Future chemical risk management

Accounting for combination effects and assessing chemicals in groups

The report of the Committe of Combination of effects and assessing chemicals in groups

Stockholm 2019

SWEDISH GOVERNMENT INQUIRIES

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To the Minister for Environment and Climate Isabella Lövin

The Government decided on the 29th of March 2018 to commission a Special Inquiry with the task to investigate how the group-wise management of hazardous chemicals can be improved, and how "combination effects" can be taken into account in regulatory risk assessment (Miljödepartementet Dir. 2018:25). On the same day, the Minister, Karolina Skog, appointed Professor Christina Rudén, Stockholm University, as chair of the Inquiry.

The following experts were employed and contributed throughout the Inquiry period:

- Professor Thomas Backhaus, environmental scientist, University of Gothenburg
- Mr Per Bergman, lawyer and former senior legal advisor to the Swedish Chemicals Agency
- Dr Michael Faust, environmental scientist and independent environmental consultant
- Dr Linda Molander, toxicologist, the Public Health Agency of Sweden
- Dr Daniel Slunge, economist, University of Gothenburg.

The Inquiry also received valuable contributions from the following experts: Professor Gunnar Johansson, Karolinska Institutet, Jan Hammar, previously vice Director General at the Swedish Chemicals Agency, professor Andreas Kortenkamp, Brunel University, London, Rolf Altenburger, Helmholtz Center for Environmental research, Leipzig, and senior professor Åke Bergman, Stockholm University. Professor Jonathan Martin and Henrik Hamrén, both from Stockholm

University, are also gratefully acknowledged for reading and improving the texts concerning language and style.

Finally, we thank all the stakeholders and scientists that provided valuable input throughout the inquiry period.

The Inquiry hereby submits the SOU 2019:45, *Future chemical risk management – Accounting for combination effects and assessing chemicals in groups*, to the Minister for Environment and Climate.

The report has been produced in close collaboration between the Inquiry Chair and the team of experts. Therefore the word ”we” is used throughout the report. However, as the Inquiry Chair I am solely responsible for the content.

The Inquiry is hereby finalized.

Stockholm October 2019

Christina Rudén

Contents

Acronyms and abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AEP	aggregate exposure pathway (framework)
AL	(regulatory) acceptable (exposure) level
Anon	Anonymous
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)
AOEL	acceptable occupational exposure level
AOP	adverse outcome pathway
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAT	best available techniques
BMAS	Bundesministerium für Arbeit und Soziales (German Federal Ministry of Labour and Social Affairs)
BP	biocidal product
BPA	bisphenol A
BPR	Biocidal Product Regulation (EU No 528/2012)

BPS	bisphenol S
BREF	best available techniques reference (document)
CA	concentration addition
CAD	Chemical Agents Directive (Council Directive 98/24/EC)
CAG	cumulative assessment group (EFSA 2013e)
CARACAL	competent authorities for REACH and CLP
CBA	component based approach
CEFIC	The European Chemical Industry Council
CELEX	Communitatis Europeae Lex
ChemSec	International Chemical Secretariat
CLP	Classification, Labelling and Packaging of Substances and Mixtures (Regulation (EC) 1272/2008)
CMR	carcinogenic, mutagenic, or toxic for reproduction
CoRAP	Community Rolling Action Plan
CSR	chemical safety report.
DDT	dichlordiphenyltrichlorethane
DEBtox	dynamic energy budget (theory)
DNEL	derived no effect level
EAP	Environmental Action Plan (of the EU)
EBM	effect-based monitoring, method, or measure
EC	European Commission
EC50	50 % effect concentration

ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
eChemPortal	Global Portal to Information on Chemical Substances (OECD)
ECx	x% effect concentration
ED	endocrine disrupter
EDA	effect-directed analysis
EDC	endocrine disrupting chemical
EDC-MixRisk	Integrating epidemiology and experimental biology to improve risk assessment of exposure to mixtures of endocrine disruptive compounds (https://edcmixrisk.ki.se/
EEA	European Environment Agency
EFSA	European Food Safety Authority
EHP	(European) Environment and Health Process (WHO)
EIA	Environmental Impact Assessment (Directive 2011/92/EU)
EL	exposure level
ELV	exposure limit value
EMEA	European Medicines Agency
EP	European Parliament
EQS	environmental quality standard
EU	European Union
EUCLEF	The European Union Chemical Legislation Finder (upcoming ECHA online service)
EuroMix	A tiered strategy for the risk assessment of mixtures of multiple chemicals (www.euromixproject.eu)

EUToxRisk	An integrated European "flagship' program driving mechanism-based toxicity testing and risk assessment for the 21st century (www.eu-toxrisk.eu/)
EU-TP	European Toxicology Programme (proposed by ANSES and others)
FQPA	Food Quality Protection Act (US Congress 1996)
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HÄMI	Hälsorelaterad Miljöövervakning (Health-related Environmental Monitoring)
HBM4EU	The European human biomonitoring initiative (www.hbm4eu.eu)
HE	hygienic effect (Arbetsmiljöverket, AFS 2015:7)
HEG	homogenous exposure group
HELCOM	Helsinki Commission: Baltic Marine Environment Protection Commission
HI	hazard index
IA	independent action
IED	Industrial Emissions Directive (2010/75/EU)
IPCHEM	Information Platform for Chemical Monitoring (JRC))
IPCS	International Programme on Chemical Safety (WHO)
IPPC	Integrated Pollution Prevention and Control (Directive 2010/75/EU)
JRC	Joint Research Centre (of the European Commission)

KEMI	Kemikalieinspektionen (Swedish Chemicals Agency)
LCID	lead component identification methodology (CEFIC 2018)
MAF	mixture allocation factor or mixture assessment factor
MCS	multi-constituent substance (as defined under REACH)
MM	mixed modelling (approach)
MoA	mode of action
MPC	maximum permissible concentration
MRA	mixture risk assessment
MRL	maximum residue level
MSFD	Marine Strategy Framework Directive (2008/56/EC)
msPAF	multi-substance potentially affected fraction of species (De Zwart and Posthuma 2005)
NC	negligible concentration
NOAEL	no-observed adverse effect level
NOEC	no observed effect concentration
NTE	non-toxic environment
NTS	non-target screening
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
OELV	occupational exposure limit value
OSPAR	Oslo and Paris Commissions: Convention for the Protection of the Marine Environment of the North-East Atlantic

p	page
PAH	poly-aromatic hydrocarbon
PBPK/PD	physiologically-based pharmacokinetics and pharmacodynamics (modelling)
PBT	persistent, bioaccumulative, and toxic
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PEC	predicted environmental concentration
PFAS	per- and polyfluoroalkyl substances
PFOS	perfluorooctane sulfonic acid
PIC	prior informed consent
PNEC	predicted no effect concentration
POD	point of departure
PODI	point of departure index
POP	persistent organic pollutant
pp	pages
PPP	plant protection product
PPPR	Plant Protection Products Regulation ([EC] No 1107/2009)
QSAR	quantitative structure activity relationship
RAC	Risk Assessment Committee (under REACH)
RBSP	river basin specific pollutant (under the WFD)
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (Regulation (EC) No 1907/2006)

RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
RMOA	risk management option analysis
Rohs	restriction of the use of certain hazardous substances in electrical and electronic equipment (Directive 2011/65)
RQ	risk quotient
RV	(regulatory) reference value
SAICM	Strategic Approach to International Chemicals Management (UNEP).
SCCS	Scientific Committee on Consumer Safety (of the European Commission)
SDG	sustainable development goal (WHO)
SFS	Svensk författningssamling (Swedish Code of Statutes)
SIN	Substitute It Now! (ChemSec campaign)
SOLUTIONS	Solutions for present and future emerging pollutants in land and water resources management. www.solutions-project.eu
SOU	Statens Offentliga Utredningar (Official Reports of the Swedish Government)
SPIN	Substances in Preparations in the Nordic Countries (database)
SVHC	substance of very high concern
SwIM	Swedish Interagency Task Force on Mixture Risk Assessment (*establishment recommended in this report*)
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalent quantity

TFEU	Treaty on the Functioning of the European Union
TU	toxic units
TUS	toxic unit summation
UN	United Nations
UNCED	United Nations Conference on Environment and Development
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
US NIEHS	United States National Institute of Environmental Health Sciences
US	United States (of America)
USSR	Union of Soviet Socialist Republics
UV	ultraviolet (radiation)
UVCB	materials of unknown or variable composition, complex reaction products or biological materials (as defined under REACH)
VOC	volatile organic compound
vPvB	very persistent and very bioaccumulative
WFD	Water Framework Directive (2000/60/EC)
WHO	World Health Organization
WMA	whole mixture approach
WMT	whole mixture testing

Executive summary

The first Europe-wide chemicals legislation was introduced more than fifty years ago: in 1967 the Dangerous Substance Directive established a hazard-based system for classification and labeling of chemicals. Subsequent risk-based regulatory frameworks, the predecessors of REACH, were then established in the eighties and nineties. The enactment of these pieces of legislation and their modern counterparts resulted in lowering of concentrations of many classical toxicants found in European citizens and ecosystems. This is as a huge success and demonstrates the power of adequate chemical regulation to safeguard and improve environmental and human health.

However, according to Eurostat, Europe still uses more than 200 million tons of hazardous chemicals per year and more than 22 000 different chemicals are registered under REACH alone. Not surprisingly, monitoring studies routinely confirm the presence of chemical mixtures in basically every analyzed environment and human tissue. That is, the typical exposure scenario has shifted from locally confined, high concentrations of individual compounds to a diffuse, widely spread mixture, composed of a myriad of individual pollutants, each one often present at low concentrations.

This report presents 11 recommendations on how modern European chemical regulation can keep up with this complexity. The proposals focus on two issues of particular relevance:

(1) Risk assessment and management of chemical mixtures, in order to increase their relevance for protecting human health and the environment.

(2) Group-wise evaluation of chemicals, in order to facilitate the identification of substances of concern and the substitution of problematic substances.

In Chapter 1 our assignment, and how we pursued it, is summarized. Chapter 2 contains a broad overview of the issues at hand and

explanations of key terms and definitions. In Chapter 3 the relevant pieces of Swedish and European chemical legislation, and important international conventions are summarized. The scientific background of our recommendations is detailed in Chapters 4 and 5, and in Chapter 6 the recommendations are presented. Each introduced by a problem description. In Chapter 7 the consequences of implementing our recommendations are outlined, and in Chapter 8 we provide a brief overview of our interactions with stakeholders. Last, the references are listed as well as explanations to the acronyms and abbreviations that are used in text.

Our analysis shows that significant improvements of the current system for chemicals control are needed in order to keep up with scientific progress as well as the dynamics of chemical discovery and use.

To develop the legislation is a prerequisite to fulfill the overarching aim of EU chemical legislation to ensure a high level of protection for human health and the environment, and the Swedish goal that the total exposure to chemical substances via all sources of exposure shall not be harmful to people or biodiversity.

Figure 1 **Our eleven recommendations**

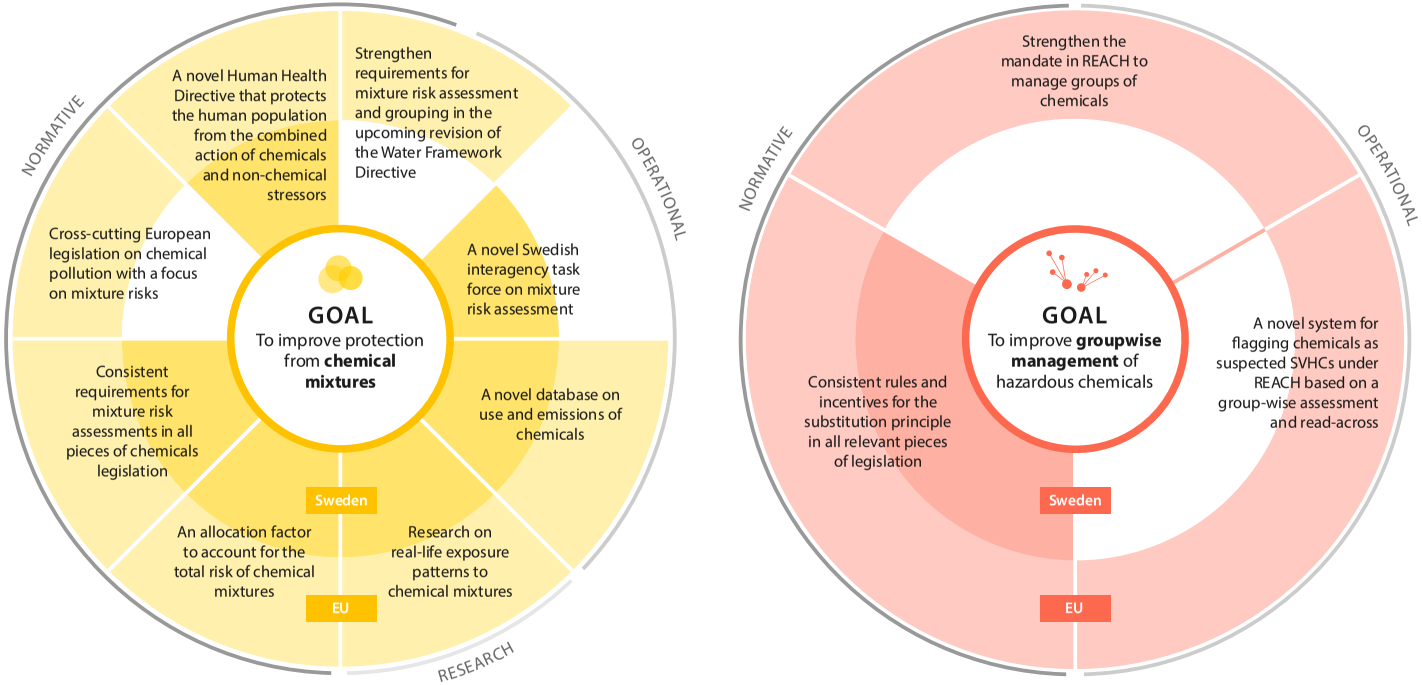

Image reference: E. Wikander/Azote.

Improve the assessment and management of mixture risks

Humans as well as organisms in the environment are exposed to complex mixtures of chemicals during their entire lives. The science behind the toxicology and ecotoxicology of mixtures is very clear: the total risk of a chemical mixture typically exceeds the risk of each individual chemical at their respective concentration in the mixture. Assessing and managing each chemical in isolation is insufficient and managing mixture risks is therefore a genuine task in order to ensure a high level of human health and environmental protection.

Already in 2009, a European state-of-the-art report on mixtures concluded that "mixture risk assessment (…) is not only necessary, but also feasible". Now – ten years later – there is an even larger body of scientific evidence to support this conclusion. The need for improving the management of mixture risks has also been addressed in several policy documents, such as the Commission Communication (2012), the EU strategy for endocrine disrupting chemicals (EC 2018a), the 7th Environmental Action Program, and the Swedish environmental objective "a Non-toxic Environment".

The concept of *Concentration Addition* is now a generally accepted common principle for mixture risk assessment, and several EU guidance documents provide details on its implementation for various mixture types. However, mixture risks are still not systematically addressed in all pieces of legislation, and cross-cutting guidance is lacking.

Our analyses show that improving the protection of human health and the environment from mixture risks requires concerted actions on different levels and within different elements of the regulatory system. In this report, we outline the necessary components of a consistent system for regulatory mixture risk assessment and management:

To introduce clear legal requirements for mixture risk assessments in all relevant pieces of EU chemicals legislation is an indispensable prerequisite for progress. Otherwise, competent authorities cannot be expected to spend time and resources on the issue (Recommendation 6.1).

Additionally, a *European policy framework that cut across the different pieces of legislations* is necessary in order to address unintentional

mixtures of chemicals that are individually subject to different pieces of EU legislation (Recommendations 6.2 and 6.3).

Any setting of normative requirements for mixture risk assessment should be combined with determined schedules for developing guidelines for their technical implementation. Otherwise, as previous experience shows, effective implementation may take a very long time (see 4.5.2).

Testing and monitoring every conceivable mixture is practically impossible. Modelling both co-exposures and combined toxicity is therefore key for regulatory progress. However, missing or insufficient data on production volumes, use patterns, emissions and exposure for the individual chemicals constitute a serious bottleneck for performing such predictive mixture risk assessments. Therefore, *collecting information on use and emissions of chemicals in a comprehensive, and publicly available, EU-wide database* is necessary (Recommendation 6.4).

Research is an important third element of a strategy towards better protection from mixture risks. We emphasize however, that the precautionary principle is a cornerstone in European chemicals management and that scientific knowledge gaps therefore should not be (mis)used as an excuse for delaying regulatory action. A plethora of relevant and reliable research results is already available. Nevertheless, with the aim to prioritise mixtures of high concern for risk reduction efforts, there is a clear need for a large-scale *research program on real-life exposure patterns to chemical mixtures* (Recommendation 6.5). The advancement of prospective co-exposure modelling techniques and monitoring-based retrospective identification of typical co-exposure patterns should be integrated in such a program.

Default assumptions for safe-guarding against mixture risks within the frame of single substance assessments (see 4.4.5) is another important element. If the available data are insufficient to allow an assessment of actual co-exposure situations, a default scenario should be assumed by means of a *mixture allocation factor* (MAF). Accordingly, we propose that each individual chemical should be allowed to only use a maximum of 10 % of the tolerable exposure level – the *risk cup* (Recommendation 6.6). An exceedance of this level should either initiate refined assessments beyond the default scenario or should prompt a systematic search for less risky alternatives (substitution).

The forthcoming *revision of the WFD* affords a specific opportunity for improving mixture risk assessment in the context of European water management (Recommendation 6.10).

Finally, we propose to create *a Swedish Interagency task force on mixture risk assessment* (Recommendation 6.11). This task force should get the responsibility to develop systems and processes that enable data and knowledge transfer across the different chemical legislations and authorities. Work of this task force should begin on the Swedish level. The knowledge and experiences gained by this work could then be used to pave the way for similar work at the EU level.

Increase and develop group-wise assessment and management of chemicals in order to facilitate the identification of substances of concern and their substitution

Organizing chemicals into well-defined groups helps to reduce the complexity of chemical risk assessment and management. In particular, a systematic group-wise assessment would facilitate a more effective application of the substitution principle and reduce the risk of regrettable substitutions.

However, the consideration of the substitution principle is still inconsistent across the different pieces of chemical regulation. Consequently, *the introduction of clear and consistent legal requirements to explore options for substitution* in all relevant pieces of chemical legislation is an important improvement. Such a consistent legal basis across legislations is a prerequisite for continuous risk reduction, and to avoid regrettable substitution, independent of the commercial use of a chemical (Recommendation 6.7). Additionally, only such clear legal requirements will allow regulatory authorities to invest enough resources and expertise.

The vast majority of chemicals on the European market is managed under REACH. We therefore provide a specific recommendation (Recommendation 6.8) to *increase and develop the use of grouping as a tool for chemical risk assessment and management under REACH*. This would enable authorities to address all substances, optimize data generation and evaluation (and minimize animal testing), and

would finally facilitate the regulatory risk management for substances of concern.

Furthermore, *substances of concern can be identified more effectively using group-based approaches and read-across* (Recommendation 6.9). This could help guide future testing efforts, the substitution towards less problematic classes of chemicals, and the implementation of adequate risk management measures.

It should be emphasized that the public dissemination and documentation of all these approaches and the resulting data is essential to get downstream users involved and to make the improved consideration of the substitution principle work in practice.

1 Terms of reference

The Inquiry Chair was given the tasks to:

1. identify opportunities, obstacles and previous measures in relevant EU legal instruments for dealing with substances by group;
2. propose strategies for future group-based regulation and, where necessary, any amendments to relevant EU legal instruments for dealing with substances by group;
3. sum up the state of scientific knowledge, identify opportunities and obstacles in different relevant EU legal instruments and previous measures in the area of combination effects; and
4. propose strategies to enable regulation based on, or taking account of, combination effects, propose other strategies to reduce the risks and, where necessary, propose amendments to relevant EU legal instruments.

The complete terms of reference (Miljödepartementet Dir. 2018:25) are reproduced in annex 1 to this report.

The analyses focus on those aspects of the regulatory system for chemicals control that are directly relevant to the two issues at hand, i.e. improving mixture toxicity assessment and developing strategies for a group-based regulation of chemicals. The state of the art, challenges and developments with respect to the regulation of individual chemicals are therefore only presented and discussed from these perspectives.

The report focuses exclusively on the (eco)toxicological consequences of the involuntary exposure to man-made chemicals (synthesized or mined). The assessment of naturally occurring contaminants (e.g. mycotoxins) in food, and microbial contamination (e.g. Salmonella) is beyond the scope. Also the consequences of deliberate and/or

controlled chemical exposure, e.g. alcohol consumption, tobacco smoke or the use of pharmaceuticals, were not evaluated.

Following the terms of reference, the recommendations focus on the Swedish and European levels.

The Inquiry team covered the necessary areas of expertise, i.e. regulatory (eco)toxicology, chemical risk assessment, environmental science, legal expertise (EU and Swedish chemicals legislation) and economy. This report is therefore the result of an interdisciplinary team effort.

Contacts and discussions with a large number of experts and stakeholders from academia, national and European authorities and authoritative bodies, NGOs, industry organizations and individual companies were initiated at an early stage and our work was communicated continuously throughout the inquiry period. The input that we received contributed significantly to the final report (for further details see Chapter 8).

The report was initially written in English, in order to allow communication with experts outside Sweden. It has subsequently been translated into Swedish. While every effort was made to ensure that the content of both reports is identical, the English report shall take precedence in case of discrepancies.

2 Introduction

2.1 Background

Tens of thousands of individual chemicals are currently available on the EU and global markets, either as more or less pure substances, or as technical mixtures, such as paint and glue.

Chemicals are abundantly used in numerous applications. They are used as such or they are incorporated into products that are either made by, or treated with, chemicals, that give them desired properties, such as “soft”, “hard”, “UV-resistant”, “water-repellant”, “non-stick”, “sticky”, “disinfected”, “nice smelling”, “flame-retardant” etcetera. We have learned to appreciate these positive aspects of chemical use, and it has been estimated that 95 per cent of all goods are directly linked to chemicals or chemical processes[1]. Therefore, the flow of products and materials in society can indeed be seen as a flow of chemicals.

Continuous exposure

Besides their desired technical properties, chemicals can also have unwanted ”side-effects”, i.e. be toxic and cause adverse effects on human health, environmental species and ecosystems.

Chemicals are emitted from all parts of the value chain, from production via use to the end-of-life and waste-phase, continuously exposing humans and the environment to complex chemical mixtures. Unfortunately, there are several examples of such exposures causing adverse effects to human health and the environment. Some well-known examples being: lead, mercury, tributyltin, PCB, DDT, trichloroethene, vinyl chloride, asbestos, chromium-6, brominated

[1] www.greenchemistryvienna2018.com/

flame retardants, perfluorinated substances, ethinylestradiol, and neonicotinoids (EEA 2013).

As a response, legislation to control environmental and health risks has developed gradually. The first step towards a European regulatory system was taken in 1967 with the Council Directive 67/548 on classification, labelling and packaging of hazardous substances. More recent EU chemicals legislation includes for instance the REACH Regulation (2006), the Marine Strategy Framework Directive (2008), an update of the rules for Plant Protection Products (2009), and the Biocide Products Regulation (2012).

Chemicals control is largely harmonized at the EU-level, and there is a significant number of legislations in force that deal with chemicals directly or indirectly. These rules have been developed at different points in time and for different purposes. Attempts have been made to harmonize and stream-line different parts of the system. The REACH regulation combined for instance more than 30 different pieces of legislations. Nevertheless, the regulatory system for chemicals control is still scattered across different laws and agencies, and between EU and national levels.

This has led to a situation where there are inconsistencies between the different regulatory frameworks, only little exchange of information between them, and no overarching or systematic attempts to harmonize across (Evans et al. 2016).

Underestimated risks

The overarching aim of EU chemicals legislation is to ensure the functioning of the common market as well as maintaining a "high level of protection for human health and the environment".

Human and environmental exposures includes a mixture of a large number of chemicals. The legal requirements for risk assessment of individual chemicals differs depending on the chemicals' intended use. Regulatory requirements are however never sufficient to enable a risk assessment that is fully relevant to the real-world situation. There is a huge number of potential hazardous effects, and also a large number of individual chemicals. In addition, the total exposure varies in time and space.

Regulatory risk assessments focus on one chemical at the time, and the complexity of the exposure and the exposed systems makes the risks inherently difficult to quantify. These are two reasons why risks associated with chemical exposures may be underestimated (Landrigan et al. 2017, UNEP/WHO 2013), and why overall chemicals management is still considered insufficient, despite several examples of successful risk management decisions for single chemicals (e.g. UNEP 2019b, KEMI 2019, Drakvik et al. 2019, Landrigan et al. 2017).

In this report, we will analyze and propose concrete actions to further develop and strengthen two important aspects of the regulatory system for chemicals control:

- *Improve the relevance of the system by taking mixtures of chemicals into account, to avoid that risks are systematically underestimated*. Scientific evidence for heightened toxicity from unintentional mixtures is mounting, yet regulation is lagging behind. The challenge is thus to reduce the risks from hazardous chemical mixtures and from the total exposure to chemicals across the different legislations.
- *The need to address groups of chemicals in order to promote data generation and support sustainable substitution*. Grouping of chemicals can help filling data gaps by read across, and grouping for risk management decisions can create incentives for data generation, and support sustainable substitution.

2.2 What do we mean by "mixtures"?

In this report, *mixtures* is a short expression for *chemical mixtures*. The term *chemical mixtures* is used to denote any set of chemicals to which an organism may be jointly exposed, and which may potentially cause an adverse combination effect, regardless of sources and exposure routes.

Chemical in this context means chemical elements and compounds of elements. In this report we use the word *chemical* and *substance* synonymously. But it should be noted that in legal terms, the term *substance* specifically denotes chemicals in the state produced or used, i.e. including technical additives and impurities.

In compliance with the Non-Toxic Environment Strategy, this report is focused on mixtures of man-made or extracted chemicals[2].

This is a broad and general understanding of *chemical mixtures* that is in line with the use of the term by the European Commission (EC 2012a), EFSA (2019), US agencies (ATSDR 2004), and the WHO IPCS (Meek et al. 2011). The general definition encompasses more specific uses under specific pieces of legislation. This particularly applies to the REACH legislation, where the term *mixtures* denotes intentionally prepared combinations of chemicals for commercial use.

Considering the whole framework of EU chemicals legislation, four different types of mixtures may be distinguished, each requiring different regulatory strategies for risk assessment and risk management:

(1) Chemicals that are legally registered as single substances on the EU market, but which are mixtures in themselves, such as so-called *multi-constituent substances* (MCS) and *materials of unknown or variable composition, complex reaction products or biological materials* (UVCBs) as defined under REACH. Examples are racemates[3] (MCS) and petroleum products (UVCB).

(2) Intentionally prepared mixtures that are placed on the EU market as chemical products. This category includes various types of chemical products for industrial and technical use, agricultural use, household use, medical and personal care use etc.

(3) Mixtures of chemicals jointly released from a single source, such as production, transportation, consumption, recycling, or waste (water) treatment processes. Typical examples are emissions into air from combustion processes, such as waste incineration or motor car driving, or emissions into rivers and lakes from waste water treatment plants.

[2] It should however, be pointed out that where mixtures components occur in the environment both naturally and as a result of human activities (e.g. metals), aggregate exposures from both sources should be considered in both single substance and mixture risk assessments.
[3] A racemate includes equal amounts of two organic molecules with the same molecular structure but opposite spacial orientation, like right and left hands.

(4) So-called unintentional mixtures of chemicals co-occurring in environmental media (water, soil, air), biota, feed, food, or human tissues as a result of releases from various sources and through multiple routes of exposure. In the literature, unintentional mixtures are also denoted as coincidental mixtures. Unintentional mixtures include degradation and transformation products of chemicals released into the environment.

Previous reviews have shown that type 1 and type 2 mixtures – and partly also type 3 mixtures – are subject to regulations under different pieces of EU law (Kortenkamp et al. 2009, EC 2012a, Kienzler at al. 2014, 2016).

Type 4 mixtures represent the main focus of regulatory concern. In 2012, the Commission concluded that "within the framework of EU legislation, there is no mechanism for a systematic, comprehensive and integrated assessment of mixture effects taking into account different routes of exposure and different product types" (EC 2012a). This situation continues to apply, as shown by the updated and extended review of the legal framework presented in Chapter 3 of this report. Recommendations derived in this report for improving the protection from mixture risks refer to *unintentional mixtures*.

What do we mean by mixture risk assessment?

The assessment of risks from exposure to chemical mixtures is denoted *mixture risk assessment* (MRA). *Cumulative risk assessment* is a synonymous term used under the EU legislation on plant protection products (PPP) and under some pieces of US legislation.

Mixture risk assessments may refer to humans or to organisms in the environment, and they may be performed for individuals, populations, species assemblages or whole ecosystems.

In congruence with established regulatory procedures for single substance assessment, mixture risk assessments are usually structured into four main steps:

(i) problem formulation
(ii) exposure assessment
(iii) hazard assessment
(iv) risk characterization.

However, the performance of these steps differs from single substance assessments, as explained in Chapter 4 of this report.

In a mixture risk assessment, *the problem formulation step* means to define the mixture of concern in terms of the chemical nature of components or in terms of common hazardous properties or a combination of both.

The *exposure assessment* step means to define the quantitative composition of the mixture in terms of component concentrations or doses. For short, the exposure assessment for chemical mixtures is denoted as *co-exposure assessment*. Co-exposure is also denoted by various similar terms such as *combined exposure*, *joint exposure*, and *cumulative exposure*.

An important distinction is made between cumulative exposure and aggregate exposure. Aggregate exposure denotes exposure to a single substance from different sources via different routes, while cumulative exposure refers to mixtures of different substances from different sources via different routes (WHO IPCS 2009).

The hazard assessment of mixtures is also denoted as *mixture toxicity assessment*. Mixture toxicity means the adverse effects on an organism that may result from co-exposure to the components of a mixture. Such effects are variously also referred to by similar expressions such as *combined effects, combination effects, cumulative effects, joint toxicity, or joint response*.

Mixture toxicity assessments may include both quantitative and qualitative aspects. In quantitative terms, the frequency or magnitude of a definite toxicological effect is typically higher for a mixture than for individual components. In qualitative terms, mixture components may contribute to effects, which they do not cause individually, such as tumor promotion by non-carcinogenic agents.

The *risk characterization* of mixtures is usually performed in terms of a risk quotient, i.e. the ratio between an observed or predicted exposure level and a regulatory acceptable exposure level,

which is considered to be reasonably safe. Formally, this approach is identical to single substance risk assessments. However, special methodologies are necessary to calculate such quotients for mixtures, as explained in Chapter 4.

Unless noticed otherwise, basic (eco)toxicological terms and concepts have the same meaning for mixture risk assessments as established for single substance assessments (see e.g. van Leeuwen and Vermeire 2007). In particular this applies to the concepts of *effect*, *endpoint*, *mechanism* or *mode of action*, *hazard*, and *risk*.

An *endpoint* is an *effect* that is measurable in a toxicity test, varying with the examined level of biological organisation from biochemical markers over cellular responses to effects on individuals and populations such as symptoms of diseases or mortality.

Mechanism, *or mode of action* (MoA) or *adverse outcome pathways* (AOP) are concepts denoting the complex chain of events from molecular interactions to adverse outcomes on the level of an individual or a population.

Hazard denotes the inherent property of a chemical or mixture to cause adverse biological effects, while *risk* denotes the probability of the occurrence of such effects as a result of exposure to a chemical or chemical mixture, for regulatory purposes often operationalized in terms of risk quotients.

2.3 Why is mixture risk assessment necessary?

During the last 10 to 15 years, a paradigm shift has taken place in regulatory toxicology and ecotoxicology. The adequacy of the conventional single substance assessment approach is questioned and mixture risk assessments are deemed necessary (see e.g. Solecki et al. 2014, EC 2018c, Kortenkamp and Faust 2018, Bergman et al. 2019). The main arguments driving this change are the following:

(1) *Humans and environmental organisms are not exposed to single substances in isolation but to mixtures of chemicals from numerous sources*. For example, the EU-project EDC-MixRisk found mixtures of 41 endocrine disrupting chemicals in urine and serum samples from 2300 pregnant woman and provided evidence on associated mixture risks for the children (Bergman et al. 2019).

Thus, combined exposures must be taken into account to make chemical risk assessments more relevant.

(2) *Combined exposures usually present a higher risk than isolated exposures to individual mixture constituents at those concentration or dose levels present in the mixture*. Mixtures may even cause significant adverse effects if all components are present at or below so-called no-observed adverse effect levels (NOAELs), i.e. concentration or dose levels at and below which no statistically significant effects are seen in single substance tests. In the literature, this has been denoted as the "something from nothing" phenomenon and demonstrated in several experimental mixture toxicity studies (Kortenkamp 2014). Thus, mixture assessments are necessary to avoid underestimations of total risks.

(3) *Regulatory reference values, which have been established to define safe exposure levels for single substances, may not be sufficiently protective in situations of combined exposure to multiple chemicals*. This is not only a theoretically derived assumption but has also been demonstrated empirically in a study led by the European Commission's Joint Research Centre on the effects of mixtures of multiple pollutants on aquatic life (Carvalho et al. 2014). Regulatory reference values are derived from NOAELs, or similar toxicity indicators, by means of assessment factors, which bridge a number of uncertainties, in particular intra- and inter-species sensitivity variations. In contrast to widespread belief, however, such assessment factors do not account for simultaneous exposures to many chemicals (Martin et al. 2013). Hence, mixture risk assessments are necessary to establish safe levels of combined exposures.

(4) *Risk reduction measures that are focused on single chemicals exceeding regulatory reference values may fall short in situations of combined exposures to multiple chemicals*. Mixture components below individual reference values may make significant contributions to an unacceptable overall risk. Mixture risk assessments are necessary for filtering out mixtures of high concern, so-called *priority mixtures* and for identifying mixture components or groups of components explaining most of the overall risk, so-called *drivers* of mixture risks. Such drivers should be the primary target of risk reduction measures. Thus, mixture risk

assessments are needed to make risk management efficient and effective.

Fortunately, mixture risk assessment is not only necessary but also feasible. Scientific methods are available for both prospective and retrospective assessments of risks from combined exposures. During the last ten years, such methods have been intensively reviewed and guidance documents for regulatory applications have been prepared. A summary review of the resulting state-of-affairs is given in Chapter 4 of this report.

2.4 What do we mean by grouping?

Grouping of chemicals is done in many different contexts, both within regulatory and voluntary frameworks, and therefore the term *grouping* can have different meanings.

In this report, grouping refers to the processes of identifying, assessing and managing health and environmental risks involving two or more chemicals (or substances) based on certain shared aspects.

According to REACH and CLP, and for the purposes of this report, a group is generally defined as two or more substances with distinct identities (REACH Article 3.1).

Chemical substances can be divided into groups in different ways depending on the purpose for grouping, e.g. if it is for screening or priority-setting, hazard identification or risk management decision-making. Chemicals may be grouped based on one or more of the following aspects:

- *Molecular structure*, e.g. a common functional group or constituent, or similar carbon range numbers.
- *Toxicokinetic and toxicodynamic similarities*, e.g. common metabolic routes, critical target organ, mechanism or mode of action (MoA), adverse outcome pathway (AOP) or breakdown products.
- *Intrinsic properties, including physicochemical, (eco)toxicological and environmental fate properties*, e.g. PBT, CMR or ED properties.
- *Technical/functional properties*, e.g. softeners, pigments, preservatives, flame retardants.

- *Areas of use and occurrence*, e.g. use in certain products or occurrence in environmental compartments.
- *Regulatory domain*, e.g. biocides, plant protection products and pharmaceuticals.
- *Exposure pattern*, e.g. exposure route, level of exposure and exposed populations.

(OECD 2014, ECHA 2008a, KEMI 2018a)

These aspects are often related to each other. For example, structurally similar chemicals can have similar intrinsic properties, and how chemicals are used is often linked to the type and level of exposure.

The group size can vary greatly, from two substances to thousands of substances. Grouping substances based on intrinsic properties, such as substances meeting the CLP criteria for CMR and/or the PBT/vPvB criteria, is common in several legislations and may result in regulatory measures including a large number of substances. One such example is the restriction of CMR substances in toys under the Toys Safety Directive (2009/48/EC).

Substances identified to belong to a certain group may either be regulated as a part of that group or individually, i.e. processed individually for different regulatory measures, such as for inclusion on the Candidate or authorization lists (KEMI 2018a).

2.5 Why is group-wise management of substances necessary?

Grouping of chemical substances for risk assessment or risk management has been highlighted as an important way forward, for the following reasons:

(1) *To make chemicals control more resource efficient*. Evaluating a group of substances may generate more detailed knowledge on the group members, as information on the individual substances in a group of structurally similar substances can increase the confidence in the reliability of the results of the individual substances and provide a more coherent picture of the properties of all the substances in the group (OECD 2014). The OECD

guidance also highlights that the application of the category approach can be more efficient and accurate than a one-by-one assessment of single compounds, since the identification of compounds as members of a category can provide insights into the potential effects of these compounds that might otherwise be overlooked. In this regard, information on the properties of chemicals that e.g. are technically difficult to evaluate following standardized test protocols may be improved (OECD 2014).

(2) *Limit the use of experimental animals*. Group-approaches can be used to fill information gaps. Available data on for example intrinsic properties of individual substances in a group of substances sharing similar structures can be used to estimate the corresponding properties of untested substances in that group. This approach is called read across and can be done from one (or a few) source substance(s) to a target substance (called the analogue approach), or within a larger group of structurally similar substances (called the category approach) (ECHA 2008a, 2017a, OECD 2014).

(3) *To prevent regrettable substitution*, i.e. that a substance with undesirable properties is being replaced by another substance with similar and/or other unwanted properties (e.g. Sveriges Regering 2013, KEMI 2014, OECD 2014, Miljödepartementet 2018). In substitution processes, substances of concern may be replaced by structurally similar chemicals as they often provide the same technical function. However, they also often show similar undesired hazardous properties and then the hazard or risk may remain similar as with the original chemicals. Grouping substances with similar chemical structures, (eco)toxicological properties, functions and/or areas of use, has therefore become a necessary strategy to process and prioritize among the large number substances on the market and to speed up the transition to less hazardous and more sustainable alternatives (KEMI 2018a, EC 2017a).

Although EU chemicals legislation primarily regulates one chemical at a time, grouping of chemicals is done in several processes under different pieces of EU legislations, e.g. for substance evaluation, identification of substances of very high concern (SVHC) and

authorization and restriction of chemicals under REACH, and to some extent in the harmonised classification of substances under CLP. However, as the Swedish Chemicals Agency recently pointed out, "additional efforts are needed if more systematic assessment and management of groups of chemical substances are to take place within REACH and CLP" (KEMI 2018a). Currently, group-wise management is unsystematic and is much dependent on the engagement and resources available at Member States Competent Authorities.

3 Legal and policy frameworks

3.1 Scope of the review of legal and policy frameworks

The following chapter gives a brief overview of legislation that has the objective (or one of its objectives) to regulate and limit chemical risks, including the issues of assessing chemical mixtures or group-wise management of chemicals.

Legislation takes the form of legally binding rules, but chemical risks are also dealt with in policy frameworks, at global, regional and national levels, which may all be relevant for our report.

Such policy frameworks may take different forms, for example as strategy documents or action programs. They are not binding for individuals in the same way as legislation but may express important principles for handling chemical risk. They may also represent essential steps in the process of developing new binding legislation.

We have structured the chapter in the following manner:

- A brief description of the most relevant policy frameworks, agreements and principles for chemicals control at international levels (global and EU).
- A review of EU policy initiatives that are relevant for our remit.
- An overview of the chemicals legislation in a broad sense. This is focused on EU law in line with the priorities set by our terms of reference.
- A brief description of Swedish legal and policy frameworks.

This is followed by some general conclusions about the need for coordination between different pieces of law in order to deal with the challenges of mixture assessment and grouping.

Only the most important EU Regulations and Directives are described. Any provisions in the legal texts that relate to mixture risk assessment are identified, as well as rules relating to the grouping of chemicals for regulatory assessment purposes.

Guidance documents are an essential complement to almost all legislation about chemicals control. These documents are generally not covered by this chapter but are described in Chapters 4 and 5. Legislation about hazards that relate to physico-chemical properties such as flammability, explosiveness etcetera is not covered by this report.

A list with full references for the most important legal acts is provided separately in the list of references.

3.2 Global policy frameworks

The Strategic Approach to International Chemicals Management (SAICM)

SAICM is a voluntary global policy framework to promote chemical safety (see saicm.org). The overarching aim of SAICM is to achieve the sound management of chemicals so that, by 2020, chemicals are used and produced in ways that lead to the minimization of significant adverse effects on human health and the environment in order to achieve sustainable development.

SAICM acknowledges e.g. the need to take actions to improve risk reduction measures in order to prevent adverse effects of chemicals on humans and the environment, but mixture risk assessment and group-wise management are not issues specifically addressed by SAICM.

Continuing SAICM activities beyond 2020 are now being discussed, and issues related to more efficient chemical risk assessment are considered, including the use of screening-level, generic risk-based approaches and grouping of chemicals with similar properties (UNEP 2019b).

Agenda 2030 and the Sustainable Development Goals (SDGs)

In 2015 the UN General Assembly adopted Agenda 2030 with 17 goals and 169 targets with the aim to bring about sustainable economic, social and environmental development by the year 2030.

There are eight goals and sixteen targets in Agenda 2030 that have clear associations to safe management of chemicals. The eight goals are: Safe food and sustainable agriculture (goal 2), Good health (goal 3), Clean water (goal 6), Safe working environments (goal 8), Sustainable cities (goal 11), Sustainable consumption and production patterns (goal 12), Protection of ecosystems and biodiversity (goals 14 and 15) (KEMI 2016).

Chemicals are furthermore mentioned specifically in three targets:

Target 12.4: Achieve the environmentally sound management of chemicals and all wastes [...] (to be achieved already by 2020), Target 3.9: By 2030 substantially reducing the numbers of deaths and illnesses resulting from hazardous chemicals and air, water and soil pollution and contamination, and target 6.3: By 2030 improving water quality by reducing pollution, eliminating dumping and minimising the release of hazardous chemicals and materials. (KEMI 2016, UN 2015).

Agenda 2030 does not propose specific actions but foresees that "all countries and all stakeholders, acting in collaborative partnership, will implement this plan." Sweden is to achieve the agenda's objectives at the national level and to contribute to the achievement of the objectives at the global level[1].

There is a substantial overlap between the Swedish environmental objectives and the SDGs (see below). This means that working to achieve the Swedish environmental objectives will also help achieving the SDGs. And vice versa (KEMI 2016, Naturvårdsverket 2019a).

Other international agreements and Conventions

In addition to the general policy frameworks, there are several international agreements and conventions at global or regional levels that regulate specific issues. The Stockholm Convention bans or limits the use of a number of specified POPs (persistent organic

[1] See SOU 2019:13, *Agenda 2030 och Sverige: Världens utmaning – världens möjlighet*.

pollutants)[2]. The Rotterdam Convention regulates trade in dangerous chemicals by ensuring that importers receive information about the chemicals' properties. States can ban or restrict the import of certain chemicals by a system of prior informed consent (PIC)[3]

There are also other international agreements that regulate specific issues, such as mercury and substances that damage the ozone layer. The UNECE Convention on Long-range Transboundary Air Pollution[4] regulates a number of air polluting substances through separate protocols, including POPs and volatile organic compounds (VOC).

Both EU and Sweden are parties to these conventions. EU implements them through Regulations that apply in Sweden and they are therefore not transferred into Swedish law.

3.3 General principles for risk management

The Precautionary Principle and other principles of EU law

The Precautionary Principle is stated in principle 15 of the Rio Declaration of 1992 (also referred to by SAICM):

> In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.
>
> (UNCED 1992)

The principle is fundamental, and part of the definition of EU environmental policy according to Article 191.2 of the Treaty on the Functioning of the European Union (EU 2012):

> Union policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Union. It shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay.

[2] The Stockholm Convention on Persistent Organic Pollutants, see www.pops.int
[3] Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, see www.pic.int
[4] See www.unece.org/env/lrtap/welcome.html.html

The application of the precautionary principle is further developed in a Communication from the EU Commission (COM 2000, 1 final) (EC 2000).

The Treaty provision also includes other principles that are relevant for our work: the need for preventive action, that damage should be rectified at source and that the polluter shall stand the costs for dealing with damage for which he or she is responsible (polluter pays principle). Any developments of EU legislation at lower levels (directives, regulations etc.) must conform to these treaty provisions.

The Swedish Environmental Code (*Miljöbalken*) contains in section 2.3 a wording that can be seen as a reference to the precautionary principle. It is stated that

> [...] precautions shall be taken as soon as there is cause to assume that an activity or measure may cause damage or detriment to human health or the environment.

The Substitution Principle

ECHA defines the substitution principle as follows:

> the replacement or reduction of hazardous substances in products or processes by less hazardous or non-hazardous substances, or by achieving an equivalent functionality via technological or organisational measures.
>
> (ECHA 2018c)

ECHA promotes so called *functional substitution* as a means to avoid *regrettable substitution*. This includes substituting groups of chemicals instead of moving to similar chemical substitutes which may have toxicology profiles similar to the chemical being phased out (Tickner et al. 2015).

The principle is a novel element of EU legislation which is not enshrined in the principles laid down in the EU treaties. Explicit legal requirements for substitution have so far only been introduced in four pieces of EU legislation: REACH, the Biocidal Products Regulation, the Plant Protection Products Regulation and a Directive about worker protection (the Chemicals Agents Directive). Among EU Member States, it is only in the Nordic countries, particularly in Sweden, that this principle has been included in the national chemi-

cals legislation. Section 2:4 in the Swedish Environmental Code (Miljöbalken) includes the substitution principle:

> Persons who pursue an activity or take a measure, or intend to do so, shall avoid using or selling chemical products or biotechnical organisms that may involve risks to human health or the environment if products or organisms that are assumed to be less dangerous can be used instead. The same requirement shall apply to goods that contain or are treated with a chemical product or a biotechnical organism.

The Swedish Government initiated in 2017 a Swedish Centre for Chemical Substitution to help to serve as an independent coordinator between industry, organizations, companies, academia, research institutes and authorities with the aim to contribute to substituting hazardous chemicals in articles and chemical products (see www.ri.se/en).

3.4 EU policy initiatives

EU environmental policy is often initially developed through policy initiatives, which are followed in some cases by legislation. Such initiatives can take the form of environmental action programs, which are foreseen in the Treaty of the Functioning of the European Union (EU 2012, article 192.3), but can also take other forms, such as Commission Communications, Green papers or White papers. A few of these that we see as relevant are briefly described below.

Communication on the combination effects of chemicals

Conclusions were adopted 22 December 2009 by the Council of the EU where the Commission was invited to

> […] assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and report back to the Council by early 2012 at the latest.

The reply to the Council came in 2012 in a **Communication from the Commission on the combination effects of chemicals** (COM 2012, 252 final) (EC 2012a).

In this Communication, the Commission concluded that current EU legislation is insufficient for addressing mixtures and that there is no mechanism for promoting an integrated and co-ordinated assessment across different pieces of legislation.

The Commission also acknowledged the potential for cumulative effects, even when chemicals are present together in a mixture below the concentration that is considered "safe" for the individual components of the mixture.

To improve the situation the Commission stated that it should e.g. establish an ad hoc working group of relevant regulatory bodies such as EFSA, ECHA, EMEA and EEA and strengthen co-ordination across the different pieces of legislation. Other actions included promoting the assessment of priority mixtures, and to develop technical guidelines to promote a consistent approach to the assessment of priority mixtures across the different pieces of EU legislation.

A report back on the progress was promised for the end of June 2015, but so far there has been little progress in the suggested actions and the progress report is still pending.

The EU strategy for a Circular Economy

An EU strategy for a circular economy was communicated by the Commission in 2015 (COM 2015, 614 final) (EC 2015b). In a circular economy, the value of products, materials and resources is maintained in the economy for as long as possible, and the generation of waste minimised. To enable reuse and recycling, a reduction of hazardous chemicals, including substitution to less hazardous alternatives, is needed.

Actions contained in the strategy are described in a final report from the Commission (COM 2019, 190 final) (EC 2019b). There is also a separate Communication on options to address the interface between chemical, product and waste legislation (COM 2018, 32 final) (EC 2018e).

A strategy for endocrine disruptors

Endocrine disruptors are chemical substances that alter the functioning of the endocrine system and negatively affect the health of humans and animals. Concerns about the effects of endocrine disruptors lead to the adoption by the Commission of a Community Strategy for endocrine disruptors (COM 1999, 706 final) (EC 1999).

One aspect raising concerns was that endocrine disruptors can work together to produce additive effects (mixture effect, or cocktail effect) such that exposure to a combination of endocrine disruptors may produce an adverse effect at concentrations at which the individual chemicals would have no observable effect.

This was followed up by another Communication in 2018 (COM 2018, 734 final) (EC 2018a), where the full understanding of combined exposure again was identified as one example of knowledge gaps that still existed. The Commission promised to launch "a comprehensive screening of the existing legislative framework on endocrine disruptors."

The 7th Environment Action Program

The Seventh Environmental Action Program (EAP) was adopted by the European Parliament and the Council in November 2013 and covers the period up to 2020 but includes a vision for 2050.

The program highlights the need to address combination effects of chemicals and to develop a Union strategy for a non-toxic environment. In order to initiate a strategy for a non-toxic environment, a comprehensive scoping study has been performed (EC 2017a, b). This study identified a number of relevant knowledge gaps and deficits in policies and legislation. The following actions were e.g. proposed: Move from the current chemical-by-chemical to groupings of chemicals approaches in risk assessment and risk management and develop appropriate regulatory approaches to address combination effects of chemicals.

Despite this comprehensive expert analysis, the Commission has not yet delivered on its obligation to produce a strategy for a non-toxic environment by 2018.

3.5 EU legislation

3.5.1 Types of EU legislation and the scope for national legislation

The following is a brief overview of EU legislation that has the objective (or one of its objectives) to regulate and limit chemical risks, and where the issue of assessing chemical mixtures or grouping may arise. Only the most important Regulations and Directives are covered and hence the list is not complete. Any provisions in the legal texts that relate to mixture risk assessment are identified, as well as rules relating to the grouping of chemicals for regulatory assessment purposes.

The issue of mixture assessment is very topical and has been a subject of many recent studies that have also covered the regulatory aspects[5]. Risk assessment of chemicals is a subject covered by many different types of legislation that are currently functioning more or less independently. The lack of coordination and cooperation between different legislations is possibly the most difficult problem to overcome when introducing rules about mixture assessment and grouping in the legislation. This overview is followed by a brief discussion of challenges related to coordination between different pieces of law in order to deal with the challenge of mixture assessment.

We divide the existing legislation into three categories based on the content of the regulation, although there may be overlap between these categories:

- *Substance-oriented:* Rules that focus on predicting the environmental or health risks arising from an individual chemical substance or a well-defined chemical mixture that is placed on the market for a specific use. The person that places it on the market is usually responsible for assessing and managing any risk, but there may also exist detailed rules (e.g. restrictions for specific chemicals) or authorisation requirements (e.g. pesticides).
- *Emissions-oriented:* Rules that limit emissions from industrial activities or waste management. Such rules also place the responsibility on the actor responsible for the pollution. The pollutants

[5] See for example Kienzler et al. (2014), Kortenkamp et al. (2009) and Rotter et al. 2018.

are often mixtures that are not necessarily known or well defined. The negative effects of the pollution often depend on local factors that influence the application of the rules.

- *Recipient-oriented:* Legislation that aims at establishing good environmental quality for a specific environmental compartment or recipient. The most developed examples relate to water quality. The rules may identify pollutants/substances that are prioritised for action. The national authorities are often required to monitor the environment and take action if the quality standards are not met.

EU legislation covers almost all aspects of chemicals control. This legislation often takes the form of EU Regulations. Such legislation is normally fully harmonised, which means that EU Member States must apply the rules directly and without deviation. They may not decide national rules that are stricter or less strict than what follows from EU regulations. CLP and REACH are typical examples of such harmonised legislation. The purpose of the legislation is to protect health and the environment, but also to ensure that harmonised rules apply in the whole internal EU market[6].

Another type of EU environmental legislation relating to chemicals is not harmonised but takes the form of minimum requirements. This means that more stringent rules may be implemented at the national level in the member states. Such legislation is normally in the form of Directives, and these may be used to set standards for environmental compartments (e.g. water framework directive), industrial emissions, waste management and worker's health.

One example of the complex interplay between harmonised legislation and minimum requirements is the plant protection products (PPP) Regulation. Authorising PPPs is governed by a harmonised Regulation, according to which a product permit is accepted in an entire environmental zone consisting of a group of member states. The actual use of the product, however, may be limited according national rules in accordance with a separate EU Directive.

Rules of the first type of legislation mentioned above are usually harmonised, while rules of the second and third type are usually minimum requirements. Harmonised rules must be followed without

[6] This description is simplified and there may be exceptions in some cases from the harmonisation requirements.

deviations, while minimum requirements allow member states to apply stricter measures.

3.5.2 Substance-oriented legislation

Classification, labelling and packaging (CLP)

The EU Regulation 1272/2008 about classification labelling and packaging of substances and mixtures (CLP) is based on the principle that chemicals placed on the market must be labelled with information about any toxicological and eco-toxicological hazards and the need for risk management measures to protect against such hazards. It is the EU implementation of the Global Harmonized System (GHS), which was developed by the United Nations[7]. Dangerous substances and mixtures are classified in hazard classes indicating the type of hazard to health or the environment and the strength of the evidence (expressed by risk phrases). The different types of hazards are linked to risk management measures (expressed by safety phrases).

This hazard information is provided to the consumer via the product label or in safety data sheets (for professional users). The person responsible for placing the chemical on the market is responsible for the classification and labelling according to extensive criteria given in the annexes to the legislation, but some substances with certain toxicological properties are subject to harmonized classification laid down by the authorities.

Classification is based on existing information in the form of experimental test results, epidemiological data etc. The availability of (eco)toxicological data is the subject of REACH since there are no testing requirements in the CLP.

The hazardousness of intentional mixtures is determined according to detailed rules given in the Regulation.

[7] See www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

REACH

The EU REACH Regulation[8] is very broad in scope and covers in principle all intentionally produced chemicals (generally not waste) that are not subject to special legislation (pesticides, food additives etc.). It is based on the requirement that all substances marketed have to be registered with the European Chemicals Agency (ECHA). The registrant (the person who places the chemical on the market or imports it into the EU) shall include a hazard assessment in the registration as well as risk assessments for all identified uses. The risk assessment must cover the use of the substance in mixtures in cases where the mixture is placed on the market. The hazard assessment shall be based on specified toxicological and ecotoxicological data that must be provided by the registrant. The risk assessment must be documented in a chemical safety report (CSR)[9].

REACH also includes rules for authorities about evaluating chemicals of concern. Substances of very high concern are subject to an authorisation procedure and general restrictions or bans apply for specified uses of some substances.

REACH focuses on substances, but a substance according to REACH is a product marketed for a commercial use, which means that it may have a number of constituents[10]. The substance may be well defined, so that it is known which components are included and within what ranges the components may vary. However, particularly for substances of biological origin or for minerals it is often not possible to indicate the components precisely, as the composition varies. Such substances are known as UVCB substances (*Substances of Unknown or Variable composition, Complex reaction products or Biological materials*).

REACH is therefore focused on the evaluation of individual substances and contains no specific methodology for assessing mixtures beyond *multi-constituent substances* (MCSs) and UVCBs, even

[8] Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
[9] Except for known SVHCs, these requirements apply fully only for substances placed on the market in quantities over 10 tonnes yearly.
[10] The legal definition: "Substance means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition."

though the risk assessment must cover the use in intentional mixtures. A registrant of a substance is in principle not required to assess and analyse co-occurrence of chemicals in environmental media. The legal text in REACH is not totally clear, however, when delimiting what is required by the registrant[11].

Combined and aggregate exposure may to some extent be assessed when the authorities evaluate a substance or consider authorisation according to Title VII in REACH[12]. As regards regulatory restrictions of chemical use (Title VIII), the legal text refers to the need to establish "adequate control" as described in Annex I.

The grouping of substances is not covered by REACH in a structured way. Grouping is mentioned in the substance evaluation chapter for substances that are similar (Article 47). The testing and assessment requirements for individual substances may be modified for chemicals that belong to a group of structurally similar substances, so that testing can be limited to one or a few substances, while the properties of other substances in the group may be predicted based on these[13] (see Annex I point 0.4 and Annex XI).

Risk management in the form of authorisation of SVHCs and restrictions under REACH have many examples of groups, such as metal compounds, PAHs, phthalates, PFASs etc.

The responsible authorities (ECHA and KEMI in Sweden) use groups in their work for all the reasons mentioned in this report. Not least important is grouping in order to avoid regrettable substitution (see Chapter 5), and to ensure an efficient use of the authorities' resources (KEMI 2018a).

Food law

The EU has an extensive legislation that regulates food safety and agricultural practises, in particular the use of pesticides and pesticide residues in food.

[11] See REACH Annex I point 6.2, especially the end of that point. See also the ECHA guidance on Information Requirements and Chemical Safety Assessment, version 3, Section E.4.5 about assessment of exposure to a substance as well as to several very closely related and similar acting chemical substances.
[12] Prioritisation for substances for evaluation by authorities shall take into account whether other substances may raise concern e.g. because of structural similarities and/or bioaccumulation (Article 44.1 a). Coincidental exposure to a substance must be taken into account in authorisation (Article 60.2).
[13] Using methods such as QSAR, read-across etc.

The basic food law (Regulation 178/2002) contains general provisions, including the establishment of the European Food Safety Authority (EFSA). This is complemented by a number of Regulations and Directives.

The food law has as its goal "a high level of protection of human life and health and the protection of consumers' interests, including fair practices in food trade, taking account of, where appropriate, the protection of animal health and welfare, plant health and the environment." (Article 5). There is also a reference to the precautionary principle. Article 14.4 states that:

> In determining whether any food is injurious to health, regard shall be had [...] to the probable cumulative toxic effects; [...].

There is neither a definition of what is meant by cumulative toxic effects nor an explanation why reference is made to health effects only.

Food contaminants, food contact materials and food/feed additives

Food containing specified contaminants may not be sold in the EU. The rules are found in Regulation 315/93, which is complemented by the list of eight groups of contaminants in the Commission Regulation 1881/2006. The restrictions regarding dioxins and PCBs as contaminants in food (such as fish from the Baltic Sea) are based on a mixture assessment by grouping congeners (PCDDs, PCDFs, PCBs) and setting limit values using toxic equivalency factors (TEFs) established by the WHO.

Food contact materials must follow EU requirements based on Regulation 1935/2004 in order to protect human health and ensure food quality. A number of regulations exist that cover different types of materials. There is no mention of combination effects (reference could perhaps be made to the general provision in food law mentioned above). For plastic materials there are migration limits for individual additives, but also overall migration limits (OML) that limit the total amount of additives that may be released from the material (Regulation 10/2011). This can perhaps be seen as a grouping approach to take mixture effects into account but is really a limit for what should be achievable in manufacture (recital point 25).

Food additives are substances intentionally added to food. They must be assessed (by EFSA) and authorised (by the Commission). Assessment includes environmental effects, when appropriate (Regulation 1333/2008, Article 1). The assessment shall take into account the probable daily intake of the additive under consideration from all sources (Article 11.1 b) but does not seem to cover a mixture assessment that includes other substances.

According to the Guidance document, grouping is allowed in test planning. Applicants are advised to design the actual testing

> on a case-by-case basis taking into account physicochemical data on the compound, toxicity data on structurally related compounds and available information on structure activity relationships.

Grouping is also allowed for acquiring quantitative toxicokinetic and toxicodynamic data for the derivation of Compound Specific Adjustment Factors (CSAFs):

> Toxicokinetic data can also be of value in developing adjustment factors for groups of related chemicals that share common physical or chemical characteristics or toxicokinetic or toxicodynamic pathways.
>
> (EFSA 2012)

There is also Regulation 1831/2003 regarding feed additives. In the Commission's associated implementing Regulation, it is stated that

> Where an additive has multiple components, each one may be separately assessed for consumer safety and then consideration given to the cumulative effect (where it can be shown that there are no interactions between the components). Alternatively, the complete mixture shall be assessed.

It is not explained further how this shall be achieved (Regulation 429/2008, Annex II, section General Aspects).

Plant protection products and MRLs

Plant protection products (PPP) are pesticides used for agricultural or horticultural purposes to limit or eliminate damage on crops, affect growth or preserve crops after harvest. They must be authorised before use according to Regulation 1107/2009. Authorisation is a two-step process, which starts with the approval of the active substance used in the PPP. This includes a hazard assessment and a risk

assessment (health and environment) for the active substance in at least one typical use.

Specific approval is also required for safeners and synergists used in PPPs. A safener is a substance or preparation (= mixture) which is added to a plant protection product to eliminate or reduce phytotoxic effects. A synergist is a substance or preparation, which, while showing no or only weak activity to control pests, can give enhanced activity to the active substance(s) in a plant protection product (Regulation Article 2.1-3).

The formulated PPP then needs a separate approval in each Member State. The assessment of risk includes both acute and long-term effects and is often performed using a whole-mixture approach. Cumulative and synergistic effects from other uses of the active substance or metabolites of other active substances have to be taken into account[14].

Approval of an active substance is a complex procedure that includes an opinion from EFSA. The agency has also developed specific guidance about the assessment of combined and synergistic effects from groups of active substances (see Chapter 4.5).

Authorisation of a PPP includes a requirement to assess maximum residue levels (MRLs) for the active substance in food. MRLs are set by EFSA according to Regulation 396/2005. The setting of MRLs have to take into account

> human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health (preamble point 6)

Directive 128/2009 on the sustainable use of pesticides gives a legal framework for minimising unwanted effects from uses of PPPs. The directive is implemented on the national level. It makes clear that Member States may introduce conditions limiting the use of pesticides when this can be motivated by e.g. local soil conditions or the need to protect sensitive areas.

The PPP Regulation is one of the EU legislations that has incurporated the substitution principle (see Chapter 5.4.3 about implementation of the substitution principle). An active substance can be flagged as a *candidate for substitution* if it fulfils certain criteria.

[14] Mentioned in the Commission's implementing Regulation 283/2013, Annex Part A point 6.9. This is also mentioned in the Annex to the Regulation 284/2013.

A PPP with a candidate for substitution as an active substance may be refused authorisation if a comparative assessment shows that there are safer alternatives (Article 50 and Annex IV in the PPP Regulation).

Pesticides: Biocidal products

Biocides are pesticides used for non-agricultural purposes (disinfectants, preservatives, rodenticides etc.). They are subject to EU Regulation 528/2012 which requires authorisation using a procedure similar to the one used for PPPs.

The Regulation clearly requires that a mixture risk assessment must be undertaken in some cases. According to Article 19.1 biocides must have no immediate or delayed negative effect on health or the environment, as such or as a result of its residues. When assessing this, cumulative and synergistic effects must be taken into account (Article 19.2).

The data requirements for products in Annex III state that product combinations shall be assessed in the case of biocidal products that are intended to be authorised for use with other biocidal products (Section I point 8.5.4). When evaluating risk assessments for biocide products, "[...] the evaluating body shall combine the results for the active substance together with the results for any substance of concern to produce an overall assessment for the biocidal product itself. This shall also take account of any cumulative or synergistic effects. (Annex VI point 53)." Substances of concern are substances with known hazardous properties (Article 3 f).

Interesting is also the reference to REACH in Article 8.3:

> Where the evaluating competent authority considers that there are concerns for human health, animal health or the environment as a result of the cumulative effects from the use of biocidal products containing the same or different active substances, it shall document its concerns in accordance with the requirements of the relevant parts of Section II.3 of Annex XV to Regulation (EC) No 1907/2006 and include this as part of its conclusions.

A reference is thereby made to the assessment of substances and mixtures in REACH.

In conclusion, mixture risk assessment is required by the Biocides Regulation, but only for mixtures of substances in the biocidal product in question or for the case of biocidal products that are intended to be used together. There is no requirement to assess combination effects from substances that come from other sources (coincidental mixtures). This is left to REACH, to the extent that such effects can be said to be covered by REACH.

With regards to grouping, Annex IV states that if certain criteria are fulfilled, validated QSAR models are allowed to indicate the presence, but not the absence of a given dangerous property.

Annex IV also says that substances with similar physico-chemical, toxicological and ecotoxicological properties or whose properties follow a regular pattern as a result of structural similarity may be considered as a group using read across, when relevant. The similarities may be based on a common functional group, common precursors and/or the likelihood of common breakdown products, or a constant pattern in the changing of the potency of the properties across the category.

Risk management is also based on grouping and the principle that active substances having the following properties shall in general not be approved: CMR 1A and 1B, Endocrine disruptors, PBT or vPvB. (Article 5). Article 10 lists these substances and some others as candidates for substitution that should not be allowed in biocidal products if there are safer alternatives.

Pharmaceuticals

The EU legislation for pharmaceuticals regulates human medicines (Directive 2001/83) and veterinary medicines (Directive 2001/82).

For human medicines, an analysis of risk/benefits for health must be performed. This includes

> forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product
>
> (Directive 2001/83 Article 59.1 c)

An environmental risk assessment shall be performed according to Article 8.3 ca) and shall include:

> Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

The discussion about effects from pharmaceuticals in the environment has led to the ongoing Commission review in the context of priority substances under the Water Framework Directive. A recent Communication from the Commission (COM 2019, 128 final) (EC 2019a) contains a review of the issues that have been under discussion, but not many concrete measures. It is acknowledged that further research is needed regarding

> The possible effects on humans of (chronic) exposure to low levels of pharmaceuticals via the environment, taking account of the potential for combined effects from multiple substances, and of vulnerable subpopulations.

For veterinary medicines an assessment must be made of risks to human health, animal health and the environment. Requirements for the environmental risk assessment are more developed than for human medicines (Directive 2001/82, Annex I Title 1 Part 3 Chapter I point 6). The whole mixture must be assessed (if the medicine is a mixture) but there is no evaluation of effects from combined or aggregate exposure in the environment.

There are no grouping approaches in these legislations.

Cosmetics

According to the EU regulation 1223/2009 on cosmetic products, every cosmetic product placed on the market has to come with a cosmetic product safety report. The report shall cover the composition of the product and the toxicological profile as well as an assessment of the safety of the finished product (Annex 1 in the regulation).

Possible interactions of the substances contained in the cosmetic product shall be assessed. This is also mentioned in a Commission Decision with guidelines on Annex 1 (Decision 2013/674) and in guidelines from the scientific committee (SCCS 2018).

Point 33 in the preamble to the Regulation underlines that

> A safety assessment of substances, particularly those classified as CMR 1A or 1B substances, should consider the overall exposure to such substances stemming from all sources.

This is also reflected in Article 15, point 2d of the Regulation. CMR substances are generally not allowed in cosmetics, but can be allowed in some limited, individual cases. The need for cooperation and data sharing between the relevant authorities (SCCS, ECHA, EFSA and EMA) when overall exposure is assessed for such substances is underlined in the guidance (Appendix 5).

The hazard assessment of some substances used in cosmetics (e.g. natural oils) can be problematic for the same reasons that apply for UVCB substances in REACH. This is also discussed in the guidance.

In relation to grouping, the Cosmetics Regulation allows for read across based on the chemical structure and properties of related substances for risk assessment of the ingredients (Annex I (8) and the guidance document) and of the finished product (bullet 41 in the preamble to the regulation). Grouping of substances and non-testing data from QSAR model outputs may be used. (Commission Implementing Decision 2013/674/EU).

The Regulation contains positive lists with the substances that may be used for specific purposes (colorants, preservatives, UV filters). More than a thousand substances are banned for uses in cosmetics or subjected to restrictions. These are listed in Annexes to the Regulation.

The evaluation of a cosmetic ingredient that is needed for the product safety report shall take into account aggregate exposure of the ingredient from different types of cosmetic products (SCCS notes for guidance point 3.4.3).

The Regulation on Cosmetic Products does not cover ecotoxicological risks of the products. REACH is applicable for such risks, but it should be noted that REACH does not generally apply for aggregate exposure from different products.

Specific products and articles

There are a number of different products that are subject to regulation regarding content of dangerous chemicals (often CMR and other SVHC chemicals). These rules generally regulate specific exposure situations and do not contain procedures for risk assessment. Pro-

ducts can also be regulated under Title VIII in REACH (restrictions).

Examples of such legislation are:

- Toys (Directive 2009/48),
- Medical devices (Regulations 2017/745 and 2017/746),
- Electronic products (RoHS, Directive 2011/65),
- End of life vehicles (Directive 2000/53),
- VOC in paint (Directive 2004/42),
- Detergents (Regulation 648/2004).

3.5.3 Emissions-oriented legislation

A number of Directives deal with large-scale activities that may pollute the environment. Such legislation traditionally regulated effects in specific environmental media (air, water etc.), but in the case of industrial emissions this has been replaced by an integrated approach.

Industrial Emissions Directive

The Industrial Emissions Directive or IED (Directive 2010/75) is the main EU instrument regulating emissions from industrial installations. The IED replaces the earlier Integrated Pollution Prevention and Control (IPPC) Directive 2008/1/EC. In addition to IPPC, the IED has also incorporated a number of earlier legal acts that regulated specific activities.

According to IED, approximately 50,000 industrial installations are required to operate in accordance with a permit granted by the authorities in Member States. This permit contains limiting conditions covering the whole environmental performance of the plant, such as emissions to air, water and land, generation of waste, use of raw materials, energy efficiency, noise, prevention of accidents and restoration of the site upon closure.

The permits contain emission limit values based on Best Available Techniques (BAT), as described in BREF documents (Best available

techniques REFerence documents) and published by the Commission for approximately 30 different sectors. These are regularly updated.

The permits shall contain emission limit values for polluting substances listed in Annex II, and for other polluting substances,

> which are likely to be emitted from the installation concerned in significant quantities, having regard to their nature and their potential to transfer pollution from one medium to another;
>
> (article 14a, 1)

The list in Annex II mentions broad categories and groups (metals and their compounds, materials in suspension, pesticides etc.). More detailed emission limit values may be specified in the BREFs.

There are no detailed rules on how risk assessment of chemicals pollution shall be carried out. This may be based on knowledge produced in other contexts (REACH for example) and can include grouping or concepts of mixture toxicology in the limit values, such as toxic equivalency factors (TEF) for dioxins.

Waste-water Treatment

Directive 91/271/EEC concerning urban wastewater treatment sets minimum requirements for waste-water treatment plants for waste waters from urban agglomerations of certain sizes and waters from some industrial activities. The requirements aim at ensuring that the water treatment achieves a certain level (primary and secondary treatment of a specified quality) but does not regulate individual chemicals.

Stricter requirements for water treatment may be set based on demands for the local environment (i.a. biological treatment). There is naturally a close link to the environmental quality covered by the Water Framework Directive (see below).

Environmental Impact Assessment

Large projects likely to have a significant effect on the environment must be subjected to an Environmental Impact Assessment (EIA). This follows from the EIA Directive 2011/92/EU. The impact assessment shall be produced by the developer and will be part of the

procedure in the Member State concerned to assess and give consent to the project.

The impact assessment must identify direct and indirect effects on health and the environment, considering humans, fauna and flora, soil, water, air, climate and the landscape as well as material assets and cultural heritage. The interaction between these factors must be described in the assessment.

The assessment must in principle identify all impacts of the project, including the impact of chemicals. This should theoretically include mixture effects, as well as coincidental mixtures[15]. The level of ambition is set very high in Annex IV point 5, where it is stated that the description should cover the direct effects and any indirect, secondary, cumulative, short, medium and long-term, permanent and temporary, positive and negative effects of the project.

The Directive in no way regulates how the impact of chemicals should be assessed, however, and information about this has to be acquired from other sources.

3.5.4 Recipient-oriented legislation

The third type of EU legislation is the one that focuses on environmental media as recipients of chemical pollution. We have included worker protection legislation under this heading because this legislation has a broad general goal, namely to provide a safe and healthy working environment. Regarding chemicals, worker protection legislation has many similarities with substance-related legislation such as REACH.

Water pollution, surface water

The Water Framework Directive 2000/60 (WFD) is a wide-ranging legislation that aims to establish good status for all surface waters and ground water. This includes measures against pollution with priority substances, i.e. pollutants selected from those presenting a significant risk to or via the aquatic environment, including such risks to waters that are used for the abstraction of drinking water. For these pollutants, measures shall be aimed at the progressive

[15] See Annex III and IV of the Directive.

reduction and, for priority hazardous substances, at the cessation or phasing-out of discharges, emissions and losses (Article 16.1).

Directive 2008/105, as amended by Directive 2013/39/EU, is based on WFD and establishes maximum acceptable concentrations, so-called environmental quality standards (EQS) for 45 pollutants (in some cases groups of related pollutants) as annual averages and maximum limits. Member states must implement measures to achieve these standards and to monitor the pollutants in water (for some cases in fish). Many of these pollutants are pesticides.

In addition, 8 pollutants have been placed on a watch list and must be monitored for the purpose of supporting future prioritisation exercises (Commission Decision 2018/840).

There is a large amount of guidance for the application of WFD. The EQS guidance document includes a chapter about mixture toxicity for groups of substances using the toxic unit (TU) approach (EC 2011b). The guidance states that the development of EQS must ensure that

> all direct and indirect exposure routes in aquatic systems i.e. exposure in the waterbody via water and sediment or via bioaccumulation, as well as possible exposure via drinking water uptake, are accounted for.

Apart from this reference to aggregate exposure and the grouping of substances for the calculation of EQS there are no rules about mixture effects in the WFD, but there are close links to pesticides regulation and to REACH. Development of the WFD is discussed further in Chapter 6.10.

Groundwater and drinking water

The Groundwater Directive 2006/118 establishes limit values for good ground water quality, including for nitrates and active substances in pesticides (0,1 μg/l per active substance, 0,5 μg/l total). The directive also has guidance about the development of other guidance values by Member States when needed.

The Drinking Water Directive 98/83 includes a list of limit values for chemicals in drinking water that includes the values in the Groundwater Directive but is more extensive. Member States must monitor these chemicals and undertake measures if the limits are exceeded.

Marine environment

The Marine Strategy Framework Directive 2008/56/EC has an approach that is similar to the WFD. The goal of the Directive is to achieve a good environmental status for marine waters by 2020[16].

Good environmental status means i.e. that biological diversity is maintained and that "Concentrations of contaminants are at levels not giving rise to pollution effects." (Annex 1). It is not defined what "pollution effects" means, but reference is made to the priority substances identified by the WFD (Annex III Table 2). Any substantial developments in the WFD regarding mixture risk assessment and grouping may therefore have consequences for the implementation of the Marine Strategy Framework Directive.

Member states are required by the Directive to develop marine strategies to reach good status. These strategies are renewed in a six-year cycle. They shall include the assessment of the water status and setting of targets for good environmental status, based on monitoring programs. A program of measures must then be developed in order to achieve good environmental status.

The implementation of the Directive is naturally linked to existing regional international agreements on water quality, such as OSPAR for the North-East Atlantic Ocean and HELCOM for the Baltic Sea.

Air pollution

The EU Air quality Directives 2008/50/EC and 2004/107/EC regulate major pollutants resulting from industrial activities, combustion plants, traffic etc.[17]. One of the aims is "defining and establishing objectives for ambient air quality designed to avoid, prevent or reduce harmful effects on human health and the environment as a whole." The Directives establish target values for the pollutants to be achieved over time as well as health-related limit values and critical levels for the environment. Monitoring and information to the public is also covered. The Directives do not regulate combination effects

[16] Waters outside the territorial line and some coastal waters that are not regulated by the WFD.

[17] Sulphur dioxide, nitrogen dioxide and oxides of nitrogen, particulate matter (PM10 and PM2,5), lead, benzene and carbon monoxide are covered by Directive 2008/50, while arsenic, cadmium, nickel and polycyclic aromatic hydrocarbons are covered by Directive 2004/107.

or grouping as such, but poly-aromatic hydrocarbons (PAHs) are regulated as a group with benzo(a)pyrene treated as a marker for the carcinogenic risk from the whole group.

Soil strategy

There is no separate EU legislation that covers chemical pollution of soils. An attempt to introduce a Directive on soil protection was voted down in Council in 2006. A brief report from the Commission on the subject was published in 2012 (COM 2012, 046 final) (EC 2012b).

Waste legislation

The framework Directive on waste (2008/98/EC) has a number of objectives, one of which is to ensure that waste with dangerous properties is handled safely. The identification of such waste is based on the hazard criteria in the CLP Regulation. If the waste is a mixture, the criteria in CLP for mixtures applies. Full mixture testing is also an option. On this basis, a separate waste list identifies waste types with dangerous properties (Commission Decision 2000/532).

For waste that is recycled or recovered, there may be established *end-of-waste criteria* for materials that no longer need to be subjected to the waste legislation. For such materials, REACH will in principle apply instead.

A communication from the Commission in the context of the circular economy package (COM 2018, 32 final) (EC 2018e) discusses various options to address the interface between chemical, product and waste legislation.

The waste legislation is focused on assessing the potential exposures of dangerous chemicals from different waste streams. When and if the chemicals legislation is developed for mixture risk assessment and grouping, the waste area should not be overlooked.

Worker's health

EU legislation about the health and safety for workers is based on the framework Directive 89/391. The general purpose is to introduce measures to encourage improvements in the safety and health of humans at the work place. This Directive is complemented e.g. by Directive 98/24 about chemical agents at work, and Directive 2004/37 about the protection from carcinogenic and mutagenic substances.

Directive 98/24 establishes an obligation for employers to gather information about any hazardous agents (substances or mixtures) that are used in the workplace, to analyse the exposure and assess any associated health risks.

Indicative occupational exposure limit values (OELVs or OELs) exist for a large number of agents to help with this. These values can be compared with, but are not identical to, DNEL values for exposure set by REACH.

According to Article 4.4 in the chemicals agents directive

> In the case of activities involving exposure to several hazardous chemical agents, the risk shall be assessed on the basis of the risk presented by all such chemical agents in combination.

Guidance for the application of these provisions include the concept of Homogenous Exposure Group (HEG) which is a combination of a particular job and the exposure in that job for chemical agents having the same adverse effect. Exposures for several agents can be combined if there are many agents causing the same adverse effect. The sum of the concentrations can then be compared with the limit value (OELV or national ELV).

Explicit general guidance on grouping and combination effects has not been produced at the EU level, but recent guidance about the derivation of OELs does not exclude that such aspects are taken into account (SCOEL 2017). As a result of the REACH refit exercise, the SCOEL Committee has been discontinued and its tasks transferred to the Risk Assessment Committee (RAC) under REACH. New guidance is being developed by EFSA, where the issue of exposure from coincidental mixtures may come up.

The EU legislation establishes minimum levels of protection, and stricter national requirements can be established when the rules are implemented in Member States. The Swedish rules are briefly discussed in the following section.

3.6 Swedish policy frameworks and legislation

The Swedish environmental quality objective "a non-toxic environment"

Sweden applies a number of political goals as a basis for environmental policy and for the application and development of legislation (nationally and internationally). One of these goals relates to a non-toxic environment by the year 2020:

> The occurrence of man-made or extracted substances in the environment must not represent a threat to human health or biological diversity. Concentrations of non-naturally occurring substances will be close to zero and their impacts on human health and on ecosystems will be negligible. Concentrations of naturally occurring substances will be close to background levels.

There are a number of more detailed aims stating what is needed to reach the general goal. Two of these aims are of particular interest for this report:

> – total exposure to chemical substances via all sources of exposure is not harmful to people or biodiversity,
>
> – knowledge about the environmental and health properties of chemical substances is available and sufficient for the purposes of risk assessment

The Non-Toxic Environment objective is far from being reached. In the most recent evaluation of progress, the Swedish EPA concludes e.g. that one step towards better goal fulfilment would be that the Swedish Government should promote development of the EU legislation to address combination effects, including processes to assess exposures from multiple sources regulated by different legislations. They also note that this would require an actor with overarching responsibilities and coordination across legislations and authorities. And finally, that EU legislation should be developed to address groups of substances when possible. (Naturvårdsverket 2019a)

Swedish Environmental Code and other national rules

The Swedish environmental code (SFS 1998:808) includes a Chapter 14 on chemicals, which is mostly limited to administrative rules. As mentioned above, Chapter 2:3 refers to the precautionary principle and Chapter 2:4 includes the substitution principle.

These provisions of general scope may mainly be applied in areas that are not subject to harmonised EU rules but only to minimum rules, such as industrial pollution, worker protection, water protection etc. The provisions are in fact often referred to in individual cases relating to measures to protect the environment. National restrictions or bans of chemicals may also be introduced in cases where detailed EU rules have not been implemented (or not been implemented yet). Some examples of this and some older Swedish chemicals regulations exist in an Ordinance[18].

Detailed national regulation may be implemented by Government Ordinances or by Regulations/guidance issued by authorities. As far as we have been able to establish, such rules do not contain general principles about the grouping of chemicals or about combination effects that are fundamentally different from the international legislation. However, individual examples exist where these concepts are applied. Establishing occupational exposure limits (OELs) in worker protection is one example where grouping has been applied nationally, so that the same OEL applies for all members in the group[19]. There are also examples of national OELs where additive effects are explicitly taken into consideration. Additive and synergistic effects are mentioned in the national guidance (Arbetsmiljöverket, AFS 2011:18). Additions (*notations*) to the OEL value, mostly a single letter, are sometimes used both in the EU and in Sweden. The noise notation (B) has been used in Sweden to manage combination effects between specific chemicals and noise that may lead to hearing impairment. This has later been implemented at the EU level.

[18] Förordning (1998:944) om förbud m.m. i vissa fall i samband med hantering, införsel och utförsel av kemiska produkter.
[19] Arbetsmiljöverkets författningssamling AFS 2018:1. Examples include diisocyanates, lactates, phthalates and proteolytic compounds and also cutting fluid aerosols and metal compounds.

3.7 Summary and general conclusions

The development of policy frameworks

Combination effects and grouping are not subjects that are covered by the global policy frameworks (such as SAICM) or the chemicals conventions (such as the POPs convention). It would not be unreasonable, however, to introduce these concepts in a discussion about the development of chemicals control in the SAICM framework.

Policy frameworks at the EU level have dealt with these issues, however (see 3.4), in particular the communication about combination effects and the foreseen non-toxic environment strategy that is part of the 7th environmental action program. Some promised contributions by the Commission to these strategies have not appeared yet. Neither have the strategies lead to new legislation. The focus recently has instead been on the development of scientific guidance (see Chapters 4 and 5).

Developments in EU chemicals legislation

In the study that formed the basis for the Commission Communication from 2012 about the combination effects of chemicals (Kortenkamp et al. 2009), a review was made of 21 existing EU legislations dealing with chemical risk. The conclusion was drawn (part 2 of the study) that only four of these were notable for their mixture toxicity perspective:

- The REACH Regulation because of guidance on how substances that are in fact mixtures are to be assessed for their PBT/vPvB properties. This applies to isomeric mixtures, multi-constituent substances (MCS), and substances of unknown or variable composition (UVCB), such as petroleum products or surfactants.
- The CLP Regulation makes detailed prescriptions for the toxicity assessment of intentionally prepared commercial mixtures. The approaches prescribed are (i) whole mixture testing, (ii) concentration addition, or (iii) the summation method, which is the toxicity-weighted summation of the relevant mixture components and subsequent analysis whether the relative amount of relevant components is above or below a pre-defined threshold.

- Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin provides incentives for the development of methodologies for mixture risk assessment. The task of developing viable assessment methods has been assigned to EFSA.
- Directive 2008/1/EC concerning integrated pollution prevention and control (IPPC)[20] refers to the directive on waste incineration as a complementary piece of legislation. This in turn includes emission limit values for mixtures of dioxins and furans that are based on the toxicological concept of Toxic Equivalence Factors (TEF).

It can be seen from our updated and extended review of the legislation that little has changed in the last decade. The only legislation in which a clear requirement for mixture risk assessment has been introduced is Regulation No. 528/2012 regarding biocidal products. Regulation (1107/2009) regarding plant protection products (PPP) also deals with combination effects.

Recipient-oriented legislation such as the water framework directive (WFD) was outside the scope of the study from 2009, but it was concluded that options for the advancement of these pieces of legislation with the aim of taking account of, and improving risk assessments of, realistic complex exposure scenarios should be explored. We propose (Chapter 6.10) that the WFD is developed to provide improved feed-back to substance-oriented and emissions-oriented legislation.

Grouping of chemicals

Regarding the grouping of chemicals when assessing chemical risk, the picture is different. There are few legal provisions that make grouping obligatory, but groups have in many cases been identified and regulated on an ad hoc basis. This is true in particular for CMR/PBT/vPvB substances. The fact that legal texts often focus on individual substances as the subject for regulation has not been seen as a hindrance for regulating groups, such as dioxins. We propose that the issue of grouping is developed in REACH (Recommendation 6.8).

[20] Replaced by later legislation, see 3.5.3.

Shortcomings in the EU legislation

In addition to inconsistent and insufficient requirements for mixture risk assessments and group-wise management, our examination of the existing legal framework identified three major shortcomings of current EU chemicals legislation:

- There are almost no links between different legislations (the problem of regulatory fragmentation). If unintentional mixtures need to be assessed, it is particularly noteworthy that very few links exist at the regulatory level between recipient-oriented legislation, such as the water framework directive, and substance/emissions-related legislation such as REACH. A number of our proposals aim at establishing such links and to ensure that enough data about use, emissions and exposure are available (Recommendation 6.2–6.5, 6.10).
- When a requirement to assess combination effects is included in the legislation it is sometimes not specified whether this applies to aggregate exposure, combined effects from a well-defined intentional mixture or if a broader scope is intended, such as for coincidental or unintentional mixtures. Food law is one example. It is then unclear what needs to be covered by more detailed subsidiary rules or guidance. This is discussed in Recommendation 6.1.
- Although the polluter pays principle should apply, individual actors placing a substance on the market cannot be held responsible for exposure originating from substances marketed by other actors. Even for legislations where individual risk assessments are made (such as registration of substances in REACH), however it should be possible to develop the legislation. One way could be to require that known information about other sources of exposure are taken into account when the risk is characterized by the individual actor. Another way could be to increase the data requirements (hazard and exposure/use) when risks from coincidental mixtures can be suspected. Some of these issues can be considered in a context of a cross-cutting framework on chemical pollution (Recommendation 6.2).

4 Mixture Risk Assessment (MRA)

This chapter provides a summary review of the scientific knowledge about mixture risks and the state of implementation of this knowledge into regulatory assessments under EU law.

Sections 4.1 to 4.3 define the scope of this review, identify key documents, and explain key terms and concepts. Sections 4.4 and 4.5 provide an overview on the scientific and the regulatory state-of-the-art. Sections 4.6 and 4.7 summarise the progress achieved during the last ten years and identify current barriers to further improvement.

4.1 Scope of the summary review

Ten years ago, a comprehensive state-of-the-art report on mixture toxicity was prepared for the European Commission (Kortenkamp et al. 2009). Subsequently, the Commission's Scientific Committees were consulted on the issue (EC 2011a). Drawing on both documents, the Commission finally prepared the Communication on *The combination effects of chemicals – Chemical mixtures* (EC 2012a) (see 3.4). Follow-up activities announced in that Communication included the development of technical guidelines for mixture assessments, the creation of a platform for chemical monitoring data, and the funding of research on (i) modes of action (MoA), (ii) grouping, (iii) predicting interactions and (iv) identifying drivers of mixture toxicity.

Now, ten years after the initial state-of-the-art report, we look at the progress made and provide an updated summary of the state of affairs. This summary is focussed on the following aspects:

- *Unintentional mixtures.* Intentionally prepared mixtures are not in the focus of this report and are only considered in terms of unwanted adverse effects. Research on intended effects of intentionally prepared mixtures is out of scope, such as therapeutic efficacy of drug combinations, or agronomic efficiency of pesticide tank mixtures.
- *Generic methodologies for assessing mixture risks and establishing safe exposure levels for both humans and the environment.* Specialized approaches in either field are not the focus, such as the so-called msPAF[1] approach for ecotoxicological risk assessments of mixtures to species assemblages. Specific mixtures or endpoints are only considered as examples.
- *Technical rules and guidance for the implementation of mixture risk assessment under EU law.* Legal principles and requirements are already detailed in the preceding Chapter 3. Approaches used in the US and other countries are only occasionally mentioned for comparative purposes.
- *All considerations in this chapter are confined to chemical risks.* Research on effects from chemicals in combination with non-chemical stressors is beyond the scope of this report.

4.2 Key documents

During the last ten years, the topic of mixture risk assessment received high attention. Various organisations and research groups repeatedly reviewed and discussed the issue from different perspectives. Resulting key documents are listed below. Together, they sum up to several thousand pages and reflect the accumulated theoretical and empirical knowledge of a few thousand original research articles in the field. This chapter provides an extract of essentials from this material.

During the preparation of this report (April 2018–August 2019), eight important review and guidance documents were published. They were written or edited by the European Commission's JRC (Bopp et al. 2018, 2019), EFSA (2019), OECD (2018), the EU

[1] msPAF – multisubstance potentially affected fraction of species (de Zwart and Posthuma 2005).

project EuroMix (Rotter et al 2018), the US ATSDR (2018), Rider and Simmons (2018) from the US NIEHS and the US EPA, and Boberg and co-workers (2019) from the Danish National Food Institute.

Prior to the preparation of this report, during the period from 2010 to 2017, important reviews, advisory documents, conceptual frameworks, and discussion papers were published (in order of appearance) by Backhaus et al. (2010), Mumtaz (2010), Boobis et al. (2011), EC (2011a), ECETOC (2011a,b), Meek at al. (2011), OECD (2011), Silins et al. (2011), van Gestel et al. (2011), Altenburger et al. (2012), Backhaus and Faust (2012), ECETOC (2012), Kortenkamp et al. (2012), Price at al. (2012a,b), Sexton (2012), Altenburger et al. (2013), Backhaus et al. (2013), EFSA (2013a,b), MacDonell et al. (2013), Meek (2013), Altenburger et al. (2014), Bunke et al. (2014), Cedergreen (2014), EFSA (2014a), Frische et al. (2014), Kienzler et al. (2014), Solecki et al. (2014), Stein et al. (2014), Bopp et al. (2015), EFSA (2015a), KEMI (2015b), Van der Linden et al. (2015), Rider and Simmons (2015), Bopp et al. (2016), Evans et al. (2016), Kienzler et al. (2016), Lamon et al. (2016), Moretto et al. (2016), Solomon et al. (2016), US EPA (2016), Health Canada (2017), van Broekhuizen et al. (2016), and WHO (2017a).

Five large collaborative EU projects addressing different aspects of mixture risks were ongoing our just finalised during the preparation of this report: EDC-MixRisk[2], EuroMix[3], EUToxRisk[4], HBM4EU[5], and SOLUTIONS[6]. In addition to a published overview on the research activities (Bopp et al. 2018), further information from these projects were included in the considerations for this chapter where relevant and publicly available from the project's websites.

Policy briefs and similar formats have been repeatedly used to communicate research findings on mixture risks and resulting recommendations to policy makers in an aggregated way. During the preparation of this report, such short opinion papers were published

[2] EDC-MixRisk – Integrating Epidemiology and Experimental Biology to Improve Risk Assessment of Exposure to Mixtures of Endocrine Disruptive Compounds. https://edcmixrisk.ki.se/
[3] EuroMix – A tiered strategy for the risk assessment of mixtures of multiple chemicals. www.euromixproject.eu
[4] EUToxRisk – An integrated European 'flagship' program driving mechanism-based toxicity testing and risk assessment for the 21st century. www.eu-toxrisk.eu/
[5] HBM4EU – The European Human Biomonitoring Initiative. www.hbm4eu.eu
[6] SOLUTIONS – Solutions for Present and Future Emerging Pollutants in Land and Water Resources Management. www.solutions-project.eu

by the European Commission's JRC (EC 2018c), Kortenkamp and Faust (2018), Bergman et al. 2019, and Brack et al. (2019). Further policy briefs from the mentioned EU projects are in preparation but were not published before the closing date for consideration in this report (August 2019).

4.3 Key terms and concepts

4.3.1 Commonalities and differences between single substance and mixture risk assessments

Mixture risk assessment (MRA) is used in this report as a short expression for *risk assessment of chemical mixtures* (see 2.2), often also denoted as the assessment of *risks of combined exposure to multiple chemicals* (e.g. OECD 2018, EFSA 2019).

Basically, key terms and concepts used for single substance risks assessment also apply to mixture risk assessments, but they require some specifications or modifications as explained in the following.

EU legislation requires both *prospective assessments*, prior to marketing, use, or release of chemicals, and *retrospective assessments* of existing exposure situations. Pro- and retrospective assessments differ in methodological details but share a common structure. They are organised into four main steps:

1. problem formulation,
2. exposure assessment,
3. hazard assessment (steps 2 and 3 can be performed in parallel),
4. risk characterisation.

For mixtures, however, these steps are not as clearly separable as for single substances. Rather than being practicable in a simple consecutive fashion, they may need to be organised as an iterative or integrated process.

Problem formulation for mixtures

For single substances, *problem formulation* (step 1) starts with defining the chemical of concern. The way of defining is usually prescribed by law and the definition is independent from the results of subsequent assessment steps. This is different for unintentional mixtures. Defining the mixture of concern already requires a hypothesis about an expectable co-exposure scenario or (preliminary) knowledge about an existing co-exposure situation (step 2). In addition, hypotheses or pre-existing knowledge about common adverse effects of (suspected) mixture components (step 3) may play an important role for the problem formulation.

Co-exposure assessment

"*Co-exposure assessment*" is used in this report as a short expression for *exposure assessment for chemical mixtures* or *assessment of combined exposure*. Depending on the context, single substance exposure is expressed in terms of:

- concentrations in environmental media (air, water, soil), food, feed, biota, or human tissues, or
- doses taken up by an organism per unit of time or per kilo bodyweight.

Extending the approach to mixtures means to define (i) the number and nature of the mixture components, (ii) the concentration or dose ratios of the mixture components (in short, the *mixture ratio*), and (iii) the total concentration or dose of the whole mixture.

For the generic considerations in this chapter, the specific exposure metrics do not play a role and the terms concentration and dose are used interchangeably, unless specifically noticed. The same applies to combined expressions, such as effect concentrations (or doses), concentration (or dose) response relationships, and concentration (or dose) addition.

Hazard assessment of chemical mixtures

Mixture toxicity assessment and *hazard assessment of chemical mixtures* are used synonymously in this report to denote the assessment of the inherent potential of mixtures to cause harm in biological systems. As for single substances, the hazard assessment of mixtures includes four sub-steps: (3a) the identification of possible adverse effects, (3b) the establishment of dose or concentration response relationships, (3c) the (statistical) estimation of so-called points of departure (POD), such as a no-observed adverse effect level (NOAEL), and (3d) the derivation of regulatory acceptable exposure levels (AL), often also denoted as regulatory reference values (RV), such as a predicted no effect concentration in the environment (PNEC), an acceptable daily intake (ADI) for humans, or various conceptually similar toxicity indicators (EQS, DNEL, TDI, ARfD, AOEL, and others).

For single substances, concentration response relationships (step 3c) are described by (statistical estimates) of two-dimensional dose-response curves. Extending the approach to mixtures results in a 3-dimensional dose-response surface for 2-compound-mixtures and an (n+1)-dimensional surface for a multi-substance mixture with *n* components. However, this complexity can be simplified and re-reduced to a 2-dimensional problem by fixing the mixture ratio (see above). Thus, for mixtures, values derived from the concentration response analyses, such as PODs and RVs, refer to a set of components in a constant mixture ratio.

This does not mean that the composition must be known from the beginning. Mixture toxicity testing may also start with environmental samples of unknown composition and identification of mixture components may be performed as a second step, if adverse effects are seen.

In addition to commonalities with single substance assessments, hazards of mixtures are often assessed in terms of agreement or departure from mixture toxicity predictions. Such predictions are derived from knowledge about the toxicities of individual mixture constituents by applying models of joint action, such as *concentration addition* (CA) and *independent action* (IA), as explained in detail in section 4.4.1 below. Departures of the real mixture toxicity from model-based predictions are generally denoted as *inter-*

actions. Toxicities which are higher or lower than expected are usually termed *synergism* and *antagonism*, respectively. However, these terms are imprecise without reference to a definite concept for prediction. Exact expressions such as *more than-concentration-additive* or *less than concentration-additive* are therefore preferable. Without such specifications, we use the terms *synergism* and *antagonism* only to denote mixture effects that are clearly stronger or weaker than expected by any non-interaction model.

Risk characterization for mixtures

Chemical *risk* is often defined as the probability to cause adverse effects. For regulatory purposes, however, the data to perform probabilistic risk assessments are mostly not available. Therefore, a simplified approach is taken. *Risk characterisation* (step 4) is often performed in terms of a *risk quotient* (RQ). In general, the quotient denotes the ratio between an observed or predicted exposure level and a regulatory acceptable exposure level, which is considered to be reasonably safe.

There are numerous variants and specifications of this approach, depending on the specific protection goals and the specific regulatory context. One prominent example is ratios of predicted environmental concentrations and predicted no effect concentrations (PEC/PNEC) determined under REACH. As long as the PEC/PNEC ratio stays below 1, the use of a given chemical is considered to be safe.

This well-established way of assessing risks of single chemicals in terms of risk quotients can be extended to MRAs. In contrast to single substances, however, the toxicity of mixtures does not only vary with the total concentration but also with the mixture ratio. This means that the total acceptable exposure concentration may be different for different mixture ratios of a given set of substances.

To deal with this complication, approaches to the calculation of risk quotients for mixtures often do not work with absolute but with relative concentrations (or doses). An important concept used for this purpose is toxic units (TU). TU are potency adjusted concentrations, i.e. absolute concentrations of mixture components divided by their respective EC50 values or other common effect concentrations

(EC10, EC20 etc) for the same (eco)toxicological endpoint, in the same species, and for each chemical in the mixture.

Toxic Equivalents (TEQ) is a similar approach that expresses the concentrations of a component in terms of equi-effective concentrations of a reference substance, calculated by means of a *toxic equivalency factor* (TEF).

TU and TEQ integrate the exposure and hazard of individual mixture components into single figures. These may then be summed up to indicators of overall mixture risks as explained in section 4.4.3 below.

4.4 State of the science

4.4.1 Hazard Assessment of Mixtures

Regulatory approaches to the problem of mixture toxicity assessment fall into two basic categories: the so-called *whole mixture approach* (WMA) and the so-called *component-based approach* (CBA). Whole mixture approach means that the mixture of concern is experimentally tested as if it were a single substance. The composition of the mixture may be unknown or not exactly known. Component based approach means that the expected toxicity of a mixture is calculated on the basis of toxicity data for individual mixture components by using models of joint action. Such modelling of the expected toxicity requires an exact definition of the mixture composition. Whole mixture approach and component-based approach both have their advantages and limitations. Therefore, they should be regarded as complementary methods rather than rival approaches. Depending on the specific context, they may be integrated in different ways for assessing the toxicities of mixtures reliably and effectively.

Whole mixture approaches (WMA)

As a research instrument, testing of well-defined whole mixtures is used for comparing observed mixture toxicities with predictions. This requires prior testing or parallel testing of the individual constituents or other ways of estimating their individual toxicities. As a regulatory instrument, whole mixture testing has a long tradition of

routine use for the bio-monitoring of complex emissions of chemicals from a common (point) source, in particular waste water treatment plant effluents. Currently, there is a strong move towards a widened use of this approach for the identification of hazards from chemical mixtures under media-oriented pieces of EU legislation, such as the WFD. The approach is usually denoted as *effect-based monitoring* (EBM) and shall complement chemical exposure monitoring (see 4.4.2).

Beyond these special applications for retrospective assessments, whole mixture approaches do not play a prominent role in the current development of regulatory approaches for MRA. For single substances and products, toxicological testing requirements have been well defined under various legislations and there is a high political resistance against any substantial widening of these requirements, both for ethical and for economic reasons. In addition, the laws of combinatorics dictate that a systematic testing of the almost infinite number of possible combinations of pollutants is practically impossible.

Hence, whole mixture testing must remain confined to well selected samples. Nevertheless, whole mixture approaches have two major advantages which make them an indispensable element of the available "tool box' for MRAs:

(i) Whole mixture testing is the only way to detect synergistic or antagonistic effects in the mixture compared to additivity models (see below).

(ii) Whole mixture testing is also the only reliable way for assessing mixture risks from unknown components in environmental samples.

Unfortunately, however, whole mixture approaches also suffer from three major limitations:

(i) Routine application is not only limited to selected samples but also to selected endpoints. Frequent testing is possible with short term assays only, such as *in vitro* screens, assays with microorganisms, or acute (non-animal) toxicity tests. Testing of chronic mixture toxicity, which is particularly important for regulatory assessments, must be confined to selected case studies.

(ii) Whole mixture approaches provide a 'spotlight' type of assessment, only applying to a mixture exactly composed as the tested one. A change in the concentration ratio between mixture components may require new testing, as does any change in the number or identity of components. "Reading-across' from a tested mixture to an untested

mixture of similar composition requires additional assumptions, such as those underlying models of joint action (see below).

(iii) Whole mixture approaches (alone) do not provide information about the chemicals causing observed toxicities. For developing targeted risk management measures, additional efforts are required to identify the so-called mixture risk drivers, such as performance of an *effect-directed analysis* (EDA) (Brack et al. 2016) and complementary use of component-based approaches.

Component-based approaches (CBA)

Most component-based approaches to mixture toxicity assessments are based on one of two basic models for joint action, *concentration* (or dose) *addition* (CA), and *independent action* (IA) (also called *response addition*). So-called *mixed modelling approaches* (MM) combine CA and IA in a common assessment procedure. Beyond these basic non-interaction models, more sophisticated approaches have been developed for special purposes which are subsumed under the term *toxicokinetic-toxicodynamic models* in this report.

Differences between Concentration Addition and Independent Action

Concentration (or dose) addition (CA) assumes that mixture components have a similar mode of action (MoA). As a consequence, a mixture component can be replaced by another compound, without changing the overall toxicity, as long as both compounds have the same toxic unit. The mathematical formulation of this assumption is given in Tab. 4.1 (eqns. [1] and [2]).

Independent action (IA) assumes that mixture components contribute to a common endpoint via dissimilar and fully independent sequences of events, so-called adverse outcome pathways (AOP), from an initial interaction with different molecular target sites to different diseases or different adverse effects seen on the level of individuals or populations. As a consequence, the individual effects can be considered to be independent events in a probabilistic sense. Under the additional assumption that the susceptibilities of the individuals of an at-risk-population are not correlated, the model is mathematically defined as given in Tab. 4.1 (eqns. [3] and [4]).

Concentration addition usually predicts a higher toxicity than independent action, i.e. risk assessments based on the assumption of independent action are usually less protective than assessments based on the assumption of concentration addition, as detailed in Chapter 13.4 of Kortenkamp et al. (2012). Furthermore, concentration addition implies that concentrations of substances below individual thresholds (zero effect levels) may still contribute to the overall toxicity of a mixture, while independent action does not.

In addition to being more protective, the proper application of concentration addition for regulatory purposes is typically much less demanding than independent action. For predicting the effect concentration of a mixture, concentration addition requires knowledge of the equi-effective concentrations of the individual components. For example, predicting the EC50 of a mixture requires knowledge of the EC50 values of the single components. Independent action, in contrast, requires knowledge of the strength or frequency of effects caused by individual components in exactly that concentration which is present in the mixture. For multi-component mixtures, this means to have good knowledge of the slopes of individual concentration response functions in the low dose region. Data from standard test protocols with relatively small numbers of organisms do not meet these statistical demands.

Table 4.1 Models for predicting the toxicity of multi-component mixtures

Predicted parameter	Concentration Addition (CA) (Dose Addition, DA)	Independent Action (IA) (Response Addition)
Effect* of a mixture $E(c_{mix})$	$E(c_{mix}) = X, if \quad \sum_{i=1}^{n} \frac{c_i}{ECx_i} = 1$ [1]	$E(c_{mix}) = 1 - \prod_{i=1}^{n} \left(1 - E(c_i)\right)$ [3]
Effect concentration of a mixture ECx_{mix}	$ECx_{mix} = \left(\sum_{i=1}^{n} \frac{p_i}{F_i^{-1}(x_i)} \right)^{-1}$ [2]	$X = 1 - \prod_{i=1}^{n} \left(1 - F_i(p_i \bullet (ECx_{mix}))\right)$ [4]

Explanations

*Effects E denote the relative intensity or frequency of a response parameter (defined as fraction of a maximum possible value) and thus can only take values between 0 % and 100 %: $0 \le E \le 1$. If effects E are not considered as a function of concentrations c but of doses d, all formulas apply in an equivalent way (all c replaced by d).

CA and IA were originally formulated for predicting effects E of binary mixtures (Loewe and Muischnek 1926; Bliss 1939) but can by extended to any number of components and transformed for the prediction of effect concentrations as explained in Faust et al. (2003).

For predicting effect concentrations of mixtures by means of IA, the value of ECx_{mix} satisfying Eq. 4 must be determined numerically by means of an iterative procedure. Transformation of Eq. 4 into an explicit expression for ECx_{mix} is not possible.

Notation

c_i = individual concentration of substance i in a mixture with n components (I = 1...n)

c_{mix} = total concentration of substances 1...n in the mixture ($c_{mix} = c_1 + c_2 \ldots + c_n$)

$E(c_i)$ = individual effect of substance i if present in the concentration c

$E(c_{mix})$ = total effect of the mixture with the total concentration c_{mix} if the mixture components are present in the concentration ratio $p_1 : p_2 \ldots : p_n$

ECx_i = effect concentration of substance i, i.e. the concentration of substance i that causes the effect X if applied individually ($c_i = ECx_i$ if $E(c_i) = X$)

ECx_{mix} = effect concentration of the mixture, i.e. the total concentration of substances 1...n in a mixture that contains the mixture components in a given concentration ratio $p_1 : p_2 \ldots : p_n$ and causes the total effect X ($c_{mix} = ECx_{mix}$ if $E(c_{mix}) = X$)

X = definite value for the effect E

p_i = relative proportion of substance i expressed as a fraction of the total concentration of substances in the mixture ($p_i = c_i / c_{mix}$)

F_i = concentration response function of substance i ($E_i = F(c_i)$)

F_i^{-1} = inverse concentration response function of substance i ($c_i = F^{-1}(E_i)$)

Symbols: $\sum$ - sum; Π - product

Combining concentration addition and independent action

Mixed model approaches (Olmstead and Le Blanc 2005), also referred to as *integrated modelling* or *two-stage procedures*, are combinations of concentration addition and independent action. The components of a mixture are grouped according to their MoAs. Concentration addition is assumed for sub-groups of similarly acting mixture components, and independent action is assumed between such groups. The mixed model approach predicts an intermediate toxicity within the "*prediction window*" defined by the alternative assumptions of concentration addition or independent action for all mixture components, irrespective of MoAs. While concentration addition and independent action require single substance toxicity data only, application of the mixed model approach additionally needs good knowledge of the MoAs of all mixture components.

Toxicokinetic-toxicodynamic models

Toxicokinetic-toxicodynamic models are sophisticated mixture toxicity modelling approaches which do not only require single substance toxicity information but also detailed knowledge or detailed assumptions about the physiology of the exposed organism and about the kinetics and/or the dynamics of the interaction between the toxicants and the organism. In the field of human mixture toxicology, such approaches are usually discussed under the key term PBPK/PD (physiologically-based pharmacokinetics and pharmacodynamics) (see e.g. US EPA 2000).

In ecotoxicology, conceptually similar approaches have been suggested as an application of the so-called DEBtox theory (dynamic energy budget theory for the evaluation of the effects of toxicants) (Jager et al. 2010). In contrast to simple generic black-box models such as concentration addition or independent action, toxicokinetic-toxicodynamic models are specific to the chemicals and for the organisms considered. They are discussed in the scientific literature as a means for supporting future MRAs (Desalegn et al. 2019). So far, they have not gained much practical relevance for regulatory MRAs.

4.4.2 Exposure assessment for mixtures

Assessment of exposures to unintentional mixtures is an under-researched issue. This applies to both the development of methodologies for prospective co-exposure assessments as well as the conduct of retrospective surveys on existing real-world co-exposure patterns.

The scientific development of methodologies that are ready for regulatory use is still in its infancy. Given this status, the recent OECD guidance document on risks of combined exposure (OECD 2018) provides a systematic overview on factors affecting co-exposure, and key data types that may inform co-exposure assessments on different levels of a suggested tiered approach. However, the suggested approach is outlined in very generic terms only, with no operational details, and it is focused on retrospective assessments on the basis of monitoring data.

Prospective modelling

Prospective co-exposure modelling means to assess the probability of co-occurrence of different chemicals at a given site in a given time-frame, and to estimate the concentrations and concentration ratios of the components of the expected mixture. The starting point is quantitative information on uses or releases of defined chemicals. Main tools are models of transport, accumulation, and transformation in the environment and ADME[7] in humans. Important auxiliary tools are models for predicting physico-chemical properties from chemical structures.

The challenge is to model multiple exposure routes for multiple chemicals simultaneously. Furthermore, for humans, modelling of indirect exposures via food and environmental media must be complemented by assessments of direct exposures through use of chemicals and chemical products both as consumers and at the workplace.

Numerous models exist which cover different sections of different exposure pathways for different types of chemicals. A non-exhaustive compilation of such tools has been prepared by Bopp and co-workers (2019, Supplementary Information Tab. S1). Teeguarden et al. (2016) developed the vision to organise all such models and all

[7] ADME – absorption, distribution, metabolism and elimination.

other sources of exposure data in an *aggregate exposure pathway (AEP) framework* which should also serve cumulative exposure assessments. Materialisation of the AEP concept is still a vision for the future. However, for the example of the aquatic environment, the EU project SOLUTIONS has taken a step forward in the modelling of unintentional co-exposures. By means of a suite of models, co-exposure calculations were performed for approximately 5 000 chemicals (REACH registered substances, pesticides, and pharmaceuticals) at 35,000 freshwater sites all over Europe (van Gils et al. 2019). These results are highly promising but further advancement of the methodology is hampered by two major obstacles. The first one is missing or imprecise information on the use or release of chemicals in terms of purposes, amounts, and sites. This input data is crucial and largely determines the possible accuracy and precision of co-exposure predictions. The second obstacle is missing monitoring data for validating modelled co-exposure scenarios. Routine monitoring data are of limited use for this purpose. They are confined to a relatively small spectrum of substances and sampling sites, and sampling frequencies may be insufficient to describe dynamics in exposure concentrations. Further research efforts are required that can integrate the advancement of methods for both pro- and retrospective co-exposure assessment.

Retrospective assessment

Retrospective co-exposure assessment means to measure current combined exposures that result from past or ongoing uses or releases of chemicals. The most important method is targeted chemical analyses of samples of environmental media and biota (*environmental monitoring*), food and feed (*food monitoring*), and human tissues or body fluids (*human biomonitoring*). Complementary approaches are so-called *non-target screening* (NTS) and *effect-based monitoring* (EBM). Concerning direct human exposures, the use of questionnaires is an additional important information source for co-exposure surveys.

Targeted chemical analyses identify and quantify pre-defined molecules for which analytical reference standards (pure substances) are available. State-of-the-art techniques can measure some hundred different compounds in a sample. More recently, so-called *non-target*

screening methods have been developed to detect thousands of different chemicals in a sample by their exact molecular mass, but the definite assignment of molecular structures remains a difficult task. Thus, even the best available chemical monitoring techniques cover only a relatively small fraction of the tens of thousands of man-made chemicals in daily use, not to mention the unknown number of associated transformation products in the environment. In addition, the information from chemical monitoring must be combined with toxicological data for assessing resulting mixture risks by means of component-based approaches. Effect Based Monitoring (EBM) can therefore be a valuable complement to chemical monitoring. EBM provides immediate information on existing risks or even acute effects. For targeting risk reduction measures, however, the causative chemicals remain to be identified by appropriate methodologies, such as effect-directed analysis (EDA) or plausibility cross-checking with results from component-based approaches on the basis of chemical monitoring data. For few pollutants, EBM methods are currently ready for regulatory use, but there are strong pleas for pushing further research initiatives in the field (Brack et al. 2019).

The current knowledge on "real-life' exposures to unintentional mixtures is scarce and fragmented. To support improvement of the situation, the European Commission has established an Information Platform for Chemical Monitoring (IPCHEM)[8] which shall provide access to publicly available chemical monitoring data. To become a valuable information source for MRAs, the database must be populated with the results from well-designed and well-performed surveys on cumulative exposures. To this end, the Commission supported some research projects which are required to feed their results into IPCHEM, such as the SOLUTIONS project on water pollution and the ongoing HBM4EU project on human biomonitoring.

[8] https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

4.4.3 Risk Assessment for Mixtures

Where possible and meaningful in a specific regulatory context, MRAs may be confined to pre-selected groups of toxicants with a common MoA to which specific populations of humans or environmental organisms are known or suspected to be co-exposed, such as the so-called *common assessment groups* (CAG) of pesticide residues defined by EFSA (see 4.5.2 below).

There is a continuous debate on what exactly constitutes a "*common MoA*" or "*common adverse outcome pathway*" (AOP), but there is consensus that the prospective MRA for such groups should be based on the assumption of concentration addition.

However, if the starting point for an MRA is a realistic and not pre-selective exposure scenario, the mixture of concern will usually include a diverse range of chemicals with different MoAs. To deal with this situation, basically two different approaches have been suggested, either starting with a mechanistic grouping of mixture components or with the default assumption of concentration addition for all mixture components, irrespective of MoAs.

A MoA-based grouping approach to component-based MRA was first developed by the US EPA (2000). The approach is built on the following simple generic scheme:

- concentration addition is assumed for mixtures of substances with a similar mode of action,
- independent action is assumed for mixtures of dissimilarly acting substances,
- a mixed model (MM) is assumed for mixtures of substances with partly similar and partly dissimilar MoAs.

From a scientific perspective, this appears to be a sound approach. From a regulatory perspective, however, this approach leads into often unsolvable practical problems.

For many environmental pollutants, knowledge about MoAs is insufficient or totally absent. In addition, the high data demands for appropriate applications of independent action and mixed models can often not be met with the single substance data that are typically available to regulatory authorities.

As a pragmatic and precautious way out of this dilemma, tiered approaches starting from concentration addition as a default assumption for all mixture components have been suggested. This is considered as a reasonable worst-case estimate. If it indicates a significant risk, refined MoA-based assessments may be conducted where the necessary data are available. Alternatively, precautionary measures may be taken.

This way of thinking has guided ecotoxicological mixture risk assessments for quite some time (e.g. ECETOC 2001, 2011a), but in the human arena it was first introduced by a WHO working group in 2011 (Meek at al. 2011). This development prepared the ground for discussing consistent and coherent approaches across the disciplinary borders (ECETOC 2011b). The first generic framework for both human and environmental mixture risk assessment was proposed by the European Commission's Scientific Committees (EC 2011a). The most recent and most refined example of a generic decision tree was developed by Price et al. (2012a). A draft SOLUTIONS proposal for an advanced tiered framework for application under the WFD has recently been made publicly available (Kortenkamp et al. 2019).

Using concentration addition as a pragmatic and precautionary default assumption can be justified by linking four arguments (EFSA 2013b):

- Data requirements for a proper application of concentration addition are much easier to fulfil than for independent action or mixed model approaches.
- Usually, the assumption of concentration addition provides a (slightly) higher estimate of mixture toxicity than the alternative assumption of independent action.
- Synergistic effects that significantly exceed the expectation of concentration addition are exceptions and not the rule, at least for multi-component mixtures with individual constituents present at low effect concentrations (Boobis et al. 2011).
- The assumption of concentration addition is protective, but not vastly over-protective. Typically, the "prediction window" between concentration addition and independent action is not very wide. For realistic assessment situations it will rarely exceed an order of magnitude on the concentration axis. Typically, it is much

smaller. Even with mixtures composed of up to 100 chemicals, predicted effect concentrations of the mixture derived from the alternative assumptions of concentration addition and independent action may usually differ by a factor of less than 5 (Kortenkamp et al. 2012, Chapter 13.4).

Pragmatic simplifications of concentration addition for regulatory assessments

To calculate risk quotients for mixtures, the so-called *toxic unit summation* (TUS) approach can be used, which is just an algebraic equivalent of concentration addition (Tab. 4.2). In regulatory practice, however, even the relatively low data requirements of concentration addition may still be unfulfillable. As a consequence, a number of pragmatic simplifications have been derived from the original concept of concentration addition, collectively denoted as *CA-based approaches* here. A comprehensive overview is provided in OECD (2018).

An illustrative selection of three prominent examples is given in Tab. 4.2: the *point of departure index* (PODI) (Wilkinson et al. 2000) and the *hazard index* (HI) (Teuschler and Hertzberg 1995), which both were originally invented for human mixture risk assessment, and the summation of PEC/PNEC ratios which was first suggested for the derivation of water quality objectives by Calamari and Vighi (1992).

A common feature of such CA-based approaches is that they basically make use of TUS as a calculation rule. However, they use input data that deviate from the strict requirements of the original concept of concentration addition, but which may be more easily available to regulators. Three basic types of such pragmatic deviations, or simplifications, can be seen in these approaches:

(i) the use of input data that do not refer to strictly identical toxicological endpoints,

(ii) the use of NOEC or NO(A)EL values instead of effect concentrations (ECx) or effect doses as input variables,

(iii) the use of regulatory acceptable levels (AL) as input data, i.e. experimental effect concentrations or NOEC or NO(A)EL values that have been multiplied by so-called assessment factors, uncertainty factors, or extrapolation factors.

Such uses of heterogenous input data can be justified with the aim to derive initial worst-case estimates for identifying mixtures of potential concern. For obtaining conclusive evidence on significant mixture risks, and in particular for ranking mixture risks for prioritization purposes, however, they may be insufficient or even misleading. Full transparency of actual input data is therefore an important requirement for ensuring the reliability of component-based mixture risk assessments. Where possible, the potential bias introduced by utilizing differing endpoints, differing assessment factors, or differing effect levels may be removed stepwise in a tiered approach.

Table 4.2 Regulatory approaches to mixture risk assessments derived from the concept of concentration addition

Approach	Assessment term		Notes
TUS Toxic Unit Summation	Effect is smaller than X % if	$\sum_{i=1}^{n} \frac{c_i}{ECx_i} \leq 1$	$\frac{c_i}{ECx_i} = TU_i = ToxicUnit$
PODI Point of Departure Index	No significant effect if	$\sum_{i=1}^{n} \frac{EL_i}{POD_i} \leq 1$	EL = Exposure Level POD = LOEL, NOAEL, NOEC
HI Hazard Index	No reason for concern if	$\sum_{i=1}^{n} \frac{EL_i}{AL_i} \leq 1$	EL = Exposure Level AL = Acceptable Level = ADI, DNEL, etc.
PEC/PNEC Summation	No unacceptable risk if	$\sum_{i=1}^{n} \frac{PEC_i}{PNEC_i} \leq 1$	PEC = Predicted Environmental Concentration PNEC = Predicted NEC

Notation for TUS as given in Tab. 4.1.

A different way of simplifying concentration addition for regulatory purposes is the so-called *toxic equivalency factor* (TEF) approach, which has been established by WHO for mixtures of dioxins and dioxin-like compounds (Van den Berg et al. 1998, 2006). The TEF approach is often equated with concentration addition, but mathematically it is a special case of concentration addition. Concentration addition and TEF are only equal under the additional assumption that

similar acting mixture components have parallel concentration response curves, which in reality is not necessarily true.

4.4.4 Prioritisation of mixtures and mixture components

Not every mixture presents a significant risk. From a risk management perspective, it is important to discriminate mixtures of high concern and to prioritise these for risk reduction measures, so-called *priority mixtures*. In addition, not every component makes a significant contribution but typically a few substances may dominate the overall mixture risk, so-called "*drivers*'. The need to identify priority mixtures and drivers of mixture risk was well recognised in the European Commission's Communication on chemical mixtures (EC 2012a), but the development of methods and criteria for mixture prioritisation and driver identification has made very limited progress since that time.

The European Commission's Scientific Committees suggested a number of general criteria for mixture prioritisations, such as "likelihood of frequent or large-scale exposure", "potential serious adverse effects (…) at the likely exposure levels", and others (EC 2011a). The specification and operationalisation of such criteria in terms of concrete decision rules remains to be worked out.

Price and co-workers (2012a, b) suggested a classification scheme for mixtures, which makes use of the hazard index approach (HI). The scheme identifies mixtures presenting a concern (HI >1) and classifies such cases in terms of the number of mixture components that explain most of the overall toxicity. The scheme is helpful for structuring the problem but may need further refinement as discussed in Faust et al. (2019a).

For integrating MRAs into prioritisation procedures under the WFD, the SOLUTIONS project proposes an approach using multiple-lines of evidence (Faust et al. 2019a, b). The approach merges all available evidence from co-exposure modelling, chemical monitoring, effect-based monitoring, and ecological monitoring. Full implementation of the proposed methodology requires changes in the legislation.

4.4.5 Accounting for combined exposures within the frame of single substance assessments: the MAF option

Concepts and tools for MRA are available. However, it is a resource intensive exercise and the unavailability of the necessary input data is often a hurdle to effective application. There are no clear perspectives for solving this dilemma in the near future. As an alternative, the so-called *MAF option* is therefore discussed in the literature. It aims to include considerations of potential mixture effects in the risk assessment of single substances, by means of a dedicated additional *mixture assessment factor* or *mixture allocation factor*, in short, the MAF. Exposure levels considered to be sufficiently safe for single substances are divided by the MAF for safeguarding against risks from combined exposures to multiple substances.

In the literature, the wording "*mixture assessment factor*" is not always used consistently and unambiguously, but may refer to two different types of uncertainties in two different types of assessment:

1. the uncertainty in single substance risk assessments that results from the fact that a chemical is not released into a pristine environment, but other pollutants may be present which contribute to the overall risk,
2. the uncertainty in a prospective mixture toxicity assessment that results from the fact that additivity models may underestimate the overall toxicity in case of synergistic toxicokinetic or toxicodynamic interactions between mixture components.

To avoid such confusion, we prefer the term "mixture allocation factor" in this report to denote an approach that covers type (i) of uncertainty and hence may be used as an alternative to performing mixture risk assessments (see Recommendation 6.6) and not as an element of mixture risk assessments for covering type (ii) uncertainties.

As a counter-argument against the establishment of a MAF, it is often claimed or presumed that conventional assessment factors are overly protective. It is assumed that they cover the simultaneous presence of other toxicants, in addition to the various extrapolations they were designed for, in particular the extrapolation from laboratory test organisms to sensitive human populations and wildlife species. However, critical examinations disprove such presumptions. In fact,

conventional single substance assessment factors do not cover mixture risks, neither for humans (Martin et al. 2013) or wildlife (KEMI 2015b).

The MAF approach is enticing for its pragmatism, but providing a sound scientific reasoning for an appropriate size of the MAF is difficult. Defining the size of a MAF means basically to make an assumption about the number, the potency and the concentration ratios of pollutants co-occurring at a site and contributing to a common adverse outcome. Suggestions in the literature range from 4 to 100 and are mostly ill justified (KEMI 2015b).

Practically, the MAF approach has been used for the derivation of environmental quality criteria for single substances in the Netherlands (van Vlaardingen and Verbruggen 2007, p. 109). To protect from combined toxicities, a factor of 100 was used to derive a so-called *negligible concentration* (NC) from a so-called *maximum permissible concentration* (MPC). The MPC is conceptually equivalent to a PNEC. The NC is the long-term target value. To the best of our knowledge, other practical applications do not yet exist.

Recently, use of the MAF has been suggested for addressing combined effects of chemicals within prospective environmental safety assessments under REACH (van Broekhuizen et al. 2016). As a default, a factor of 5 to 10 was suggested. The proposal is based on an analysis of Dutch freshwater monitoring data which indicate that, typically, no more than 5 to 10 chemicals make a significant contribution to the overall toxicity to aquatic organisms. Under these conditions, the assumption of concentration addition implies that a MAF of 5 to 10 safeguards against mixture effects.

4.5 State of regulatory implementation under EU law – technical rules and guidance

This section summarises the current regulatory use of the methods and approaches for MRA outlined in the preceding section. In normative terms, the existing requirements for mixture risk assessment under EU law have been summarised in Chapter 3. As a complement, this section informs about rules and guidance for implementing those requirements in technical terms.

Legal requirements for MRA have not changed during the last ten years except for biocidal products. The novel biocidal product regulation came into force in 2012 and implementation guidelines were developed subsequently. In addition, the preceding reform of the legislation on plant protection products (PPPs) in 2009 necessitated novel implementation guidelines, which were developed in subsequent years only. Furthermore, in 2011, considerations on MRA were included in a revised Technical Guidance Document for the derivation of environmental quality standards (EQS) under the Water Framework Directive (WFD) (EC 2011b). All other rules and guidance documents for MRA under EU law were also already reflected in the 2009 state-of-the-art report (Kortenkamp et al. 2009).

4.5.1 Intentionally prepared mixtures

Under *REACH* and the Regulation on classification, labelling and packaging (*CLP*), guidance on the assessment of mixtures is confined to hazard classifications, not including risk assessments.

The CLP implementation guidelines offer four possibilities for classifying intentionally prepared mixtures (ECHA 2009). Two of these are whole mixture testing and CA-based mixture toxicity calculation. The other two follow the so-called *bridging principle*, which assumes similar toxicity of similar mixtures, and the so-called *summation rule*, which is based on hazard classifications of individual mixture components. These options may be combined in tiered approaches. An overview and a discussion of quantitative differences between different approaches is given in Backhaus et al. (2010).

Under REACH, rules have been established for the assessment of the PBT[9]/vPvB[10] properties of MCS[11] and UVCB[12]. The overall classification depends on the content of constituents that are classified as PBT or vPvB individually (ECHA 2008c).

To prepare safety data sheets for mixtures under REACH, industry has developed the lead component identification (LCID)

[9] PBT – persistent, bioaccumulative, and toxic.
[10] vPvB – very persistent and very bioaccumulative.
[11] MCS – multi-constituent substance (e.g. isomer mixture).
[12] UVCB – materials of unknown or variable composition, complex reaction products or biological materials.

methodology (CEFIC 2018a). The methodology is based on the premise that the risks of a mixture are controlled, if the risk of the most hazardous component is adequately controlled.

Under the plant protection product Regulation (PPPR)[13] and the biocidal product Regulation (BPR)[14], guidance has been released for environmental MRAs of products containing more than one active ingredient.

Under the PPPR, procedures for MRA have been included in the risk assessment guidelines for birds and mammals (EFSA 2009a, section 2.5, and Appendix B), for aquatic organisms (EFSA 2013c, section 10.3, and 2015b, section 10.2), for bees (EFSA 2013d, section 8), and for non-target terrestrial plants (EFSA 2014b, sections 8.1, 8.2, and Appendix F).

Under the BPR, rules for mixture toxicity assessment have been included in the guidance on the environmental assessment of biocidal products (ECHA 2017c).

In all these documents, terminologies and suggested tiered approaches are not fully consistent. As a common feature, however, they are all based on the default assumption of concentration addition. Typically, they start with a pragmatic simplification of the original concept of concentration addition, such as a summation of PEC/PNEC ratios. If this signals an unacceptable risk, the analysis is taken forward towards compliance with the conceptual premises of concentration addition, as far as possible with available data. If concerns about a significant risk cannot be removed, whole mixture testing is considered as an ultimate option for clarification.

To assess the regulatory significance of deviations between predicted and experimentally observed mixture toxicities, the BPR guidance provides a quantitative criterion: "The experimentally derived effect of a mixture which is greater than that predicted by concentration addition by a factor of 5 or more should be reviewed and discussed with respect to potential synergistic interactions" (ECHA 2017c, p. 355).

[13] Regulation (EC) No 1107/2009.
[14] Regulation (EU) No 528/2012.

4.5.2 Unintentional mixtures

Under the chemical agents directive (CAD)[15] for the protection of workers health, a CA-based approach is used to assess the overall risk of occupational exposure to air contaminants with a similar mechanism of action. The approach is not laid down in an EU-wide guidance but on the Member States level, such as the Swedish provisions on Occupational Exposure Limit Values (OELV). In Sweden, the calculated risk indicator is denoted as *hygienic effect* (HE) (Arbetsmiljöverket 2015, § 9, p. 10). The HE is a specific form of the hazard index approach (HI).

The calculation of OELVs for similarly acting air contaminants at the workplace is the oldest regulatory application of the concentration addition model. In the early 1970's, the approach was already used in the former USSR (Bustueva and Roscin 1975). More than a decade later, western European countries adopted the approach. In Germany, for example, it was introduced in 1985 (BMAS 1985).

Under the frame of the former IPPC[16], which was replaced by the Industrial Emissions Directive (IED)[17] in 2014, the toxic equivalency factor approach (TEF) was established in 2000 under the daughter directive on waste incineration[18] for setting exposure limit values (ELV) for dioxins and furans. The approach has been transferred to the assessment of dioxins and furans under other EU legislation too, such as legislation on food contaminants (see Chapter 3) and the WFD. Whole mixture testing (WMT) is another approach practically used in many EU Member States for assessing complex urban and industrial emissions, in particular waste waters. A survey on WMT use was included in Part 3 of the 2009 state-of-the-art report (Kortenkamp et al. 2009).

The water framework Directive (WFD)[19] aims to achieve a good chemical and ecological status of waters and thus entails a need for assessing overall exposures but does not include a clear requirement for MRAs (see Chapter 3). Nevertheless, a guidance on the calculation of quality standards for "*substances occurring in mixtures*" was prepared in 2011 (EC 2011b, section 7) but has not gained practical

[15] Council Directive 98/24/EC.
[16] IPPC – integrated pollution prevention and control; Directive 2008/1/EC.
[17] Directive 2010/75/EU.
[18] Directive 2000/76/EC (repealed by Dir 2010/75/EU).
[19] Directive 2000/60/EC.

application. The guidance continues efforts for establishing quality standards for mixtures in the aquatic environment which began more than 25 years ago (Calamari and Vighi 1992). The new guidance suggests three possible approaches: toxic units (TU), toxic equivalency factors (TEF), and specifically for petroleum substances the *PETROTOX model*, which is an application of concentration addition. To become fit for practical use, however, the guidance still leaves much room for improvement. To this end, the SOLUTIONS project made detailed recommendations (Faust et al. 2019a).

Since 2005, the Regulation on maximum residue levels (MRL)[20] of pesticides in food and feed includes a requirement to consider "known cumulative and synergistic effects, when the methods to assess such effects are available" (Article 14, 2b). To develop such a methodology, EFSA built on pre-existing concepts of US agencies (US EPA 2002). In 2008, EFSAs work yielded a proposal for a tiered CA-based approach (EFSA 2008) which was tested in a case study on conazole fungicides (EFSA 2009b). The approach shall be applied to pre-selected groups of pesticides with a common toxicological profile in humans, so-called cumulative assessment groups (CAG). In 2013, EFSAs work on the identification of such CAGs resulted in the definition of CAGs effecting the nervous system or the thyroid hormone system (EFSA 2013e). CAGs for several other target organs were proposed in a contract study for EFSA (Nielsen et al. 2012) but did not find consensual acceptance by the competent EFSA panel. No further progress on CAG definition has been reported since then. The issue is further addressed in Chapter 5 (sections 5.3.2 and 5.4.2).

Beyond the specific case of MRLs for multiple pesticide residues, the overarching EU food law, which came into force in 2002, includes a general requirement to consider "*probable cumulative toxic effects*"[21] on human health, however with no clear definition of terms (see Chapter 3). Now, in 2019, EFSA has presented a generic guidance on MRA. In accordance with EFSAs legal mandate, the guidance is focused on human health risks from dietary exposure to chemicals and on environmental risks of chemicals falling under EFSAs remit, i.e. pesticides and food and feed additives. EFSA considers the guidance ready for use by EFSA panels but recommends a testing

[20] Regulation (EC) No 396/2005.
[21] Regulation (EC) No 178/2002, Article 14(b).

phase, the development of case studies, and further research on many elements of the suggested generic framework.

4.6 Summary appraisal of scientific and regulatory progress during the last 10 years

All in all, the last ten years have been a phase of confirmation and consolidation of knowledge about mixture risks and available methodologies for their regulatory assessment. The subject gained wider attention than ever before, and the expertise for performing MRAs is now spread among a much wider community of both researchers and regulators. The overall conclusion from the 2009 state-of-the-art report for the European Commission was that "mixture risk assessment (…) is not only necessary, but also feasible". This view is no longer scientifically disputed, but the focal point of discussion has now shifted towards developing guidance to decision makers "on when and how to assess the risk from combined exposure to multiple chemicals" (EFSA 2019, p. 9). Converging initiatives on various levels (OECD, WHO, EU, Member States) support the development of a consistent terminology and the harmonisation of principles and methodologies for both human and environmental MRAs. As a common principle, all these initiatives now recommend "adoption of the mixture assessment concept of dose addition as a pragmatic and precautious default assumption" (EFSA 2019, p. 15). In detail, however, the exact conditions for applying this default assumption and the needs and ways for refining the assessment in a specific regulatory context continue to be debated, and progress is slow.

The 2009 state-of-the-art report gave six main recommendations. Developing European guidance for MRA and using concentration addition as a default assumption were two of them, and some progress has been made as stated above. The same applies to a third recommendation which was to support research on the identification of typical co-exposure situations, priory mixtures, and determinants of synergistic effects. Some frontier research initiatives have taken these challenging tasks and pursued them for selected cases. They improved our knowledge on these issues and suggested novel tools and approaches for dealing with them. However, considering the

dimensions of these problems, much more concerted research activities are needed.

No progress has been made concerning a fourth recommendation which was to take quality assurance measures for single substance toxicity data which are needed for MRAs. The problem of insufficient input data for component-based MRAs has turned out to be much wider and more fundamental than recognised in the 2009 report. For thousands of chemicals known or suspected to occur in environmental media, available information on uses, releases and toxicity is not just of a poor quality, but totally absent. The high expectations once imposed on REACH concerning the improvement of data availability have not materialised.

No significant progress has been made concerning the remaining two 2009 recommendations. These were to strengthen the legal requirements for MRAs and to explore options for MRAs in media-oriented legislation such as the WFD. The legal basis for MRAs has not changed since 2009, except for intentional combinations of chemicals in biocidal products (see Chapter 3). The WFD will be subject to a forthcoming revision, and researchers have made detailed proposals for dealing with risks from pollutant mixtures in the aquatic environment (Brack et al. 2017, Faust et al. 2019b). Whether any of these find acceptance in the political process remains to be seen.

4.7 Conclusions from the literature review

Improving the protection of humans and the environment from mixture risks requires concerted actions at different levels and on different elements of the regulatory system. Identified short-comings in the current regulatory system include:

- Clear and consistent legal requirements for MRAs are absent in most pieces of EU chemicals legislation.
- Overarching rules to enable management of unintentional mixtures of chemicals regulated by different pieces of legislation are missing.
- There is no comprehensive database that collects information on uses, emissions and toxicity for all chemicals.

- There are no large-scale and long-term research programs in place for improving our scarce knowledge about real-life exposure patterns to chemical mixtures, using both prospective modelling and retrospective monitoring techniques.
- No use is made of the so-called "MAF-option", i.e. safe-guarding against mixture risks within the frame of single substance assessments by means of simple default assumptions.

Improvements of EU legislation could be made step-wise by utilizing windows of opportunity, such as the forthcoming revision of the WFD.

5 Group-wise management of chemicals

This chapter provides a summary review of different research areas where grouping of chemicals is addressed, and examines how the use of different grouping approaches has been implemented under EU chemicals legislation.

Section 5.1 defines the scope of this review, and 5.2 explains key terms and concepts. Sections 5.3 and 5.4 provide an overview of the scientific and the regulatory state-of-the-art. Section 5.5 summarises current barriers to further improvements identified in the review. Based on this, recommendations on how group-wise management of chemicals can be improved are derived in Chapter 6.

5.1 Scope of the summary review

A number of methods and approaches have been suggested in the scientific literature for grouping chemicals for various purposes. The focus of this scientific overview is on methods and approaches related to regulatory risk assessment or risk management measures.

The section on regulatory implementation under EU law provides an overview of key guidance documents and approaches used for grouping of chemicals under different processes and by different actors.

5.2 Key terms and concepts

There are different methods used to fill information gaps by grouping chemicals together, but they have in common that they are based on the *similarity principle*, i.e. the hypothesis that structurally similar chemicals have similar biological activities (ECHA 2008a).

Read *across* is one of these methods, which is used to predict the properties of a (target) substance using relevant information on similar (source) substances. This method is used for regulatory hazard identification and assessment within what is called the analogue and category approaches. The *analogue approach* refers to the grouping of a target and one (or a few) source analogue(s), whereas the *category approach* often refers to the grouping of a larger number of similar substances to predict properties of the category members (ECHA 2008a, OECD 2014). The properties of a target chemical within a category are assessed based on the evaluation of the category as a whole (OECD 2014).

Chemicals within a category are often related by a trend in an effect for a specific endpoint. This means that the properties of the category members change with structure in a predictable manner and that a pattern can be seen in the changing potency across the category. A *trend analysis* can be carried out by deriving a model based on the data of the category members (OECD 2014).

Quantitative *Structure-Activity Relationship* (QSAR) is another data filling technique which, based on the chemical structure, predicts the chemical's physico-chemical, toxicological and environmental fate properties (KEMI 2018a, ECHA 2008a).

5.3 State of the science

This section describes three research areas where grouping approaches have been developed, applied and/or evaluated. These include grouping for filling information gaps, grouping for mixture risk assessment, and grouping to support substitution of hazardous chemicals.

5.3.1 Grouping for filling information gaps

The development and use of different data gap filling techniques, such as read-across and QSAR methods, have increased as a response to new requirements to provide information on chemical hazards and the aim to reduce animal testing (Patlewicz et al. 2017).

Although there are technical guidance documents available which describe the use of read-across (e.g. ECHA 2008a, 2017a, OECD 2014), the applicability and validity of read-across approaches for the prediction of specific endpoints have been questioned. Concerns have been raised due to inconsistencies in read-across predictions, insufficient evidence to substantiate read-across predictions and poor documentation of justifications for these predictions (Patlewicz et al. 2017). This has spurred research on how grouping strategies and read-across can be improved for regulatory purposes (e.g. Patlewicz et al. 2017, Pradeep et al. 2017).

Studies evaluating and refining read-across and QSAR approaches aim to improve their consistency in predicting different endpoints (Patlewicz et al. 2015). Despite development of these methods, a recent study on substitution and grouping conducted on behalf of the European Commission (EC 2017a) concluded that further research on grouping strategies for regulatory purposes is needed and that it should be focused on

> the association between chemical structures and trends in (Q)SAR predictions in order to scale up their adoption and move from the current incremental substitution practice to a more effective substitution of hazardous substances. (EC 2017a).

Alongside computational methods, there has also been a shift towards increased use and regulatory acceptance of *in vitro* testing approaches for hazard identification and risk assessment. This development is also mirrored in the research area of data gap filling techniques, where approaches are evolving to incorporate more mechanistic data, e.g. making use of knowledge about so-called adverse outcome pathways (AOPs) to substantiate read-across for the prediction of chemical toxicities (Patlewicz et al. 2017). An AOP describes the mechanistic relationship between a molecular initiating event, subsequent perturbations at the cellular and organ levels, and the final adverse phenotypic outcome on the level of an individual or a population, such as malformations or symptoms of diseases.

The scientific literature includes several examples of read-across approaches, which integrate both chemical and biological data. Such methods have been developed e.g. for categorization of chemicals into different chemical classes, for predicting different endpoints and for hazard classifications (Low et al. 2013, Gebel et al. 2014, Grimm et al. 2016, Shah et al. 2016).

To increase regulatory acceptance of using read-across predictions for filling information gaps in hazard and risk assessments, the need for a transparent and systematic approach for assessing similarity and uncertainty in read-across applications has been addressed (Blackburn and Stuard 2014, Schultz et al. 2015). Schultz et al. (2015) developed templates to assist in assessing similarity with regard to chemistry, toxicokinetics and toxicodynamics and to guide systematic characterisation of uncertainties in the context of the similarity rationale, the read across data, the overall approach, and the conclusions drawn. The authors also suggested a workflow for transparent and consistent reporting of read-across predictions (Schultz et al. 2015).

Due to the specific characteristics of nanomaterials, a number of studies have looked into how knowledge on these characteristics can be used to categorise nanomaterials into hazard groups. To avoid the testing of all individual nanomaterial, and to fill information gaps, different approaches to the grouping of nanomaterials based on shared properties have been investigated (Landvik et al. 2018, Arts et al. 2014, Braakhuis et al. 2016, Oomen et al. 2014).

5.3.2 Grouping for mixture risk assessment[1]

Whether and how chemicals should be grouped for performing mixture risk assessments is the subject of a long-lasting and sometimes controversial debate. Views on the issue differ with (i) the assessment perspective (prospective or retrospective), (ii) the methodological approach (whole mixture testing or component-based modelling), (iii) the protection goal (human health or environment), and (iv) the regulatory context which may pre-define a group of chemicals under consideration, e.g. pesticides in food governed by the Regulation on maximum residue levels.

[1] See Chapter 4 for explanations of key terms and concepts used in this section.

In addition, a difference must be made between the use of grouping approaches for (i) defining the mixture of concern (the starting point of an assessment) or (ii) refining an assessment on a higher level of a tiered assessment framework.

The definition of the mixture of concern, i.e. the initial problem formulation step of a mixture risk assessment, may either start from evidence on combined exposures (exposure-based definition) or from evidence on a common hazard (hazard-based definition), or a combination of both. Exposure-based definitions may be derived from retrospective chemical analyses or prospective co-exposure modelling. Hazard-based definitions may stem from toxicological test data or may be derived from similarities in physicochemical properties as a proxy for similar hazards. Hazard-based definitions may be further confined to substances causing a specific adverse outcome by a common mode of action (MoA), but this is a disputed issue as explained below.

The discussion about grouping of mixture components is mainly associated with component-based approaches to mixture risk assessments, which require an exact definition of the substances included in the assessment. In contrast, where mixture risk assessments start with whole mixture testing, such as effect-based monitoring (EBM), the mixture of concern is automatically defined in terms of the hazardous effects that can be seen with the assays used. These may be specific mode-of-action screens (e.g. estrogen-receptor binding) or tests on so-called apical endpoints (e.g. algal growth inhibition). Identifying the causative agents is a second step of whole mixture approaches and grouping does not play a significant role in this.

EFSA denotes the substances included in a component-based assessment as a "common assessment group" and distinguishes between "grouping based on (i) regulatory criteria, (ii) exposure, (iii) physicochemical similarities, and (iv) biological or toxicological effects" (EFSA 2019). In this list, the grouping criterion "exposure" may appear to be tautologic if a mixture is defined as a group of chemicals to which an organism may be jointly exposed (see 2.2.2). However, the idea of "grouping based on exposure" becomes understandable under the premise that a regulatory authority works on a legally predefined selection of a relatively small number of chemicals with clearly different probabilities for co-occurrence in a specific exposure scenario. For example, the typical spectrum of pesticide

residues in a vegan diet may be significantly different from the spectrum in a diet including meat.

However, for more comprehensive assessments of combined human exposures, not limited to one use group of chemicals (pesticides) and one exposure route (food), the idea of "grouping based on exposure" may need to be developed further into a broader methodological concept for identifying typical co-exposure situations.

Differing views on MoA-based groupings

Component-based approaches presume that mixture components contribute to a common toxicological endpoint by similar (concentration additive) or dissimilar (independent) modes of action, or by a mixture of both. Therefore, the discussion about grouping of chemicals for mixture risk assessments is mainly focused on the identification of common modes of action. However, there are ranging views on the importance of this point. In human toxicology, many experts consider MoA-based grouping as a key step in mixture risk assessment and a top research priority (e.g. Rotter at al. 2018, Boberg et al. 2019). In eco-toxicology, in contrast, MoA-based grouping is not generally considered as a crucial bottleneck for component-based mixture risk assessments; rather it is the unavailability of comparable single substance toxicity data.

These differing views on the importance of MoA-based grouping reflect different opinions about the appropriate regulatory use of component-based approaches. The general assumption of concentration addition, irrespective of modes of action, is now widely accepted as a cautious and not vastly over-protective first tier approach in both ecotoxicology and human toxicology (see Chapter 4).

However, if such an initial assessment signals significant mixture risks, there are different views on the needs and the ways for refining such an assessment for regulatory decision making. In the human arena, MoA-based grouping is considered as an essential refinement step (EFSA 2019). For environmental assessments this is usually neither possible nor considered necessary (Backhaus and Faust 2012). If toxicity data for individual components refer to the same endpoint in the same taxonomic group (irrespective of MoAs) this is usually the highest achievable refinement level.

Chemicals act differently in different species

One of the various reasons for such differing views is the fact that mode of action is a species-specific concept. While human risk assessment deals with one species, environmental risk assessments aim to protect millions of different species with different physiologies. Modes of action in algae are something very different from modes of action in insects, for example. Two substances may act similarly in one species, but dissimilarly in another. Some modes of action may be common to large taxonomic groups, others may be confined to sensitive sub-populations of only a single species.

For most of the chemicals and most of the species, knowledge about modes of action are missing, and there are no prospects for changing this situation fundamentally in the foreseeable future. Some years ago, there were great expectations that novel toxicogenomic-approaches could change the situation very rapidly (Altenburger et al. 2012), but so far these have not materialised. Thus, waiting for the scientific clarification of MoAs for tens of thousands of pollutants in millions of species appears to be a deadlock and not an effective way forward towards better protection from mixture risks.

What is the protection goal?

Another reason for differing views on the importance of MoA-based grouping are different types of endpoints and protection goals. Human risk assessments seek to protect individual humans from diseases or other adverse health outcomes that may be caused by specific types of chemicals with specific modes of action, such as certain forms of cancer caused by genotoxic carcinogens for instance. Environmental risk assessments, in contrast, consider so-called apical endpoints such as mortality or population growth, which may be affected by a multitude of chemicals with diverse and mostly unknown modes of action.

For these different assessment situations, there are different opinions about the risk assessment of mixtures if the components (i) have different MoAs and (ii) are present at low doses or concentrations, whereby "low" denotes levels below regulatory acceptable

levels for individual chemicals, such as ADIs or DNELs for humans, and PNECs for organisms in the environment.

In 2011, the European Commission's Scientific Committees came to conclude that in relation to human health the level of concern about such mixtures "should be assumed to be negligible", while in relation to ecological effects, such mixtures should be "considered as a possible concern" (EC 2011a). Given this paradigm, it becomes reasonable to pursue MoA-based groupings for human mixture risk assessments but not for ecological risk assessments.

Mode of action is not a precisely defined term, and details of knowledge about MoAs may be very different for different chemicals. In the literature, MoA-based classifications of chemicals vary from definitions of target molecules (e.g. a specific enzyme), to definitions of affected metabolic pathways (e.g. cholesterol biosynthesis), and descriptions of affected target organs or general modes of functional disturbance (e.g. endocrine disruption) (Busch et al. 2016).

A novel and more precisely defined concept for grouping are adverse outcome pathways (AOP) (Ankley et al. 2010, see descriptiton under 5.3.1). The AOP concept is considered to have potential for future regulatory use, but so far has found little practical application in mixture risk assessment (EFSA 2019).

In the literature, the MoA-based grouping of chemicals for mixture risk assessment is discussed largely in isolation from considerations about grouping of chemicals for hazard classifications under REACH and CLP, and from criteria for identifying candidates for substitution. To our knowledge, concepts for linking regulatory grouping approaches for all three purposes have not yet been developed.

5.3.3 Grouping to avoid regrettable substitution

In the scientific literature, different challenges and obstacles that could hamper successful substitutions are identified, and approaches for how they could be addressed are presented. One approach proposed to prevent regrettable substitution is to group chemicals by functional use (Tickner et al. 2015, Fankte et al. 2015, Howard 2014). This is referred to as *functional substitution* and aims to

encourage searching beyond *chemical-by-chemical* substitution, i.e. replacing one chemical with a structurally similar chemical (so called "*drop-in*" chemical), to find less hazardous alternatives to meet product performance (Tickner et al. 2015).

According to Tickner et al. (2015), substitution may occur at three different levels, i.e. by substituting:

(i) a chemical, commonly by a structurally similar chemical, e.g. bisphenol A (BPA) with bisphenol S (BPS),

(ii) the end-use function, which entails a change in material, product or process, e.g. low density polyethylene instead of high density polymers which require plasticizers, or

(iii) the service function, which entails a change of the system, e.g. digital receipts instead of printing receipts.

(Tickner et al. 2015, Sackmann et al. 2018).

To avoid regrettable substitutions, it is emphasized that preference should be given to substitution of the end-use or service function over drop-in chemical substitutions (Tickner et al. 2015, Sackmann et al. 2018).

To identify suitable substitutes, chemical alternatives assessments are performed. Methods and tools for chemical alternatives assessments typically combine hazard and risk assessment with economic and technical feasibility to different extents and they have mainly been used with a focus on chemical-by-chemical substitution (Howard 2014, Fankte et al. 2015).

Chemicals currently used for obtaining a particular function may not be the best option from a health or environmental perspective. Sometimes there may also be non-chemical alternatives available to achieve that particular function.

Grouping chemicals according to functional use can provide valuable information for the alternatives assessment to look for different and/or entirely new chemical structures and materials and non-chemical solutions (Howard 2014, Tickner et al. 2015).

In a literature review and stakeholder consultation study, the benefits of applying functional substitution was emphasized, contrasted by chemical-by-chemical substitution. In relation to this, a need to create a system for consistent definitions, classification and characterisation of functions of chemicals was identified (EC 2017a).

Sackmann et al. (2018) also points out that grouping chemicals according to technical functions, e.g. plasticizers, flame retardants and surfactants, will be useful for identifying safer alternatives as well as patterns of substitution, i.e. which substance might be substituted by which substitute.

However, it is not certain that functionally equivalent alternatives can always be found outside a group of structurally similar chemicals. If so, and in the absence of sufficient information on (eco)toxicological properties and environmental fate of structurally related alternatives, Fankte et al. (2015) suggest that it should be assumed that the alternatives exhibit the same hazardous properties as the substance(s) to be substituted, based on similarity in chemical structure. The authors suggest that this default assumption may be dropped if the manufacturers of the alternatives can demonstrate that it is wrong. The assumption that structural similarity can be used as a proxy for similarities in (eco)toxicological and environmental fate properties is an accepted principle and the basis of in silico models used in regulatory contexts to identify chemicals of potential concern and to avoid regrettable substitution.

Attention has also been paid to grouping chemicals in the context of biomonitoring as a way of responding to shifts in chemical use and the emergence of new chemicals on the market. Biomonitoring of groups of chemicals could enable identification of chemicals that may emerge as health or environmental concerns, e.g. as a result of a replacement of a restricted chemical with a chemical with a similar toxicity profile. According to Krowech et al. (2016), it is therefore important to include groups of chemicals in monitoring and intervention programs.

5.4 State of regulatory implementation under EU law

This section informs about regulatory guidance and approaches for implementing the existing requirements and possibilities for grouping of chemicals as summarised in Chapter 3. Grouping is not generally and consistently applied across regulations, but implementation is fragmented and confined to specific purposes under specific legislations and performed by the corresponding competent authorities.

This is mirrored in this section, which includes grouping for (i) hazard identification and risk management measures under REACH and CLP, (ii) mixture risk assessment under the EU food law, and (iii) supporting substitution under REACH, the BP and PPP Regulations. Guidance that considers grouping is also available for the implementation of the regulations on food additives and cosmetics. These are briefly mentioned in Chapter 3 and not further discussed in this chapter.

5.4.1 Grouping for hazard identification and risk management measures under REACH and CLP

Guidance on grouping approaches and read-across

REACH Annex XI lays down general rules for adaptation of the data requirements. These include rules for when chemicals may be grouped and read-across of data used to fill information gaps as an alternative to test each chemical for every required endpoint.

Under REACH, structural similarity is a pre-requisite for any grouping and read-across approach (ECHA 2017a). Chemicals whose physicochemical and (eco)toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be grouped and considered as a category (REACH Annex XI).

Using read-across to fulfill the test data requirements for the registration process under REACH is one of the most commonly used alternative approaches to fill data gaps (Ball et al. 2016, ECHA 2017a). The read-across approach needs to be justified by scientifically plausible explanations and sufficient supporting information. Such information could come from QSARs or experimental data addressing specific aspects of the read-across hypothesis (ECHA 2017a). However, many registrations that have used the read-across approach have been found to be of poor quality, or to apply unfounded or insufficiently justified groupings (KEMI 2015a, 2018a).

As a means to improve the quality of registration dossiers and to avoid the future misuse of read across, the Swedish Chemicals Agency has previously suggested that ECHA should explore the feasibility of grouping within the framework of substance evaluation (KEMI 2015a). Since then, ECHA has e.g. integrated a systematic

analysis of structural similarities in the IT screening of candidate substances for evaluation (EC 2017a, KEMI 2018a).

ECHA has issued guidance on how to group chemicals, the use of read-across approaches and the technical and scientific justifications of such assessments (ECHA 2008a, ECHA 2017a).

Guidance on grouping and read-across has been developed by other organisations as well, with the Organisation for Economic Co-operation and Development (OECD) guidance and the QSAR Application Toolbox software for making read-across assessments being the most advanced guidance for addressing current regulatory needs (Patlewicz et al. 2017). A brief overview of the ECHA and OECD guidance is given in Table 5.1.

Table 5.1 Regulatory guidance on grouping of chemicals and read-across

Reference/ Organisation	Scope and purpose	Grouping based on:
ECHA (2008a): Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals	General guidance on grouping, QSARs and read-across as alternative approaches to fill data requirements under REACH	Common functional group, constituents or chemical classes, similar carbon range numbers, common precursors and/or breakdown products
ECHA (2017a): The Read-Across Assessment Framework (RAAF)	A complementary resource to the general guidance for structuring the read-across justification and making the different sources of uncertainty transparent	Mentions that grouping may be based on e.g. common functional groups, precursors and/or breakdown products, or a constant pattern in the changing of the potency of the physico-chemical or biological properties across the group
OECD (2014): Guidance on grouping of chemicals, second edition	General guidance to and different applications of grouping approaches and data gap filling techniques for hazard assessment	Common functional group, mode or mechanism of action (MoA) or adverse outcome pathway (AOP), constituents or chemical classes, precursors and/or breakdown products, an incremental or constant change across the category (e.g. a chain-length category) or a constant pattern in the changing of the potency of the physico-chemical or biological properties across the group

In the ECHA and OECD guidance, the analogue and category approaches are described as techniques for grouping chemicals. A chemical category is described as a group of

> chemicals whose physical-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (OECD 2014).

ECHA (2008a) uses a similar definition of chemical category.

More specifically, grouping of chemicals may be based on e.g. common functional groups, modes/mechanisms of action or breakdown products (see Table 5.1). Due to more chemicals generally being present in a chemical category than upon application of the analogue approach, trends across endpoints may be easier to detect using the category approach (OECD 2014).

Although chemical grouping and read-across of data is commonly used for industrial chemicals under REACH, it is acknowledged that these approaches may introduce additional uncertainty into hazard and risk assessment (ECHA 2008a, OECD 2014). To reduce uncertainty, access to good quality data is fundamental, as well as mechanistic understanding for specific endpoints to assess the biological plausibility and to justify the grouping (OECD 2014).

Specific guidance

In addition to the general guidance, both ECHA and OECD provide more specific guidance for read-across application and assessment of QSAR approaches. The *Read-Across Assessment Framework* (RAAF), developed by ECHA, is a complementary resource to the guidance that provides principles and examples for scientifically examining read-across predictions of human health hazards, environmental fate and environmental hazards of chemicals in the context of REACH (ECHA 2017a). To increase the regulatory acceptance of QSAR methods, the OECD has developed a QSAR Toolbox (OECD 2019). The Toolbox consists of a set of tools supporting the use of QSAR models in different regulatory frameworks, e.g. by providing estimates for commonly used endpoints together with guidance on the interpretation of the estimated data (OECD 2019).

As a response to the identified need to assign nanomaterials to hazard groups (see 5.3.1), ECHA has also developed principles and guidance for grouping of nanomaterials (ECHA 2017b).

The possibility and suitability of grouping chemicals is also addressed in the "Guidance for the preparation of an Annex XV dossier for restrictions" (ECHA 2007). The guidance mentions two scenarios where grouping of chemicals may be relevant in the restriction process when (i) registrants have already grouped chemicals for the chemical safety assessment (Annex I, Section 0.4) as it will affect the information available for the restriction procedure, and (ii) an authority wishes to cover a number of related substances by the same restriction dossier. This could be the case when the key hazardous property, in combination with the exposure that causes the risk addressed in the restriction proposal, is shared by two or more substances.

Grouping approaches to identify, assess and restrict chemicals of concern are increasingly used within EU regulatory frameworks, both by EU agencies and by Member State Competent Authorities. The following sections provide examples of grouping activities at ECHA and the Swedish Chemicals Agency.

Grouping activities at the European Chemicals Agency

ECHA is increasingly working with groups of substances as a means to address substances of concern as effectively as possible. Grouping is an essential part of ECHA's Integrated Regulatory Strategy, which supports authorities to use the most appropriate combination of REACH and CLP processes to manage chemicals of concern (ECHA 2019a).

Mapping the "chemical universe"

One of ECHA's most recent and ambitious activities in support of a grouping approach is to "map the chemical universe" of REACH registered substances (ECHA 2019a). This work was initiated in 2018, and ECHA's ambition is to categorize all registered substances that are manufactured or imported in quantities above

100 tonnes per year by the end of 2020. By 2027, ECHA intends to have covered all registered substances.

The aim of the screening and mapping work is to assign registered substances to any of the following three regulatory bins:

1. *High priority for further risk management*
   These are substances with identified concern and further regulatory work can start based on currently available data, i.e. there is sufficient information within the registration dossier or complemented with other available information to initiate either:

– hazard classification according to CLP, or identification as a SVHC for PBT and/or ED properties, or

– a restriction or authorisation process under REACH, or regulatory risk management measures under other EU legislation.

2. *High priority for data generation*
   These are substances of potential concern for which data generation is expected to address current uncertainties, thus enabling a decision whether these require further regulatory risk management or can be considered as a low priority. These substances are then prime candidates for compliance check and/or substance evaluation.

3. *Low priority for further regulatory action*
   These are substances for which available data is sufficient to conclude that they are of low concern at present, or which are already subject to sufficient regulatory risk reduction measures.

Due to the current lack of hazard and/or exposure information in the REACH dossiers, a considerable "uncertain' area exists which contains substances for which no immediate allocation to any of these three bins can be made. The intention is to reduce the uncertain area by allocating substances for further work (either information generation, initiate hazard confirmation or regulatory risk management), or concluding that a substance is of low priority. Such conclusion is time-dependent and should be regularly reviewed based on new information on hazards or uses. Ultimately, all substances should be regarded as low priority for further regulatory action, either because they are of low concern or because the relevant regulatory action is already in place.

Step-wise mapping of the "chemical universe"

In a first step of the mapping, the substances are grouped based on structural similarity. Starting from a specific substance, also called a 'seed', structurally similar substances are identified within the chemical universe. Examples of "seeds' are substances in Annex VI of CLP, on the Candidate List and the Community rolling action plan (CoRAP), i.e. substances which are already undergoing further regulatory work.

Another type of starting point for grouping are substances which have a certain type of use or function with high potential for release, e.g. a substance used as a plastics additive.

In a second step, following the structural grouping, an assessment of the individual substances in the group begins. The aim is to conclude by determining to which bin each substance in the group belongs.

In the following steps, the outcome of the regulatory processes, e.g. incoming information as result of compliance checks or the outcome of the harmonised classification process, will be assessed and used to identify whether further regulatory actions are needed or if the substance can be regarded as low priority for further action at this stage.

This cycle of allocating substances to regulatory bins and requesting new information, confirming hazard properties, and setting up regulatory risk management measures will form feedback loops that will lead to a systematic refinement of the "chemical universe' picture. ECHA will disseminate information on which substances have been allocated to which of the three regulatory bins.

According to ECHA (2019a), working with groups of substances is fundamental in this 'chemical universe' approach. This is because it allows enhanced coherence of the work of ECHA and Member States Competent Authorities through all steps, from screening through further information generation (compliance check, substance evaluation, other means including direct contacts with industry), to risk reduction measures (harmonised classification and labelling, SVHC identification and authorisation, restriction, and possibly also actions under other legislation).

Grouping activities at the Swedish Chemicals Agency

In 2017, the Swedish Chemicals Agency published a report on grouping of chemicals under REACH and CLP (KEMI 2018a). Although work using group-based approaches is advancing, the report is still up-to-date (communication with the Swedish Chemicals Agency). The Swedish Chemicals Agency works with grouping of chemical substances in all processes under REACH and CLP, and the activities described below are mainly based on their 2017 report.

The possibility to handle substances as a group depends on the purpose of the grouping, and some processes have been identified to be more feasible than others for grouping of chemicals (KEMI 2018a).

Screening and regulatory management option analysis (RMOA)

In the prioritisation of substances for different risk management measures under REACH and CLP, groups of substances with similar structures, intrinsic properties and areas of use are identified. This is done within ECHA's annual common screening programme, in which the Swedish Chemicals Agency participates. The screening includes an automated and a manual component and uses information primarily from REACH registrations collected in ECHA's registration database to systematically prioritize substances for e.g. substance evaluation, harmonised classification and the Candidate List.

Group-wise handling of substances in the common screening and risk management option analysis (RMOA) was identified in the "Roadmap on substances of very high concern" (EC 2013a) as an important activity in order to achieve the Commission's strategic aim that all relevant SVHC substances shall be identified and placed on the Candidate List by 2020 (ECHA 2013).

The Swedish Chemicals Agency has developed a tool, a Prioritisation Table, for identification and prioritisation of chemicals of potential concern for different regulatory measures, e.g. under REACH and CLP processes. The Prioritization Table contains information on a large number of substances and can be used to generate groups of substances based on e.g. structural similarities, toxicological or environmental fate properties, as well as function and use. The

Prioritisation Table complements ECHA's automated IT screening approach primarily used for identifying structurally similar substances (KEMI 2018a).

Substances that are identified as candidates for potential regulatory measures by manual screening, i.e. the screening performed by Member State Competent Authorities to further assess the outcome of the IT screening, move forward to RMOA. Substances identified as candidates for substance evaluation move forward to CoRAP.

RMOA is a case-by-case analysis carried out by the Member States. It aims to identify whether regulatory action is needed for a given substance, or group of substances, and to identify the most appropriate measures to address the concern.

The Swedish Chemicals Agency has performed manual screenings and presented RMOAs for groups of substances, including skin sensitizers in textiles based on intrinsic toxicological properties and use patterns.

Grouping in the screening and selection of substances for further regulatory measures does not require the same high scientific level and knowledge about the substances as does grouping intended for read-across of data, and can therefore be more widely applied (KEMI 2018a).

Substance registration

Many REACH registrations that have used read-across have been found to be of poor scientific quality and to use insufficiently justified groupings (KEMI 2018a). ECHA has performed different activities to improve the registration quality, including those concerning groups of substances. One such activity was to assess smaller groups of substances in which ECHA, selected Member State Competent Authorities including the Swedish Chemicals Agency, and registrants participated. ECHA has also reviewed registrations for groups of substances in sector-specific dialogues with affected stakeholders as another way to improve the quality of these registrations. The Swedish Chemicals Agency also participated in this activity.

Substance evaluation

In the substance evaluation process, grouping is done to achieve a higher efficiency, but also to check that Competent Authorities make consistent decisions about structurally similar substances. As an outcome of the common screening, structurally similar substances are published annually in the Similarity Report and can support Member State Competent Authorities in identifying and selecting groups of substances for evaluation. ECHA recommends Competent Authorities to evaluate structurally similar substances in a group, but there is no legal requirement to do so. The Swedish Chemicals Agency belongs to those that have evaluated groups of structurally similar substances within CoRAP.

Due to confidentiality of the decisions, substance evaluations for groups of substances are administratively processed as individual substance evaluations. Nevertheless, it is still more resource efficient in a longer perspective to evaluate chemicals in a group of structurally similar chemicals than to evaluate them separately, i.e. the cost is lower per substance in a group evaluation. According to the Swedish Chemicals Agency, to administratively process group evaluations would require major changes of the evaluation process and supplements in REACH (KEMI 2018a).

Classification according to CLP

Harmonised classification in accordance with CLP often constitutes the basis for further regulation of substances under REACH, as well as other legislations restricting the use of chemicals. Classification of groups of substances under CLP can therefore be an effective measure to achieve group regulation in subsequent legislative processes.

In the hazard classification of a substance according to CLP, all available information shall be used, including "information from the application of the category approach (grouping, read-across)" (Annex I to CLP, section 1.1.1.3). The Swedish Chemicals Agency has made several classification proposals for groups of substances using read-across of data between structurally similar substances.

There are examples of both defined and undefined group entries in Annex VI to CLP. Most of the more wide and undefined entries were, however, adopted under the previous Council Directive

67/548/EEC. The number of new group entries under CLP are still limited, and decisions to work with groups of substances are taken on a case-by-case basis. The Swedish Chemicals Agency concludes that further support and tools are needed to facilitate grouping in the classification process (KEMI 2018a).

The Candidate List and authorization

The Candidate List contains group entries that are both well and poorly defined. Undefined, wide groups entries could result in more substances being subject to the information requirement for articles and to authorization – if they are included in Annex XIV to REACH. However, it may be difficult to prioritise substances to Annex XIV if they are included in a group that is very wide because the prioritisation is based on the intrinsic properties, use and the annually produced or imported tonnage of each individual substance.

An alternative method to prevent one SVHC being substituted by another chemical with similar hazardous properties is to process the listing of substances on the Candidate List, and in Annex XIV as individual substances, although in close succession to each other.

However, according to the Swedish Chemicals Agency (KEMI 2018a), chemicals management would be more efficient if similar substances could be processed as one group instead of individual substances, and if these groups reoccurred in different regulatory processes, e.g. in the CLP classification, SVHC identification and authorization process.

Restriction

Restricting groups of substances under REACH (Annex XVII) is quite common, and grouping is used to a greater extent in the restriction process than for classification in accordance with CLP and in the REACH authorisation process. Annex XVII contains group restrictions for various substances and uses.

According to the Swedish Chemicals Agency (KEMI 2018a) it has been shown to be a feasible route for regulating groups of substances, although recognizing that it may be associated with significantly more work for a Member State compared to a restric-

tion proposal for a single substance. The restriction proposal has to show that the use of the group of substances results in an unacceptable risk to human health or the environment, and that the proposed restriction is also motivated from a socio-economic perspective.

Grouping chemicals under REACH has historically primarily been based on similarities in molecular structure, but now more examples are seen where grouping proposals are based on toxicological data, such as the recent proposal by Sweden and France to restrict the use of over a thousand chemicals being classified as skin sensitising, irritating and/or corrosive in textile and leather articles (ECHA 2019b, communication with the Swedish Chemicals Agency).

In summary, REACH and CLP allows for group-based assessment and management of substances, but grouping approaches could be further developed and supported by guidance and tools to ensure that chemicals are grouped more systematically and ultimately that grouping of substances is always considered the first choice (communication with the Swedish Chemicals Agency).

5.4.2 Grouping for mixture risk assessment under the EU food law

Considerations on grouping of chemicals for mixture risk assessments have been included in two guidance documents prepared by the European Food Food Safety Authority (EFSA). A specific guidance for identifying so-called "*cumulative assessment groups*" (CAGs) of pesticides was released in 2013 (EFSA 2013e). A generic guidance on "risk assessment of combined exposure to multiple chemicals" was recently published (EFSA 2019). The new generic guidance includes considerations on the "grouping of chemicals into common assessment groups" (EFSA 2019). The guidance applies to assessments "in all areas of EFSA's remit" which is defined by the EU food law[2]. Practically, this means that it is focused on (i) exposure of humans, farm animals and pet animals to any chemicals in food and feed, and (ii) exposures of wildlife species to pesticides only. Other exposure routes or substance groups are beyond the remit.

[2] Regulation (EC) No 178/2002.

The authority uses common *assessment group* as an overarching term for denoting any set of "chemical substances that are treated as a group by applying a common risk assessment principle (e.g. dose addition) because these components have some characteristics in common (i.e. the grouping criteria)". In contrast, the term *cumulative assessment group* (CAG) is used to denote a specific

> type of Assessment Group in which the active substances could plausibly act by a common mode of action, not all of which will necessarily do so (EFSA 2019).

As these definitions indicate, the grouping criteria are not sharply defined but leave much room for specification and future refinements. The guidance documents describe the meaning of the criteria and provide examples on how these may be operationalized, but no strict rules for implementation.

The new generic guidance distinguishes between (i) grouping for the initial definition of an assessment group, and (ii) the refinement of grouping during a tiered component-based assessment procedure.

For the initial definition, the authority may use four different types of criteria, which are explained in section 5.3.2: "regulatory criteria", "exposure", "physico-chemical similarities", and "biological or toxicological effects".

For the refinement of an assessment, the authority may use (i) "weight of evidence approaches", (ii) "dosimetry" (i.e. toxicokinetic information), or (iii) "mechanistic data", such as information on modes of action (MoA) or adverse outcome pathways (AOP).

The approach to be taken shall be "determined by the available data and expert judgement". If the authority chooses a weight of evidence approach, this may include various aspects such as (i) "dose–response relationship", (ii) "consistency throughout studies and species", (iii) "robustness of the evidence (if the effect was defined only at one exposure level)", and (iv) "understanding of the effect as supported by a MoA/AOP knowledge" (EFSA 2019).

The applicability of this new generic guidance shall be assessed through a testing phase. The outcome remains to be seen.

Cumulative assessment groups

The earlier specific guidance on pesticides grouping for human health risk assessments yielded the definition of two *cumulative assessment groups* (CAGs), as discussed in section 4.5.2. These include (i) 68 pesticides affecting the nervous system, and (ii) 103 pesticides affecting the thyroid or thyroid hormone systems. Considering that roughly 500 pesticides are currently approved for use in PPPs in the EU, these CAGs make up significant fractions of the total number of PPPs.

Three features of these CAGs are important to note:

- The grouping methodology requires the availability of *in vivo* toxicity data, such as from chronic rat studies. Hence, it is not transferable to other groups of chemicals for which such tests are usually not performed.
- The grouping is non-exclusive. There are many pesticides interfering with both the nervous system and the thyroid system. With more endpoints taken into consideration, such a grouping will evolve into a complex system of toxicological substance profiles.
- Due to insufficient knowledge on modes of action in humans for many pesticides, the grouping was based on phenomenological effects on the physiological target systems. Considering that pesticides are one of the best researched group of chemicals, it is clear that the idea of a full MoA-based grouping of chemicals is largely a vision for the future.

The EFSA guidance from 2013 announced the development of further CAGs for other endpoints such as effects on liver, adrenals, eye, and developmental and reproductive systems. However, none of these has been delivered so far.

5.4.3 Grouping to support substitution under REACH, the BP and PPP Regulations

Both hazard-based and risk-based approaches to substitution are used in European chemicals policy where it either encourages the substitution of hazardous chemicals directly, by explicitly requiring substitution and/or an assessment of alternatives, or indirectly, by restricting certain uses or requiring expensive risk management measures that provide incentives for substitution.

The substitution principle is a novel element of EU legislation which is not enshrined in the principles of environmental and chemicals legislation laid down in the treaties for the function of the Community. Explicit legal requirements for substitution have, so far, only been introduced in four pieces of EU legislation: the REACH Regulation (EC) No 1907/2006, the Plant Protection Products (PPP) Regulation (EC) No 1107/2009, the Biocidal Products (BP) Regulation (EU) No 528/2012, and the Council Directive 98/24/EC on Chemical Agents at Work.

The substitution principle has been implemented differently under the different pieces of legislation. This section is focused on REACH, the BP and PPP Regulations since they, in contrast to the Chemical Agents Directive, include specific criteria for the identification of substitution candidates. The substitution requirement in the Chemical Agents Directive is given a general, risk-oriented wording:

> substitution shall by preference be undertaken, whereby the employer shall avoid the use of a hazardous chemical agent by replacing it with a chemical agent or process which, under its condition of use, is not hazardous or less hazardous to workers' safety and health, as the case may be (Article 6.2).

Under REACH, the substitution requirement relates to the identification and phase-out of SVHCs. According to the authorization chapter in REACH, SVHCs shall be progressively replaced by suitable alternative substances or technologies where these are economically and technically viable (Article 55). SVHCs are identified in Article 57 as substances with serious health hazards (CMR) or environment hazards (PBT, vPvB). Individual substances with other hazardous properties – such as endocrine disruptors – can also be identified as SVHCs. REACH requires that identified SVHCs

should undergo authorisation for continued used. The criteria for authorization are complex (Article 60), but require substitution in some cases where alternatives are available.

In a survey, Member State Competent Authorities, industry stakeholders and external consultants were asked about substitution, its drivers, barriers and challenges. Legislative requirements were considered to be the main driver of substitution by industry stakeholders, with 95 per cent of the respondents specifying REACH as important or very important. Specifically, the placement of a substance on the Candidate List has been indicated to be a key mechanism that initiated companies to search for safer alternatives (EC 2017a, Danish EPA 2019).

Based on annual use volumes in the SPIN database, Sackmann et al. (2018) showed that the use of identified SVHCs was reduced, as compared to unregulated compounds during the same time period. The same authors showed that phthalates on the authorization list have decreased over time for all Scandinavian countries, and that they seem to have been replaced mostly by unregulated non-phthalate plasticizers from 2012 onwards. The decrease in use of the phthalates to be authorized under REACH did, however, start before REACH entered into force, suggesting that substitution may have already been triggered by awareness that these substances might become subject to regulation (Sackmann et al. 2018).

In another study, conducted on behalf of the European Commission, over 80 per cent of industry stakeholders reported having substituted hazardous chemicals in the last 10 years as a result of the identification of SVHCs under REACH (Jacobs and Tickner 2016, EC 2017a). However, although not only related to substitution of SVHCs, over 35 per cent of the respondents answered that an alternative that had been adopted was later found to be a substance of concern, in terms of its hazardous properties, and that it is now subject to regulatory and non-regulatory pressures, e.g. through inclusion in the REACH candidate list, the authorization process, or black-listing by non-governmental organisations (EC 2017a).

Some of the group entries on the Candidate List are the same as those in Annex VI to CLP, demonstrating that grouping substances in one process can be used in another as a way to more efficiently manage health and environmental risks. Some group entries on the Candidate List are further listed in Annex XIV and subject to

authorization. Among these, there are examples of grouping based on structural similarity, and use of read-across of data for identification of hazardous substances.

Under the BP and PPP Regulations, candidates for substitution are identified with the aim of replacing the most hazardous active substances, and products containing active substances with those requiring less risk mitigation, or by non-chemical control or prevention methods. The criteria for identifying such candidates overlap with the criteria for identifying SVHCs under REACH, but are broader and include more generally worded examples which also take exposure into account[3]. Under REACH, exposure is considered in the subsequent step of including SVHCs on the authorisation list (REACH Article 58). Member States may refuse to authorize a PPP or BP that includes a candidate for substitution if safer alternatives are available, and if some other conditions are fulfilled (PPP Regulation Article 50, BP Regulation Article 10).

The BP and PPP Regulations entered into force in 2012 and 2009 respectively, so the process of identifying candidates for substitution has been ongoing for a limited period of time. It is, therefore, too early to draw definite conclusions on the workings of the substitution process in this context. However, so far, few substitutions have taken place because the available alternatives are not considered to be sufficiently effective to replace those substances currently in use (communication with the Swedish Chemicals Agency).

5.5 Conclusions from the literature review

The overview of the state of science and regulatory implementation of group-wise management of chemicals identifies a number of shortcomings in the current regulatory system that hampers a systematic assessment and management of chemicals in groups. The shortcomings include:

[3] For example: "– there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)" (Annex II part 4).

- Clear and consistent legal requirements to continuously identify and substitute chemicals of concern are missing in most pieces of EU chemicals legislation.
- Explicit requirements to always consider assessing and managing chemicals in groups is lacking across EU chemicals legislations.
- Substances identified as candidates for substitution based on group-wise assessment and read-across are not publically disclosed and disseminated to all relevant downstream users.

Improved group-wise management of chemicals would facilitate a more effective application of the substitution principle and minimize the risk of regrettable substitutions. This could be achieved step-wise through a combination of normative and operational actions at the EU and national levels.

6 Our recommendations

This chapter presents eleven recommendations to

(i) improve the regulatory assessment and management of risks from exposures to unintentional mixtures, and

(ii) strengthen group-wise approaches to hazard and risk assessment with the aim to support implementation of the substitution principle, and to make chemical regulation more efficient.

The recommendations are derived from the reviews of the existing legislation and the scientific state-of-the-art in the preceding Chapters 3 to 5.

The first six recommendations 6.1 to 6.6 are different elements of a comprehensive strategy for better dealing with risks from chemical mixtures. The strategic elements are the following:

(6.1) legal requirements for managing mixtures in individual pieces of EU chemical legislation,

(6.2) a cross-cutting policy framework for dealing with mixtures of chemicals falling under different legislations,

(6.3) a novel regulatory framework for protecting humans from complex exposures to chemicals and other environmental stressors,

(6.4) a database on use and emissions of chemicals to facilitate predictive assessments of aggregate and cumulative exposures,

(6.5) a long-term research program on real patterns of co-exposure to multiple chemicals, and

(6.6) a default allocation factor approach for setting acceptable exposure limits for single substances, if data and knowledge on actual co-exposures to other chemicals are missing or insufficient to support state-of-the-art mixture risk assessments.

The three subsequent recommendations, 6.7 to 6.9, are different elements of a strategy for the enforcement of the substitution principle and the avoidance of so-called "regrettable substitutions' by

means of group-wise assessment approaches. The strategic elements are the following:

(6.7) amending or strengthening legal provisions for substitution in all relevant pieces of EU chemical legislation where they are currently missing or insufficient,

(6.6) strengthening the mandate in REACH to manage chemicals in a group-wise fashion, and

(6.9) a novel system for flagging suspected SVHCs under REACH and CLP based on structural similarities with known SVHCs.

Recommendation 6.10 focuses on the EU Water Framework Directive (WFD), which is subject to a forthcoming revision. The revision provides an opportunity for strengthening both mixture risk assessments and group-wise assessments for water pollutants.

The final recommendation 6.11 deals with institutional arrangements and suggests establishing a novel Swedish Interagency Taskforce on Mixture Risk Assessment (SwIM). SwIM shall perform part of the tasks outlined in the first ten recommendations.

The recommendations are quite different in nature. Ranging from very concrete short-term actions, such as the establishment of the SwIM task force, over medium-term aims, such as establishing research programs or amending existing legislations, to more long-term goals, such as creating a novel regulatory framework for better protection of human health from cumulative exposures to chemicals and other stressors. Therefore, the possible level of detail when estimating economic impacts and other consequences of these recommendations varies largely, as discussed in Chapter 8.

The following presentations of the eleven recommendations have a common structure. First, a summary is given in a box, briefly stating the aims and the expected achievements, and clearly listing the actions that the Swedish government is recommended to take. Thereafter the text is divided into two main sections, a background section that outlines the problem, and then a detailed explanation of the recommended way to solve it. The background recapitulates the main findings from the detailed reviews in Chapters 3 to 5.

Due to the complex structure of EU chemical legislation with shared competence[1] between the EU Commission, EU Parliament and the Member States, we recommend tackling most of the identified problems by means of a dual strategy, including actions on both

[1] Article 4 TFEU (EU 2012).

the EU and Swedish levels. To this end, our recommendations explicitly state which actions the Swedish Government should take on each of these levels.

The recommended national activities will provide experience, examples, and demonstrations of feasibility. This should give Sweden a strong position in the complementary activities on the EU level. The recommended activities on the EU level will usually require forming alliances with other Member States, non-governmental organisations, and economic actors that are willing to take forward political actions for improving chemical safety in Europe. Sweden is well placed to take a leading role in this process.

6.1 Establish consistent requirements for mixture risk assessments in all pieces of chemical legislation

We recommend establishing clear and consistent requirements for mixture risk assessments in all relevant pieces of legislation, both on the national and EU levels[2].

EU chemical legislation focuses on single chemicals and is highly fragmented. Most of the numerous pieces of legislation do not include any clear requirement for assessing and managing risks from exposure to chemical mixtures. In particular if the mixtures are not intentionally produced but result from releases of chemicals from different products and processes.

Establishing such legal requirements is a crucial step towards effective protection against risks from exposure to mixtures. Where no such requirements exist, progress towards the sound management of risks from chemical mixtures cannot be expected to occur.

We recommend that the Swedish Government:

- Together with Swedish competent authorities, take a leading role in strengthening the requirements for mixture risk assessment in all relevant pieces of EU chemical legislation. Whenever a piece of legislation is up for revision, Sweden should propose to include a requirement for mixture risk assessment.
- Give all relevant Swedish authorities the task to systematically check the options to include adequate requirements for mixture risk assessment in national legislations, where not already existing.

[2] A list of relevant pieces of legislation is provided in section 9.2 of this report.

6.1.1 Background

Humans and the environment are continuously exposed to mixtures of chemicals, but EU legislation focuses on risks from single substances.

Rules that address risks caused by cumulative exposures to multiple chemicals from different sources are therefore lacking under most pieces of legislation. The only exception are mixtures of pesticide residues in food. In the Communication on Chemical Mixtures from 2012, the European Commission recognized the fragmentary legal basis for mixture risk assessments (EC 2012). However, follow-up activities focused on research for closing knowledge- and data gaps and did not include measures for strengthening and harmonising legal requirements.

Clear and consistent requirements

Assessing and managing risks from cumulative exposures is a demanding and resource-intensive task. To spend efforts on this task, regulatory authorities need clear legal mandates. Experience shows the importance of such legal stimuli. The European Food Safety Authority (EFSA) did not start developing methods for regulatory mixture risk assessments until a requirement was introduced in the Regulation on Maximum Residue Levels (MRLs) of pesticides in food and feed in 2005[3].

Under the Plant Protection Products Regulation, the requirement for assessing mixture risks from pesticide residues was phrased in 2009 as follows:

> The residues [...] shall have no [...] harmful effect on human health [...], taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available[4].

This requirement has three shortcomings:

(i) The key terms "known cumulative and synergistic effects" are not defined, leaving much room for interpretation.

[3] Regulation (EC) No 396/2005.
4 Article 4(3.b) of Regulation (EC) No 1107/2009.

(ii) No timeline for establishing "methods accepted by the Authority" is set; EFSA has been working on the issue for a decade now.

(iii) The requirement is confined to human health risks, while environmental risks remain uncontrolled. The European Parliament failed to change this during the legislative procedure (EP 2008).

Future attempts to improve the legal basis for mixture risk assessments should avoid such deficiencies.

Current policy initiatives

Much of the concern about mixture risks has been triggered by research on endocrine disrupting chemicals. In a recent resolution on the *European Union framework on endocrine disrupters* (EC 2018a), the European Parliament called on the Commission "to take mixture effects and combined exposures into account in all relevant EU legislation" (EP 2019).

We share the view of the Parliament. However, to achieve the aim of a high level of protection of human health and the environment, requirements for mixture risk assessment should cover all kinds of adverse effects, including, but not limited to, endocrine disruption.

6.1.2 Recommendations

Improving existing EU legislation

Establishing clear legal requirements for mixture risk assessments in all existing pieces of EU chemical legislation is a critical step towards better protection of humans and the environment.

The aim should be to ensure an equivalent protection from risks of exposure to single substances and to mixtures. This is a strategic goal, which requires forming alliances between Member States, non-governmental organisations and economic actors that are willing to take forward political actions for improving chemicals safety in Europe. The Swedish government is encouraged to take a leading role in this process.

To make this fundamental and important change in European chemical legislation, a general and understandable rule is needed, that can be inserted into different legislations. As a tentative generic

phrasing, we suggest including the following sentence in all relevant EU legislations:

> The environmental and health risk assessments performed under this legislation shall take mixture effects into account, which may result from combined exposures to multiple chemicals from the same or from different sources.

Such a normative requirement should be combined with a time-line for an explicitly named entity to develop detailed rules and technical guidance for implementation. Such guidelines will need to be tailored to the specific context but should follow common principles.

To start, the initiative may give primary attention to EU Regulations[5] that authorize specific uses of hazardous substances (such as veterinary medicinal products, biocidal products, plant protection products, etc.) and any uses of *substances of very high concern* (SVHC)[6]. EU Directives which are subject to transposition into national law may be considered at a later stage.

Windows of opportunity for including requirements for mixture risk assessments in EU legislation may open whenever a legislation becomes subject to regular or occasional revision. The current work on an EU framework on endocrine disrupters may provide such opportunities. The forthcoming revision of the Water Framework Directive is another one (see 6.10).

Improving existing national legislation

On the national level, all relevant legislations should be subject to a systematic check of options for including adequate requirements for mixture risk assessment, where not already existing. The government should request all Swedish competent authorities to perform such checks within their remits. This action should include:

(i) issues which are exclusively subject to national legislation, such as the protection of soils or indoor air quality.

(ii) issues which are subject to minimum requirements that are laid down in EU Directives but for which Member States may

[5] See Chapter 3 for an explanation of the differences between EU Regulation and Directive and for guidance to the legislations mentioned in the text.
6 SVHC as defined in Article 57 of the REACH Regulation.

choose to apply stronger provisions, such as occupational safety or measures against industrial emissions and water pollution.

This national initiative sets an example that will strengthen Sweden's position in the complementary activities on the EU level.

Towards an overarching framework

Within single pieces of chemical legislation, mixtures can only be handled effectively if the components are subject to the same law. Therefore, including requirements for mixture risk assessment in individual legislations is a necessary step, but it is only the first one. For dealing with mixtures of substances from different sources, governed by different laws and managed by different agencies, cross-cutting initiatives are required as a second step. This issue is addressed in Recommendation 6.2.

6.2 Establish cross-cutting European legislation on chemical pollution with a focus on mixture risks

We recommend establishing an EU-wide legal framework on chemical pollution, focusing on mixture risk assessment and –management, with a clear vision and specific interim targets.

Such an overarching framework is needed in order to protect human health and the environment against possible impacts from chemical mixtures, which cannot be fully evaluated and managed by sectorial pieces of legislation. This framework should build on the "non-toxic environment"-concept, as it is currently applied in the Swedish environmental and health policy and in the 7th Environmental Action Programme (EAP).

We specifically recommend the Swedish Government to

- Take concrete action to ensure that an EU-wide non-toxic environment strategy is implemented in the near future.
- Work towards extending the scope of mixture considerations in the upcoming 8th EAP in order to consider all groups of hazardous chemicals and to provide specific provisions for environmental and biodiversity protection.
- Include dedicated feedback loops between the different stakeholders and regulatory authorities, as well as a mechanism for continuous progress monitoring in a new 8th EAP.
- Establish a dedicated European framework on chemical pollution that cuts across regulatory silos and provides (a) common definitions and assessment principles, (b) agreed goals and targets, and (c) suitable policy options to act on the fact that typical exposures are characterized by complex chemical mixtures

6.2.1 Background

Already in 2012, the EU Commission acknowledged that

> there is no mechanism for a systematic, comprehensive and integrated assessment of mixture effects taking into account different routes of exposure and different product types (EC 2012).

but did not propose any concrete ways forward to tackle the problem. It is therefore not surprising that the European Environmental Agency concluded as recently as in 2018 that

> concerns persist, around […] chronic exposure of the population to mixtures of chemicals (EEA, 2018a).

Meeting these concerns requires a move away from the narrow focus on individual pollutants and the exclusive consideration of single emission sources and exposure routes towards a broader, more holistic approach. The strategy must be based on the analysis of the combined effects from all sources and exposure routes.

Chemical mixtures pose a major challenge for the structure of the current European system of chemical regulation and management. This system is currently organized into separate legislations along commercial uses, but not along likely co-exposure patterns. The European Food Safety Authority (EFSA) assesses exclusively pesticides, food additives and food contact materials. The European Chemicals Agency (ECHA) handles industrial chemicals and biocides. And the European Medicines Agency (EMA) deals exclusively with human and veterinary pharmaceuticals. Moreover, each of these European authorities interacts with the corresponding regulatory authorities of the individual EU member states in its own, very specific way.

This organizational division, and the ensuing complexity of the European system for regulating chemicals, also results in inconsistent and insufficient sectorial mixture assessment frameworks. For example, the Pesticide Regulation EC 1107/2009 and the accompanying Regulation 396/2005 on maximum residue levels (MRLs) in food, stipulate that cumulative effects of pesticides residues in food should be taken into account. In sharp contrast, a similar provision is missing for veterinary drugs, although there is obviously little scientific reason why mixed residues of “animal protection chemicals”

should be assessed differently from mixtures of "plant protection chemicals".

Additionally, no provision exists that requires the toxicological assessment of the total levels of pesticides, veterinary drugs, biocides, food additives and non-intentionally added substances in a given food commodity.

Contrary to the situation on the European level, Sweden already has a dedicated strategy for a non-toxic environment (NTE) which aims to ensure that the

> total exposure to chemical substances via all sources of exposure is not harmful to people or biodiversity (Naturvårdsverket 2019a).

However, such a national strategy is insufficient alone, in view of the increasing trade of chemicals and consumer goods across national borders, and the inherent trans-national nature of environmental pollution.

It is therefore encouraging to see that the notion of a non-toxic environment is taken up by the 7th European Environmental Action Program (EAP) (EP 2013). Unfortunately, implementation is lagging behind. The 7th EAP certainly did not reach its goal to establish "appropriate regulatory approaches to address combination effects of chemicals". In fact, the EAP implementation report to the EU Parliament in 2018 "regrets the lack of progress on developing a Union strategy for a non-toxic environment" (EP 2018).

Furthermore, the consideration of mixture toxicity under the 7th EAP focusses almost exclusively on endocrine disrupters and human health. Other groups of hazardous chemicals, for example neurotoxicants or immunotoxicants, are not given equal weight.

Also, biodiversity protection is not mentioned in the context of the European non-toxic environment strategy, despite the facts that biodiversity is declining EU-wide and globally (Diaz et al. 2019), and that chemical pollution has been highlighted as a major underlying cause (Malaj et al. 2014, Bernhardt et al. 2017).

6.2.2 Recommendations

We recommend that the Swedish Government should work towards establishing an overarching EU-wide legal framework on chemical risk assessment and management. Such a framework should provide

common definitions, structures, rules and protection goals that can be adapted by the EU to specific policy contexts and by individual Member States to their different national circumstances.

It should also provide a structure for the EU-wide coordination of national policies. The recommended framework should overcome the inconsistent approaches of the various sectorial regulations, avoid inconsistent assessments of one and the same chemical subject to different regulations and provide an umbrella for the consistent consideration of mixture risks, including a clear vision to be reached at a set date and specific interim targets. The new framework can be introduced stepwise, starting with the environmental action program. At a later stage, it should be shaped into a Directive or Regulation.

The new framework should provide recommendations for prospective (substance oriented) as well as retrospective (ecosystem/media oriented) mixture-aware risk assessment approaches for human health and environmental protection, in fulfillment of article 3 of the Treaty of the European Union. In the end, the policy frameworks should strive to ensure that European citizens can enjoy a non-toxic environment and that biodiversity is not unduly impacted.

Although the 7th EAP has tremendous potential, its implementation is severely lagging behind. In order to protect European citizens and the environment against detrimental chemical exposures, we therefore recommend to take specific steps towards publishing a Europe-wide strategy for a non-toxic environment in the nearest future. The 7th EAP covers the time period up to and including 2020. Work on the 8th EAP is therefore expected to commence in the near future. However, no specific timeline seems to be available currently (in May 2019). We therefore recommend taking appropriate political action to ensure that:

(i) An EU-wide strategy for a non-toxic environment is developed and implemented

(ii) an 8th EAP is in place at the end of 2020, when the 7th EAP runs out

(iii) the aim of a non-toxic environment for European citizens and the environment continues to be included as a central part of the EAP.

We also recommend that regulatory authorities develop a clear strategy for interacting with the various stakeholders, as well as implementing a mechanism for continuous progress monitoring.

We further recommend extending the current consideration of mixture effects to include all groups of hazardous chemicals and establish biodiversity protection as a specific protection goal, equal in importance to the direct protection of human health.

The need for long-term consistency

Due to their integrating nature, EAPs can prepare the ground for the cross-sectorial consideration of mixture toxicities. However, EAPs are comparatively short-lived (less than 10 years duration) and their content is re-negotiated for every new EAP. Therefore, they do not provide the necessary long-term consistency for the implementation of cross-sectorial mixture toxicity risk assessment and management. Such a holistic consideration of mixture toxicities also requires revisiting other issues of chemical risk assessment and management, such as chemical grouping, comparative assessments, the substitution principle and the problem of hazardous chemicals in a circular economy.

6.3 Establish a Human Health Directive that protects the human population from the combined action of chemicals and non-chemical stressors

We recommend working towards a Human Health Directive that aims to achieve "good public health", protecting humans from the combined action of chemical and non-chemical environmental stressors.

Such legislation should put human health at the center by seeing humans as a "recipient" in a recipient-oriented perspective, learning from the ecosystem-oriented approaches of the Water Framework Directive and the Marine Strategy Framework Directive that aim to achieve good ecological and environmental status, respectively.

We recommend the Swedish Government to

- Evaluate which WFD/MSFD instruments could be adapted for a Human Health Directive. In particular, this relates to the holistic assessment perspective, the identification of (mixtures of) priority pollutants to guide regulatory action, the setting of legally binding maximum acceptable levels, and the implementation of systematic long-term monitoring programs.
- Analyze how the different Swedish and international environmental and health objectives should be considered in such a legislation.
- Assess potential conflicts and synergies between the various goals (societal, environmental, public health-oriented) specified in the different pieces of existing legislation and develop strategies to minimize conflicts and promote synergies.
- Explore how a national Human Health Directive could be best linked up with similar and complementary work on the European and international level.
- Evaluate which legal instrument (Directive or Regulation) is most appropriate for such an instrument on the European level.

6.3.1 Background

There is no overarching EU legislation that puts public health front and center, i.e. a legislation that aims to protect the human population from the total impact of chemical exposures and non-chemical environmental stressors.

Such legislation is in place to protect European surface and ground water from complex chemical and non-chemical pollution. The Water Framework Directive (WFD) and the Marine Strategy Framework Directive (MSFD) both aim to achieve a good ecological and environmental status, respectively, and set the conditions for targeted water management. Both Directives take an ecosystem perspective and consider the joint impact of anthropogenic stressors, chemical or otherwise (changes in hydromorphology, oxygen depletion, acidification, etc.).

The WFD established a systematic strategy for the identification of (groups of) priority hazardous chemicals, their monitoring and restriction, as well as a watch list mechanism in order to fill data gaps. For these chemicals, EU-wide and legally binding maximum regulatory acceptable concentrations are identified in the form of so-called Environmental Quality Standards (EQS values), see also Chapter 6.10.

In sharp contrast to the holistic strategy put forward in the WFD and MSFD, no legislation exists that provides a comparable framework for protecting human health from the total impact of chemicals and the physical environment (noise, etc.), encountered at the work place as well as in private life. In contrast to the WFD strategy, no systematic evaluation is performed to identify the priority chemicals and chemical groups that are most relevant for public health amongst the thousands of chemicals found in consumer products, food, air and water. And maximum acceptable human body burdens, equivalent to biota-based EQS values, are currently neither agreed upon nor used as tools for chemical management.

EU-wide and river-basin specific priority pollutants are systematically monitored in the aquatic environment. The lack of a dedicated and holistic Human Health Directive that employs a similar strategy for chemicals relevant to human health has led to a situation in which we know more about chemical pollution of aquatic ecosystems than about the total chemical exposure in humans.

The WFD and MSFD put the recipient (aquatic ecosystems) at the center of their protective action. Such a recipient-oriented perspective would also improve public health protection. Not only would it improve the assessment of the joint action of the entirety of chemical and non-chemical stressors, it would also facilitate acting on interactions between chemical exposure and confounding processes that might increase the vulnerability of exposed populations. Scientific evidence which, for example, links exposure to perfluorinated compounds (such as perfluorooctane sulfonate, PFOS) with a reduced effectiveness of tetanus and diphtheria vaccines (Grandjean et al. 2012) makes it clear that such a holistic approach is needed.

6.3.2 Recommendations

We recommend initiating a systematic evaluation of how to establish a Human Health Directive, i.e. a legislation that puts public health front and center.

This piece of legislation should aim to protect the human population from the total impact of chemical exposures and non-chemical environmental stressors, analogous to the ecosystem-oriented philosophy of the WFD and MSFD. This would improve the coordination of national health-related policies and promote a holistic culture of prevention. It would also provide the opportunity to further clarify and assess the interlinkage between specific human health-oriented objectives and environmental objectives, along the lines of the "one health" concept (Zinsstag et al. 2011) and the integrated assessment concept (Péry et al. 2013) of the WHO.

Such a legislation would be a natural extension of the non-toxic environment strategy, which focusses on chemical exposures only. Other Swedish environmental objectives that would need to be merged into a Human Health Directive would include "Reduced Climate Impact", "Clean Air", "Protective Ozone Layer", "Safe Radiation Environment", "Good Quality Groundwater", "Good Built Environment", and "Varied Agricultural Landscape".

Human chemical exposure is characterized by deliberate, voluntary exposure to selected hazardous substances such as alcohol and tobacco smoke. Additionally, humans might also be deliberately exposed to

hazardous chemicals from pharmaceuticals (e.g. anti-cancer drugs). We consider such deliberate chemical exposures to be out of scope of the suggested Human Health Directive, which should target involuntary chemical exposures whose extent and health consequences are typically almost impossible to assess by individual consumers. Such work would also provide the opportunity to pro-actively acknowledge and analyze goal conflicts and synergies, and to develop strategies to minimize conflicts and promote synergies.

Start nationally

Health policy is mainly implemented by individual EU member states. Work on a Human Health Directive should therefore, at least initially, focus on the national level.

The Swedish public health policy acknowledges the importance of tackling environmental problems, such as air pollution, exposure to hazardous chemicals, biodiversity loss and climate change, to achieve "good and equal health" (Sveriges regering 2018). Consequently, the inconvenience concept ("olägenhetsbegreppet") of the Swedish Environmental Code ("Miljöbalken"), which also aims to protect particularly vulnerable parts of the population, such as infants, could also be further strengthened in a new Human Health Directive.

The holistic perspective of the suggested Human Health Directive would thus directly contribute to the overarching aim of public health in Sweden to create societal conditions for good health on equal terms for the entire population, and to close avoidable gaps in health within one generation.

However, special considerations need to be taken in this process to identify and mitigate potential inequities in environmental health. Given that chemicals and chemical products are widely traded across national borders, that health policies are affected by trade and trade policies, and that emissions in other countries might have direct impacts on Swedish citizens, efforts should be taken to coordinate this work with European and international activities and institutions. In particular, it should be analyzed whether a new European Regulation or a Directive would be a productive option. In this context, links to Agenda 2030 and the Sustainable Development Goals, and the WHO European Environment and Health Process (EHP)

should be specifically considered as a tool for achieving the SDGs (WHO 2019a). The EHP aims to eliminate the most significant environmental threats to human health and, most recently, resulted in the Ostrava Declaration (WHO 2017c) with one of the professed aims to minimize the adverse effects of chemicals on human health. Other important activities and frameworks include the EU Strategic Framework on Health and Safety at Work (EC 2014), the European Observatory on Health Systems and Policies (WHO 2019b), and the Strategic Approach to International Chemicals Management (SAICM) (UNEP 2019a).

6.4 Establish a database on use and emissions of chemicals

We recommend establishing a database that facilitates aggregate and cumulative exposure assessments[7] across legislations.

For any chemical, the database should include information on the amounts used for all relevant purposes, amounts contained in all relevant products and articles, and amounts released from all relevant processes. This information is not available in the regulatory system today.

Such a database will help to avoid systematic underestimations of risks from aggregate exposures to individual chemicals. In addition, it will pave the way to better assessments of cumulative risks from co-exposure to different chemicals.

To achieve this aim, we recommend the following actions by the Swedish Government:

- Give the Swedish Chemicals Agency (or SwIM[8]) the mandate and the resources to expand the national product register by including all chemicals and all possible sources and routes of exposure of both humans and the environment.
- Support long-term efforts on the EU level: Give the Swedish Chemicals Agency (or SwIM) the task and resources for a pilot study assessing aggregate exposures and risks for (a selection of) chemicals which are subject to more than one regulation and for which sufficient use and exposure information is already available to Swedish authorities via the national product register.
- Work at the EU level by forming alliances between Member States and between governmental and non-governmental organisations, as well as industries, to provide the resources and mandates to establish a central European database which facilitates comprehensive aggregate and cumulative exposure assessments, using the Swedish product register as an example and as a starting point.

[7] *Aggregated exposure* is used here to denote exposure to a single substance from different sources via different routes, while *cumulative exposure* refers to mixtures of different substances from different sources. See section 2.2 for further explanations.
[8] Swedish Interagency Task Force on Mixture Risk Assessment (Recommendation 6.11).

6.4.1 Background

Exposure to a chemical may result from many different sources and occur via different routes, and a comprehensive risk assessment of a chemical must account for the total exposure from all sources. Unfortunately, however, different uses of a chemical, different emission sources, and different sites and routes of exposure to a chemical may be subject to different pieces of legislation. Different data requirements and different assessment rules may apply, and different authorities may be responsible for the enforcement of these rules.

Currently, it is a demanding task to identify all "multi-regulated' substances. To enable searches for all legislation applicable to a single substance, ECHA has announced *The European Union Chemical Legislation Finder* (EUCLEF) online service. The service shall be available from 2020 onwards and will initially cover 40 pieces of EU legislation[9]. This will be a valuable step forward. For aggregate exposure assessments, however, the information on applicable legislation must be complemented with factual data on amounts used or released from different sources.

Where different legislation applies to different sources or uses of the same chemical, assessments performed under a single piece of legislation may systematically underestimate total exposure and risks. Aggregate exposure assessments cannot be performed by a single economic actor, such as an individual registrant of a chemical under REACH. The task requires an authority that has an overview of all relevant uses, pollution sources, exposure pathways, and applicable legislations.

Clear legal requirements for performing aggregate exposure assessments across different regulatory sectors currently exist only in some pieces of legislation. Examples include the provisions of Article 15 (2d) of the EU Cosmetics Regulation, which requires to assess the safety of chemicals in cosmetic products which are classified as CMR category 1A or 1B substances by "taking into consideration the overall exposure from other sources". The aggregated assessment is to be performed by the European Commission's Scientific Committee on Consumer Safety, and a guidance has been developed for the necessary

[9] https://newsletter.echa.europa.eu/home/-/newsletter/entry/which-pieces-of-eu-legislation-apply-to-your-substances-

exchange of data with relevant EU agencies on a case-by-case basis (EC 2015a).

In general terms of implementing legal requirements for performing aggregate exposure assessments, this example points in the right direction. In procedural terms, however, the approach cannot be extended to include all other toxicological or eco-toxicological endpoints or all other uses of chemicals. The case-by-case consultation mechanism between agencies and committees is manageable only for rare occurrences. For a routine application it would be an impractical bureaucratic monster, and more efficient procedural arrangements are needed.

Assessing aggregate exposures to single substances via different routes is part of the more complex problem to assess cumulative exposures to different substances. Cumulative exposure assessments require reliable knowledge about the aggregate exposure to individual mixture components. Therefore, the following recommendations aim to facilitate aggregate exposure assessments in the first place, but they also pave the way towards better assessments of co-exposure to multiple chemicals.

6.4.2 Recommendations

Strong long-term efforts should be made to establish a central European database, which facilitates comprehensive aggregate and cumulative exposure assessments.

In contrast to IPCHEM[10], which compiles monitoring data for retrospective assessments, the novel database shall facilitate prospective assessments. To this end, the database should include all necessary information on:

(i) all purposes for which a chemical is used, and the amounts used for each purpose

(ii) the articles and products in which a chemical can be found and the corresponding amounts

(iii) the sources from which a chemical is released, the amounts released, and the nature of the environmental compartment into which it is released.

[10] Information Platform for Chemical Monitoring (see recommendation 6.5).

For subsequent aggregate and cumulative risk assessments, this information should be linkable with existing data collections on hazardous properties of substances, such as those included in the OECD eChemPortal[11].

Information on tonnage bands and broad use categories provided in the REACH registration database are too imprecise for serving the purpose of aggregate and cumulative risk assessments. However, a good starting point for building the envisaged comprehensive database is provided by the national product register of the Nordic countries, which is made publicly available in an aggregate non-confidential format in the SPIN database on Substances in Preparations in Nordic Countries. The Swedish Government should expand and further develop this valuable and unique approach.

A first step should be to expand the information from the national product register by including information on chemicals and uses which are currently not covered but which are available from other information sources. Examples are pesticides[12], pharmaceuticals[13] and substances released from industrial facilities[14]. Performing aggregate exposure and risk assessments for these compounds may be an intermediate goal and serve as a pilot study supporting the long-term efforts on the EU level.

Transfer the approach to the EU level

As a second step, the Government should seek to transfer the approach to the EU level, ultimately requiring all Member States to contribute to the database and including all substances that are subject to any piece of European chemical legislation.

A relevant and ongoing initiative is the collection of information about ingredients in hazardous chemical products for consumer use at the poison centers, with support from legal requirements in Annex VIII of the CLP.

[11] www.oecd.org/chemicalsafety/risk-assessment/echemportalglobalportaltoinformationonchemicalsubstances.htm
[12] Data from the pesticide registry (https://webapps.kemi.se/BkmRegistret/Kemi.Spider.Web.External/) and the pesticides use/sales statistics (www.scb.se/MI0501).
[13] Data from FASS (www.fass.se).
[14] Swedish data reported to the E-PTR (European Pollutant Release and Transfer Register) (www.eea.europa.eu/data-and-maps/data/member-states-reporting-art-7-under-the-european-pollutant-release-and-transfer-register-e-prtr-regulation-18).

To generate a novel and comprehensive database for chemical exposure assessment in the EU is a technical recommendation, but its realisation will require considerable changes of the legal framework and a reallocation of responsibilities between the agencies involved. Dedicated efforts are required to explore the different options to establish the database and to negotiate them with the other EU Member States. This includes detailed considerations of

(i) appropriate legal settings,

(ii) measures to ensure sufficient data quality

(iii) ways of dealing with the conflicting interests to protect data that are considered confidential.

6.5 Establish a research program on real-life exposure patterns to chemical mixtures

We recommend developing and strengthen long-term exposure survey studies on the national and EU levels. The studies should be designed to provide better information on exposures to chemical mixtures.

Important knowledge gaps that need to be addressed include the identification of typical patterns of co-exposure to multiple chemicals that may cause significant risks, and the number and nature of substances typically driving the overall risk.

The empirical knowledge generated by these surveys will support (i) the development and validation of modelling approaches for the predictive assessment of cumulative exposures, and (ii) the identification of cumulative exposure profiles that provide a reason for concern and require targeted risk reduction measures, so-called "priority mixtures'. In addition, where needed and relevant, they could (iii) help to decide if the default mixture allocation factor proposed in Recommendation 6.6 needs adaptation.

We recommend the following actions by the Swedish Government:

- Establish a national long-term research program on combined exposures to multiple chemicals from different sources and give the Swedish Chemicals Agency (or the interagency task force proposed in 6.11) the mandate and the resources to design and to supervise the program.
- Engage with the Commission and the other Member States to establish funding of complementary EU-wide studies under *Horizon Europe*.

6.5.1 Background

Toxicological and eco-toxicological sciences have developed methods for the predictive assessment of risks from exposure to multi-component mixtures. As a starting point, the mixture of concern must be defined in terms of the number and nature of components and their concentrations or doses. Unfortunately, however, our knowledge about co-exposure of humans and the environment to different chemicals under real-world conditions is scarce and fragmentary. This knowledge gap was well recognized in the European Commission's Communication on mixtures in 2012 (EC 2012). Since then, research efforts have been made to reduce the gap, but the progress is slow. To speed up the process, more resources must be invested, and concerted actions must be taken.

Better understanding of cumulative human and environmental exposures may be achieved through both measuring and modelling. Both approaches have specific advantages and limitations and therefore they complement each other.

The availability of data for modelling is still insufficient

For predictive risk assessments performed for regulatory decisions under EU legislations, modelling approaches play a dominant role. The models used for predictive exposure assessments vary, from crude default assumptions that are typically made under REACH, to data intensive and more sophisticated approaches, used for example for pesticide authorisation. In any case, these standard modelling approaches can be used for single substance assessments only. They are inappropriate to predict the co-occurrence of chemicals from different sources at a given point in time and space and in a given matrix, such as soil, air, water, or biota.

In recent years, considerable research efforts have been made to develop co-exposure modelling tools, in particular for surface waters (van Gils et al. 2019). However, these fate and transport models require reliable input data in terms of exact uses or sources of chemicals, and the amounts marketed or released. Currently, such data are largely unavailable or inaccessible due to confidentiality issues. In addition, validation and refinement of such modelling tools requires chemical analyses of actual co-exposure situations. Such data are

currently missing for many chemicals, sites, and matrices. The problem of missing use and tonnage information can be reduced through the establishment of the database suggested in Recommendation 6.4. Solving the validation and refinement problem requires targeted co-exposure monitoring studies.

Monitoring

Minimum requirements for routine monitoring have been established under different pieces of EU legislation for specific types of chemicals and matrices, such as pesticide residues in food or priority pollutants in waters. Such routine monitoring is usually focused on compliance checks with regulatory acceptable levels for selected substances, such as maximum residue levels for pesticides or environmental quality standards for priority water pollutants. Routine monitoring programs were not designed for co-exposure surveys of many substances from many sources. In the past, monitoring data were often not even documented in a way that would allow to assess whether two substances occurred in the same sample. This situation has been improved during recent years, but other limitations remain, such as insufficient sampling for assessing the spatial and temporal dynamics in exposure concentrations. In particular, there are no routine monitoring programs that would allow to assess simultaneous exposures of humans or wildlife via all relevant routes, such as air, water, soil, and food, and for humans also via chemical products and consumer articles and both at the workplace and in private life. To this end, special research programs are needed.

A new platform requires generation of new data

As a follow-up activity from the Communication on chemical mixtures, the European Commission has launched IPCHEM[15], the Information Platform for Chemical Monitoring. IPCHEM shall provide an open access point to chemical monitoring data. This is a desirable initiative. However, to become valuable for the advancement of our knowledge about mixture risks, the database must be populated with the results from well-designed and well-performed

[15] https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

surveys on cumulative exposures. Currently, there are very few efforts of this kind, such as the recently completed SOLUTIONS project[16] on water pollution, the EDC-MixRisk project on endocrine disrupting chemicals in pairs of mothers and children[17], and the ongoing HBM4EU project[18] on human biomonitoring, that will end in 2021.

6.5.2 Recommendations

Long-term monitoring studies on cumulative exposures and associated risks should be established both on the national and the EU level. EU-wide studies shall provide information on general exposure patterns across Europe that may require risk reduction measures at the Community level.

National studies shall provide information on specific exposure patterns in Sweden, which may require targeted action for specific media, populations or regions. Wherever possible, national and EU-wide studies should be organised as a collaborative work. Studies should mobilise the collective expertise and use the facilities of academic institutions, competent regulatory authorities, and private analytical chemical laboratories. Surveys should be designed for a time-frame of at least ten years to allow the identification of trends.

On the EU level, projects may be funded under *Horizon Europe*, the future framework programme for research and innovation. On the national level, the Government should establish a dedicated research program on combined exposures. Implementation and supervision of the program should be assigned to SwIM, a new *Swedish Interagency Task Force on Mixture Risk Assessment* (Recommendation 6.11).

The work of funded projects should include:

(i) the development of efficient strategies to detect typical co-exposure patterns for different types of organisms in the environment, different human populations, and different regions and exposure situations, such as agricultural landscapes or urban environments,

(ii) the complementary use of targeted chemical analyses, so-called non-target screening, and effect-based methods[19], where possible and favourable,

[16] www.solutions-project.eu/
[17] https://edcmixrisk.ki.se/
[18] www.hbm4eu.eu/
[19] See section 4.4.2 for an explanation of the different techniques.

(iii) the integration of chemical and effect-based analyses with the development and validation of co-exposure modelling approaches,

(iv) the combination of exposure information with toxicological or epidemiological data for the identification of so-called "drivers' of mixture risks, i.e. mixture components which contribute the most to the risk to a specific organism for a specific endpoint,

(v) the development of quality control measures for analyses of chemicals for which standardised protocols do not yet exist.

The work should be supported by regulatory measures for ensuring the availability of necessary analytical standards[20]. Where needed, the establishment of legal obligations for industry to provide such standards should be considered.

Results of the research may have an impact on the design of future routine monitoring programs.

[20] Highly purified samples of chemicals required as a reference for chemical analyses.

6.6 Use an allocation factor to account for the total risk of chemical mixtures

We recommend applying a mixture allocation factor, in order to account for the fact that hazardous chemicals are not emitted into a pristine environment or human body.

To this end, we recommend the following strategy:

- Risk assessment and management should ensure that no individual chemical occupies more than a certain percentage (the allocation factor) of the maximum regulatory acceptable concentration (the risk cup).
- Apply the risk cup concept to all hazardous chemicals co-occurring in a human body or an environmental compartment, irrespective of their intended use or mode of action.
- A default allocation factor of 10% should be used when establishing acceptable exposures. That is, the exposure to an individual chemical via all pathways and emission sources should only occupy a maximum of 10% of the risk cup.
- Sweden should initiate further research in order to collect solid empirical or validated modeling data on the optimum size of mixture allocation factors. This, however, should not postpone the implementation of a pragmatic interim allocation factor.
- Chemicals that contribute to the risk cup by more than 10% should be classified as substitution candidates. This will generate incentives to search for less risky alternatives and/or implement risk mitigation measures, without immediately jeopardizing business operations.
- The size of an optimum allocation factor is driven by actual co-exposure patterns, which might be unknown to individual chemical producers/importers. Therefore, the setting and adjustment of allocation factors is a genuine task of competent authorities.

6.6.1 Background

Regulatory risk assessment is based on assumptions that lead to a systematic underestimation of actual environmental and health risks.

Chemical risk assessment is often based on the risk quotient, i.e. the ratio between a measured or an expected exposure and the maximum regulatory acceptable concentration. The acceptable concentration is estimated using a predefined set of (eco)toxicological data. The amount of data available differs depending on the legislation, and on the intended use of a substance. For some types of chemicals, a large data set is required, while for others, very little (or no) data are required. In any case, empirical datasets are always only coarse approximations of the real world, simply because it is impossible to test all effects on all endpoints in all potentially exposed species.

Therefore, in order to extrapolate from the limited set of (eco) toxicological data to the real world, so-called assessment factors (also termed uncertainty factors) are applied to the result from the most sensitive endpoint and test species used. For example, the knowledge gaps and uncertainties accounted for during the environmental assessment of a REACH chemical relate to the intra- and inter-laboratory variation of data, biological variance, acute to chronic toxicity extrapolation and laboratory to field extrapolation (ECHA 2008b). The assessment factors used in the human health risk assessment of REACH chemicals are provided in a separate guidance document (ECHA 2012).

Assessment factors do *not* cover the simultaneous presence of other compounds, i.e. the reality of mixed exposures (Martin et al. 2013). Basically, the current system for chemical risk assessment and management assumes that each chemical is emitted into its own pristine environment. REACH, with its more than 20 000 registered substances, therefore assumes *de facto* that the EU comprises 20 000 separate environments, each occupied by just one chemical. And even this scenario still ignores the likely simultaneous exposure to pesticides, pharmaceuticals, biocides and non-intentionally produced chemicals. As a consequence, current risk evaluations are systematically underestimating the real-world risks for humans and the environment.

The risk cup concept

The *risk cup* concept of the Food Quality Protection Act (FQPA) (US Congress 1996) improves the relevance of risk assessment of pesticides in the US. The concept is based on the notion that every organism has a certain overall tolerance for chemical exposure before unacceptable toxic impacts might occur. Each chemical, from each exposure pathway, in proportion to their corresponding individual risk quotients, contributes to filling this risk cup.

For example, a chemical that is exposing a human population at a risk quotient of 0.1 via food, and 0.05 via drinking water, would fill the risk cup by a total of 15 per cent. Adding exposure to a second chemical via food at a risk quotient of 0.1 would yield a risk cup that is filled to 25 per cent. The risk-cup based risk management aims to ensure that the sum of all contributions does not exceed 100 per cent.

The FQPA currently only applies the risk cup concept to pesticides, and only to groups that share the same mode of action. The implicit rationale behind the latter is that low-dose contributions of chemicals that do not share a common mode of action do not increase mixture risks. This notion, however, is not supported by the current understanding of mixture (eco)toxicology (see Chapter 4).

The risk cup concept is also the basis for the allocation factors that are used for the relative source allocation during the setting of drinking water standards by the World Health Organization (WHO 2017b). Allocation factors are employed for deriving human health-oriented guidance values, by allocating an estimate of the safe concentration, such as the ADI, among the different routes of exposure. The WHO assumes as a default that drinking water contributes between 20 per cent (e.g. for the herbicide atrazine) and 80 per cent (e.g. for disinfection byproducts) of the total human exposure to the chemical of interest. The remainder is attributed to exposure via food and air.

Mathematically speaking, using an allocation factor is the same as applying an additional mixture assessment factor (MAF), which has been discussed previously (KEMI 2015b, van Broekhuizen, 2016). The MAF is driven by the number of components in the mixture, and existing implementations and suggestions for the size of MAF range between 4 and 100, see Chapter 4.

However, the allocation factor is conceptually different from an assessment factor. The latter can be adjusted during a tiered risk assessment if additional information on the (eco)toxicological profile of a chemical is collected. In contrast, the size of an optimum allocation factor depends on the actual co-exposure patterns, which is likely unknown to a chemical producer/importer and which will constantly change in relation to chemical production and use.

Optimizing the size of an allocation factor beyond a simple default value is therefore a task for competent authorities, which have, in principle, the means to provide the necessary up-to-date overview of the chemicals on the market and their uses. Such work would obviously imply an increased workload for authorities, for which adequate resources (trained experts, staff time) need to be made available.

6.6.2 Recommendations

We recommend applying the concept of the risk cup to all chemicals. Furthermore, the risk cup should be combined with the concept of Concentration Addition (see Chapter 4) for first tier mixture risk evaluations in general.

The application of a risk cup concept lends itself naturally to a broader application for mixture risk assessments in data-poor situations. This approach would also help overcome the obviously oversimplistic notion that each chemical possesses its own, otherwise pristine, environment.

Scientific evidence on actual chemical composition and occurrence patterns of real-world mixtures is still scarce and fragmented. In particular it is largely unknown which compounds that actually co-occur. Also, knowledge on synergistic interactions is still insufficient. Consequently, the actual fraction by which a given chemical contributes via a particular pathway to filling the risk cup is largely unknown. More data on mixed exposure are needed in order to provide better estimates. However, it will take considerable time and effort to generate those data.

In order to improve the currently inadequate protection of human health and the environment, we therefore suggest setting an interim default allocation factor of 10 per cent for the cumulative

exposure to each chemical until, and unless, solid empirical data become available. In other words, every exposure to an individual chemical via all pathways should only occupy a maximum of 10 per cent of the risk cup. This suggestion takes a middle ground between the factor of 4 and 100 that are currently used or discussed (see Chapter 4).

The approach is equivalent to reducing the default critical value of a risk quotient that considers all uses and exposure pathways of a given chemical from 1 to 0.1. Such a strategy is in line with previous suggestions from the Dutch National Institute of Health (RIVM), academics, and various non-governmental organizations (see Chapter 4).

Given the preliminary nature of setting a generic allocation factor at 10 per cent, we suggest classifying hazardous chemicals that have an interim risk quotient between 0.1 and 1 as candidates for substitution. This would generate incentives to search for less risky alternatives and/or implement risk mitigation measures, without immediately jeopardizing business operations.

Separate strategy for chemicals with low toxicity

It should be pointed out that this strategy is straight forward to apply to hazardous chemicals, i.e. substances for which the maximum regulatory acceptable concentration is based on actual numerical (eco)toxicity estimates (EC50 values, NOECs etc). A specific strategy needs to be developed for compounds with a low toxicity, for which often only semi-quantitative data in the form of e.g. "toxicity is lower than the solubility limit" are available. Simply applying an allocation factor of 10 per cent to those chemicals might otherwise overestimate their contribution to the risk cup.

Lack of data must not delay the implementation

The lack of empirical or reliable modeling data on chemical co-exposure is a serious knowledge gap and more research is clearly needed (see recommendation 6.5). This, however, should not be taken as an argument to delay the implementation of a default mixture allocation factor across all pieces of chemical regulation. The science on mixture (eco)toxicology is very clear (Chapter 4), in that mixture

risks are usually higher than the risks of each individual chemical (at the concentration at which it is present in the mixture). This is currently not accounted for in chemical risk assessment. Implementing a default mixture allocation factor would therefore increase the relevance of current chemical risk assessment approaches substantially.

With this, the probability that a specific exposure situation (be it a wastewater effluent or a specific worker or consumer exposure situation) would result in unacceptable risks effects as a result of the presence of multiple chemicals, would be reduced significantly.

Better empirical data on co-exposures would in the future also allow analyses of where, and under which conditions, the risk cup might overflow, which could trigger targeted risk management and risk reduction measures.

6.7 Establish the substitution principle in all relevant pieces of legislation

We recommend introducing consistent rules and incentives for substituting hazardous chemicals in all relevant legislations.

The substitution principle is currently only implemented in a few pieces of EU chemical legislation. Clear and consistent requirements across all relevant legislations are needed. This would strengthen incentives for industry to identify chemicals of concern and to search for safer alternatives, both chemical and non-chemical.

A systematic implementation of the substitution principle promotes a step-wise lowering of risks and encourages continuous innovation for a non-toxic environment. This will also support the goal of a circular economy and the reduction of risks from chemical mixtures.

We recommend the Swedish Government to

- give all relevant Swedish authorities the task to check for options to improve requirements for substitution in national legislation, where missing or insufficient,
- work together with Swedish Competent Authorities and take a leading role in strengthening requirements and harmonizing criteria for identifying substitution candidates in EU chemical legislations.

6.7.1 Background

Use restrictions or other regulatory measures for risk reduction typically refer to single substances rather than whole groups of chemicals with similar molecular structures, (eco)toxicological properties, or technical functions. As a consequence, economic actors may replace such substances of concern with similar ones, which have the same technical features but are not less hazardous. There are several examples of such “regrettable substitutions”, including e.g.

the replacement of bisphenol A by bisphenol S in thermal paper (see 5.3.3).

The substitution principle aims to prevent such void substitutions while encouraging effective risk reductions. The principle states that, whenever possible, hazardous chemicals should be replaced by less hazardous alternatives, chemical or non-chemical (ECHA 2018d).

The importance of substituting hazardous substances has been emphasized in a number of international agreements and policies. The 7th Environment Action Program identifies innovation and the development of sustainable substitutes, including non-chemical solutions, as basic aspects of a strategy for a non-toxic environment (EC 2013b). The EU strategy for a circular economy (EC 2015b) also considers substitution as a crucial element. Single hazardous substances or mixtures of hazardous substances in chemical products or finished articles may prevent safe recycling and safe reuse of materials. It is therefore important to consider substitution of substances of concern early, in the phase of product design (EC 2018b).

Continuous reduction of risks

Conventional risk assessments aim to ensure that regulatory acceptable exposure levels for individual substances are not exceeded. Where exposures stay below such thresholds, substances are considered to be of no concern or adequately controlled. There is no incentive for reducing risks any further. This changes with the introduction of the substitution principle which requires to achieve a desired purpose with minimal risks. This entails a need for comparative risk rankings of all available options, and it provides momentum for continuous improvement with technological progress. Providers of less risky products get a competitive advantage, and the filling level of the overall "risk cup" (see 6.6) may be continuously reduced.

Although the importance of substitution is well recognized, the substitution principle is still a relatively novel element of EU legislation which is not enshrined in the principles of environmental and chemical legislation laid down in the Treaty on the Functioning of the European Union. Up to now, explicit legal provisions on substitution have been laid down in only four pieces of EU legislation. These include the REACH Regulation (EC) No 1907/2006, the

Plant Protection Products (PPP) Regulation (EC) No 1107/2009, the Biocidal Products (BP) Regulation (EU) No 528/2012, and the Council Directive on Chemical Agents at Work.

Under REACH, provisions on substitution are linked to the identification and authorisation of substances of very high concern (SVHC). Under the PPP and BP Regulations, competent authorities shall not grant authorization to products containing substances classified as "candidates for substitution" if a chemical or non-chemical alternative is available for the same use which presents a "significantly lower risk" (PPP Regulation Annex IV, and BP Regulation Article 23). Under the Chemical Agents Directive, employers are generally required to ensure that risks in the workplace are eliminated or reduced to a minimum, preferably by substitution. Decision criteria and procedures are not detailed in the Directive but left to Member States.

Other pieces of EU legislation create some indirect incentives for substitution by means of excluding selected substances from specific uses under specific conditions. An example is Directive 2011/65/EU on the restriction of certain hazardous substances in electronic equipment. However, such listings may cause one-time risk reduction effects only, while the substitution principle triggers continuous improvements.

In contrast to the situation on the EU level and in other Member States, the substitution principle has been firmly embedded in the national legislation of the Nordic countries, particularly in Sweden, since the beginning of the 1990s (see Chapter 3). However, in Swedish law, provisions focus on chemical-by-chemical substitutions. Considerations of non-chemical alternatives are not explicitly required. This is a weak point that should be addressed.

6.7.2 Recommendations

Legislative requirements have been reported by industry stakeholders to be the main drivers of substitution (Lohse et al. 2003, EC 2017a). We therefore recommend including the substitution principle in all relevant pieces of legislation where it is currently not explicitly stated.

We propose to use existing provisions on substitution under the PPP, BP, and REACH Regulations as the basis for developing similar

provisions for other types of substances and products which require approval or authorization, such as human and veterinary medicines, cosmetics, and food contact materials.

The situation is different for chemicals which require registration only, such as the majority of REACH chemicals. For such substances novel legislative approaches may need to be developed for promoting desirable and preventing regrettable substitution.

There are different views on whether substitution should be hazard or risk-based (EC 2017a). The existing provisions for substitution under EU Regulations use hazardous properties as criteria for classifying substances as so-called "candidates for substitution". For identifying safer alternatives, however, comparative risk assessments are required to support regulatory decision making, such as the refusal of a product authorisation. Transferring this already existing two-step approach to other legislations may hence be a basis for consensus finding across the EU.

Further investigations are needed to (i) identify all pieces of legislation in which the substitution principle should be introduced and (ii) clarify how this should be done more precisely to be most effective for reducing risks to human health and the environment.

Sweden should take a leading role

Sweden has a unique tradition of implementing the substitution principle in legislation. The Swedish Government is therefore encouraged to take a leading role in strengthening and harmonising requirements for substitution in EU chemical legislations, in addition to improving national provisions further.

Promoting the implementation of the substitution principle in EU legislations may be combined with efforts to establish requirements for mixture risk assessment (see 6.1), and with the ongoing horizontal initiative for a European Union framework on endocrine disrupters (EC 2018a).

Strengthening legal requirements for substitution will provide a strong stimulus for the advancement of strategies and methods for identifying groups of chemicals with similar (eco)toxicological properties as a means to avoid regrettable substitution. The issue is addressed further in the following recommendations on group-wise management of chemicals (6.8 and 6.9)

6.8 Strengthen the mandate in REACH to manage groups of chemicals

We recommend that substances registered under REACH are allocated to groups of structurally similar substances and that the mandate to manage chemicals in groups is strengthened.

To make regulatory risk assessment and management less fragmented, more efficient, and more transparent, chemicals should be systematically assigned to groups. Such groups should include chemicals known or suspected to have similar hazardous properties. Where test data are missing, similar chemical structures should be assumed to cause similar hazards.

Group-wise approaches will help (i) to identify, prioritize and manage chemicals of concern more efficiently, (ii) to avoid regrettable substitution, and (iii) to reduce mixture risks.

Options for grouping depend on data requirements which differ largely between legislations. To start, we suggest focusing on REACH which covers the highest number of chemicals with the lowest test data requirements.

We recommend the Swedish Government to:

- Engage on the EU level to strengthen REACH requirements for assessing and managing similar substances as groups rather than individually. Sweden should work to give ECHA a clear mandate to allocate all REACH chemicals to groups of structurally similar compounds. The results should be made publicly available and searchable.
- On the national level, wherever possible, the Swedish Chemicals Agency should use a group-wise approach for manual screening, compliance checks, substance evaluation, SVHC identification and authorization, and restriction proposals under REACH, as well as classifications under the CLP Regulation.

6.8.1 Background

Handling chemicals in groups has been identified as a key approach for preventing regrettable substitution (e.g. EC 2017a, KEMI 2018a). Relevant grouping criteria include chemical structure, (eco)toxicological properties, technological function and use categories. The use of in silico methods, such as read across and QSAR approaches, is being increasingly used and accepted for the identification and assessment of chemical groups for regulatory measures (see Chapter 5).

Despite these regulatory efforts, group-wise handling of chemicals needs to be expanded and performed more systematically under REACH, both on the EU and the Member State levels (ECHA 2018a, KEMI 2018a). Currently, it is largely dependent on the engagement of individual authorities and suffers from resource constraints. To improve the situation, legal provisions must be strengthened, and clear tasks assigned to ECHA.

Under the REACH and CLP Regulations, chemicals may be grouped in different ways for different purposes, such as compliance checking, substance evaluation, identification of testing requirements, hazard classification, SVHC identification, authorisation, and restriction (ECHA 2018a). In the REACH Regulation, the use of group-wise approaches is explicitly mentioned in Annex XI as a possible way to fill data gaps in the registration process, and in Article 47 on substance evaluation.

In addition, the guidance document on restriction proposals points to the potential need for restricting groups of chemicals, when two or more substances of concern share hazardous properties and exposure patterns (ECHA 2007).

As a consequence, grouping of chemicals is a prioritized working area of ECHA. The agency's efforts include developing grouping methodologies and providing guidance for both authorities and companies on grouping approaches for different types of substances and processes. The Swedish Chemicals Agency is also active in the field and has made several group-wise proposals for regulatory measures under REACH and CLP (see 5.4.1).

6.8.2 Recommendations

We recommend that Sweden should work to promote that ECHA is assigned the task to allocate the substances registered under REACH to groups of structurally similar substances. The result of such grouping should be made publicly available and searchable in the registration database.

Grouping based on structural similarity is a proxy for grouping based on hazards or hazard profiles for which test data are missing or insufficient. Thus, it is a first step which may be refined if test data should reveal significant (eco)toxicological differences between structurally similar compounds. Or *vice versa*, if dissimilar structures can be demonstrated to cause similar hazards.

To comply with the precautionary principle, structural similarities may therefore only be used as a positive indicator for hazards similar to those known for a similar compound, but not as evidence for the absence of hazardous properties.

Initial grouping on the basis of structural similarity is the only way for efficiently dealing with tens of thousands of chemicals for which experimental (eco)toxicological data or epidemiological data are missing or are limited to a few endpoints.

IT-tools for mass screening

Currently, the identification of structurally similar substances is already brought forward within ECHA's annual screening program, called the common screening, which is performed for identifying substances of potential concern and prioritizing substances for further regulatory measures (ECHA 2015). The automated IT mass screening tool and the grouping algorithm developed for the common screening is likely able to identify all structurally related substances, to the extent that the submitted information allows one to do so (ECHA 2018b). ECHA is also identifying chemicals with similar structures in their effort to map the chemical universe to address substances of concern (ECHA 2019a, see also 5.4.1). Thus, currently available IT algorithms should allow implementing systematic grouping of all registered substances.

Our recommendation is in line with ECHA's strategy to promote substitution by making relevant information from REACH

registrations available (ECHA 2018c). The strategy considers structure-based grouping as valuable information for "downstream users who are considering substituting away from hazardous substances – as similar substances are likely to have similar hazardous properties" (ECHA 2018c).

To implement our recommendation of a systematic structure-based-grouping of REACH chemicals, the Swedish Government may raise the issue in the ECHA Management Board and/or the Competent Authorities for REACH and CLP (CARACAL) and propose to consider it as part of the tasks assigned to ECHA under REACH Article 77. The initiative may be taken in the context of establishing the 8th Environment Action Program.

Legal requirements to handle chemicals in groups

Beyond initiatives that can be taken under the existing REACH Regulation, we also recommend working on the EU level to promote an amendment to the Regulation. The amendment should introduce a legal requirement to consider groups of similar chemicals, rather than individual chemicals, as a default in all assessment and management processes under REACH. The existing possibility to group chemicals in the registration and substance evaluation processes should hence be strengthened and expanded to become part of the authorisation and restrictions processes under REACH Title VII-VIII.

However, in this context, we stress the importance of ensuring that a sufficient set of reliable and relevant data is made available for all chemicals. To ensure sufficient quality of the registered data set is vital to all processes under REACH and serves as the fundament for appropriate risk management. The use of grouping and read across to conclude that a chemical *lacks* a certain property is, from a scientific perspective, more problematic compared to using read across for identifying (potential) hazards. This should also be reflected in the legal applications.

Group-wise assessment under CLP

These recommendations are confined to the REACH Regulation which covers the largest share of chemicals and a wide range of different uses on the EU market. However, wherever possible, chemicals should also be handled in groups under the CLP Regulation. Furthermore, a more systematic handling of groups of chemicals under REACH and CLP will likely also support substitution of hazardous substances under legislation on consumer products, as data generation, hazard classification and SVHC identification performed under these legislations often provide the basis for use restrictions. Examples are Regulations on toys and electronics (KEMI 2018a).

Our recommendations are supported by the latest report on the implementation of the roadmap for SVHC identification (ECHA 2018a). The report points to the need for strengthening the grouping of substances to ensure that authorities address all substances that matter, to optimize data generation and assessment, and to ensure that substances of concern are progressed towards regulatory risk management measures without delay.

A group-wise approach to the assessment and management of hazardous chemicals will reduce the risk of regrettable substitution, thereby supporting the implementation of the substitution principle across the EU chemical legislation, as recommended in the preceding section 6.7.

6.9 Establish a system for flagging chemicals as suspected SVHCs under REACH based on a group-wise assessment and read-across

We recommend that chemicals are identified as suspected SVHCs under REACH based on structural similarity and read-across. These should be flagged and publicly disclosed.

We support a move towards systematically assessing chemicals as groups in the process of identifying substances of very high concern (SVHCs) under REACH. To further promote substitution with non-hazardous alternatives and innovation in safer technologies, we propose that all chemicals belonging to a group of chemicals that are structurally similar to a known SVHC are flagged as suspected SVHCs.

Flagging chemicals of potential concern in this way will provide useful information to downstream users, strengthen the substitution principle and improve mixture risk management and the work towards a circular economy.

We recommend the Swedish Government to:

- Work to assign ECHA with the task to establish a flagging system where chemicals identified as suspected SVHCs, based on structural similarity, are publicly disclosed and communicated to downstream users unless registrants submit the data needed to conclude on the properties within a given time frame.

6.9.1 Background

The 2019 in-depth evaluation of the environmental objective of "A non-toxic environment" states that the objective will not be met in 2020, due to the continued use of substances of high concern that affect human health and the environment (Naturvårdsverket 2019b). The same conclusion was reached in the European Environment Agency's (EEA) State of the Environment Report, where the outlook for 2030 is that both human and environmental exposure to complex mixtures of hazardous chemicals is likely to increase (EEA

2019). Therefore, moving towards a circular economy requires strengthening the use of the substitution principle.

Several advantages with group-wise approaches

Different initiatives have been taken to speed up the legislative process of identifying substances for substitution. Addressing groups of substances will contribute to identifying new chemicals of concern and to support informed substitution.

ECHA has moved towards addressing groups of structurally similar substances in their work to identify substances of potential concern and regulatory action (ECHA 2018a). Since 2016, ECHA, together with Member States and the Commission, has actively identified groups of structurally similar substances as part of their common screening.

ECHA has applied an approach where substances are grouped together based on similarity in molecular structure and read-across. This means that, as soon as a substance of potential concern is identified, ECHA also identifies:

- related substances of concern,
- substances for which there is a lack of information on hazard and exposure, and
- substances of lower priority at the time.

In the manual screening, i.e. the part of the screening process where Member States' Competent Authorities evaluate substances identified by ECHA and recommend further management measures, approximately 77 % of the substances in groups required further follow-up actions, whereas the respective percentage for single substances was 60 %. According to ECHA, this seems to confirm a trend identified in the 2016 annual report on the implementation of the SVHC roadmap: that it gets increasingly difficult to find single substances for further regulatory action. This shows the need to address groups.

The group-wise approach ensures that substances with similar molecular structure that are not currently registered, or only registered as intermediates, are identified and assessed as well. With the group approach, it is possible to avoid that these, and the other registered

substances with similar hazards to the ones listed on the Candidate List, are seen as viable alternatives (ECHA 2018a).

Lack of data is an obstacle to substitution

According to ECHA (2018a), all currently known CMR, PBT/vPvB and ED substances, i.e. substances for which these hazardous properties have been confirmed, have been either included in the Candidate List or identified for other regulatory risk management measures, e.g. substance evaluation, classification and restriction.

ECHA is currently working towards assigning all registered substances to one of three bins – *high priority for further risk management, high priority for data generation, and low priority for further regulatory action* – where substances that are structurally similar to the currently known SVHCs are identified and allocated to any of these bins (described in 5.4.1).

The lack of data is one of the major obstacles to substitution. For most of the substances under scrutiny to confirm or refute SVHC properties, the first step is to request from the registrants the hazard data that are needed to clarify the activity on these endpoints. In connection to the screening process, Member States consult expert groups in the process of defining the best testing strategy, and the data to be requested. Expert groups also support Member States in assessing the information generated to decide whether a substance fulfills the SVHC criteria or not, and whether it should enter the formal regulatory process, e.g. to be included on the Candidate list (ECHA 2018a).

Another common strategy to encourage and speed up substitution is to list substances of potential concern (Lohse et al. 2003). To "flag" (suspected) hazardous chemicals, and make such information available, creates incentives for downstream users to look for alternatives. The efficiency of the list as a tool for substitution depends, however, on whether the listed substances are believed to become regulated or not (Løkke 2006).

6.9.2 Recommendation

In support of ECHA's work with addressing groups of substances, we propose that the suspected SVHCs identified and assessed under the common screening process and/or ECHA's ongoing work with mapping all REACH registered substances, are publicly disclosed and openly communicated to downstream users. Industry can avoid the flagging if data to conclude on the properties of concern are submitted to ECHA within a specified period of time. The option to provide sufficient data for an improved assessment is foreseen to push data generation and speed up the process of identifying SVHCs.

The flagging would have a similar function as the Member States' or ECHA's registry of intentions, which aim to make interested parties aware of the substances for which regulatory measures are planned, e.g. for which an SVHC dossier is planned to be submitted to ECHA (ECHA 2019c).

If the new data and their assessment show that a suspected SVHC indeed has the hazardous properties of concern, it would become a confirmed SVHC. If the concern can be refuted, the suspected SVHC flag should instead be removed.

We propose that the flagging system is introduced in connection to the identification of SVHCs under REACH, where there is already a system established in the screening process for identifying suspected SVHCs by using a group approach and if there is a need for more information to clarify a concern. Authorities have looked into whether, and when, respiratory and skin sensitisers could be regarded as SVHCs (ECHA 2018a). We emphasize the importance of also including these substances in this process.

The suggested task would fit into the described tasks of ECHA according to REACH Article 77. The issue could be raised by Sweden in ECHA's Management Board and/or the CARACAL.

If the flagging system works well, it may be expanded within REACH to include chemicals that are restricted (Annex XVII). This means that if a chemical is (to be) restricted, all chemicals belonging to the same group of structurally similar chemicals as the restricted chemical should receive a flag and be considered for restriction too.

The flagging system could also be expanded outside REACH. Substances identified as suspected SVHCs could be flagged under other legislations which regulate their use(s), including for example the Cosmetics Regulation and the Food contact materials Regulation. This would contribute to moving away from regulatory silos.

Such a system of structural alerts could also make use of the identification and formation of groups of structurally similar chemicals as suggested in Recommendation 6.8.

6.10 Strengthen requirements for mixture risk assessment and grouping in the upcoming revision of the Water Framework Directive

The Water Framework Directive (WFD) is the most developed regulatory system in the EU dealing with a specific environment. A number of issues may be raised in an upcoming review of the WFD that relate to the subjects of our assignment:

(i) a requirement in the WFD to take combination effects into account,

(ii) ensuring that groups are always considered when identifying priority pollutants and when setting environmental quality standards (EQS),

(iii) introducing Effect-Based Methods (EBMs) in the Directive, (iv) coordinating the two systems used by the WFD to establish chemicals standards.

We recommend that:

1. Sweden works actively on issues related to mixture assessment of chemicals and grouping when the WFD is reviewed. This includes provisions about combination effects in the Directive, further development of grouping when developing quality standards, and the introduction of effect-based methods.
2. Sweden takes the initiative to further study the scope for coordinating EU chemical legislation and the WFD in order to improve the assessment of mixture effects and grouping.

6.10.1 Background

As we concluded in Chapter 3.7, chemical legislation is often fragmented under separate regulations that function more or less independently and use different types of regulatory techniques to achieve the goal of protecting health and the environment. The lack of contact and coordination between legislations can be problematic if the goal is to ensure that mixture risks are fully assessed for chemi-

cals that fall under different regulatory domains. Effective grouping of chemicals for different purposes may also be made more difficult because of regulatory fragmentation.

More effect-based legislation

The Water Framework Directive (WFD) is an example of legislation that primarily aims to identify adverse effects in the environment, including human health effects via the environment.

Such effects-based legislation monitors the environment and human health status. Problems that emanate from chemical mixtures should be possible to identify, and a basis thereby established for solving any problems. Measures to solve the problems could be based on the WFD itself, but the Directive could also provide information to legislation in other regulatory domains, such as REACH, which may provide more suitable and efficient instruments for action. Using instruments such as REACH is in line with the Treaty requirement that environmental damage should as a priority be rectified at the source.

One difficulty is that effects-based or retrospective legislation of this kind cannot easily identify the components in a chemical mixture and identify the extent to which individual components contribute to an overall negative effect. It may therefore be difficult to establish a causal link between the pollution and a specific chemical that may be the main cause of it. But this type of legislation is still extremely important, i.a. by providing indications as to whether the component-based rules really work (substance-oriented and emissions-oriented legislation, see 3.5.1).

The WFD has the aim of ensuring good environmental quality that takes the monitored state of the environment as the starting point, irrespective of the source of any pollution. The legislation is recipient-oriented and in principle, should be able identify and undertake measures against chemical pollution created by chemical mixtures of any kind, including coincidental mixtures. Furthermore, a review of the Directive will take place starting in 2019, which creates an opportunity to develop and amend the legislation, in particular with respect to combination effects.

Upcoming review of the WFD

The water legislation covers both environment and health effects when the exposure takes place via water or via food (fish, mussels etc.). There is also EU legislation about air pollution and the marine environment is subject to a separate legislation that is similar to the WFD (see Chapter 3). Parallels can also be drawn to general legislation about health effects; most importantly, probably food law and rules about workplace protection. We have chosen to concentrate on the WFD because of the importance to tackle water pollution and because a review of the Directive is imminent. A large number of reports and studies have been produced as input to the review (see for example EEA 2018b, Voulvoulis et al. 2017, Brack et al. 2017).

One aim of the WFD is to achieve and maintain good chemical status of water bodies. To achieve this, a number of environmental quality standards (EQS) have been laid down for individual substances (at present 45 substances). The list contains many well-known problematic individual substances (pesticides, solvents etc.) but also some groups (e.g. PAHs, PFOS and derivatives, dioxins, metal compounds).

The quality standards have to be applied by all member states and corrective measures have to be undertaken when the limit values are exceeded. There is also a short watch list with substances that have to be monitored in the environment. The present watch list includes six individual substances (antibiotics, pesticides, hormones), and also two groups of 3 antibiotics and 5 neonicotinoids (insecticides). In addition to this system of EU-wide standards, quality standards can be set by member states that indicate the highest acceptable level for individual river basins (river-basin specific pollutants, RBSPs). The number of identified RBSPs vary considerably between member states.

The studies conducted for the upcoming review of the WFD have identified a number of problems that are clearly related to the main issues of our report – mixture assessment and group-wise management of chemicals. These problems can be summarised as follows:

- The existing focus on a limited number of priority chemical substances is insufficient to deal with the present situation, where hundreds of different organic chemicals can be found in fresh-

water samples, many of them with unknown toxicological properties. Chemical stress in the environment cannot be assessed based on a few individual chemicals. The focus on a few well-known substances may lead to overlooking emerging problems from other substances and mixture effects.

- The WFD does not contain any obligation to perform mixture risk assessments for combined exposure from multiple chemicals. However, assessing mixtures using toxic units (TU) and toxic equivalency factors (TEF) is mentioned in a guidance document (EC 2011b).
- There is a lack of links between observed ecological status and the chemical status of water bodies as defined by the directive.
- There are bio-analytical effect-based methods (EBMs) available that can be used to complement traditional methods for identifying substances or mixtures that need to be prioritised for action. These methods have not been introduced in the Directive (Brack et al. 2019).
- There is no clear mandate in the Directive to group substances when developing quality standards.

6.10.2 Recommendation

A developed WFD could improve chemicals control and provide an important input to other types of chemical legislation. The review of the WFD is an opportunity to modernise the legislation, which clearly needs to be updated to account for developments in the science of evaluating chemical risk. We recommend that the review of the Directive is treated as a priority issue by Sweden.

New requirements to take combination effects into account

The following suggestions for improvements link to the two topics of our assignment – mixture risk assessment and grouping.

It will be necessary to introduce into the WFD a requirement to take combination effects into account when risks are assessed, and priorities are identified. Whenever relevant, mixture assessments

should be performed when developing environmental quality standards, and also for identifying river-basin specific pollutants and setting monitoring requirements. Grouping should always be considered in order to avoid unsuitable substitution.

Include effect-based approaches

One problem with the present approach to deal with chemicals in the WFD is the concentration on a limited number of priority substances. The concern is that monitoring efforts and risk management will be overly focused on these chemicals, while the water may in fact contain hundreds of organic substances, many of them unknown. The focus on individual chemicals (priority substances and RBSPs) should therefore be complemented in the Directive by the introduction of Effect-Based Methods (EBMs), whether to identify trigger values/quality standards or as instruments for screening or monitoring. The possibility to establish standards based on EBMs should also be introduced in the legal text, complemented by guidance. There seems to be agreement that a number of endpoints (or modes of action) can be covered already today by EBMs: estrogenicity, mutagenicity/genotoxicity, dioxin-like effects and selected herbicidal effects. In the future, neurotoxicity should also be covered.

The EBMs may possibly be initially used for monitoring of the environment, as a basis for future screening and as input to more developed risk assessments. The concept of a watch list in the WFD is interesting in this context. As mentioned, investigative monitoring already forms part of the WFD.

Create feed-back to other legislations

Other issues that may come up are the need for coordination between the two systems used to establish standards (EQSs at EU level and national RBSPs).

There is a lot of supporting material in the studies and reports produced for the WFD review that can form a basis for improvements in these areas. The outcome of the WFD review should also be of great interest and have consequences for other legal instruments that deal with chemicals safety. A developed WFD could

provide important input to other types of chemical legislation that do not contain efficient legal instruments to assess environmental effects. A direct link should be established between legislation about environmental status, such as the WFD, and legislation that limit releases of problematic chemicals or groups of chemicals, such as REACH, food law, pesticides, and industrial emissions.

It is often said in policy reports and scientific papers that the challenge of assessing combination effects leads to a need to co-ordinate different types of chemical legislation, but it is seldom presented how such a feed-back loop of information would look like in practice, nor what problems may arise when one tries to implement it. The same could be said about coordination when assessing groups of chemicals. A study that discusses the development of such coordination measures would be essential to undertake. This could provide input to the WFD review but would also be of great general interest.

6.11 Establish a Swedish interagency task force on mixture risk assessment

A Swedish interagency task force should be given the responsibility to explore how agencies can collaborate to facilitate mixture risk assessments across national legislations.

A comprehensive and science-based approach to cumulative exposures and mixture risk assessment can only be achieved in close collaboration between agencies responsible for the different relevant chemical legislations. Therefore, we propose the following actions by the Swedish Government:

- Give the Swedish Chemicals Agency the mandate to create a Swedish Interagency task force on Mixture risk assessment (SwIM) and to decide on its organization.
- The SwIM should have the responsibility to develop systems and processes that permit data and knowledge transfer across the relevant chemical legislations and authorities, to enable mixture risk assessments nationally.
- Provide the SwIM with sufficient resources to fulfill such a novel and complex task as well as a timeline for implementing the results and reporting on the findings.
- A body for interagency collaborations is clearly also motivated at the EU level, and the Swedish Government should actively promote such a development. The knowledge and experiences gained by the SwIM can help pave the way.

6.11.1 Background

As previously described, chemical substances are currently regulated at the EU level by several different legal frameworks. The scope and purposes of the different legislations vary and depend on the hazards, exposures and risks generally foreseen. Therefore, priorities, data requirements, risk assessment processes, and division of tasks and responsibilities differ between legislations. To add to the complexity, some aspects are regulated on the EU level, while some are subjected

to national rules. There are also different agencies, at the EU and the national level, set up to implement these legislations.

Despite this apparently scattered organization of chemicals control, there are currently little or no efforts to integrate and harmonize requirements and processes in a comprehensive and systematic way. This is true both for the EU level and nationally.

The need for coordination has previously been identified. As early as in 2012, the Commission announced the establishment of "an ad hoc working group of relevant services and associated Agencies and Authorities (EFSA, ECHA, EMEA and EEA) to strengthen coordination across the different pieces of legislation and to promote the integrated assessment of priority" in its Communication on chemical mixtures. But this proposal has not yet been realized.

Nevertheless, interactions at the EU-level occur regularly between e.g. ECHA and EFSA under the Classification and Labelling Directive (CLP), where there is a clear overlap in responsibilities. In addition, collaborations have been initiated *ad hoc*. A recent example is EFSA's review of phthalates under the Food Contact Materials Regulation, during which EFSA was specifically asked by DG SANTE to interact with ECHA, and to take the REACH restrictions for the same substances into account. There is also an ongoing collaborative initiative between ECHA, EFSA and interested Member States on bisphenol S. The aim of this initiative is to ensure that the actions decided for this substance are aligned and coordinated across legislations.

Despite these examples, there is no formal process or organisation set up to ensure the coordination of risk assessments and management actions taken under different pieces of chemical legislation. Hence, there might be issues and actions that are not identified, and that work is duplicated. Notably, the aforementioned examples of collaborations are limited to address single substances or groups of substances, but coordination activities are clearly also needed to address broader and more general issues such as aggregate and combined exposures. ECHA and EFSA have identified this as a concern, and the two authorities have started a dialogue to explore mechanisms and processes that could help to increase mutual awareness of ongoing work, and to avoid duplication and incoherencies. (Jack de Bruijn, ECHA, personal communication).

6.11.2 Recommendations

The Committee proposes to create a Swedish Interagency task force on Mixture risk assessment (SwIM). This task force should be given the responsibility to develop systems and processes that enable data and knowledge transfer across the relevant chemical legislations and authorities to enable mixture risk assessments nationally.

The task force could start addressing several of the proposals that are put forward in this report, but in particular we propose three prioritized areas:

- *Identify multi-regulated substances and perform aggregate risk assessments.* The task force should identify chemicals that are regulated under the different legislations, compile use and exposure data for these substances, and make both aggregate and cumulative risk assessments. A preliminary analysis (unpublished) identified approximately 250 chemicals that are regulated by the Cosmetics Regulation (implemented in Sweden by the Medical Products Agency), the Biocidal Products Regulation and REACH (implemented in Sweden by the Swedish Chemicals Agency).
- *Identify specific exposure scenarios to be prioritized for mixture risk assessment.* Possible examples of such prioritized scenarios related to human health are e.g. combinations of chemicals identified in human blood and urine, chemicals emitted from building materials and consumer articles to indoor air, or chemicals released from toys.
- *Contribute to designing, assessing and supervising long-term monitoring studies on cumulative exposures and risks*. The task force should also have the responsibility to inform monitoring programs and help set up a call for research projects that will design and establish long-term survey studies on cumulative exposures and risks. This should be coordinated with, and feed into, the existing national monitoring programs, including the health-related environmental monitoring (HÄMI). A review of Swedish monitoring (SOU 2019:22), including HÄMI, is ongoing, so it is timely to consider the possibility to include monitoring efforts that include analyses of combined exposures and mixtures.

The Swedish Chemicals Agency has overarching responsibilities for chemicals control including cooperation within the EU and across national agencies.[21] In addition there is already a body for inter-agency collaboration set up through SamTox. SamTox was established by the Swedish Government in 2016 as a coordination group to ensure processes for easy transfer of knowledge and information between authorities[22]. The Director General for the Chemicals Agency is chairing SamTox.

SamTox has a support function in the Toxicological Council. The Toxicological Council consists of representatives from Swedish agencies in the field of chemical regulation, and scientists from Swedish universities from relevant disciplines. The purpose of the Toxicological Council is to improve monitoring and use of scientific information for identifying new and emerging risks as well as known, but insufficiently managed risks with chemicals, and provide this information to SamTox. Combined exposures to chemicals can be seen as a known but insufficiently managed risks and would hence fit well into the scope of SamTox.

We propose that the Swedish Chemicals Agency is given the responsibility to set up and find an organisational structure for the SwIM. This includes an analysis of the relevant agencies to be included, as well as other stakeholders of relevance. In particular, the organization should be set up so that the relevant scientific expertise is included. To make SamTox and the Toxicological Council hosting the SwIM is one option that could be considered. Regardless of how the SwIM is organized, it will require clear responsibilities and mandates, in combination with sufficient funds and deadlines for reporting on progress and implementing the results.

A body for interagency collaborations is clearly also motivated at the EU level, between e.g. EFSA, ECHA, EMEA and EEA as proposed by the Commission already in 2012. The Swedish Government should actively promote such a development. Recently, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) proposed to create a standing and permanent European Toxicology Programme (EU-TP). The aim of the EU-TP would be

[21] Förordning 2009:947 med instruktion för Kemikalieinspektionen.
[22] www.kemi.se/en/about-us/organisation/the-coordination-group-for-new-and-emerging-chemical-threats-samtox

> to finance the development, execution and application of toxicological studies for generating data (mechanistic, in vitro and in vivo data) for agents of interest for public health.

The idea is furthermore that emerging issues such as assessment and management of unintentional mixtures and grouping approaches should be handled within this proposed constellation (Anon 2019). The EU-TP proposal is in an early phase, but Sweden is active in that development.

A Swedish national initiative, focusing on mixture risk assessment could pave the way for developments at the EU level by generating important experiences and knowledge.

7 Impact analysis

Our recommendations aim at improving the assessment and management of chemicals in groups and the reduction of risks from combined exposures to multiple substances. The recommendations are primarily oriented towards improving rules and practices at the European level, as chemical management is a highly harmonized policy area within the European Union. A detailed assessment of the impacts of these rules and practices can only be done when one has to decide on concrete proposals or legal acts.

An overall assessment of the impacts of the recommendations is presented in section 7.1. An account of the impacts of specific recommendations with potentially large impacts on public- and private sector organisations is included in section 7.2. Section 7.3 describes other impacts and section 7.4 discusses the financing of the recommendations. The final section discusses alternative courses of action.

7.1 Overall assessment

Motivation of public commitment

The recommendations address chemical pollution arising from combined exposures to multiple substances and their effects on human health and ecosystems. These effects (see Chapter 2) cause economic costs that are currently external to the firms producing, manufacturing or importing chemicals to the Swedish and European market. These external effects represent market failures which motivate further regulation (Hammar and Drake 2007)[1].

[1] The presence of externalities does not necessarily motivate government intervention. In some cases, market actors can reach a negotiated solution where polluters compensate those suffering from pollution. However, in the case of combined exposures to multiple substances, the transaction costs involved in a negotiated solution would most likely be pre-emptive.

Further action is also motivated by the precautionary principle which is an important pillar in European environmental policy. It stipulates that, if there is a threat of serious or irreversible damage to the environment or human health, lack of scientific evidence should not be used as an excuse to postpone cost-effective measures to prevent environmental pollution. It is generally more cost-effective to prevent chemical pollution compared to addressing the effects of pollution at a later stage (EEA 2013).

The recommendations contribute to achieving important health and environmental objectives as well as the sustainable development goals.

The implementation of the recommendations outlined in the present report contributes to achieving the Swedish generational goal[2], the environmental quality objective of a non-toxic environment as well as several other environmental quality objectives. Implementing the recommendations would also contribute to reaching the overarching aim of public health in Sweden to create societal conditions for good health on equal terms for the entire population and to close avoidable gaps in health within one generation. At the European level, the recommendations help to achieve a high level of protection of human health and the environment as laid down in Article 191 of the Treaty on the Functioning of the European Union, in line with the seventh Environmental Action Programme.

Implementing the recommendations would also contribute towards achieving the eight sustainable development goals that have clear associations with a non-toxic environment: safe food and sustainable agriculture (goal 2), good health (goal 3), clean water (goal 6), safe working environments (goal 8), sustainable cities (goal 11), sustainable consumption and production patterns (goal 12), protection of ecosystems and biodiversity (goals14 and 15) (KEMI 2016).

[2] The overall goal of Swedish environmental policy is to hand over to the next generation a society in which the major environmental problems in Sweden have been solved, without increasing environmental and health problems outside Sweden's borders.

Benefits and costs of implementing the recommendations

In principle, the benefits to society of implementing the recommendations should be compared with the societal costs of a more restrictive use of chemicals. Such a comparison is complicated by data gaps and considerable uncertainties.

Recent evaluations of European chemical regulation – which do not take mixture risks into account - indicate that benefits of current chemical legislation outweigh the costs by a considerable margin. For example, the recent REACH REFIT evaluation of the European Commission concludes that the "costs seem to be justified by the benefits"[3] but that the limited data available on costs and benefits makes a robust statistical comparison impossible (EC 2018d). An evaluation of the costs and benefits related to the first 18 restriction proposals in REACH found that the estimated annual cost of the restrictions is more than EUR 170 million per year, while the monetised benefits reach EUR 380 million per year (ECHA 2016). A study commissioned by the European Commission finds that the cumulative health and environmental benefits of European chemicals legislation over the last 50 years "are likely in the high tens of billion Euro per year" (EC 2017c). The same study highlights that it was only possible to quantify and monetise a subset of benefits, largely due to a lack of available data.

All those studies have only analysed single chemicals. Comparing costs and benefits of recommendations to regulate chemical mixtures is even more challenging, due to increased amounts of data that need to be considered and the higher uncertainties involved (see Chapter 4). Data gaps and uncertainties should not be interpreted that health and environmental costs are low. Rather, there is growing evidence that chemical pollution carries larger health and environmental costs than previously documented (Grandjean and Bellanger 2017, Landrigan et al. 2017). For example, recent studies initiated by the Nordic Council of Ministers indicate that the health and environmental costs from the diffuse and widespread pollution from mixtures of PFAS (per and polyfluoroalkyl substances) are very substantial

[3] The main direct costs incurred under REACH was assessed to be associated with registration and the communication of information along the supply chain. These costs were estimated at EUR 2.3–2.6 billion for the first two registration deadlines. The estimated scale of potential benefits for human health and the environment was estimated to be in the order of EUR 100 billion over 25–30 years.

(Goldenman et al. 2019). Also, a growing number of studies find large health costs linked to the effects of mixtures of endocrine disrupting substances on male reproductive health and other health endpoints (Olsson 2014, Trasande et al. 2015). The research project ''EDC-MixRisk'[4] under the European research programme Horizon 2020 concluded that ''current regulations of man-made chemicals systematically underestimate health risks associated with combined exposures to EDCs or potential EDCs'. Furthermore, there are strong indications that mixtures of chemicals strongly impact the biodiversity of European water bodies, with taxonomic losses up to 42 per cent (Beketov et al. 2013). Only 38 per cent of monitored lakes, rivers and other surface water bodies in Europe are in good chemical status (EEA 2018b). The decline in insect populations observed in Europe is also likely associated to exposure to multiple pesticides (UNEP 2019b).

The societal benefits of implementing our recommendations would be the avoided health and environmental costs resulting from a reduced chemical pressure. Children and other groups who are especially vulnerable to chemical pollution would benefit the most. As the effects from chemical pollution during the fetal period and childhood often only manifests later in life, several large benefits from implementing the recommendations will be long-term. From a societal perspective, measures that protect children's health are particularly cost effective since lifetime costs from increased illness, hospital care and reduced productivity can be avoided. Beyond the improved protection of human health from direct effects of chemicals and chemical mixtures, implementing our recommendations will also help to maintain and restore a good status of environmental media (air, water, soil) and the functioning of ecosystems and the numerous ecosystem services they provide.

The societal costs of implementing the recommendations can be divided into direct and indirect costs. The direct costs consists of additional administrative costs for authorities in relation to legislative changes, policy frameworks, databases and monitoring programmes. Direct costs for industry from implementing the recommendations are mainly related to additional costs for reporting information needed for mixture risk assessments and for grouping of substances.

[4] https://edcmixrisk.ki.se/ EDC – Endocrine Disrupting Compounds.

In line with the polluter pay principle, we suggest that the additional costs for authorities should be financed via fees paid by industry.

Indirect costs are more long term and involve the effects of the recommendations on industrial competitiveness and consumer prices. These indirect costs are largely dependent on the availability of relevant substitutes to the chemicals of concern and the rate of innovation.

There is a growing empirical literature on the effects of environmental regulation on competitiveness. In a recent review, Dechezleprêtre and Sato (2017) on the one hand find little evidence to support the hypothesis that environmental regulations had a large adverse effect on competitiveness. Taking the lead in implementing ambitious environmental policies can lead to small adverse effects on trade, employment, plant location, and productivity in the short run, particularly in pollution-and energy-intensive sectors. However, the scale of these impacts is small compared with other determinants of trade and investment location choices such as transport costs, proximity to demand, quality of local workers, availability of raw materials, sunk capital costs, and agglomeration. On the other hand, there is also little empirical evidence that environmental regulation has had large positive effects on competitiveness – the so-called "Porter hypothesis" (Dechezleprêtre and Sato 2017). However, there is growing evidence that environmental regulation enhances innovation, for example through increased resources invested in R&D (Ambec et al. 2013, Dechezleprêtre and Sato 2017).

The conclusions of the REACH REFIT evaluation about effects on competitiveness and innovation after the first 10 years with REACH largely confirm the above mentioned empirical literature on environmental regulation and competitiveness. The evaluation finds some evidence of increasing innovation in the chemical sector, but it is difficult to say whether this is due to REACH or not. The evaluation does not find any big positive or negative impacts on the competitiveness of the European chemical industry that can be specifically associated with REACH. However, the need for continued support to small and medium sized enterprises to understand and comply with the REACH regulation is recognized (EC 2018d).

Summary assessment

Our recommendations address important deficiencies in chemical policy. The implementation of the recommendations is assessed to be a cost-effective way to tackle serious environment and health concerns compared to treating chemical pollution at a later stage. In similarity with the implementation of REACH, which is arguably the most ambitious chemical regulation in the world, the implementation of the recommendations put forward in this investigation is not foreseen to significantly impact competitiveness in Sweden or Europe.

A detailed assessment of benefits and costs to society, including impacts on small and medium sized enterprizes and on vulnerable groups, should be made when concrete legislative proposals are tabled.

While recognising that several uncertainties exist, available evidence indicate that the benefits associated with the implementation of the recommendations outweigh the costs. However, the distribution of the costs and benefits over time requires that decision-makers have a long-term perspective. Several of the costs for improving chemical risk management are tangible in the short term, but many of the benefits are long term.

7.2 Impacts of specific recommendations

Several of our recommendations focus on changing existing chemical legislation or creating new legislation at the EU level (recommendations 6.1–6.3, 6.7–6.8 and 6.10). These recommendations can have large impacts when implemented. However, a detailed assessment of these impacts can only be made when there are concrete proposals for legislative changes.

In this section we focus on the five recommendations with the potentially most tangible impacts for Swedish and European authorities as well as the private sector.

7.2.1 A database on use and emissions of chemicals (Rec. 6.4)

The cost of developing and maintaining a national and European database on use and emissions of all chemicals will depend on the requirements specified in associated regulations.

Based on estimates of the costs for existing European databases at ECHA and JRC[5] and adding approximate costs for an expansion with information on use and exposure of chemicals, we estimate the cost for developing the suggested database at the European level to approximately 15 million SEK per year during a five year period. The cost for subsequently managing the database is estimated to around 3–4 million SEK per year[6]. These cost estimates refer to costs at ECHA and JRC, costs for additional data collection efforts at member state level are not included. Further information about these costs would be gathered in the proposed pilot study.

The cost of conducting the suggested pilot study on aggregate exposures and risks for (a selection of) chemicals covered by several pieces of legislation should be covered by the proposed budget for the Swedish interagency task force on mixture risk assessment (see below). This study would also help to refine the scope, specific requirements and budget regarding the proposed databases on national and European levels.

7.2.2 Establish a research program on real-life exposure patterns to chemical mixtures (Rec. 6.5)

Financing the proposed research programmes on combined exposure to multiple chemicals may be made either through expanding national and European research funds and/or through prioritizing these studies within existing research funds.

The proposed research would build on the methodologies and results developed in recent research programmes on mixture risks[7] (for an overview see Bopp et al. 2018). The EU funding for these 4 to 5-

[5] ECHA's REACH database as well as the Information Platform for Chemical Monitoring (IPCHEM) at the Joint Research Centre of the European Commission.
[6] Based on information provided by ECHA and JRC. The estimated costs for developing the database is based on ECHA's costs for developing other databases. To maintain and update the database there would be 3–4 full time employees.
[7] For example, EDC-MixRisk, EuroMix, EUToxRisk, HBM4EU and SOLUTIONS.

year research programmes varies between 20 and 100 million SEK per year. Based on these experiences we estimate the cost for one European long-term research program on combined exposures to multiple chemicals from different sources to around 200 million SEK, or 20 million SEK per year over a ten-year period.

We estimate the cost of establishing a national long-term research program on combined exposures to multiple chemicals from different sources to around 100 million SEK, or 10 million SEK per year over a ten-year period.

7.2.3 Use an allocation factor to account for the total risk of chemical mixtures (Rec. 6.6)

Introducing an allocation factor of 10 % for all chemicals would fit well into the structure of current chemical regulation and would directly reduce tolerable exposures and hence risks. Implementing an allocation factor would have significant consequences for the use of chemicals in the EU. Since data on exposure and use volumes are incomplete there are large uncertainties on how many of the chemicals on the European market that have a risk quotient between 0.1 and 1, i.e. would be classified as candidates for substitution. Given this uncertainty, we suggest that the allocation factor is introduced gradually across the different pieces of chemical legislation in Europe. An adequate transition period should be implemented, in order to allow industry to adjust to the new requirements.

In order to allow for increased use volumes in the future, producers/importers of industrial chemicals are likely to have registered the maximum production volumes for which the available (eco)toxicological data still allow to demonstrate safe use. This implies that the use volumes reported under REACH might be considerably higher than the actual use volumes. As a result, a probable consequence of introducing the allocation factor is a revision of the use volumes reported under REACH for chemicals with a risk quotient between 0.1 and 1. Introducing the allocation factor would require chemical industry to report realistic production and import volumes and refine their risk assessment accordingly. This information would in turn help European authorities to better understand typical exposure situations for people and the European environment. In the end, this might also allow to more precisely estimate the size of an

allocation factor (or different allocation factors for the different environmental compartments and human health).

The allocation factor would most likely have the strongest impacts on the agricultural sector as many of the Plant Protection Products have risk quotients close to 1. As part of our investigation we asked the Swedish chemical agency to make a preliminary assessment of the share of the plant protection products currently used in Sweden that would end up with risk quotients below or above 0.1 if an allocation factor of 10 was introduced. The assessment concluded that only a few percent of the plant protection products currently used in Sweden would have risk quotients below 0.1. A little less than half of the substances would most likely be able to reach risk quotients below 0.1 based on further testing with higher tier hazard and exposure assessments. For a bit more than half of the plant production products currently on the market, it would not be possible to reduce the risk quotient to below 0.1, even with further testing. These substances would be flagged as candidates for substitution.

The European regulation on Plant Protection Products allows for continued use of substances that have been identified as candidates for substitution for a specific time period until substitutes are available. A similar procedure could be applied for the substances that would have risk quotients above 0.1. By allowing for continued use of these substances under the current authorisation period for a specific plant protection product, it would be ensured that a sufficient number of pesticides remain on the market. At the same time, testing and technological development would be stimulated, which would reduce risks in the long run.

The introduction of an allocation factor would incur costs on producers and importers of chemicals for reporting additional information, additional testing, risk management measures and technological development. Costs for users of pesticides and other chemicals of concern depend on the availability of relevant substitutes and the rate of innovation. Based on ex-post assessments of the costs and benefits of implementing REACH, it is likely that these costs would be considerably smaller than the benefits from introducing the allocation factor.

The implementation of the recommendation would imply new work tasks for competent authorities in Europe (primarily ECHA, EFSA and EMA) as well as industry. Industry would need to factor

in the allocation factor when applying for market approval and would need to revise and perhaps improve existing risk assessments with higher tier hazard and exposure assessments. Authorities would need to consider the allocation factor in their risk assessment procedures and could work, based on evaluations of data on substance use and co-exposure patterns, towards refining the allocation factor(s). National competent authorities are foreseen to play an important role in this work. There will also be an increased need for coordination between authorities in the implementation and refinement of the allocation factor. In order to more precisely estimate the impacts on authorities and the private sector of introducing an allocation factor we suggest that a pilot study be undertaken by the proposed Swedish interagency task force on mixture risk assessment.

7.2.4 Establish a system for flagging chemicals as suspected SVHCs under REACH based on a group-wise assessment and read-across (Rec. 6.9)

It is currently unknown how many chemicals would be flagged as potential substances of very high concern (SVHCs) based on group wise assessments and the read across of hazard data. The Candidate List of SVHCs for authorisation currently (Aug. 2019) contains 201 chemicals. Based on criteria for identification of SVHCs within REACH, the International chemical secretariat (ChemSec) has developed the "SIN[8] List" consisting of 919 chemicals. Most of these belong to one or several of 31 groups of structurally similar chemicals. It is likely that a considerably larger number of chemicals would be flagged as suspected SVHCs as soon as our recommendation would be implemented.

This would lead to increased testing and reporting costs for producers and importers of substances flagged as suspected SVHCs. The affected companies would need to provide the data needed for a conclusive assessment of those substance properties that gave rise to the concern. For high-volume chemicals, much of this information should ideally already form part of the REACH registration dossiers, but in practice, additional data might be needed to address specific concerns. For instance, if the particular test needed to revoke the

[8] SIN stands for ""Substitute It Now".

suspicion is not required for registration, or if the registered data is deemed to be of insufficient quality.

The signaling effect of the flagging system is likely to lead to market advantages for producers of chemicals not flagged as suspected SVHCs. Implementing the recommendation could also lead to fewer cases of regrettable substitution, as it would be easier to identify substances of concern at an early stage.

7.2.5 Establish a Swedish interagency task force on mixture risk assessment (Rec. 6.11)

We propose that the Swedish interagency task force is allocated a budget of 10 million SEK per year, which corresponds to the budget of the Swedish Climate Policy Council. This would allow for a small secretariat and funds for smaller investigations.

7.3 Other impacts

In accordance with the Committees Ordinance (SFS 1998:1474) impacts of the proposed recommendations on gender equality, crime, employment, integration and local and regional administrations were analysed. We foresee no significant impacts on any of these qualities or administrations.

The Committees Ordinance also specifies that an environmental assessment should be conducted. We do not anticipate any significant negative environmental impacts associated with the recommendations. In contrast, the implementation of the outlined recommendations would have significant positive long-term impacts on ecosystems and humans, by reducing the total pressure from multiple chemicals in water, soil and air.

7.4 Financing of the recommendations

The implementation of the recommendations will generally require additional efforts by the Swedish Chemicals Agency, ECHA, EFSA and other relevant authorities. Besides efforts to analyze and design proposals, the authorities will need to expand contacts with EU

institutions and other member states to discuss and seek support for proposals. Contacts regarding these issues will also be needed between authorities and the research community, NGOs, industry bodies and companies. Managing these new obligations may to some extent be possible through reallocation of existing resources, but additional resources will also be needed. Additional analytical and coordinating capacity will be created through the proposed Swedish interagency task force on mixture risk assessment. The Swedish Chemical Agency will also need additional resources in order to meet the proposed increased ambition regarding mixture risk assessment and grouping of chemicals. The resources needed for the Swedish Chemical Agency to expand the national product registry with information on chemicals and uses as well as other tasks resulting from our recommendations should be assessed as part of the agency's work with the annual budget plan (KEMI 2018b).

European chemical policy follows the Polluters Pay Principle, and places responsibility on industry to manage the risks from chemicals and to provide safety information on the substances it manufactures, uses or places on the market. Under REACH, for substances with a use exceeding 1 tonne per year, manufacturers and importers have to gather and register information on the properties of their chemical substances in order to guarantee safe handling. Without providing this information it is not possible to manufacture, import or place chemical substances on the market ("No data no market").

In line with the Polluters Pay Principle, the costs for taking aggregate and cumulative exposures from chemicals into account as well as grouping of chemicals should be paid by the actors causing these costs. This includes the additional costs for authorities for developing and maintaining the recommended database on use and emissions of chemicals as well as the cost for conducting cumulative risk assessments and for grouping chemicals. A separate investigation on a revised fee structure for chemical management that covers the costs for administrating a sustainable system for chemicals management in Europe as well as creates incentives for substituting away from using SVHCs should be initiated.

7.5 Alternative courses of action

Our recommendations include alternative courses of actions as they range from very concrete short-term actions, such as the establishment of the SwIM task force, over medium-term aims, such establishing research programs or amending existing legislations, to more visionary long-term goals, such as creating a novel regulatory framework for better protection of human health from cumulative exposures to chemicals and other stressors.

Several recommendations aim at generating more and improved data and making them publicly available, which would facilitate the assessment and management of mixture risks. This is important for creating a sustainable system for chemical management in the long term.

Since we cannot wait to address the problems associated with chemical exposure from multiple sources until we have generated this improved information, we also recommend the introduction of an allocation factor and the flagging of suspected SVHCs. These recommendations would directly reduce exposures to hazardous chemicals, and hence risks in the short and medium term.

We also recommend a dual strategy relating to actions at the national and European levels. As responsibilities for chemical legislation are shared between the EU Commission, EU Parliament and the Member States, we recommend tackling most of the identified problems with actions on both the EU level and on the national Swedish level. The recommended national activities will provide experience, examples, and demonstrations of feasibility that will give Sweden a leading position in the complementary activities on the EU level.

8 Stakeholder dialogues

Contacts and discussions with stakeholders were initiated at an early stage and our work was communicated continuously throughout the inquiry period.

We are very grateful for the many detailed and constructive suggestions for refinements or amendments to the text. They helped us to sharpen the argumentation, to rule out ambiguities, and to remove potentially misleading wording. A very brief overview of (a selection of) input received, and the full list of stakeholders that we were in contact with, is provided below.

Summary of input

Some stakeholders called for a ranking of our eleven recommendations and a prioritisation of selected ones, while others explicitly recognised that it is good to have a wide range of concerted actions which address both problems, mixtures and grouping, from different angles and on different levels simultaneously. That was our intention, as explained in the Executive Summary of this report.

Some stakeholders stressed the responsibilities of producers and importers of chemicals for the safety of their products and were concerned that our proposals place a high burden of work on authorities. However, assessing the risks from unintentional mixtures, as well as grouping chemicals for avoidance of regrettable substitution, cannot be done by a single economic actor but requires an authority that has an overview on all relevant substances. Under these conditions, the responsibility of industry must be to provide the necessary input data.

In general, most comments on the recommendations related to mixtures were very positive, welcoming our recommendations on the issue and providing many ideas and opinions on how they should be worked out in further detail as a follow-up from this report. A few stakeholders, however, were skeptical about the relevance of

our assignment. They casted doubts on the need for mixture risk assessments, arguing that existing regulatory schemes for individual chemicals should provide sufficient protection and that it would be disproportionate to take an array of measures against a problem that they considered to be minor. For reasons summarized in Chapter 2, we do not share this view but consider mixture risk assessments both necessary and feasible.

The comments received on the recommendations related to grouping were also overall positive. Stakeholders pointed out that there are many grouping activities for regulatory purposes going on, but that there is a need to support this development with further efforts in order to avoid regrettable substitutions and promote innovation in safer alternatives. One stakeholder did, however, not believe that "government substitution instructions" is the best solution. Instead, improved support for development of efficient screening methods for substance evaluation and risk characterization, and communication and knowledge transfer within the supply chain and between academia and industry were suggested.

Another stakeholder posed the question of whether action may be delayed if we argue that a change in the legal text is necessary to assess and manage groups of substances, i.e. undermining current regulation which allows for grouping. However, as our review shows, explicit legal requirements to substitute are generally considered to be the most effective tool to spur innovation in safer chemicals and technologies. For the same reason, we deem that a strengthening of the legal text regarding group-wise handling of chemicals is important for it to be done systematically and to a larger extent.

The recommendation to flag, and publicly disclose, suspected SVHCs received mainly positive comments, but potential drawbacks as a result of "blacklisting" substances were expressed, e.g. that the market would start asking for alternatives for substances of suspected concern which may be found not to be hazardous after being assessed. Several stakeholders however emphasized the need to speed up the process of data generation by registrants. The recommendation was revised so that substances identified to be suspected SVHCs based on structural similarity and read-across are not immediately disclosed publicly, but only if the registrant(s) do not submit the data needed to conclude on the properties within a given time frame, with the aim to push data generation.

List of stakeholders

The following stakeholders have contributed to the inquiry. Some have been in more or less regular contact with us throughout the inquiry period, while others have contributed occasionally.

National authorities

Swedish Chemicals Agency
Swedish Medical Products Agency
Swedish Food Safety Authority
The Public Health Agency of Sweden
Swedish Environmental Protection Agency
Swedish Work Environment Agency
Danish Environmental Protection Agency
Ministry of Environment and food of Denmark
National Institute for Public Health and the Environment, RIVM, in the Netherlands

European agencies and authoritative bodies

European Chemicals Agency, ECHA
European Food Safety Authority, EFSA
European Environment Agency (EEA)
European Parliament
European Commission
European Environment Bureau (EEB)

NGOs

International Chemicals Secretariat (ChemSec)
ClientEarth
Swedish Consumer's organisation

Water and waste organisations

The Swedish Waste Management Association
Swedish Water and Waste Water Organisation

Industry organisations and companies

Joint Secretariat of Swedish Chemical Products Associations (KTF)
Chemical and innovation companies in Sweden (IKEM)
Swedish Forest Industries
The researched based pharmaceutical industry (LIF)
H&M
IKEA

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EU Legislation[1]

Substance-related legislation

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.

Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food.

Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs.

Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC.

Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food (Text with EEA relevance).

Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives.

[1] The list refers to the basic legal acts. The often numerous amendments to the acts are not included in the list. The inofficial consolidated versions including amendments can be found by searching for the number (e.g. 1907/2006) at https://eur-lex.europa.eu/homepage.html and choosing ”latest consolidated version” under the heading for the legal act in question.

Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition.

Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives.

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC.

Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides.

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal product.s

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. *Repealed by Regulation (EU) 2019/6.*

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Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

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Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products.

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Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 on the safety of toys.

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment.

Directive 2000/53/EC of the European Parliament and of the Council of 18 September 2000 on end-of life vehicles.

Directive 2004/42/EC of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC.

Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 on detergents.

Emissions-oriented legislation

Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control).

Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment.

Directive 2011/92/EU of the European Parliament and of the Council of 13 December 2011 on the assessment of the effects of certain public and private projects on the environment.

Recipient-oriented legislation

Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy.

Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council.

Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives.

Commission Decision of 3 May 2000 replacing Decision 94/3/EC establishing a list of wastes pursuant to Article 1(a) of Council Directive 75/442/EEC on waste and Council Decision 94/904/EC establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste.

Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration.

Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption.

Directive 2008/56/EC of the European Parliament and of the Council of 17 June 2008 establishing a framework for community action in the field of marine environmental policy (Marine Strategy Framework Directive).

Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe.

Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air.

Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work.

Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC.

Committee terms of reference 2018:25

Combination effects and dealing with substances by group

Decision at a government meeting on 29 March 2018

Summary

An Inquiry Chair will investigate how risk assessments for hazardous chemicals being carried out by group can be increased, and how "combination effects' can be taken into account.

Among other things, the Inquiry Chair will:

- identify opportunities, obstacles and previous measures in relevant EU legal instruments for dealing with substances by group;
- propose strategies for future group-based regulation and, where necessary, any amendments to relevant EU legal instruments for dealing with substances by group;
- sum up the state of scientific knowledge, identify opportunities and obstacles in different relevant EU legal instruments and previous measures in the area of combination effects; and
- propose strategies to enable regulation based on, or taking account of, combination effects, propose other strategies to reduce the risks and, where necessary, propose amendments to relevant EU legal instruments.

The Inquiry is to present its report by 29 September 2019.

Background

Traditionally, substances have been dealt with one at a time. Account is rarely taken of overall exposure to the same substance or similar substances from different sources or routes of exposure, known as ''cumulative exposure'.

There is growing awareness of the fact that there can be combination effects, although knowledge about this remains low. This means that the current risk assessment methodology systematically underestimates the risks of exposure to hazardous chemical substances. The issue of how different substances interact in the human body or the environment is not taken into account when risk assessments are conducted for chemical substances and they are regulated.

Dealing with substances by group, according to chemical structure, mode of action, qualities or area of use would lead to a considerable improvement of chemical controls. In the Government Bill *Towards a toxin-free everyday environment* (Govt Bill 2013/14:39), the Government outlines the measures needed to achieve the interim targets of the environmental quality objective *A non-toxic environment*. The Government states, among other things, that general knowledge-building is needed concerning the combination effects of chemicals. Moreover, methods that take account of combination effects and cumulative exposure in risk assessments must be developed and the relevant regulatory frameworks must be amended. In recent years, there has been an increase in knowledge about and interest in the effects on human health and the environment of simultaneous exposure to several different chemicals. These effects are called combination effects or cocktail effects.

Risk assessments for chemicals are usually carried out for one substance at a time and do not take account of the combined effect of several chemicals. The possibility of carrying out overall assessments of several substances is currently limited by the lack of simple tools to assess the overall risk.

In December 2009, the Council of the European Union adopted conclusions on combination effects of chemicals (17820/09). In response to the environment ministers' Council conclusions from December 2009, in spring 2012 the European Commission presented a communication on combination effects (COM/2012/0252). The communication contains commitments aimed at strengthening guid-

ance and coordination between various EU legal instruments, but no commitments on reviewing relevant EU legal instruments. The Commission has not implemented the measures contained in the communication. The 7th General Union Environment Action Programme (PE-CONS 64/1/13) establishes that strategies are needed to tackle combination effects, and methods need to be developed and applied. On numerous occasions, the European Parliament has pointed out that the EU's chemicals legislation must take account of the combined effects of different chemicals on human health and the environment.

The environmental quality objective *A non-toxic environment* includes eight interim targets on hazardous substances. Dealing with substances by group and combination effects are included in two interim targets. The interim target *Knowledge about substances' health and environmental qualities* states that decisions taken at EU and international level must contain measures to ensure that "conditions are in place by 2015 for relevant regulatory frameworks to take account of combination effects in exposure to chemicals". The interim target *Development and application of the EU's chemical rules* states that the REACH Regulation and other relevant EU legislation will be applied or, if necessary, revised by 2020 so that "it is possible to a greater extent to assess and test groups of substances with similar inherent qualities, chemical structure or area of use". In Chapter 9.2 of the Bill *Towards a toxin-free everyday environment* (Govt Bill 2013/14:39), the Government describes the measures needed for the interim target to be achieved and to facilitate dealing with relevant groups of substances.

Combination effects and how substances are best dealt with by group have long been subjects of discussion. These are complex issues and very little has happened in recent years. An Inquiry Chair will therefore investigate how risk assessments of hazardous substances can be carried out by group and how combination effects can better be taken into account.

More details on the remit

Remit on dealing with substances by group: identify opportunities, obstacles and previous measures in relevant EU legal instruments.

Traditionally, hazardous substances have in most cases been dealt with one at a time. There is a risk here of ''false substitution'. This is when a hazardous substance is banned and substituted with a very similar substance with the same desirable technical qualities. Unfortunately, the new substance often has the same or similar hazardous qualities. To avoid this, a holistic approach to groups of substances is needed. For substances to be dealt with by group, any opportunities and obstacles currently in relevant EU legal instruments need to be identified. The approach of dealing with substances by group is not new; some trials have been successful, whereas others have not. To learn lessons and to benefit from previous experiences, these trials should also be surveyed. The Inquiry is to:

- identify what opportunities and obstacles there are in relevant EU legal instruments for dealing with substances by group;
- survey previous trials, whether successful or not, of dealing with substances by group in relevant EU legal instruments; and
- report conclusions from these surveys.

Remit on dealing with substances by group: propose strategies for future regulation by group and, where necessary, amendments to relevant EU legal instruments.

A prohibition of a hazardous substance has often led to a similar and equally hazardous substance being used instead, known as false substitution. The basis of EU chemicals legislation is that substances are dealt with one at a time. However, in some cases it must be possible to deal with substances by group. The Inquiry is to:

- analyse the results of the surveys and other relevant sources;
- propose strategies for how substances with similar hazardous qualities can be dealt with by group in the implementation of different EU legal instruments; and

- analyse and, where necessary, propose amendments to relevant EU legal instruments to enable regulation of groups of chemicals.

Remit on combination effects: sum up the state of scientific knowledge and identify opportunities and obstacles in different relevant EU legal instruments and previous measures in the area.

Knowledge about combination effects is currently inadequate. The state of scientific knowledge about combination effects therefore needs to be summarised. Only a few EU legal instruments currently prescribe that account should be taken of combination effects. A survey is needed of the opportunities and obstacles in relevant EU legal instruments when it comes to considering exposure to several different chemical substances simultaneously. Measures that could help achieve the interim target on knowledge about substances' health and environmental qualities are contained in the 7th General Union Environment Action Programme, the Council conclusions adopted during the Swedish Presidency in 2009 and the Government Bill *Towards a toxin-free everyday environment* (Govt Bill 2013/14:39). The Inquiry is to:

- compile research in the area;
- identify opportunities and obstacles in relevant EU legal instruments; and
- survey previous measures.

Remit on combination effects: propose strategies to enable regulation based on, or taking account of, combination effects, propose other strategies to reduce the risks and, where necessary, propose amendments to relevant EU legal instruments.

A clear picture of possible success factors is needed, based on existing opportunities and obstacles and what has previously been done. The Inquiry is to:

- propose strategies to enable account to be taken of combination effects;

- propose, where necessary, other measures that could lead to a reduced risk of undesired combination effects; and
- on the basis of the itemised remits specified above, propose any necessary amendments to relevant EU legal instruments to enable account to be taken of combination effects.

Impact assessments

The Inquiry's proposals and background material must follow the requirements of the Committees Ordinance (1998:1474) concerning impact assessments and cost estimations. The proposals must be followed by economic impact assessments and analyses of their cost-effectiveness. The proposals must contain alternative courses of action. If the Inquiry proposes measures entailing costs, the Inquiry must propose financing for these measures. The Inquiry must also provide an environmental assessment of the proposals.

Consultation and reporting of the remit

The Inquiry is to conduct its work in close dialogue with relevant agencies, researchers, stakeholders, companies, industry organisations and other actors in this area. The Inquiry is to survey and draw on the experiences of similar work in other relevant EU countries.

The report (including an English translation) is to be submitted to the Government Offices (Ministry of the Environment and Energy) by 29 September 2019.

(Ministry of the Environment and Energy)

Swedish Government Official Reports 2019

Chronological list

1. Santiagokonventionen mot organhandel. S.
2. Ingen regel utan undantag – en trygg sjukförsäkring med människan i centrum. S.
3. Effektivt, tydligt och träffsäkert – det statliga åtagandet för framtidens arbetsmarknad. A.
4. Framtidsval – karriärvägledning för individ och samhälle. U.
5. Tid för trygghet. A.
6. En långsiktig, samordnad och dialogbaserad styrning av högskolan. U.
7. Skogsbränderna sommaren 2018. Ju.
8. Kamerabevakning i kollektivtrafiken – ett enklare förfarande. Ju.
9. Privat initiativrätt – planintressentens medverkan vid detaljplaneläggning. N.
10. Stöd för validering eller kompetensåtgärder i samband med korttidsarbete. Fi.
11. Biojet för flyget. M.
12. Nya befogenheter på konsumentskyddsområdet. Fi.
13. Agenda 2030 och Sverige: Världens utmaning – världens möjlighet. Fi.
14. Ett säkert statligt ID-kort – med e-legitimation. Ju.
15. Komplementär och alternativ medicin och vård – säkerhet, kunskap, dialog. S.
16. Ny kärntekniklag – med förtydligat ansvar. M.
17. Bebyggelse- och transportplanering för hållbar stadsutveckling. N.
18. För flerspråkighet, kunskapsutveckling och inkludering. Modersmålsundervisning och studiehandledning på modersmål. U.
19. Belastningsregisterkontroll i arbetslivet – behovet av utökat författningsstöd. A.
20. Stärkt kompetens i vård och omsorg. S.
21. Effektivt investeringsfrämjande för hela Sverige. UD.
22. Sveriges miljöövervakning – dess uppgift och organisation för en god miljöförvaltning. M.
23. Styrkraft i funktionshinderspolitiken. S.
24. Stärkt integritet i idrottens antidopningsarbete. Ku.
25. Genomförande av ändringar i utstationeringsdirektivet. A.
26. Organbevarande behandling för donation. S.
27. Rasistiska symboler. Praxisgenomgång och analys. Ju.
28. Komplementär och alternativ medicin och vård – ny lagstiftning. S.
29. God och nära vård. Vård i samverkan. S.
30. Moderna tillståndsprocesser för elnät. I.
31. F-skattesystemet – en översyn. Fi.
32. Straffrättsligt skydd för barn som bevittnar brott mellan närstående samt mot uppmaning och annan psykisk påverkan att begå självmord. Ju.
33. Ökad statlig närvaro i Härnösand. Fi.
34. Förbättrat skydd för totalförsvaret. Fö.
35. Demokrativillkor för bidrag till civilsamhället.
    + Demokrativillkor för bidrag till civilsamhället. Vägledning för handläggare. Ku.
36. Skattelättnad för arbetsresor. En avståndsbaserad och färdmedelsneutral skattereduktion för längre arbetsresor. Fi.
37. Kontroller vid högskoleprovet – ett lagförslag om åtgärder mot fusk. U.

38. Stora brottmål
– nya processrättsliga verktyg. Ju.
39. En moderniserad radio- och tv-lag
– genomförande av ändringar
i AV-direktivet. Ku.
40. Jämlikhet i möjligheter
och utfall i den svenska skolan. Fi.
41. Företagare i de sociala trygghets-
systemen. N.
42. Digifysiskt vårdval. Tillgänglig
primärvård baserad på behov
och kontinuitet. S.
43. Med tillit följer bättre resultat
– tillitsbaserad styrning och ledning
i staten. Fi.
44. Ett bättre premiepensionssystem. S.
45. Framtidens kemikaliekontroll.
Hantering av kombinationseffekter
och gruppvis bedömning av ämnen. M.
Future chemical risk management.
Accounting for combination effects
and assessing chemicals in groups. M.

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Systematic list

Socialdepartementet

Utbildningsdepartementet

Utrikesdepartementet