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# Mixtures in the Environment – Development of Assessment Strategies for the Regulation of Chemicals under REACH



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## **Mixtures in the Environment – Development of Assessment Strategies for the Regulation of Chemicals under REACH**

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## Abstract

This report describes and discusses approaches for the environmental risk assessment (aquatic compartment) of mixtures under REACH. Different types of mixtures are defined. The focus lies on technical mixtures and discharge mixtures. Cumulative and aggregated exposures are considered. Interfaces to other regulations (e.g. Water Framework Directive) and consideration of substances not regulated under REACH (e.g. biocides) are briefly discussed.

A tiered component based approach for the risk assessment of technical mixtures is proposed. It links the state of the art in mixture risk assessment methodology with data requirements and the assessment philosophy according to REACH. Therefore the use of REACH generated data, necessary amendments, and feasibility constraints under REACH in order to perform such a mixture risk assessment are analysed. The tiered approach has been tested on real technical mixtures from a tannery. As possible supplemental elements, mixture assessment factors and whole mixture testing are considered.

Current limitations for risk assessment of technical mixtures under REACH are identified and acknowledged. Those are, inter alia, the generic and very crude substance exposure levels (PECs) generated by REACH risk assessment tools, the disparity in the availability of suitable data across the supply chain limiting the possibilities of different actors to assess mixture risks and the missing link between the responsibilities of the single REACH actor (producing or using technical and discharge mixtures and the components (quantitatively and qualitatively) of the actual local coincidental mixture in the receiving water volume which, however, determine the real environmental risk.”

Priority setting is essential for the risk assessment of mixtures. For this purpose, “Mixture Assessment Triggering Substances (MATS)” are proposed. MATS are selected based on single substances’ risk related data indicating a relevant contribution to mixture effects according to concentration additivity assumptions, if they are present in a specific technical mixture. Further approaches for the identification of priority mixtures refer to critical components in mixtures, critical composition and critical uses of mixtures. End-users of technical mixtures can focus on aggregated exposures due to the parallel use of the same substance in more than one technical mixture.

Options to assess technical mixtures under REACH have been developed for industry and for authorities. The feasibility of these options is analysed. Possible next steps for validating and refining the proposed mixture risk assessment strategy and for implementation are described.

## Kurzbeschreibung

Dieser Bericht beschreibt und diskutiert Herangehensweisen, um technische Gemische unter REACH zu bewerten, bezogen auf den Schutz der Umwelt. Unterschiedliche Arten von Gemischen werden definiert. Der Schwerpunkt liegt auf technischen Gemischen, und den aus ihnen entstehenden Gemischen im Vorfluter. Es werden kumulative und aggregierte Expositionen berücksichtigt. Kurz angesprochen werden Schnittstellen zu anderen Regulierungen (z.B. der Wasserrahmenrichtlinie) und die Betrachtung von Stoffen, die nicht unter REACH geregelt sind (z.B. Biozide).

Für die Risikobewertung technischer Gemische wird ein gestuftes Vorgehen vorgeschlagen. Es verbindet den derzeitigen Stand der wissenschaftlichen Diskussion zur Risikobewertung von Gemischen mit dem Bewertungsansatz für Stoffe unter REACH. Die vorgelegte Analyse bezieht sich deshalb auf die Nutzung von Daten, die durch REACH erhoben werden, notwendige Anpassungen und Begrenzungen einer solchen Bewertung. Das gestufte Vorgehen wurde am Beispiel tatsächlich verwendeter Gemische für die Ledergerbung getestet. Als mögliche Ergänzungen werden Bewertungsfaktoren für Gemische und das Testen des gesamten Gemisches aufgeführt.

Bestehende Begrenzungen für eine Risikobewertung technischer Gemische werden identifiziert und ernst genommen. Hier zählen, unter anderem, die generischen Expositionshöhen für Stoffe, die mit den für REACH benutzten Instrumenten berechnet werden und oftmals nur grobe Schätzungen darstellen und die ungleiche Verfügbarkeit erforderlicher Daten für die Akteure in den Lieferketten. Hinzu kommt, dass ein unmittelbarer Zusammenhang zwischen der Verantwortung eines einzelnen Akteurs unter REACH, und der aktuellen Zusammensetzung im Vorfluter bzw. einem tatsächlichen Umweltrisiko fehlt.

Schwerpunktsetzungen sind unbedingt erforderlich für die Bewertung von Gemischen. Hierfür werden sog. MATS vorgeschlagen: "Mixture Assessment Triggering Substances (MATS)", Stoffe, deren Vorhandensein die Risikobewertung eines Gemisches auslöst. Außerdem werden Möglichkeiten beschrieben, "prioritäre Gemische" anhand inhärenter Eigenschaften der Gemische zu bestimmen. Für Anwender von Gemischen wird vorgeschlagen, aggregierte Expositionen zu bewerten, wenn sie ein- und denselben Stoff in mehreren Gemischen verwenden.

Für Industrie und Behörden werden Möglichkeiten beschrieben, um Bewertungen von Gemischen durchzuführen. Ihre Umsetzbarkeit wird analysiert. Nächste Schritte werden vorgeschlagen, um die entwickelte Bewertungsstrategie für Gemische zu verfeinern und umzusetzen.

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## List of Abbreviations

ACR	Acute to Chronic Ratio
AF	Assessment Factor
CA	Concentration Addition
CAG	Common Assessment Group; also used for “Cumulative Assessment Group” with identical meaning
CRA	Cumulative Risk Assessment
CRVTL	Chronic Reference Value specific for Trophic Level
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DNEL	Derived no Effect Level
DU	Downstream User
ECHA	European Chemicals Agency
ES	Exposure Scenario
EPM	Equilibrium partitioning Method
ETNCaq	Environmental Thresholds of no toxicological Concern for Freshwater Systems
HC5	Hazard Concentration 5: Concentration at which 5% of species are at risk
HI	Hazard Index, $HI = RQPEC/PNEC = \sum_{i=1}^n \frac{PEC_i}{PNEC_i} = \sum_{i=1}^n RCR_{,i}$
i	Index for Chemicals contained in a Mixture
I	Importer of a Substance
IA	Independent Action
IF	Interaction Factor
Koc	Organic Carbon normalized Adsorption Coefficient
M	Manufacturer
MA	Mixture Risk Assessment
MAF	Mixture Assessment Factor
MATS	Mixture Assessment triggering Substance(s)
MCR	Maximum Cumulative Ratio
MIAT	Mixture Assessment team (A CEFIC team)
MoA	Mode of Action (identical to TMoA)
MoE	Margin of Exposure
MS	Member State
NOAEC/ NOAEL	“no observed adverse Effect Concentration / Level”
PBPK Models	Pharmacokinetic based Models

PEC	Predicted Environmental Concentration
PNEC	Predicted no Effect Concentration
POD	Point of Departure
QSARs	Quantitative Structure Activity Relationships
RCR	Risk Characterization Ratio = $PEC_i/PNEC_i$
RCRTL	RCR for Trophic Level: $RCRTL = PEC_i/CRV_{i,TL}$
RQSTU (TL)	Risk Quotient from the Sum of Toxic Units for a Trophic Level: $RQSTU (TL) = (\sum_{i=1}^n \frac{PEC_i}{EC50 (TL)_i}) \times AF$
RQSTU	$RQSTU = MAX (RQSTU (TL))$ , TL = Algae, aquatic Invertebrates (inv.) and Fish
SDS	Safety Data Sheet
SEA	Socio-economic Analysis
SEV	Substance Evaluation
SSD	Species Sensitivity Distribution
THI	Trophic Level Hazard Index: $THI = MAX (THITL)$ , TL = Algae, aquatic Invertebrates (inv.) and Fish
THITL	Trophic Level Hazard Index for the specified Trophic Level: $THITL = \sum_{i=1}^n RCRTL_i = \sum_{i=1}^n \frac{PEC_i}{CRV_{i,TL}}$
TMoA	Toxic Mode of Action (identical to MoA)
TTC	Threshold of Toxicological Concern
TU	Toxic Unit

## Summary

This report describes and discusses approaches and options for the environmental risk assessment of technical mixtures - under REACH. It presents the results of a research and development project of the German Federal Environmental Agency (project short title: “4M: Mixtures under REACH”). The project took into account findings regarding the assessment of mixtures under other legislations. Key questions of the project have been:

1. What are the requirements for and the relevance of an environmental assessment of mixtures under REACH? How can risks for the environment from technical mixtures be assessed? Which approaches relevant to REACH are discussed in the state of the art in mixture risk assessment methodology?
2. How can priorities be set which technical mixtures should be subject to mixture risk assessment? Which criteria exist to define “priority mixtures”?
3. Which options for industry and for authorities exist to assess technical mixtures under REACH? How feasible are these options? Which options would require changes in the legal text of REACH or in the guidance documents?

Focus in the project has been on the aquatic compartment. Several options are described in this report to assess technical mixtures under REACH. They refer not only to registrants, formulators and end-users. Also options to act for the national competent authorities are presented – related to substance evaluation, restriction and authorisation. External experts have been invited to discuss major findings of the project at a workshop. The results of the discussions are considered in the final report and the conclusions of the project<sup>1</sup> (see Annex 7, chapter 9.7).

The following sections give a summary of the main findings and conclusions of the project 4M. References are made to more comprehensive descriptions in the main chapters and the related annexes. Important terms and definitions are introduced in the glossary, chapter 5.

The chapters have the following main authors:

- Chapter 1: Background: Dirk Bunke.
- Chapter 2: Concepts for Environmental Risk Assessment of Mixtures and for Priority setting: Fritz Kalberlah.
- Chapter 3: Evaluation of Options to implement Mixture Assessment under REACH: Antonia Reihlen (Options to act for authorities were described by Ninja Reineke).
- Chapters 4-6: Dirk Bunke.

The different aspects of each chapter have been discussed in the project team. However, not always a common position has been found. The chapters reflect primarily the opinion of the respective main author.

## Central terms

Within European legislation, there are no harmonized definitions for different types of “mixtures”. Furthermore, important terms – such as “combined exposure” and “aggregated

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<sup>1</sup> The workshop documentation summarises the discussion results. It is publicly available from the Federal Environment Agency (contact: Ms Aust, Ms Hassolt). The main findings of the workshop are documented in chapter 9.7 of this report.

exposure” – are used differently in the scientific discussions. In this report, the following definitions for central terms are used (chapter 1.2):

- **Mixture:**<sup>2</sup> generic term for all different types of combinations of two or more substances. Mixtures can be produced on purpose or can be the unintended result of a magnitude of different processes.
- **Substance:** a single pure element or a single pure chemical compound without impurities and without additives.
- **Mixture assessment:** Risk assessment of mixtures. It consists of hazard assessment, exposure assessment and risk characterisation.
- **Aggregated exposure:** Exposure to one substance from different sources, pathways and/or routes.
- **Cumulative exposure:** Exposure to two or more different substances. Exposure can result from different emission sources, emission pathways and exposure routes.
- **Combined exposures:** Exposure to two or more different substances or to one substance from different sources, pathways and routes. This term is used if no differentiation between aggregated and cumulative exposure is made.

### Where to look? Types of mixtures addressed in the project

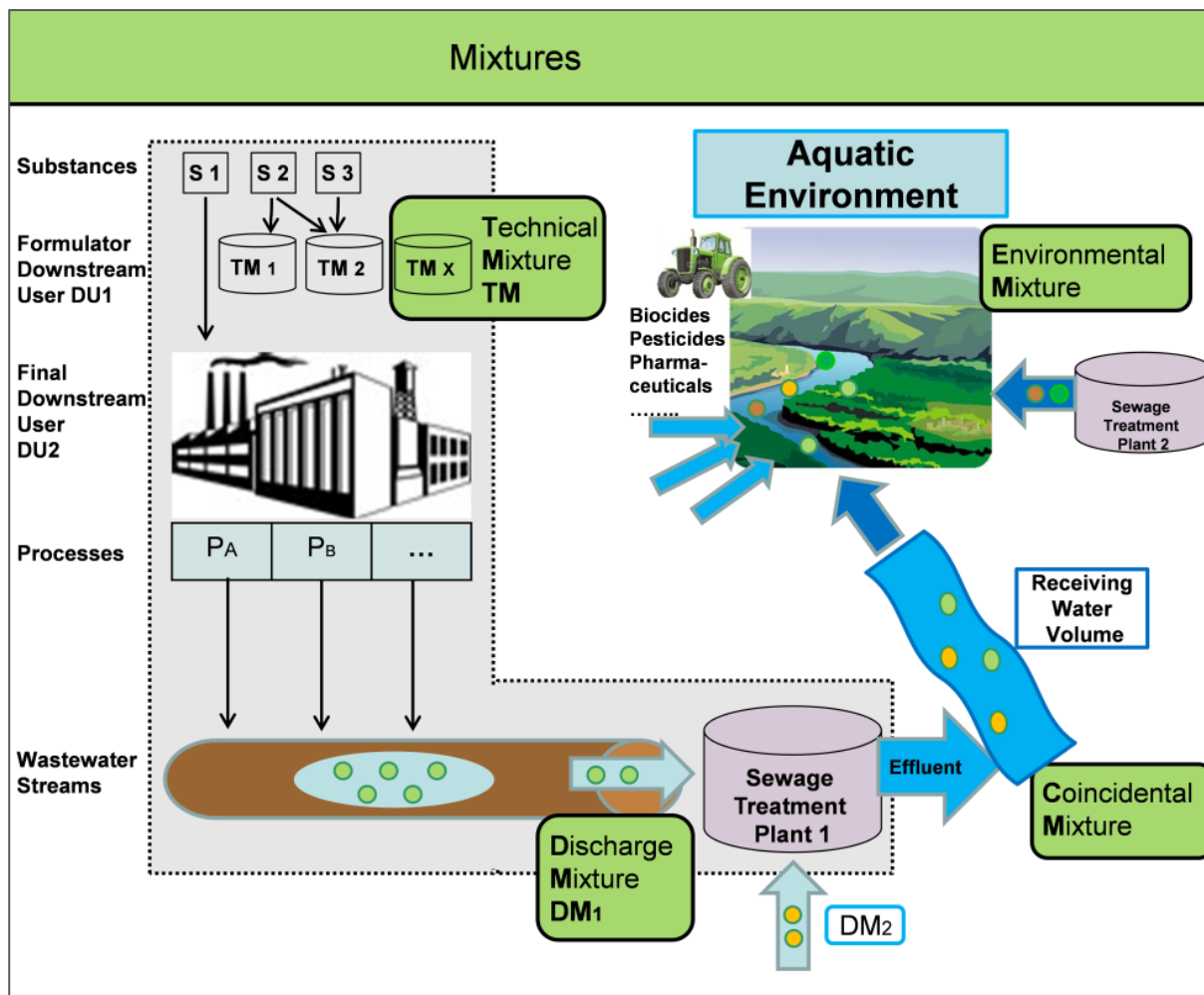
This report discusses the assessment of technical mixtures under REACH. They consist of at least two substances. They are produced on purpose by formulators (under REACH, such technical mixtures are called “mixtures”). They are used by downstream users (Figure 1). **Discharge mixtures** are substance combinations present directly at the “end of the pipe” of a single discharging production unit. For the aquatic compartment, the discharge mixture is the influent to the sewage treatment plant. After treatment in the sewage treatment plant and after dilution in the receiving water volumes, the resulting mixture in the receiving water volume is called a “**Coincidental mixtures**”. It can result from one or more discharge mixtures. Finally, substances can be further distributed between the environmental compartments. They contribute to **environmental mixtures**, which often show a large complexity.

In this report, assessment methods and options to act refer to **technical mixtures** and the discharge mixtures which result from the use of these technical mixtures. This is due to the fact that principally the REACH actors can be identified, which handle these mixtures: manufacturer or importer of a substance, formulator of a technical mixture or end user of a technical mixture. The link between effects of coincidental mixtures or complex environmental mixtures and a specific substance is much more indirect. Responsibilities may not be easily attributed to a specific REACH actor.

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<sup>2</sup> The Competent Authorities in Germany propose the term „substance combination“ as a generic term for all different types of combinations of two or more substances.

Figure 1: Schematic presentation of the types of mixtures addressed in this report (source: own illustration)



### Why? Relevance and requirements for mixture assessment under REACH

There are several indications that certain environmental mixtures, coincidental mixtures and technical mixtures can cause adverse effects in the environment, which would not be predicted only based on the risk assessment of the single substances (see chapter 1.3). Regarding **technical mixtures**, for biocides and pesticides, comparative testing of components of the products and of the whole products show that toxicity of the whole product is larger than the toxicity of the individual substances. Studies on „mixture toxicity“ with different groups of chemicals, including industrial chemicals, show that in most cases the toxicity of the substance combination can be predicted using the concept of concentration addition (CA), a component based approach. This means: in many cases it has to be assumed that toxicity of a mixture is underestimated by isolated assessments of the toxicity of its components (see chapter 2.2).

Significant concentrations of a large number of substances are measured in monitoring programmes. The phenomenon of concentration addition has been shown to be a plausible assumption for such multiple substances' exposure effects. Therefore the existence of mixture effects in the environment can be assumed (chapter 1.3).

Already now, REACH and the CLP Regulation assume concentration additivity within a mixture in classification and labeling requirements (e.g., the *aggregated* percentage in content of irritating substances within a mixture has to be added up). However, due to different physico-chemical properties, percentages and absolute amounts of individual substances will change

significantly, when this mixture is discharged into the environment. Therefore the *exposure term* in environmental mixture risk assessment may not be based on the original percentages of the single components as addressed in the CLP – process, but has to account for, e.g., volatility, sewage treatment plant effectiveness, water solubility, retainment processes etc., which may differ from substance to substance. All these changes in mixture composition, toxicity and resulting risk are currently not addressed under REACH. With other words, current understanding of mixture risk assessment in classification is only restricted to the quantitative information on the composition of the formulated technical mixture as such and does not cover changes in toxicity and resulting risk due to discharge and resulting exposure characteristics.

An analysis of 21 European legal acts shows that current legislation does not properly take into account potential mixture toxicity aspects and potential risks from mixtures (Kortenkamp et al. 2009). Four pieces of legislation have been identified as particularly noteworthy regarding the assessment of mixtures: the REACH-Regulation, the CLP-Regulation, the Pesticide Residues Regulation and the Industrial Emissions Directive. In addition, the Water Framework Directive could address single industrial chemicals, if they are relevant for the quality of European water systems and if they are included in the directive as priority pollutants.

Within these legislations, REACH plays a central role addressing the safe use of ten thousands of single substances. Chemical safety assessments and exposure scenarios cover the whole life cycle of the substances. REACH defines obligations for the producers of the substances, for the formulators and the end users. It demands a structured communication in the supply chains on the safe use. In addition, REACH is based on the precautionary principle. Potential effects have to be evaluated by methods of risk assessment. These elements can be used to strengthen the assessment of mixture effects for technical mixtures within REACH.

Under REACH, safe use of a substance has to be demonstrated for the whole life cycle of a substance (REACH Art. Annex I, 0.3). This includes uses of a substance in technical mixtures. In these mixtures effects due to concentration addition can take place. They are not reflected in a risk assessment of a single substance.

So far, exposure estimation and risk characterization start with the assumption that exposure is related to the substance itself – without considering the parallel exposure to other substances. For single substances, a risk characterisation ratio (RCR) <1 is accepted as an indication for the safe use of a substance under a given set of conditions.

At present, in REACH no indicator exists to show on a theoretical base the safe use of a given technical mixture - comparable to the RCR for a single substance. Such an indicator should take into account of the cumulative (potentially simultaneous) exposure to multiple substances as components of a technical mixture or discharge mixture. The indicator should reflect scientific approaches that have been discussed in mixture toxicology, e.g. the concentration addition model. Such an indicator has been developed in the project 4M (see section 2.5.2).

### **REACH actors and mixture assessment: legal obligation, voluntary action or product responsibility?**

REACH is a substance-focused legislation. The registration process was primarily designed to address the lack of knowledge on the hazardous properties and on the types of uses of substances. Mixtures and their specific aspects have not been included with high priority and much detail in the legal text.

However, **registrants** have to demonstrate the safe use of substances as such, in mixtures or as part of articles. This includes the use in mixtures. In the single substance assessment they have to consider all available knowledge. This could be interpreted in such a way that knowledge on

mixture effects – if available – has to be considered and potentially communicated. However, no guidance is available on how to do this, yet. REACH Annex 1 obliges the registrant to assess (for the amount of substance which he produces) aggregated exposures from different routes (In the headings of the CSR, this aggregated exposure is called “combined exposure”).

**Downstream users** are responsible to ensure their uses are covered by the exposure scenarios they receive. Otherwise, they have to make their own CSA and demonstrate safe use or communicate upstream to have the use reassessed or to cease the use. **Formulators** have to assess, whether the use of a substances in their mixtures is covered by the exposure scenarios which they receive. In their safety data sheets, they have to describe the conditions of safe use for their product – which are mixtures. End-users and formulators have to be compliant with the exposure scenarios which they receive from their suppliers. If they use at the same time the same substance in different technical mixtures, aggregated exposures can occur.

**Authorities** have several possibilities but no obligations to take into account possible effects of aggregated and cumulative exposure to the multitude of substances in their tasks.

However, REACH sets no formal obligation to make a cumulative risk assessment of mixtures with exposure estimation and quantitative risk characterisation. There is no indicator for „safe use“ of a technical mixture equivalent to the indicator „RCR < 1“ for single substances.

### **How to assess? Concepts for the environmental risk assessment of technical mixtures**

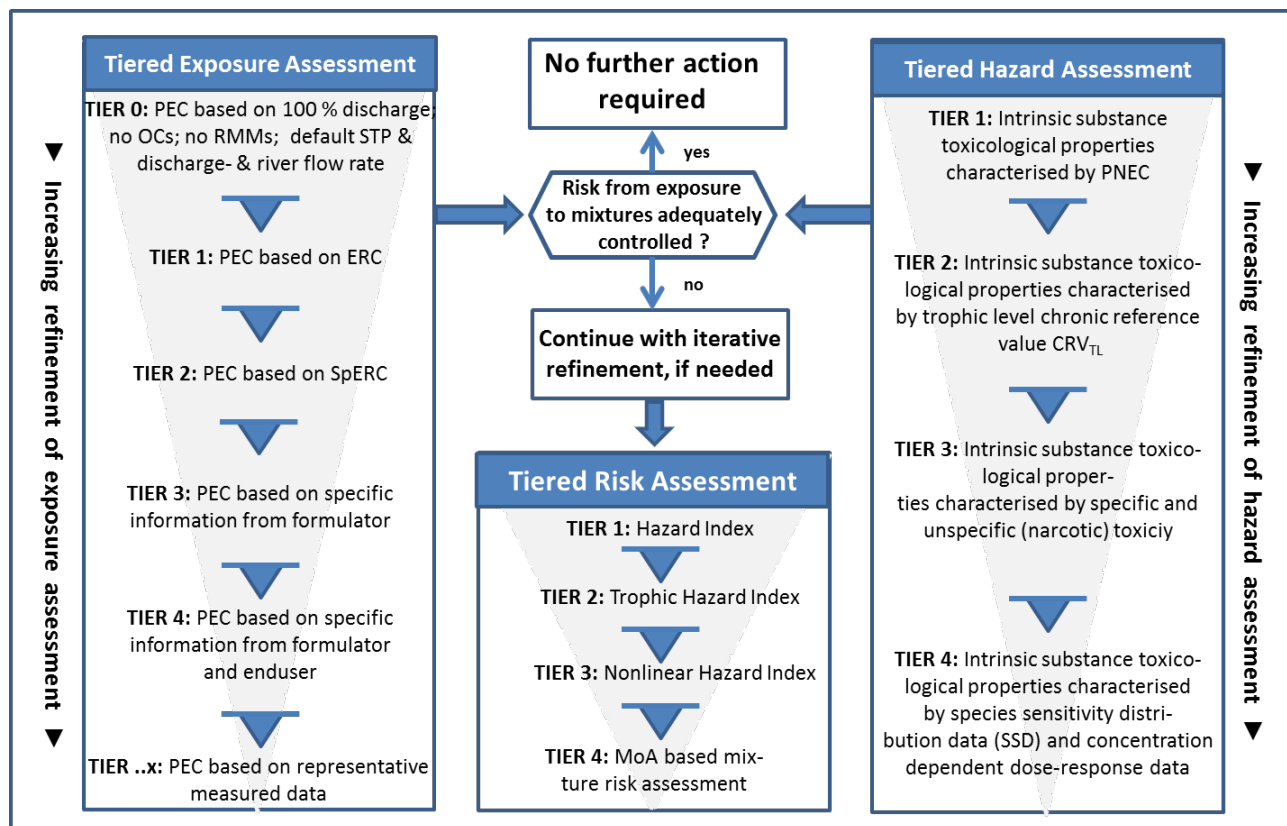
How to demonstrate the safe use of a technical mixture of known composition? Three principle methods – and combinations of them - can be used to for a quantitative risk assessment of technical mixtures under REACH.

- A tiered approach;
- Mixture Assessment Factors (MAF) for single substances and
- Whole Mixture Testing.

In this project, tiered approaches, discussed for other regulations, have been further developed- considering the regulatory framework of REACH and considering the data, which will be available for the different actors. The following figure shows the structure of the proposed **tiered approach** for the risk assessment of technical mixtures. It consists of three components: a tiered exposure assessment (left column), a tiered hazard assessment (right column) and a tiered risk assessment (central part). As usual, the resulting risk is calculated as quotient of the figures from the exposure assessment and the hazard assessment.



Figure 2: Schematic presentation of a tiered approach for assessment of technical mixtures under REACH3 (source: adapted from Meek et al. (2011)4, modified and specified for REACH)



The tiered approach: Which type of data is used for the different tiers? What indicators result from the assessments? What are the differences between the tiers?

At **tier 1**, concentration addition is applied in its simplest form. As for the chemical safety assessment of single substances, for each substance in the mixture risk characterisation ratios are calculated. For this purpose, **PECs** and **PNECs** are used. The ratios of the substances are summed up. The result of this addition is most commonly called “**Hazard Index**” **HI** for the technical mixture:<sup>5</sup>

$$HI = \sum_{i=1}^n \frac{PEC_i}{PNEC_i}$$

If this index is below 1, no risk for environmental effects from the exposure to the mixture is expected. This approach is relatively simple. However it may overestimate the risk to a certain extent: predicted environmental concentrations often overestimate the real exposure situation. In addition, the PNEC as a single value must be protective for all three trophic levels – for algae, daphnia and fish. Species specific toxicity data (e.g. chronic toxicity values for fish) are not evaluated specifically at this tier.

<sup>3</sup> Note that numbering of tiers is flexible and not necessarily identical to tiers as used in similar schemes.

<sup>4</sup> This figure only demonstrates the principle factors and hierarchies schematically. For a final guidance, numbering and assigned definitions may have to be adopted.

<sup>5</sup> The term “hazard index” is somewhat confusing: it really describes risks instead of hazards.

At **tier 2**, the assessment is refined. On the hazard side, a new element is introduced. PNECs are replaced by so-called “chronic reference values specific for trophic level” (**CRV<sub>TL</sub>**). They are based on species-specific ecotoxicity data. For each trophic level, such a reference value is calculated for the substances in the mixture. Risk characterisation ratios for the substances are calculated using these reference values and the respective exposure levels. The substance “RCRs” for each trophic level (**RCR<sub>TL</sub>**) are added up to calculate a hazard index for the mixture (**HI<sub>TL</sub>**) for each trophic level. Finally, the highest of these hazard indexes is chosen to characterise the risk posed by the mixture. This index is called “**trophic level hazard index**” (**THI**). It is directly comparable to Hazard Index HI at tier 1 – but does not add up effect data from different species to estimate mixture effects. It will usually be lower than the risk quotient calculated at tier 1, based on PNECs. This step allows to take out the best of given data under REACH. It avoids overestimation of mixture ecotoxicity at least to some degree due to the separate assessment of each trophic level

At **tier 3** and **tier 4**, even more sophisticated elements are introduced on the hazard side (differentiation between specific and unspecific (narcotic) toxicity and knowledge on the mode of action). For tier 1 – 3 of the hazard assessment, concentration addition is assumed as the basic principle for emerging mixture effects. In the fourth tier, independent action (IA) and even more detailed information may be used for mixture risk quantifications. However, already tier 2 of the hazard assessment requires expert knowledge. This is even more the case for hazard assessments at tier 3 and tier 4. It is not feasible to realize a hazard assessment at tier 3 and 4 with the set of data usually generated (and published) under REACH (chapter 2.5.2.).

**Mixture assessment factors (MAFs)** are sometimes proposed if a tiered approach is not feasible. A MAF is used as an additional assessment factor to calculate a PNEC for all those single substances known to be present within a mixture. However, as the appropriate size of a MAF depends on the number of components within the mixture (assuming concentration additivity), there is a high uncertainty about the appropriate size of a MAF (chapter 2.5.3).

**Whole mixture approaches / whole effluent approaches** are proposed to assess effects of mixtures with (partly) unknown substances. In addition, they are used for mixtures of known composition – to assess whether and which kind of mixture effects occur. This assessment includes testing of the complete technical mixture/ discharge mixture/ coincidental mixture or environmental mixture. Because of infinity of resulting potential mixtures, this approach would not be feasible as a routine regulatory procedure to assess mixture toxicity. It may, however, be very helpful a) to validate CA (concentration addition) or IA (independent action) assumptions or interactive behaviour (synergism/ antagonism) for specific mixtures with known substances and b) to compare such assessments with known substances with the additional influence by unknown further substances within a mixture, and c) to assess constant immission scenarios, where (known and unknown) substances are present in stable compositions in environmental media. Therefore in this case representative results may be derived from whole effluent testing (chapter 2.5.4).

Examples for the exposure tiers and for the use of the tiered approach are given in chapter 9.5.

### **Priority setting: How to find technical mixtures which should be assessed for mixture effects?**

Due to the large number of existing technical mixtures, priority setting is an important step. **Criteria** are required to decide in which cases risk assessments of technical mixtures should be performed and where to start if risk assessment of technical mixtures is integrated as a general principle into REACH. At present, experience and guidance is missing how to set priorities in

mixture assessment. In chapter 2.6, two different concepts for such a priority setting are described:

- Nomination of “**Mixture Assessment Triggering Substances**” (MATS). These substances initiate (trigger) risk assessments of technical mixtures which contain such substances. They indicate that a technical mixture requires an assessment which goes beyond the isolated assessment of the substances contained in it.
- Identification of “**priority mixtures**”. These mixtures have specific properties (from composition or critical use/exposures) which increase the likelihood of mixture effects. Therefore priority mixtures need an additional assessment of mixture effects

The two concepts have different starting points. The concept of MATS aims to identify substances which occur already in relevant concentrations in the environment. The starting point for “Priority mixtures” is the composition of the mixtures and their uses.

### **MATS: Mixture assessment triggering substances**

One trigger for an additional assessment of technical mixtures could be that the mixture contains substances of specific concern. This means: substances which indicate that the mixture requires an assessment which goes beyond the isolated assessment of the substances themselves. Such a substance is called a “Mixture Assessment Triggering Substances” (MATS).

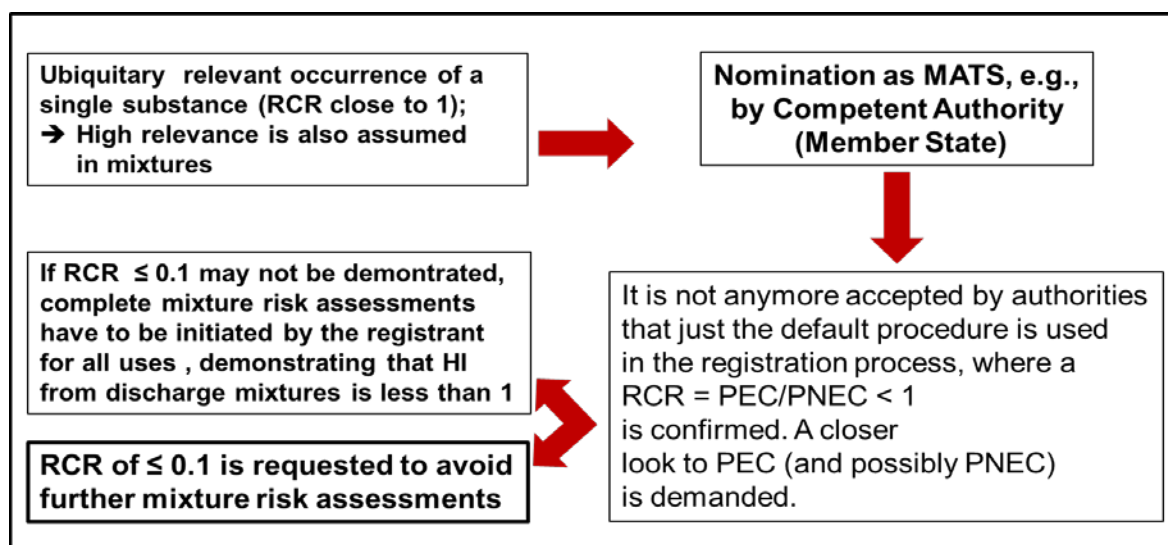
A MATS is a substance which causes concern, because it already occurs in relevant concentrations in the environment in relation to its inherent ecotoxicity. The proposal foresees that in most cases such substances will be nominated and selected by a regulatory decision from authorities. MATS will usually be identified based on measured data at regional level not locally.

A “relevant occurrence” may be defined as an ubiquitary occurrence with an RCR close to 1 in many locations. Examples for such substances are the priority substances of the Water Framework Directive. A more precise quantification of what is meant by “close to 1” is open for discussion with regulatory experts and is not fixed in the project’s proposal. However, for illustration and in order to work with quantitative figures, a  $RCR \geq 0.8$  is suggested as key criterion for “relevant occurrence”. The PEC in this RCR is derived from representative monitoring or other high quality exposure data provided by registrants or downstream users in their chemical safety assessments.

“Relevant occurrence” may not merely be defined by the RCR of  $\geq 0.8$  as only criterion. Other properties may also be considered, e.g. the type of adverse effects or critical substance properties, like bioaccumulation or persistence, specific toxicity characteristics, such as endocrine disruption, or amount and type of uses.

If a technical mixture, discharged by any actor within the supply chain under REACH, contains a MATS above a specified concentration limit, a mixture risk assessment has to be performed. This aims to demonstrate that no relevant additional occurrence of the MATS causes a concern of mixture effects in the environment. “Relevant *additional* occurrence” means: a significant increase to background occurrence. For illustration and in order to work with quantitative figures, a starting point of  $RCR \geq 0.1$  (calculated local above regional background) is suggested as key criterion for “relevant additional occurrence”.

Figure 3 shows the function of MATS for the assessment of technical mixtures under REACH.



If any of the RCRs derived by a registrant in his CSR for any of the intended uses of a MATS exceeds the cut-off of 0.1, this triggers a mixture risk assessment of technical mixtures containing this MATS. The principles of a tiered approach are presented in section 2.5.2.

Priority mixtures: Which technical mixtures should be assessed for mixture effects first?

There is a huge amount of technical mixtures placed on the market by formulators. What are the technical mixtures which should be assessed first? The identification of „priority mixtures“ has been proposed by different actors as a possible first step to implement mixture assessment. However, criteria which determine priority are usually not provided. In this report a mixture is called a “priority mixture” in five cases:

- There is a high probability that a “hazard index” of 1 will be exceeded (assuming concentration additivity).
- There is a high probability that – due to exposure to this mixture – certain adverse effects, which themselves are prioritised, may occur.
- The type of use of a mixture implies a high probability of a combined exposure of the environment to the substances in the mixture (e.g. use of chainsaw oils in forestry, leading to a contamination of soil from the technical mixture.)
- There is a higher probability that concentration additivity as a mixture effect occurs (in comparison, where concentration additivity is just a conservative default, without explicit support from the specific similarity properties of the ingredients), or
- there is a higher probability that synergistic effects as a mixture effect occur (in comparison to the usual additivity default assumption).

Up to now, a systematic identification of priority mixtures did not take place. The five cases above more describe principles than give actual examples. The following criteria can help to decide whether the mixture should be assessed for mixture effects (chapter 2.6.3.2):

- Relevant occurrence of one or more substances of the mixture in the environment
- Specific critical properties of one or more substances of the mixture
- Critical use characteristics of the mixture
- Critical combinations of substances in the mixture

- Closely related substances in the mixture, which occur frequently together

Table 1 indicates which actor could use the criteria for priority mixtures described above.

Table 1: Conformity of the option to require the use of MAF in the registrants' CSRs with core REACH principles

Criterion for priority setting	Actor	Reasoning
Relevant occurrence / MATS	Registrants + formulators	Registrants have to show for MATS RCR < 0.1 or to perform a tiered risk assessment, probably in cooperation with formulators
Specific critical properties	Formulators	Formulators can check which technical mixtures contain substances with these properties (if it has been defined what are these critical properties).
Critical uses	Formulators	Formulators know which of their technical products have critical uses (if criteria for such uses have been defined).
Critical combinations	Formulators	Formulators can check which of their technical mixtures contain critical combinations of substances (if it has been defined what are critical combinations).
Closely related substances	Registrants	Registrants know for which substances grouping and read-across have been used in the registration of these substances.

**How to find Mixture Assessment Triggering Substances and priority mixtures?** Existing monitoring programs are one of the most interesting approaches to find MATS and other single substances for priority mixtures (section 2.6.6.1). Moreover, two procedures address the search for priority mixtures quite differently with other strengths and weaknesses:

- a “reporting tool”, providing tier 1 RCR calculations from downstream users and end-users for further analysis by administrative bodies (section 2.6.6.2),
- a SPIN linked approach related to product register evaluations (section 2.6.6.3).

In addition, formulators and end-users of technical mixtures can use two approaches for priority setting: the tiered assessment of MATs/priority mixtures (for formulators, see section 2.6.4), and the assessment of aggregated exposures (by end-users, see section 2.6.5).

### Options to assess technical mixtures for industry and for authorities under REACH

Various forms of mixture risk assessments could be implemented in different REACH processes. A formulator could use a tiered approach as an indicator for safe use of a specific technical mixture. An end-user of technical mixtures could assess the aggregated exposure if he uses the same substance in different mixtures. A national authority could consider combined exposures of structurally related substances if it prepares a restriction dossier. Registrants and formulators could communicate mixture effects in the supply chains.

Which options to act exist for registrants, downstream users and authorities if they want to take possible mixture effects into account? In chapter 3, the different methods to assess risks from technical mixtures described before are specified with regard to the actor who should perform them and with regard to the processes in which they could be implemented. For industry, ten options to act are described; for authorities, six options.

**How feasible are these options?** A first and preliminary, qualitative assessment of the options' feasibility was conducted. It aimed to sort out the unrealistic options and to pinpoint further

assessments to those options, which are not limited by missing data access of industry actors. The most feasible options for industry to consider assessment of technical mixtures under REACH are:<sup>6</sup>

- **Downstream users aggregate substances amounts, when they check compliance with exposure scenarios.** If they use a specific substance from more than one mixture in parallel, an exposure scenario has to be compared with the total amount of the substance which is applied for a specific use.
- **Registrants and formulators communicate information on mixture hazards in the supply chain.** Registrants could provide information on mixture effects or synergisms to ECHA as part of the registration dossier and/or include it in the safety data sheets. Formulators would consider this information in their safety data sheets.
- **Registrants use the tiered approach to assess mixture risks from ‘similar substances’ along the supply chain.** These substances have either been registered as / in a group (category approach) of read across has been applied for them. There should be indications that these substances co-occur in the supply chains.
- **Formulators use the tiered approach to assess mixture risks along the supply chain.** They make a mixture risk assessment for their technical mixture at their site (formulation) and for the uses of the technical mixture down the supply chain.
- **Registrants use a Mixture Assessment Factor in the CSR to assess mixture risks along the supply chain.** The assessment is substance based and covers all discharges of the substance in mixtures along the lifecycle, including from manufacture.

A further option could be used under the Industrial Emissions Directive (IED): Substance manufacturers, formulators and end-users can conduct a mixture risk assessment for their effluents, either using a tiered approach or whole effluent testing. This action could support the priority setting and further method development of options to be implemented under REACH. (see chapter 3.7.5 for a discussion of further options for industry, not regarded as feasible). Almost all of the industry options require changes of the legal obligations under REACH; some may be implementable at the level of guidance documents. The implementation of most options is limited due to the lack of necessary data to the respective industry actors. It is not likely that confidentiality of business information can be circumvented. All options would lead to improved knowledge on potential mixture risks; however the degree of possible risk reductions cannot be determined, yet. Also the potential costs to conduct assessments and implement consequences cannot be estimated yet.

**Authorities** have different options to implement aspects of mixture risk assessment into their REACH task. Which are the most feasible options for authorities?

- **Priority setting for the Community Rolling Action Plan (CoRAP).** Mixture risks could be a trigger for the inclusion of substances in the CoRAP. The concern “mixture risk” could be included in addition to other reasoning for substances in the CoRAP.

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<sup>6</sup> The following results reflect the evaluation of the authors of this report. Chapter 3 of this report contains for some options remarks on diverging evaluations.

<sup>7</sup> C.f. details on how the term “similar substances” are understood in the respective chapter.

- **Checking mixture risks in CSRs during substance evaluation.** In the scope of substance evaluation, Member States could check how combined exposures are considered in registration dossiers of “similar substances” (these substances are registered in groups, or read-across has been applied by the registrant).
- **Assessing mixture risks and requesting information during substance evaluation.** During substance evaluation, Member States could carry out mixture assessments or make related considerations of environmental exposures. If relevant, they could request additional information regarding these aspects from registrants.
- **Prioritisation for authorization.** ECHA could propose substances on the candidate list for inclusion in the authorisation procedure based on concerns related to combined exposures. This would require a respective justification in the prioritisation proposals.
- **Mixture risks in restriction dossiers.** Authorities could propose restrictions for groups of substances with the justification that mixture risks could occur. Reasons could be the close relation of the substances, similar hazard profiles and the likelihood of combined exposures.

All authority options except one (Consideration of mixture risks in granting authorisations, not mentioned above), could be implemented without changes to the legal text and based on the Member States’ or ECHA’s initiative. In the implementation of most options the availability of data on uses and combined exposures may limit the possibilities to prioritise substances or make assessments of mixture risks. Authorities have limited possibilities to obtain information on technical mixtures and their uses other than from the registration dossiers. They could in principle initiate specific monitoring campaigns or request respective information from industry (formally or informally).

All options would achieve benefits regarding the level of knowledge on mixture risks and some are likely to result in concrete improvements of risk management measures. Furthermore, authorities could contribute to method development and promote awareness on the issue. Due to the voluntary nature of all options as well as the low number of substances involved, the efforts necessary to implement the options are comparatively low in absolute terms but may be rather high in relative terms, as method development and information search would be concentrated on few cases.

**Proposals for Changes in ECHA Guidance Documents.** All of the options for industry and authorities could be implemented on a voluntary basis. For example the communication of mixture hazards in safety data sheets as well as the aggregation of substances amounts before compliance checking could be implemented with low efforts starting from now on. The provision of respective alerts and guidance on “when and how” to consider mixture aspects under REACH in the available ECHA guidance documents would be a first step to raise awareness and support REACH actors willing to act on a voluntary basis - industry as well as the authorities. In a large number of guidance documents topics can be included addressing the environmental risk assessment of mixtures under REACH (see chapter 3.12).

**Next steps for different actors.** Criteria for prioritisation of mixtures have not been sufficiently developed and agreed yet. There is lack of experience with the concepts for priority setting and lack of experience with the application of approaches for the assessment of technical. Already now different actors can test the approaches developed (chapter 4). This will help to gain more experiences and to clarify the open questions on the assessment of technical mixtures under REACH.

## Conclusions

Results of the analysis done in the project 4 M start out with the finding that there is evidence for environmental effects caused by mixtures. The arguments to include risk assessment of technical mixtures under REACH could be supported if more examples were described for the causal link between the use of a technical mixture and adverse effects in the related coincidental mixture or in a complex environmental mixture.

REACH requires that manufacturers and importers of substances show the safe use of their substances along their entire life cycle. This includes use in mixtures. Formulators have to identify and communicate conditions of safe use for substances and mixtures which they place on the market. A risk characterisation ratio below 1 is agreed to under REACH as an indication for the safe use of a substance. However, REACH does not define an indication for the safe use of a mixture as a whole.

The analysis of the state of the art in mixture risk assessment methodology shows that concentration addition is a conservative default to consider mixture effects. Several tiered approaches have already been proposed for the assessment of mixtures, which, so far, are not linked to technical mixtures of substances registered under REACH. The tiered approach developed in the project 4M allows the environmental assessment of technical mixtures in the aquatic compartment with increasing degrees of precision. It uses different variations of hazard indexes as indicators for safe use. In its simplest form (tier 1), the proposed approach requires to sum up the risk characterisation ratios using PEC-values and PNEC-values as used for single substances under REACH.

Taking examples of real mixtures, it has been shown that the tiered approach can be used for the assessment of technical mixtures under REACH. However, it became evident that assessment of technical mixtures requires more precise exposure data on exposure than the assessment of single substances. In the first step of the tiered approach for mixture assessment, risk characterisation ratios for the components are added up to calculate the hazard index for a technical mixture. If these risk characterisations are already close to 1, the hazard index for the whole mixture will be above one. Even if the real exposure to the components is lower than assumed.

Regarding hazard assessment within the tiered approach, publicly available PNEC values can be used only for calculation at the first tier. For more precise calculation, ecotoxicity data for specific trophic levels are required. Obviously, expert knowledge is necessary to carry out assessments on hazards tiers of 2 and higher. More testing of the proposed tiered approach is needed to gain experience with its application on real technical mixtures. Based on this, recommendations can be given how to proceed for hazard indices above 1.

Current limitations for risk assessment of technical mixtures under REACH are identified and acknowledged. Those are, inter alia, the generic and very crude substance exposure levels (PECs) generated by REACH and the disparity in the availability of suitable data across the supply chain. This limits the possibilities of different actors to assess mixture risks. In addition, there is at present no link between the responsibilities of the single REACH actor (producing or using technical mixtures) and the components of the actual local coincidental mixture in the receiving water volume which, however, determine the real environmental risk.

Due to the large number of technical mixtures, setting of priorities is a key requirement. Two approaches have been proposed which should be tested and further developed in parallel: Mixture Assessment Triggering Substances (MATS) and priority mixtures.



REACH offers several options for the risk assessment of technical mixtures for **industry**. In the short term, the obligation to assess aggregated exposures during compliance checking of the ES by downstream users and the obligatory communication on known mixture hazards of substances could be implemented. These options require fairly low efforts and have benefits regarding an improved risk management (aggregated exposures) and knowledge dissemination and awareness raising. All other industry options identified as possibly feasible should not be discussed for short term implementation. They should be subject to further assessment, testing and discussion with all stakeholders. **Authorities** should use the possibilities to assess mixture risks in the different tasks they perform under REACH. More coordination with other legislations is required to develop a common strategy not only on REACH, but including also other regulations.

### **Recommendations for further activities (case studies and research)**

The analysis of possible starting points, existing requirements and options to act under REACH as well as the discussions at the expert workshop clearly show that there are a number of items to clarify in order to integrate (elements of) mixture assessment into REACH. For clarification the following five activities are recommended– based on the findings and conclusions described before (for details see chapter 6):

- Assessment of aggregated exposures by end-users
- Communication and use of existing knowledge on mixture effects in the supply chains
- Development of prioritisation criteria for mixtures
- Application and further development of the tiered approach by formulators
- Mixture assessment as an element of the tasks of authorities

The proposals 3 and 4 lead to case studies of tiered risk assessment of technical mixtures. These case studies can be used to assess the added values of these mixture assessments. The proposed risk management measures for a technical mixture can be compared to the measures proposed for the substances of the mixture without considering mixture effects. In addition, the proposal of MATS can be tested by authorities. As long as no official MATS are nominated, priority substances from the Water Framework Directive can be used. In cooperation with formulators the risk characterisation ratio can be assessed. If it exceeds 0.1 the consequences of this finding can be determined.

These activities would

- help in gaining a better understanding of what can be done under REACH to address mixture effects;
- help to support the required horizontal approach on mixture effects in the EU;
- start to reduce the impact of technical mixtures on the environment.
- raise awareness that mixture risk assessment is part of the general producer responsibility.

They give valuable input for the development of accepted concepts for the environmental risk assessment of technical mixtures under REACH and further development of the related guidance, supported by practical experience.

Regarding the assessment of aggregated exposures by downstream users, it would be helpful to clarify the legal requirement within REACH at European level. In addition, it should be clarified that the requirement to consider all available knowledge within a registration includes scientific evidence for mixture effects.

The proposed activities refer to REACH and technical mixtures.<sup>8</sup> At the same time clarification of what can be done under REACH supports the horizontal discussions on mixtures. It helps to identify interfaces to other regulations such as the WFD and the Industrial Emissions Directive. Such activities are necessary to identify and to agree on areas where technical mixtures of industrial chemicals regulated under REACH lead to relevant risks which go beyond the impact of single substances and which require additional action.

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<sup>8</sup> An important element in each of these activities should be workshops with external experts. They allow an in-depth discussion with all stakeholders on which actors should make the mixture risk assessment (registrant / formulator / end-user) and at which local dimension (discharge mixture, coincidental mixture, environmental mixture – local or regional assessment).

# 1 Background: Relevance and Requirements for an Assessment of Mixtures under REACH

## 1.1 Introduction: Mixtures under REACH

Real exposures of humans and the environment are always exposures not to a single substance from a single source, but to mixtures of substances from one or several sources. They can reach humans and the environment by different pathways.

The following sections address the relevance and the requirements for an assessment of mixtures under REACH. They aim to structure the broad variety of aspects relevant for mixtures and their environmental impact. However, mixtures and problems resulting from mixtures do not only refer to industrial chemicals as regulated by REACH. Complex environmental mixtures consist of many different classes of substances, e.g. pesticides, biocides, pharmaceuticals and others. In addition, the quality of the environmental compartments is apart from REACH also influenced by the implementation of sectoral environmental laws. A sound recommendation on how to regulate (substances in) mixtures should

- have an integrated view on the responsibilities and possibilities for mixture assessment of the different market and regulatory actors
- assess the possibilities, substance coverage and potential impacts of different regulations, also other than REACH, with regard to regulating mixture toxicity assessment and/or exposures to multiple chemicals (not only industrial chemicals– in addition biocides, pesticides, pharmaceuticals and other substances)
- include the option that the current REACH regulation is modified and adapted to better address mixture effects.

The European Commission has been asked in 2009 to assess whether and how relevant existing Community legislation adequately addresses risks from exposures to multiple chemicals from different sources and pathways. The Commission has been invited to consider appropriate modifications, guidelines and assessment methods. The report of the EU Commission has been launched in a form of a Commission Communication, published June 2012. It is based on the review of Kortenkamp and colleagues on mixture toxicity (Kortenkamp 2009) and the respective opinion of the EU Commission's scientific committees (Toxicity and Assessment of Chemical Mixtures, 2011). A summary of the most important findings from these activities in respect the assessment of technical mixtures under REACH is given in chapter 2.2.

Compared to the task of the EU Commission, the focus of this report is much more limited: the topic are approaches and options to act for different actors under **REACH**. However, it takes into account findings regarding other legislation (as documented e.g. in Kortenkamp et al. 2009). This allows first recommendations which options to act under REACH could be effective and in which situations options related to other legislation could make more sense.

This chapter is divided into 8 sections:

- Mixtures: Types, terms and definitions (1.2)
- Relevance of assessment of mixtures (1.3)
- Priority setting (1.4)
- From substance properties to sectors of use? Possibilities to group substances (1.5)
- Assessment of mixtures: data requirements and data availability (1.6)

- Responsibility of actors under REACH (1.7)
- Industrial chemicals in environmental mixtures (1.8)
- Mixtures and European legislation (1.9)

## 1.2 Mixtures: Types, Terms, Definitions

Within European legislation, there are no harmonized definitions for different types of “mixtures”. REACH defines a mixture as a combination of two or more substances (it has been called a “preparation” before the CLP regulation<sup>9</sup> entered into force). Such a mixture is the result of an **intended combination** of substances by a formulator.).

It is a kind of common understanding, that a mixture is more than one substance. However, even this first approach can cause difficulties. This is due to a different use of the term “substance”,

- In a narrow scientific understanding, a substance is a pure element or a pure chemical compound of a defined structure. Under REACH, from a legal perspective a broader definition of substance is used. “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”.
- Due to this definition, “substances” as defined under REACH include isomeric mixtures, substances of unknown or variable composition and biological materials (UVCB) and multi-constituent substances (MCS)). These “substances” are themselves mixtures from a scientific point of view.
- A “substance” as defined under REACH can contain several contaminants.
- In addition, chemical reaction products are considered as “substances” under REACH – although they can consist of multiple distinct substances
- A specific substance can be emitted from several sources. Exposure can take place via different pathways. In this case, the “mixture” consists of one substance from different origins.

Basic terms for the assessment of mixtures have been defined, e.g., in the publications of Kortenkamp et al. 2009, and Backhaus et al. 2010. Recently, an overview on frequently used terms and a proposal for a consistent terminology have been prepared by Gross et al. 2010.

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<sup>9</sup> 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

Based on this overview, we use the following terms in our study:

- **Mixture**<sup>10</sup>: generic term for all different types of combinations of two or more substances. Mixtures can be produced on purpose or can be the unintended result of a magnitude of different processes.
- **Substance**: a single pure element or a single pure chemical compound without impurities and without additives.
- **Substances** which are part of a mixture are simply called “substances”. In most cases, it is specified in which type of mixtures they occur, e.g. “substance in a technical mixture”.
- In the following, the term “**mixture assessment**” is used for the risk assessment of mixtures. It consists of hazard assessment, exposure assessment and risk characterisation.
- “**Mixture toxicity**”, refers to the hazard assessment of mixtures only. It is a synonyme to “**mixture effects**”.

We distinguish between the following four types of mixtures:

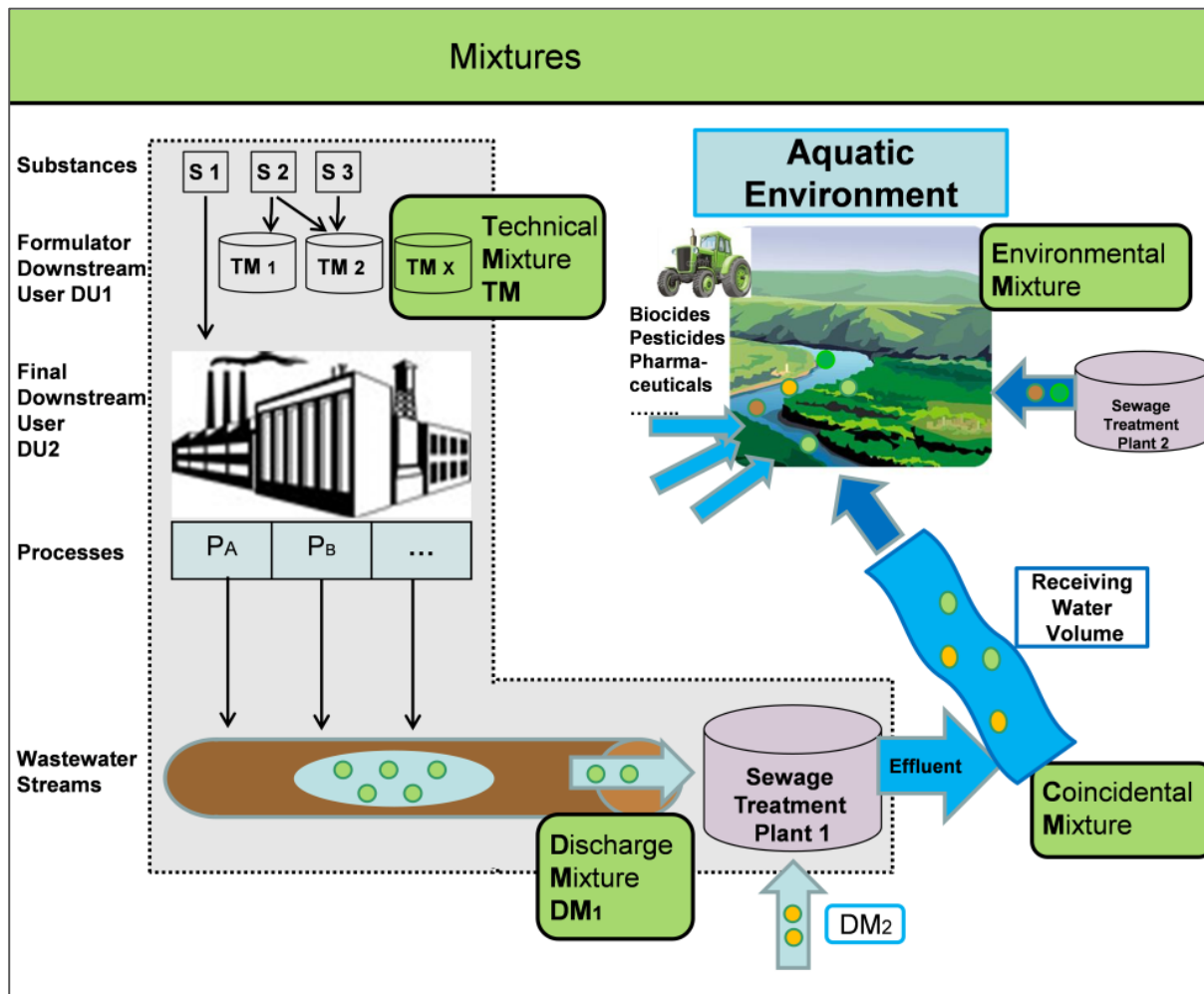
- **Technical mixtures**: they consist of at least two substances. They are produced on purpose by formulators (under REACH, such technical mixtures are called “mixtures”).
- **Discharge mixtures**: these are substance combinations which are present directly at the “end of the pipe” of a single discharging production unit of different actors (substance manufacturers, formulators of mixtures, end-user of substances and/or mixtures or actors carrying out simultaneous manufacturing and/or formulating and/or end-using activities). For the aquatic compartment, the discharge mixture is the influent to the sewage treatment plant.
- **Coincidental mixtures**: These are mixtures in the water compartment which receives the emissions from the sewage treatment plant, i.e. the receiving water volume after the STP (or after a direct discharge point, if there is no STP). They can result from one or more discharge mixtures after treatment in the sewage treatment plant and after dilution in the receiving water volumes.
- **Environmental mixtures**: Substances in coincidental mixtures can be further distributed between the environmental compartments. Finally, they contribute to environmental mixtures: substance combinations in environmental compartments including biota. They result from substances accumulating according to their environmental fate properties and degradation after emissions from different sources and uses to different pathways. In many cases, these environmental mixtures show a large complexity.

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<sup>10</sup> The Competent Authorities in Germany proposes the term „substance combination“ as a generic term for all different types of combinations of two or more substances.

These four types of mixtures are visualised below (Figure 4).

Figure 3: Mixtures in the environment: Origin and contribution of technical mixtures, discharge mixtures and coincidental mixtures to environmental mixtures (source: own illustration)



In the following, we will give some examples for the different types of mixtures.

### 1.2.1 Technical Mixtures

In technical mixtures, the number of substances can range from two to 30 and more substances. Regarding the number of substances, we distinguish between technical mixtures of low, medium and high complexity.

As an example for a technical mixture of medium complexity, Table 2 gives the composition of an oven cleaner. It consists of five substances.

Table 2: Recipe of a spray oven cleaner intended for private households (Bunke et al. 2010)

Nr.	Substance	Comments	Concentration of pure substance	Classification & Labelling
1	Water		91.50 %	Non hazardous
2	Sodium hydroxide 33%		2.50 %	C – R 35
3	Sodiummethylhexyl-sulfate	(43% in water) Anion. tenside	4.00%	Xi – R 38, R41
4	Lithium Sodium Magnesium Silicate		1.90%	non hazardous
5	Xanthan Gum		0.10 %	non hazardous

Technical mixtures are placed on the market by formulators or importers / distributors and are used by further downstream users or consumers. They can either be used by formulators to produce further technical mixtures or they can be finally applied to fulfil a specific purpose, e.g. an adhesive or a lubricant. Downstream users, which apply a mixture for its final purposes are a second type of downstream users. They are called „final downstream users”.

Remark: At present, no representative overview is available regarding “typical” composition of technical mixtures. Analysis of a restricted number of technical mixtures from several branches (Bunke et al. 2011) shows that the number of substances in technical mixtures ranges from a few substances (2–5) up to more than 30. In rare cases, systematic compilations of technical mixtures placed on the market are available (e.g. the catalogue of textile auxiliaries, TEGEWA 2011). It can be assumed that formulators know typical compositions of technical mixtures in specific branches. The same is the case for the occurrence of problematic substances in specific branches. However, this kind of information is not communicated in general. In order to get a better understanding of “typical” mixtures, knowledge of formulators in specific sectors would be important source of information. In addition, in some countries databases on hazardous substances in technical mixtures have been established (e.g. the SPIN database). They allow a research in which sectors specific problematic substances are used (for details on the SPIN database, see chapter 2.6.6.3).

### 1.2.2 Discharge Mixtures and Coincidental Mixtures

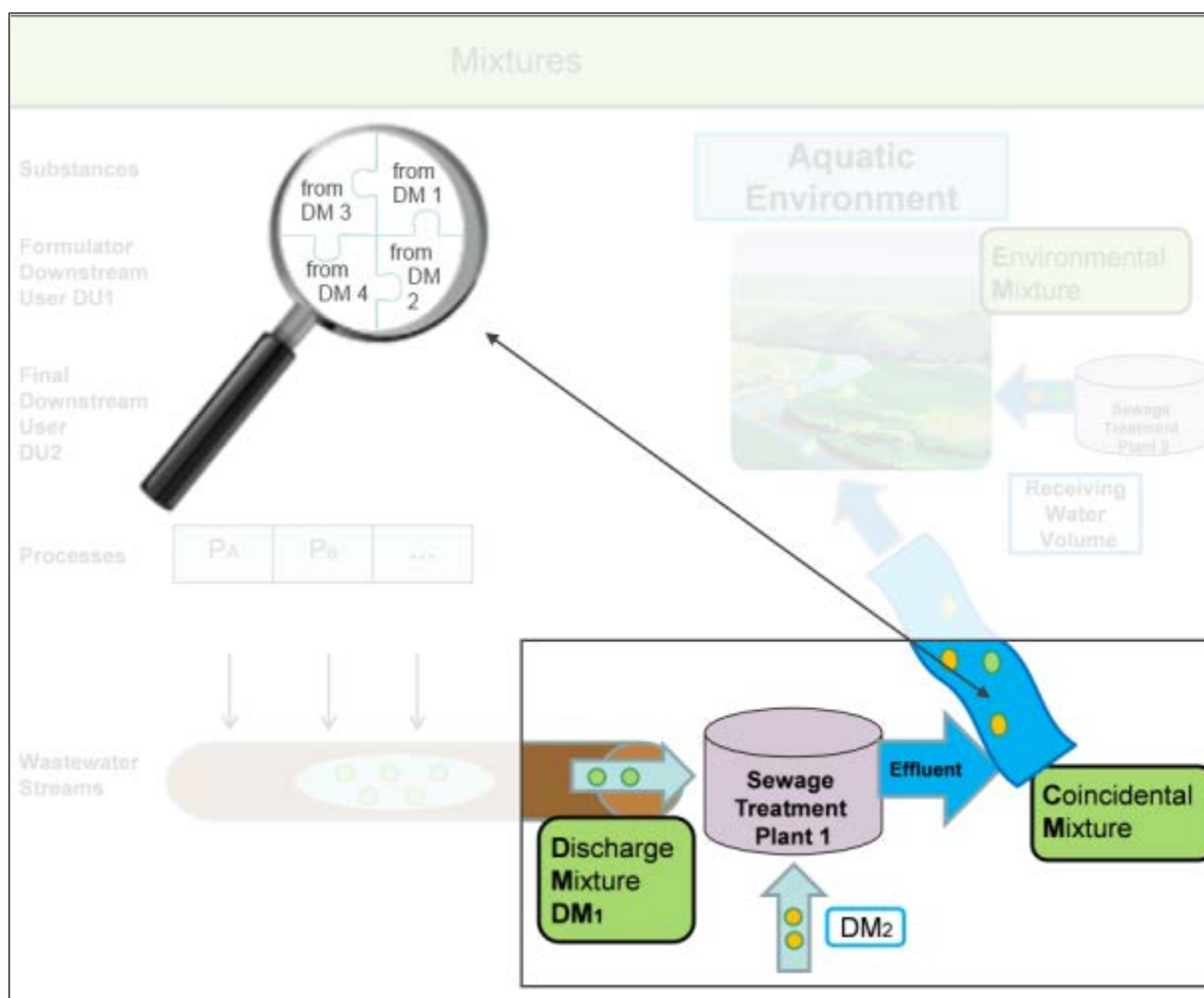
In this report focus is set on the use of technical mixtures by downstream users<sup>11</sup>. Normally, several substances and mixtures are used simultaneously in industrial and professional applications resulting in emissions of combinations of substances to water, air or soil and sediment. These emissions we call discharge mixtures. In the following only discharge mixtures in water are considered.<sup>12</sup>

<sup>11</sup> Consumers are not discussed here, because they have no obligations under REACH. However, identified consumer uses have to be considered in the chemical safety assessments of registrant.

<sup>12</sup> This is due to the fact that risk assessment for the air compartment is not very developed and respective standards are missing as yet. For soil and sediment, PNECs are derived in the registration dossiers. Due to time constraints, detailed analysis in the 4M project in WP 2 is restricted to surface water. Differences in methodology and in data availability for other environmental compartments are discussed in chapter 2.4.6.

The influent to a sewage treatment plant comprises discharge mixtures from one or more discharging units (substance manufacturers, formulators (DU1) and/or end-users (DU2)). Those influents are treated in sewage treatment plants before they are emitted to the environmental compartments. The effluents from the sewage treatment plants are diluted in the receiving environmental compartments. Substance combinations in the receiving environmental compartments are called “**coincidental mixtures**” – see the following figure.

Figure 4: Coincidental mixtures (source: own illustration)



Environmental compartments receive the discharge mixtures from one or several discharging sources after first dilution and changes due to the wastewater treatment plant, which include degradation, adsorption and evaporation processes of the substances contained therein. Potential mixture effects of the substances in a coincidental mixture may not necessarily be attributed to a single discharging source, if the sewage treatment plant is connected with several discharging sources.

Usually coincidental mixtures contain substances from more than one discharge mixture after treatment in sewage treatment plants and dilution in the receiving water volume. They may include aggregated exposure to some substances from different downstream users.

**Note:** In this report focus is on the assessment of technical mixtures and to the discharge mixtures which result from the use of these technical mixtures. The reference point of the exposure assessment is the coincidental mixture: it includes sewage treatment of the discharge



mixture and dilution in the receiving water volume. It is the same reference point as chosen in the chemical safety assessment of the registrant.

The use of such a technical mixture leads to a discharge mixture of a composition which can be predicted. However, in practice it is not possible to isolate this fraction of the coincidental mixture from the whole coincidental mixture.

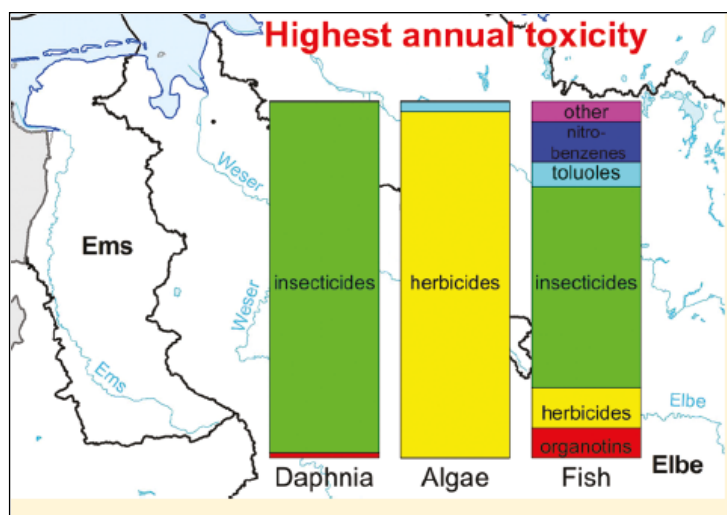
Similar to technical mixtures, coincidental mixtures can differ widely in their complexity. Coincidental mixtures of low complexity result from the application of a single mixture in a single process. Coincidental mixtures of high complexity result from the parallel use of many different products in several installations which discharge to the same receiving surface water body via the same sewage treatment plant or by direct discharge at a similar location.

### 1.2.3 Environmental Mixtures

Environmental compartments such as surface waters, sediments, soil, marine waters and air receive substance combinations from many different sources. Apart from industrial and municipal waste water treatment plants, substances enter the compartments from natural sources, from historical stocks, from different transport processes. Finally this results in very complex combinations of substances. In this report, the term „**environmental mixture**“ is used for complex combinations of substances in environmental compartments from different sources. Environmental mixtures include multiple coincidental mixtures. They consist of industrial chemicals, which may have to be registered under REACH, and further classes of substances such as biocides and pharmaceuticals. They originate from different industrial, agricultural and municipal sources. Processes such as transport, dilution and degradation, evaporation, sorption and desorption diffuse immissions and a combination thereof influence the site-specific composition of environmental mixtures. Therefore they resemble the most complex mixtures present in our environmental media (e.g. rivers, lakes or the sea).

The publication of Schäfer et al. provides an example for the analysis of environmental mixtures. It refers to organic pollutants in large rivers in North Germany (Schäfer et al. 2011). In total, 331 substances have been included in this analysis. Different types of substances contribute to the total toxicity of environmental mixtures. Schäfer et al. distinguishes between insecticides, herbicides and different groups of industrial chemicals such as nitrobenzenes, toluoles and organotin compounds (which are used as biocides and for other uses). The following figure shows the contribution of these types of substances to the total toxicity of the environmental mixtures calculated from exposure data for rivers in Northern Europe.

Figure 5: Contribution of different types of chemicals to the total toxicity of environmental mixtures (source: Schäfer et al. 2011<sup>13</sup>)



#### 1.2.4 Aggregated Exposures – another Perspective on Mixture Toxicity

In the previous sections, four different types of mixtures have been introduced. They are characterized by the actors who contribute to the mixture and to the location where it occurs. In this section, another differentiation is explained: exposures can be cumulative or aggregated. This applies to all of the different mixtures described above.

- **Cumulative exposures:** these are exposures to two or more **different** substances. Exposure can result from different emission sources, emission pathways and exposure routes.<sup>14</sup>
- **Aggregated exposures:** these are exposures to **one** substance from different sources, pathways and/or routes.<sup>15</sup>

Remark: The terms “cumulative exposures” and “aggregated exposures” are not used in the same way in different legislations. For biocides, the two terms are used reversed.

In any mixture, a cumulative exposure takes place because two or more substances are present at the same time. With increasing complexity / number of substances, the cumulation

<sup>13</sup> Reprinted with permission from Schäfer, R.B. et al.: Occurrence and toxicity of 331 organic pollutants in large rivers of North Germany over a decade (1994 to 2004), Environm. Sci. Technol. 2011, 45, 6167–6174, Copyright (2011) American Chemical Society.

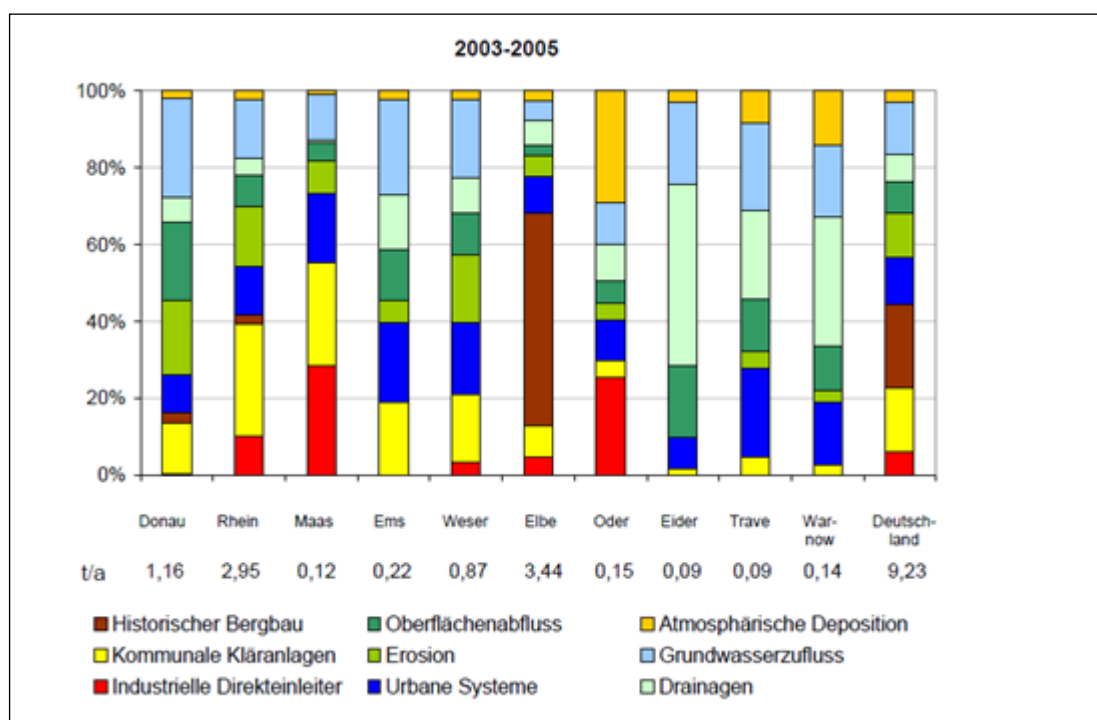
<sup>14</sup> The emission pathway only indicates into which compartment a substance is emitted from a product or process. The exposure route with regard to the environment is expressed as the environmental compartment for which an environmental concentration is determined. For short term assessments, the emission pathway is frequently the same as the exposure route and normally only water, air and soil are considered. Exceptions are e.g. highly volatile substance which may, shortly after emission to water evaporate to air. For long term assessments the exposure routes can be very different and also sediments, marine waters and biota are considered. This is due to the fate and partitioning of substances in the environment.

<sup>15</sup> If no differentiation is made between aggregated and cumulative exposure, the term “combined exposure” is used.

increases. Aggregated exposures only occur, if the mixtures contain the same substance from different emissions, i.e. the total dose or concentration of one substance in a mixture is added up.

Figure 7 gives an example for aggregated exposures in environmental mixtures. It shows the total emission of cadmium into the catchment area of ten rivers in Germany in the period from 2003 – 2005 (UBA 2008). Total emissions are given in tons/year. They originate from nine types of sources, including direct discharges from industrial sources. The contribution of industrial sources is indicated in red colours. The sum of the emissions is given in the last column of the figure. For cadmium, industrial sources are of minor importance for the total emission (contribution to the total emission: less than 10%) (UBA 2010).

Figure 6: Emission of cadmium into the catchment areas of rivers in Germany. Contribution of the total emission (in tons / year) to different sources (source: UBA 2010)



Direct discharges from industrial installations („industrielle Direkteinleiter“) are marked in red. Further emissions result from mining (historical), municipal waste water treatment plants, surface run off, erosion, urbane systems, deposition from atmosphere, groundwater and drainage

A further example for an aggregated exposure is given in the following Table 3. It refers to the situation of a downstream user in a tannery. In this case, three different technical mixtures are used. Each of these technical mixtures contains the same alkylsulfonate – in differing concentrations. In the resulting discharge mixture of the tannery, substances from the three technical mixtures occur together and hence an aggregated exposure to alkylsulfonate from the three products occurs.

Table 3: Simultaneous use of three products with the same substance (here: Alkylsulfonate) by DU. Source: own survey, related to TEGEWA 2011

Technical mixture	Amount of product used per day by DU [kg]	Content of alkylsulfonate [%]	Amount of alkylsulfonate used per day [kg]
Degrace 14	50	5	2,5
Protube 25	40	10	4
Solomud TB	20	10	2

In this report, aggregated exposures are considered as a specific case of cumulative exposure. A concept for the assessment of aggregated exposures under REACH has been published by the Federal Environmental Agency (Gross et al. 2010).

The following table summarises the key characteristics of the different types of mixtures.

Table 4: Terminology of mixtures. Short characterisation of the different types of mixtures.

Type of mixtures	Knowledge on composition	Assessing mixture toxicity	Risk assessment
Technical mixture	Formulator: „complete“ End-user: classified substances known	Formulator: calculated during classification considering classified substances. Measurement possible	Summation of individual RCRs possible
Discharge mixture	All actors: could be estimated based on the use of mixtures; however limited by degree of knowledge on technical mixture	Could be calculated by dilution of original mixtures used in the volume of wastewater from the discharger Measurement of effects of discharge mixture as part of emission monitoring possible	Addition of individual RCRs possible aggregation and cumulation of different mixtures → more complex
Transformed and diluted Individual discharge mixture in coincidental mixture	All actors: could be estimated based on the use of mixtures; however limited by degree of knowledge on technical mixture	Calculation for discharge mixture in coincidental mixture possible with many uncertainties (fate in STP and theoretical dilution)	RCRs of individual discharge mixtures may be derived; however this represents only a share of the coincidental mixture. Measurement of discharge mixture in coincidental mixture not possible
Coincidental mixture	Generic, qualitative estimation of composition may be possible based on the type of dischargers. Individual discharge mixtures cannot be distinguished	Calculation for coincidental mixture with many discharge mixtures not possible Measurement of effects of STP effluent possible but no allocation of effects to mixtures / substances	RCR of coincidental mixture requires knowledge of all discharge mixtures. Measurement of effects in coincidental mixture possible

Type of mixtures	Knowledge on composition	Assessing mixture toxicity	Risk assessment
Environmental mixture	Predictions based on EUSES for “all” substances in the EU theoretically possible	Effect measurements of environmental samples possible. Calculations based on predictions probably not reasonable	

### 1.3 Relevance of Assessment of Mixtures

Risk assessment of a substance under REACH aims to show safe use of the substance under a given set of conditions of use. Exposure estimation and risk characterization start with the assumption that exposure is related to the substance itself – without considering the parallel exposure to other substances. However, there are several indications that certain environmental mixtures, coincidental mixtures and technical mixtures can cause adverse effects in the environment, which would not be predicted based on the risk assessment of the single substances.

- Environmental mixtures:** Biological monitoring of environmental samples reveals adverse effects for specific endpoints. For example monitoring of surface waters showed estrogenic activities (e.g. Krüger et al. 2011). In some cases, it can be shown that specific industrial chemicals are responsible for the effects. However, in many cases it is difficult to identify the individual chemical stressor (Brack et al. 2007).  
Fortunately, the environmental quality of aquatic media has improved for some substances during the recent years (EEA 2012). At the same time many emerging substances are not covered in routine monitoring programmes which are a reason for concern in Europe’s aquatic ecosystems due to hazardous properties such as persistence, bioaccumulation or endocrine disruption. It is expected that registration under REACH supports identification of such problematic substances (and vice versa inclusion of them into monitoring activities). Assessment of the surface quality of European rivers shows in many cases insufficient quality of the water bodies. Discharge of industrial chemicals is one of several sources of pollution. Some of the observed adverse effects may be attributed to high environmental concentrations of single substances; in particular after direct emissions or in hot spot areas (Brack et al. 2007). However, in many cases the toxicity observed in sample fractions cannot be assigned to a specific substance.

The Water Framework Directive sets Environmental Quality standards for priority substances. Risk characterisation ratios (RCRs) for specific substances are reported in Annex XI to the monitoring-based prioritisation report for Water Framework Directive implementation (IOW/INERIS, 2009). These RCRs may be considerably elevated (a RCR above 1 is already regarded as not safe in a single substance assessment). If concentration addition is assumed for the substances in the environmental mixture, adverse effects due to the cumulative exposure should be expected.

- Coincidental mixtures:** Whole effluent testing of wastewater streams of single plants in Europe shows environmental toxicity of process-specific wastewater streams. A comparison between different sectors regarding the effluent toxicity in fish eggs have been published by Ecklartz-Nolden and Vietoris 2007. In total 202 effluents have been assessed. The study includes 166 municipal wastewater treatment plants. In 37% of the samples toxicity in the fish egg test has been found. In most cases, for effluents from municipal waste water treatment plants no toxicity in this test system has been reported. If these effluents are

excluded from the analysis. 75% of the remaining effluents show adverse effects in the test system. Effluents from chemical industry belong to the five sectors with a frequent occurrence of enhanced toxicity in the fish egg test (Ecklartz-Nolden and Vietoris 2007).

Whole effluent toxicity testing has been used in the COHIBA-Project to enhance waste water control (COHIBA: “Control of hazardous substances in the Baltic Sea region”). The project studied sources and inputs of 11 hazardous substances/ substance groups (e.g. polybrominated diphenylethers, bisphenol A, mercury, cadmium). The Baltic Sea countries have been advised to increasingly apply whole effluent toxicity testing to complement conventional chemical analysis. This advice is based on the experience that it is not possible to assess – without direct testing - the high number of possible environmental mixtures in the Baltic Sea, including all chemicals and their metabolites. Results of toxicity testing and ring tests have been used to develop recommendations for whole effluent testing (COHIBA/FEI 2010).<sup>16</sup>

- **Technical mixtures:** For biocides and pesticides, comparative testing of components of the products and of the whole products show that toxicity of the whole product is larger than the toxicity of the individual substances. Studies on „mixture toxicity“ with different groups of chemicals, including industrial chemicals, show that in most cases the toxicity of the substance combination can be predicted using the concept of concentration addition. This means: in many cases it has to be assumed that toxicity of a mixture is underestimated by isolated assessments of the toxicity of its substances (see Kortenkamp et al. 2009; see the summary of recent mixture toxicity studies in work package 2 (interim report 3, chapter 2.1)).

In these experimental studies it has been shown that substances can act together and that their toxicity is enhanced. The established concept of concentration addition (CA) would be a plausible, conservative and fairly correct model to assess combined exposures when toxicity data of the substances of the mixture are known. Looking at the measured exposure data of many single substances in monitoring programmes and the number of substances found in aquatic media it appears very plausible that mixture effects become true in realistic exposure scenarios due to concentration addition (or even assuming the concept of independent action).

Such mixture effects therefore may be assumed for environmental mixtures which contain pesticides, other chemicals from agricultural use, pharmaceuticals, veterinarian medicals, metals and industrial chemicals. Industrial chemicals may enter the environment by diffuse immissions (e.g. dyes washed out from consumer textiles during use and processed to the municipal sewage treatment plant) or direct discharges.

Based on the findings, described above, we conclude

- that adverse effects from environmental mixtures appear to be relevant,
- that mixture effects in technical mixtures are convincingly demonstrated by experimental testing,
- that industrial chemicals (in technical mixtures) may contribute to mixture effects in the environment,
- that evidence for adverse effects on the environment from industries’ discharge mixtures has been demonstrated less clearly, but still is plausible.<sup>17</sup>

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<sup>16</sup> The recommendations are available at [www.cohiba-project.net/identification/recommendations](http://www.cohiba-project.net/identification/recommendations)

<sup>17</sup> Chemical safety assessment under REACH includes diffuse emissions by consumer uses.

Due to the fact that any substance in a mixture may contribute to the mixtures' overall toxicity any exposure reduction is useful to minimize effects for human health and the environment. The report describes concepts for the assessment of technical mixtures under REACH and for the related priority setting (see chapter 2). The REACH processes registration, evaluation, authorisation and restriction address industrial chemicals, their manufacturers, industrial and professional users. Therefore REACH-induced activities on the safe use of chemicals can influence the composition of complex environmental mixtures - with regard to industrial chemicals.

Chemical safety assessment under REACH as described in REACH Annex I relate to the assessment of single substances. For single substances, a RCR <1 is accepted as an indication for the safe use of a substance under a given set of conditions. At present, no comparable indicator exists in REACH to show on a theoretical base the safe use of technical mixtures. In the last years several scientific approaches have been discussed in mixture toxicology for the assessment of technical mixtures (assuming e.g. the concentration addition model). In work package 2 we give an overview on these concepts. It includes indicators such as the hazard index (addition of risk characterisation ratios of the substances in a mixture).

At present only limited knowledge is available regarding the relevance of direct discharges of industrial chemicals for mixture effects. This report describes in section RCRs for substances in technical mixtures. Effects for discharge mixtures and coincidental mixtures have been calculated under use of the concentration addition model. Based on this experience, existing approaches for assessment of technical mixtures have been further developed (see section 2.5).

The calculations documented in section 2.4.4.7 are based on data of real technical mixtures. Knowledge on combined uses of technical mixtures in specific sectors is used to predict the composition of discharge mixtures of final downstream users. Exposure estimation and risk characterisation with EUSES are used in 2.4.4.7 to model the exposure in the coincidental mixture after the sewage treatment plant. Although this may not reflect the actual environmental concentrations of substances in the environment, it corresponds to the current implementation of REACH. Results of this work allow a better understanding of possibilities and limitations in using REACH data for mixture assessments (see section 2.4.4).

Under which circumstances it is likely that risk assessment of mixtures shows a risk which is significantly higher than the risk described for the single substances?

In the following section, we make a first description of circumstances under which risks may be underestimated, if mixture effects are not considered.

Prior to this, it should be noted that the RCRs derived under REACH in the chemical safety assessment may differ from RCRs derived from measured environmental concentrations. In addition, predicted effects may differ from measured effects in the respective compartments. There are two main reasons for this:

1. there are several safety factors and assumptions made in the emission estimation and exposure modelling, which may influence the calculated PEC and PNEC values and
2. registrants tend to calculate the possible use amounts “backwards” from a PEC/PNEC ratio of 1. Due to this the maximum “allowed” environmental concentration is estimated rather than a realistic concentration based on the implemented conditions of use (c.f. below).

Validation of modelled exposure data by measurements is not foreseen as a standard element in the chemical safety assessment. It seems to be an exception that data from environmental monitoring are used for the environmental exposure assessment under REACH – e.g. for metals.

Regardless of these REACH-inherent reasons for uncertainties about the actual levels of exposure and risks, several cases can be distinguished, in which risk assessment of a mixture is likely to indicate a higher risk than an isolated assessment of a single substances:

Technical mixtures: A formulator may carry out a risk assessment for a specific formulation<sup>18</sup> and discover risks, which are not indicated by the assessments of the substances in the mixture

- RCR of one substance in the technical mixture is already close to 1, further substances are contained in the mixture with effects on the environment. Due to concentration addition, the RCR of the mixture is likely to exceed the value of 1.
- RCR of many substances with environmental effects add up to > 1
- RCR of all substances in the mixture is below 1 but they have synergistic effects.

Coincidental mixtures.<sup>19</sup> Emission sources are the applications of substances and technical mixtures by REACH actors.

- Aggregated exposure: RCR of substance A in technical mixture P1 close to 1, total amount of substance A in all technical mixtures P1,P2, P3.... significantly higher than amount in technical mixture P 1 only.
- RCR for single technical mixture close to 1. Parallel use of different technical mixtures. Additivity of substances.
- RCR for single technical mixture below 1. Parallel use of different technical mixture. More than additivity of substances.

Environmental mixtures: Emission sources are the many installations of manufacturers and downstream users as well as waste water treatment plants. Substances from non-REACH applications are also present in environmental mixtures.

- Aggregated exposures: substance A accumulates from different sources and different pathways. RCR for a single emission already significantly above 1.
- Complex substance combinations with many substances which have impacts on the environment.

At present, robust estimations of the frequency of occurrence of these cases can't be given. This requires a more profound knowledge on typical compositions of mixtures for different branches. As described above, in this report priority is given to the assessment of technical mixtures – and the part of coincidental mixtures which can be linked to the use of such a specific technical mixture (see Figure 5).

How safe are single substance RCRs, if we consider cumulative and aggregated exposure? In which cases do deviations from single substance RCRs occur? How large are they? How often do they occur?

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<sup>18</sup> Formulators are not required to carry out risk assessments for their formulations under REACH. However, they may do so either voluntarily or in the scope of a downstream user chemical safety assessment (DU CSR).

<sup>19</sup> An assessment of discharge mixtures (see Figure 4) is not foreseen. First environmental impacts of the discharge mixture can take place in the sewage treatment plant. This is taken into account in the chemical safety assessment.



According to the chemical safety assessment under REACH, “safe use” of a substance means that the exposure to humans and the environment is below the DNELs and PNECs derived from the registrant. This is expressed by a risk characterisation ratio (RCR) below 1.

In most cases exposure characterization is made by modelling instead of using measured data. Risk characterization is done in an iterative process. If the calculated risk characterization ratio is above 1, further steps are made to refine the assessment, e.g. considering additional risk management measures in the emission estimation.<sup>20</sup> Calculation is finished if the RCR is below 1.

Analysis of a limited number of registration dossiers within the REACH Baseline Study (EUROSTAT 2012) has shown that for the majority of substances for the impact on workers a RCR close to 1 is reported. It is reasonable to assume that this is a consequence of the objective to reach a RCR below 1. It does not mean that in reality the exposure levels are as high as calculated. The compliance check of the downstream user with the exposure scenarios should ensure that the real exposures are not higher than the calculated ones. At present there are no data available in how many cases the real exposures are above, at or below the exposures assumed in the chemical safety assessments.

**Remark:** A deeper understanding of the relation between real exposures and REACH exposure estimates would be an important element in a quality assessment of REACH registrations. Such a comparison could be made for substances which are subject of environmental monitoring programmes. In parallel the analysis requires access to the chemical safety reports of these substances which contain the REACH exposure estimates.

As many RCRs are just below 1, theoretically there is little room for additional risks posed by the same substance from other sources or by other substances – without causing a total risk characterization ratio above 1.<sup>21</sup>

**Note:** Robust answers to these questions can only be given on basis of examples with realistic exposure data in comparison to lower tier modelled data (as actually done under REACH).

## 1.4 Priority Setting

Due to the high number of mixtures in reality, any approach to implement mixture assessment in a specific regulation requires a decision on priority setting. It depends on the objective of the individual legislation and the related actors how such a priority setting can be done.

We assume that the priorities for implementing mixture assessments under REACH would be to

1. identify the substances or exposure situations which contribute a large proportion to enhanced risks from mixture toxicity and
2. to address industrial chemicals which can be tackled under the regulatory framework of REACH (to ensure that the required data on substance properties and exposure will be generated under REACH).

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<sup>20</sup> These are then to be communicated as obligatory measures to ensure the safe use of the substance.

<sup>21</sup> As stated above, no data are available in how many cases the real exposures are properly described by the exposure estimations of the registrants or of the formulators.

The first point, the identification of priority substances is based on science and evidence for risks in the environment due to different types of mixtures. The second point depends on the regulatory setting and the possibilities to assign responsibilities to different actors. In any case, REACH actions can only influence

- the substances used in a technical mixture by limiting the use of substances based on safety considerations and
- the composition and nature of the discharge mixtures from processes by defining the conditions of use and risk management measures that determine the emissions of substances / technical mixtures from processes.

Under REACH, activities of manufacturers, importers and downstream users can only target the formulation and use of technical mixtures. Priorities for authorities how to regulate single substances under REACH may also be triggered by considerations and issues related to environmental and coincidental mixtures.

In the following sections, first considerations on priority setting relating to the different types of mixtures are introduced. They are further elaborated in section 2.6.

#### 1.4.1 Priority Setting related to Environmental Mixtures

Priority setting for **environmental mixtures** could be based on evidence from environmental monitoring. However, this is restricted to substances which are covered by environmental monitoring activities. Indicators reflecting chemical pressures and state of the environment could be used to identify environmental compartments in which adverse effects caused by cumulated or aggregated exposures to substances already take place or which show an unacceptable chemical quality.

It will be valuable to draw on the experience and data gathered in the context of the designation of priority (hazardous) substances for water. The EU Water Framework Directive (WFD) prioritises substances that present a significant risk to or via the aquatic environment, based on risk assessment or simplified risk assessment approaches (see WFD article 16.2). In the context of the recent revision of the directive on environmental quality standards (EQS), a daughter directive of the EU Water Framework Directive, a comprehensive priority setting exercise was carried out: One of the screening results of the expert group was a list of nearly 300 substances that pose risks to aquatic ecosystems which were selected in the first step out of more than 2000 water relevant chemicals. This list includes industrial chemicals, pharmaceuticals and pesticides and can potentially be of value also for this project. The list was further condensed and 44 substances were evaluated in detail. The outputs were reviewed by experts from the Member States and stakeholders and the evidence was considered sufficient to designate them as priority substances – based on their hazard and their presence in the aquatic environment and an RCR exceeding 1. In January 2012 the European Commission published their revised proposal with additional substances (adding to the existing 33) and currently the political negotiations are ongoing in the European Parliament and EU Council. Recently, an overview on data from environmental monitoring programmes and their use for REACH has been prepared in a project for the German Federal Environmental Agency (Gross et al. 2010).

Götz et al. published a screening method to identify high priority “micropollutants”. These are substances from different sources, e.g. biocides and pesticides (see Annex 1 (section 9.1) for the list of substances). They define 6 exposure categories. Substances of exposure category 1 have the highest priority. These substances are persistent and are continuously emitted (Götz et al. 2007).

In a recent study of a large number of environmental pollutants occurrence in four river systems has been determined. In addition, the contribution of the substances to the toxicity of the environmental mixtures has been assessed. It has been found that the substances with the highest contribution have not been addressed in the Water Framework Directive (Schäfer et al. 2011). On-going research projects aim to identify additional priority substances, e.g. RiSKWa (Risikomanagement von neuen Schadstoffen und Krankheitserregern im Wasserkreislauf) and PRiMaT (Präventives Risikomanagement in der Trinkwasserversorgung).

Sydberg et al. proposes to take a ratio  $PEC/PNEC > 0.1$  as initial trigger for the assessment of substances in environmental mixtures (Sydberg 2011).

#### 1.4.2 Priority Setting related to coincidental mixtures

For coincidental mixtures, the IPPC Directive gives priority to sectors which are known to have problematic discharges into the environment. The IPPC Directive refers to best available techniques and emission limit values as main instruments for pollution prevention. This leads to a sector-specific decision on key processes and priority substances. Whole effluent testing is used to identify locations where additional risk management measures are required. Experience with the assessment of coincidental mixtures by whole effluent testing leads to the recommendation that such a testing should be done carefully and selectively. Due to the high variability of test results depending on local environmental conditions no standard procedure for whole effluent testing can be made (SEATC 2000; Chapman 2000).

#### 1.4.3 Priority Setting related to Technical Mixtures

For the enormous number of **technical mixtures** of industrial chemicals no assessment of mixture toxicity has been foreseen yet. However, the classification rules for mixtures under the CLP directive include the application of concentration addition for substances classified for the environment. Consequently, at least some aspects are already implemented for some substances in technical mixtures. No approaches for priority setting are yet available.

The number of technical mixtures placed on the market exceeds the number of substances registered under REACH by more than one order of magnitude.

For some sectors estimations can be made on the number of substances and technical mixtures used. In the textile industry, 600–800 substances are used by formulators to produce more than 16.000 technical mixtures. Textile finishers use these technical mixtures in individual combinations if they finish textiles. It can be estimated that this finally leads to more than a million different coincidental mixtures in the effluents of the waste water treatments plants – only from this sector.

Based on 600–700 substances, large producers of paints put more than 10.000 different technical mixtures on the market. They are used by a large number of professional downstream users in many different combinations. Finally, also for this sector a huge number of discharge mixtures can be expected.

Several criteria have been proposed to identify technical mixtures of high priority for an assessment. Having in mind the enormous number of mixtures produced from a high number of substances, priority setting should not be based only on properties of the substances or properties of the technical mixtures.

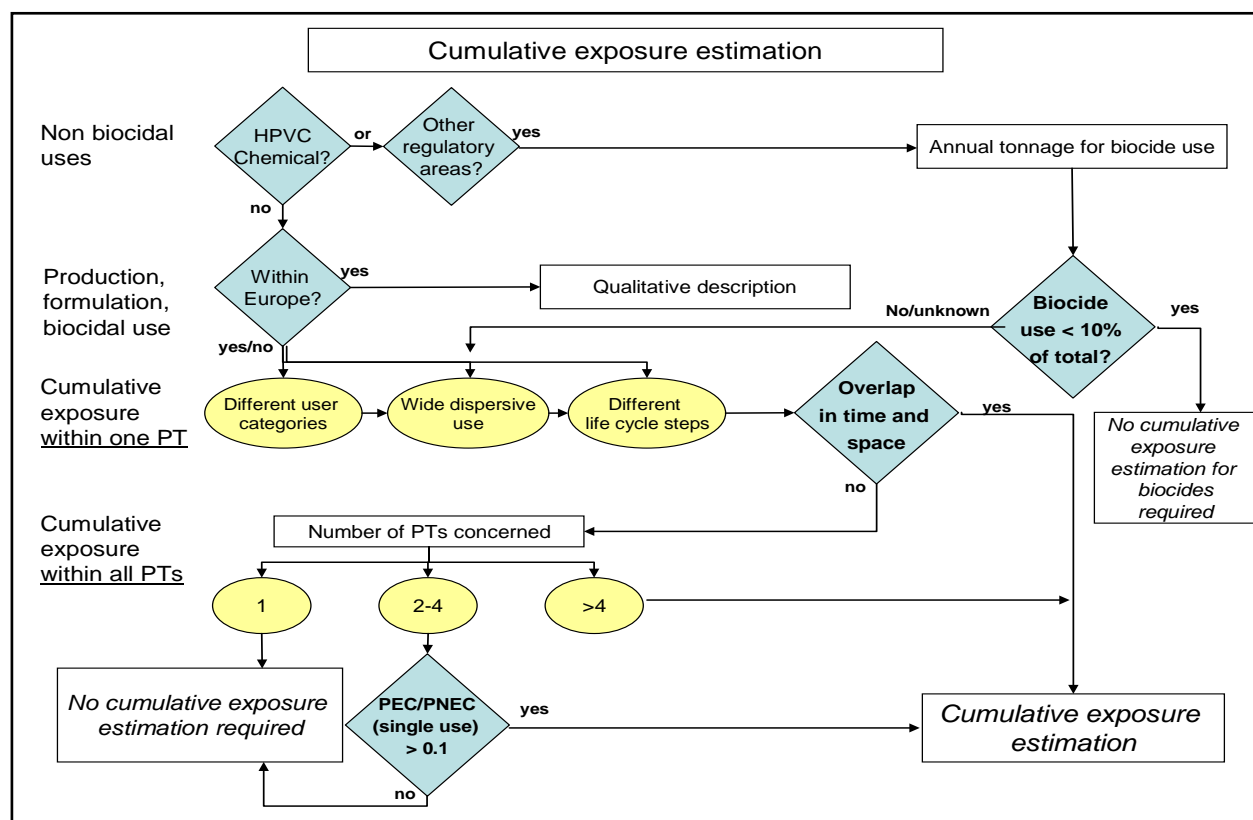
Up until now, no detailed discussion on possibilities to prioritize technical mixtures for a mixture assessment has taken place. Priority setting should include indications for a real risk

posed by a technical mixture or its substances. Classification of the substances as harmful for the environment alone cannot be taken as criterion for prioritisation. Classification of a substance refers to a limited set of hazardous properties (for an analysis of environmental impacts which are not covered by classification see analysis in Reihlen et al. 2011 and ECHA 2012, Scope of exposure assessment). In addition, substances which are emitted in high amounts, can pose a relevant environmental risk, even if their PNECs are below the thresholds for classification (see ECHA 2011, Scope of EA).

Regarding aggregated exposures of biocides, a first proposal of key parameters indicating the need of additional assessments have been made for the technical mixtures by Groß et al. 2010. The following parameters have been assessed: product type, user category/use sector, entry pathways into the environment, tonnage, PEC-values, PNEC values, risk characterization ratios. Regarding the PEC/PNEC ratio, a risk quotient of  $>0.1$  for the single use has been suggested as a trigger value in the decision tree for aggregated exposure assessments. For biocides, the following decision tree has been developed for aggregated exposure estimations:

(Note: Currently no harmonization of the terms “aggregated” and “cumulative” exposure is available. In contrast to the definitions of this report, in the following figure, the term “cumulative exposure” is used to address a situation in which one substance is used in different products).

Figure 7: Decision tree to assess the need for aggregated exposure estimations for biocides (source: Gross et al. 2010)



In chapter 2.6, concepts to prioritise technical mixtures for mixture assessment under REACH will be further elaborated. This includes the following indications:

- Mixtures with substances with a measured environmental concentration (MEC) close to or higher than the predicted no effect concentrations (PNECs); data from environmental monitoring could be used to identify such substances, e.g. within the implementation of the

Water Frame Work Directive (see Gross et al. 2010 for the use of environmental monitoring data under REACH).

- Mixtures in uses with high emissions to the environment
- Mixtures with substances which – in this combination - are known to have more than additive effects
- Mixtures for which environmental data show actual adverse effects in the receiving waterbodies, other environmental compartments and biota.
- Mixtures with substances which have already a risk characterisation ratio close to 1.
- Special attention could be given to mixtures which contain substances of very high concern, including PBT substances and vPvB substances and substances of equivalent concern such as endocrine disrupters. This could refer to all substances which fulfil the criteria defined in REACH Art. 57 (independent from the question whether they are already on the candidate list).

An important element could be the identification of substances which are already problematic on their own. This could be the case due to their intrinsic properties, or because they are emitted in high amounts.

In section 2.6.2, a concept is described to identify so called “**Mixture Assessment Triggering Substances**”, (MATS). Use of such a substance in a technical mixture could be the first indication in a decision process, that an assessment of the technical mixture is required. Besides the occurrence in environmental mixtures, MATS could also be defined by additional substance properties (e.g. persistence, accumulation in environmental compartments and others).<sup>22</sup>

**Remark:** In general it can be assumed that substances which on their own already have adverse effects at a low level in aquatic ecosystems, they are likely to belong to the dominating substances in coincidental mixtures for the respective sensitive endpoint at the same time. As a consequence, MATS could be identified by MEC/PNECs ratios. Identification of such MATs is not within the scope of this report. However, indications for such substances are likely to be found in projects addressing industrial chemicals in the European environment, as mentioned above, e.g. RiSKWa and PRiMaT). For more details on the concept of MATS, see section 2.6.2.

**Cut off values:** Technical mixtures can consist of a high number of substances (thirty and more, Bunke et al. 2011). Assessment of such complex mixture would be easier if not all substances have to be considered. Criteria could be defined to exclude specific substances in a technical mixture from the assessment (“cut-off criteria”). An example for a cut-off criterion could relate to the total amount of the produced or emitted substances in the mixture (“low tonnage cut off”). Another cut-off criterion could be a low risk quotient of 0.01 or less (“low risk cut off”).

Where it is possible to demonstrate with experimental or measured data that no adverse effects take place in a coincidental mixture, this would make a model-based assessment of the technical mixture unnecessary.

<sup>22</sup>

In addition, it might be that the prospective assessment of technical mixtures leads to the identification of further substances which have the potential to result in adverse effects in the environment. These results could be important information for local authorities, national authorities or European institutions like ECHA to consider these substances in national or European activities (REACH, WFD, IPPC).

These first ideas and approaches for priority setting are further developed in chapter 2.6.

## 1.5 From Substance Properties to Sectors of Use? Possibilities to Group Substances

Grouping of substances may be one option to increase the efficiency of the assessment of mixture toxicity. Different criteria can be discussed to find substances which build a group to be assessed together:

- Structural similarity,
- Common endpoint.
- Common mode of action,
- Common mechanisms of action,
- Common use in specific sectors.

Structural similarity is used as starting point for structure activity relationships and for read-across to determine the hazardous properties of a substance. First groupings of substances have been used in the OECD database on existing chemicals (e.g. alkyl chlorosilanes, ethylene-glycoles, secondary amines, for details see <http://webnet.oecd.org/hpv/ui/ChemGroup.aspx>).

However, the use of structural similarities for the assessment (of substances and of mixtures) requires that predictions are possible for the specific endpoint under consideration. This has not been proved in many cases. For the assessment of mixtures, structural similarity could be used (in QSAR models) to derive toxicity estimates for substances for which no hazard data are available (see section 2.4.2)

Any mixture toxicity assessment should consider that data for different substances should be used only if they apply to the same endpoint. Hence, if substances in a mixture have data for different endpoints, they would naturally be grouped together due to this basic rule. Nevertheless it is commonly accepted that effects on a certain species can be extrapolated within and across the trophic levels.

PAKs, PCBs, dioxines and furans, certain phthalates are examples for groups of closely related substances with a similar mode of action. In these cases, a cumulative assessment can be made for these groups. For the majority of industrial chemicals such a grouping has not been done yet. Mode of action and mechanisms of action as grouping criteria require detailed knowledge on these properties. Such knowledge is not available for most of the substances. Therefore the approach of Common Assessment Groups (CAGs) as proposed by the US EPA (US EPA 2002, EFSA 2009) is difficult to put into practice – at least for the next years.

In practice, approaches for mixture toxicity assessment in the context of REACH should normally not consider mode or mechanism of action as criteria for grouping and/or simplifying an assessment because this information is normally not available and too detailed for any pragmatic approach.

The use of the same substances in mixtures in different sectors has not been discussed yet as a possibility to group industrial chemicals in the context of mixture assessment. Such an approach could start with the identification of typical compositions of technical mixtures used in specific sectors. This grouping would contribute to priority setting for selecting mixtures for further assessment.

Sector-specific knowledge on the composition of technical mixtures could help to identify typical mixtures which require a specific assessment, because they contain critical substances

(see section 2.6.3 ). In addition, an assessment for specific types of technical mixtures may already been available in specific branches (due to experience with this specific type of technical mixture). In such a case, it would not be necessary to apply a default assessment procedure such as assumption of concentration addition.

Therefore a survey on typical compositions of technical mixtures should use the sector specific knowledge on mixtures. In a parallel approach, mixture assessment triggering substances could be identified (as described in section 2.6.2). In a second step it could be analysed in which sectors they are used – and in which technical mixtures. Both ways could supplement each other.

At present, there are no approaches available to group a significant number of industrial chemicals for mixture assessment. Therefore it is even more important to identify substances which indicate the necessity of an additional assessment of technical mixtures, as described in section 2.6 (concepts for priority setting).

## 1.6 Assessment of Mixtures: Data Requirements and Data Availability

The following section gives a first discussion on data requirements and data availability for the risk assessment of technical mixtures. It is elaborated in more detail in chapter 2.4.

Risk assessment of technical mixtures can be based on direct testing of the whole mixture. For industrial chemicals, such data are not available in most cases. Which data are available for technical mixtures?

- Technical mixtures of industrial chemicals are classified according to the CLP regulation.
- Risk management measures and conditions for safe use are communicated based on the information available for the substances in the technical mixture and experience from the use of the mixture.
- Safety data sheets of substances and technical mixtures are used in the supply chains to transport this information (from the registrant to formulators; from formulators to end-users of the technical mixtures).

For technical mixtures, predictions on the risk of the whole mixture can be made based on the toxicity assessment of the substances in the mixture.

This predictive assessment of the risk from a technical mixture requires:

- Information on hazardous properties of the substances;
- Information on physic-chemical properties related to the distribution and fate of the substance in the environment (e.g. molecular weight, vapour pressure, water solubility, partition coefficients, bioconcentration factors);
- Information on the use of the mixture and the resulting exposure situations;
- Information on the composition of the technical mixture.
- Information on interactions between substances of the technical mixture, if they occur.

The first two sets of information are part of registration dossiers of the substances, they are communicated in the safety data sheet or available from the ECHA dissemination database. Information on interaction is expected to be rare. It will be available only for a limited number of substances.

Information on the composition of the technical mixture is available for the formulator who produces the technical mixture. However, in many cases formulators by themselves use technical mixtures as raw materials when they produce technical mixtures. In these (frequent) cases the formulators know only substances listed in section 3 of the safety data sheets of the technical mixtures which they use. Here information is given only for substances classified as hazardous and present in the technical mixture in concentrations above the limits set in REACH Annex II, Article 3.3.

Which data are available under REACH (e.g. depending on tonnage, classification)? What quality do they have?

For the environmental assessment of technical mixtures under REACH, two types of information generated under REACH are relevant:

- The **hazard information** for substances forms the basis for the toxicity assessment of mixtures except when it is determined via measurements. Hence, the existence and the quality of information on the aquatic toxicity and the environmental fate and behaviour properties determine the achievable quality of any mixture toxicity prediction.
- The **exposure information** forms the second essential part for the risk assessment of mixtures. Therefore, the quality of the environmental exposure assessment is of decisive importance for the risk characterisation – of the single substances and of the mixture. In most cases exposure is estimated by modelling. The quality of the exposure predictions depends on the quality of the data on the environmental fate and behaviour of the substance. In addition, it depends largely on the knowledge about operational conditions and risk management measures for the different uses.

### 1.6.1 Data Availability

As discussed by Kortenkamp (Kortenkamp 2012), for most of industrial chemicals limit values for human toxicity and ecotoxicity are not yet available. An analysis of data availability for all known industrial chemicals has been made by Scheringer et al. (Scheringer 2012). It has been part of a screening analysis for further PBT/ vPvB substances. The screening started with a set of approximately 100.000 substances. Only for a small fraction (around 2.400 substances) experimental data on ecotoxicity of the substances were available yet.

QSAR predictions have been used by Scheringer and colleagues to derive ecotoxicity estimates for the majority of industrial chemicals. A similar approach is possible if ecotoxicity data are missing for an assessment of the toxicity of technical mixtures and coincidental mixtures. However, use of QSAR data introduces an additional degree of uncertainty in the assessment. A recent discussion of the use of QSAR models for registration under REACH came to the conclusion that QSAR data could support other sources of information in a weight of evidence approach. It is questionable to use them as the only source of information in an assessment process (Simon 2012). Note: The decision on which instrument is applicable and how the results can be used requires expert knowledge. This limits the number of actors able to do these predictions on their own.

Limit values for human toxicity and ecotoxicity, exposure assessments and risk characterisation ratios should become available due to registration of substances under REACH.

By End of August 2012, more than 4 600 unique substances have been registered under REACH. In addition, more than 5 200 substances have been notified before REACH. According to an estimation of ECHA, approximately 3 000 substances have to be newly registered by May



2013. It is expected that by end of 2018 registrations have been made for more than 10 000 substances.

- For all substances with a production volume of 10 tons/year and more a chemical safety assessment is required for registration (apart from those registered as intermediates only). Most of the substances registered until May 2013 have production volumes of 100 t and more. Therefore, for a large number of substances data on hazardous properties, uses, exposures and risk characterization ratios become available in the chemical safety reports.
- For substances with a production volume below 10 tons/year a chemical safety report is not required. Only a base set of hazard information has to be compiled for registration. Regarding the environment, it includes data on aquatic toxicity, log K<sub>ow</sub> and degradability. Regarding exposure assessment, only limited information on uses has to be reported (according to REACH Annex VI). For these substances neither PNEC values nor detailed data on the exposure situation will become available. Therefore the data generated under REACH are not sufficient for an environmental assessment of the substances itself. Furthermore, they cannot be used to perform additional mixture assessment, e.g. based on the concept of concentration addition.
- Substances with a production volume below 1 ton/year will not be registered at all and hence, no additional on hazard properties and exposure will be generated under REACH.

It has to be seen that only a restricted part of the information from registration dossiers is publicly available in the ECHA dissemination database: PNEC values, information on uses, information on uses advised against, and results of the PBT/vPvB assessment. Information from the exposure assessment and the risk characterisation part of the CSR are not made available. It is only available for a limited number of authorities who have access to the registration dossiers.

**Remark:** Within the supply chains, communication on substances in technical mixtures by safety data sheets is restricted to substances which are classified as dangerous or have PBT/vPvB properties – if their concentrations in the technical mixture are above the threshold values set in REACH Annex II, 3.2. It might be that in specific cases substances which are not classified make a significant contribution to the toxicity of the whole technical mixture. These substances are not listed in the safety data sheet. This will be analysed more in detail in work package 2.

The following table gives an overview of the availability of information for the different REACH actors.

Table 5: Availability of data relevant for mixture assessment (own compilation)

Information	Source	Documentation	Communication	Available for ...
Substance properties, including PNECs	Registrant (R)	CSR	ECHA Chem, SDS	R, F, final DU, CA
Use pattern, substance (use descriptor system, UDS)	Registrant (R)	CSR	ECHA Chem (UDS)	Registrant, formulator, final DU, CA
Use pattern, mixture	Formulator (F)	Internal	No communication	Only formulator
Generic information on exposure, PECs, substances	Registrant	CSR	Optional in SDS, rarely	Mostly restricted to R, CA
Exposure situation end-users, generic information	Formulator, sector associations	spERCs, sector-specific information,	Exchange Formulator / Registrant (via associations)	Registrant, formulator, CA, if communication takes place
Exposure situation end-user, local	Final DU	Internal documentation	No communication	Only final DU
Generic operational conditions (OC) and RMMs, substance	Registrant (R)	CSR	SDS Substance	Registrant, formulator, final DU, CA
Composition of mixture	Formulator (F)	Internal documentation	No communication	Only formulator
Hazardous substances in mixture above threshold concentrations	Formulator (F)	SDS Mixture	SDS mixture	Formulator, final downstream user
Generic OC and RMMs, mixture	Formulator (F)	Internal documentation	SDS Mixture	Formulator, final downstream user
Specific (local) OC and RMMs, mixture	Final downstream user (DU)	Company specific	No communication	Only final downstream user
Risk Characterisation Ratio, substances	Registrant	CSR	Optional: SDS substances	ECHA, CA / if included in SDS: F, final DU substances
Risk Characterisation Ratio, mixture	Not yet established. Probably source of information: formulator. Could be communicated to final DU by SDS mixture.			

It depends largely on the quality of the data in the registration dossiers of the substances, whether they can be used for an assessment of a technical mixture and the related coincidental mixture.

### 1.6.2 Data Quality

Compliance check of registration dossiers is made by the European Chemicals Agency. A minimum of 5% of the dossiers are to be checked. Cases of incompliance are followed-up by ECHA decisions whereas concerns relating to the dossier quality and in particular the quality of the exposure and risk assessment are addressed via quality observation letters to the registrant,

which are not binding.<sup>23</sup> Member States are involved in the process of substance evaluation. For this purpose, registration dossiers of selected substances are assessed. The national authority can require further information from the registrants if necessary for the evaluation.

The second progress report on evaluation under REACH published in 2012 states that the quality of the assessed chemical safety assessments (from 146 dossiers) has been mixed (ECHA 2012). In 105 cases, evaluation resulted in a decision asking the registrant to provide further information. Deficiencies have been observed in all parts of the registration dossiers. Advice to improve the quality of the dossier refers to the hazard assessment, the PBT/vPvB assessment, the exposure assessment and the risk characterization.

From this it can be concluded that registration of a substance under REACH does not automatically mean that data on hazard and exposure are available in sufficient quality. This means that any mixture assessment based on the hazard and exposure data in registration dossiers starts in many cases with a potentially low data quality and will also be of low quality.

The 5 Years Update of the REACH Baseline Study (EUROSTAT 2012) shows that there is a significant improvement in the quality of the data available for toxicity estimates and exposure estimates – compared with the situation in 2007. However, as mentioned above, according to the results published in the ECHA Evaluation Reports, for a larger part of registration dossier improvements are requested. However, this indicates that the data quality may rise in the future, hence providing a better information base for any mixture assessments.

At present, no specific analysis is available regarding the quality of the PNECs developed in the registration dossiers. For human toxicity data, an analysis has been made by Püringer on the quality of the Derived Minimal Effect Levels (DMELs). It refers to 293 substances registered as proven carcinogens or mutagens. The author concludes that the currently registered limit values for these substances do not appear to be comprehensible or trustworthy (Püringer 2011). Analysis of a restricted number of registration dossiers by the Federal Environmental Agency regarding new information on PBT/vPvB candidates found no new information on these properties in the dossiers (Biegel-Engler 2012).

In most registration dossiers exposures are modelled using exposure estimation tools such as ECETOC TRA. Iterations are targeted to achieve a RCR < 1. Consequently, the exposure assessment can be regarded as providing upper bounds of exposures rather than realistic exposure levels. As already discussed in section 1.3, analysis of a limited number of registration dossiers regarding exposure of workers shows that in many cases RCR is close to 1. It is reasonable to assume that this reflects the aim to demonstrate safe use. It does not mean that real exposures are similar. They might be lower or higher, this is a challenge for the REACH enforcement authorities.

## 1.7 Responsibility of Actors under REACH

Table 6 gives an overview about potential starting points to consider mixture toxicity under REACH. It refers to the specific tasks and to the responsibilities of the different actors.

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<sup>23</sup> Quality observation letters are sent to the registrant – and to the national competent authority. The national authority can request further information to improve the quality of the data.

Table 6: Potential starting points for considering mixture toxicity under REACH: Overview on tasks and responsibilities.

REACH title / task	Actor	Action
<b>I. Specific REACH mechanisms</b>		
Registration	Registrant: Manufacturer, Importer	Preparation of registration dossiers with CSR according to Annex I
		Assessment of substance properties
		Exposure estimation on a local and regional scale
		Risk characterisation
Supply Chain Information	Registrant, Formulator	Communication on operational conditions and risk management measures ensuring safe use
	Registrant	Preparation of SDS for substances
	Formulator	Compilation of SDS for mixtures
	Downstream User	Communication of new information on hazardous properties or conditions of safe use upstream
Downstream User (DU)	Formulator, final DU	Chemical safety assessments of downstream users / obligations of DU to report information
	Final downstream user	Check of coverage by exposure scenarios, including assessment of aggregated exposures
Evaluation	MS,ECHA	Dossier evaluation and substance evaluation
	ECHA	Dossier evaluation: priority setting / check of information in registration dossiers
	MS	Substance evaluation: check risk characterization, request for further information, dossiers for restrictions / authorisations
Authorisation	MS, ECHA,	Candidate list, Annex XIV
	MS	Identification of substances of very high concern
	ECHA	Proposal for inclusion of SVHC in Annex XIV following prioritisation
Restrictions	MS, ECHA,	Annex XVII
	MS, ECHA	Proposals for inclusion of substances in Annex XVII
<b>II. Success control</b>		
Authorisation and restrictions	MS	Control by authorities (enforcement (related to single companies) and success control (regional/national/EU scale)).
	M, I, DU	Self-monitoring/success control by companies
RMMs, SDSs	M, I, DU, MS	Self-control by companies/ enforcement by authorities.
<b>III. REACH Regulation as a whole</b>		
Information/Art. 117, 121	MS, Commission	Evaluation of the Efficiency of the REACH regulation, including assessment of total impact of all chemicals on human health and the environment

List of abbreviations: MS: Member state; M: manufacturer; I: Importer; DU: Downstream user; RMM: Risk management measures; SDS: Safety Data Sheet.

Before elaborating on the different obligations of the REACH actors, it should be clearly stated that REACH is a substance-focused legislation. The registration and chemical safety assessment process was primarily designed to address the lack of knowledge on the hazardous properties and the types of uses of substances.

Mixtures and their specific aspects have not been included with high priority and much detail in the legal text. This is – among others – currently visible in the difficulties of formulators to prepare extended safety data sheets for mixtures. For them it is a difficult task to consolidate the information on safe use which they receive for the substances of their technical mixtures.

Possible starting points for the assessment of technical mixtures under REACH are described in the following section. We distinguish between three actors: registrants, downstream users (formulators and final downstream users) and authorities (ECHA and MS authorities). In addition, we distinguish between responsibilities related to aggregated exposures and cumulative exposures.

**1. Registrants (manufactures/importers = M/I):** They are responsible to register and demonstrate safe use of the **substances** as such, in mixtures or as part of articles, if a CSR is required (REACH Annex I). For substances with PNECs: Explicit requirement to demonstrate safe use in a quantitative risk description. Indicator: RCR substance < 1 for the assessment of identified uses of the individual substance. For PBTs/vPvBs no risk characterization is necessary but an emission estimation is required.

Aggregated exposures:

- Obligation to make an estimation of the regional exposures / background concentration for individual substances. Regional exposures are documented in the chemical safety report; they are not communicated in the safety data sheets (safety data sheets have to show the derived PNEC values; optionally they can give risk characterisation ratios as additional information).
- No legal obligation to take into account used amounts of other manufacturers/importers (beyond estimation of regional concentration) or parallel use of several products with the same substance by DU. If joint CSRs are prepared in a SIEF, the M/I may however take amounts of other registrants into account. Outside of SIEFs, this information will not be communicated in the supply chains.
- Annex 1 obliges the REACH registrant to look at their own aggregated exposures from different routes (concerning the same substance) (in the headings of the CSR, this aggregated exposure is called “combined exposure”).

Cumulative exposures:

- The ECHA Guidance document on “information requirements and chemical safety assessment” obliges the REACH registrant to consider exposures *to several very closely related and similar acting chemicals (e.g. different salts of a metal or closely related derivatives of organic substances)*. However, this is not specified in further detail.
- Apart from the one reference in Annex 1 mentioned above, there is no obligation to assess the chemical safety of the substances when it is used in a mixture in terms of considering mixture toxicity. The term “safe use” of a substance on its own, in a mixture or article rather addresses that the entire lifecycle is to be assessed than making reference to the simultaneous occurrence of other substances.
- There is a general obligation to consider all available knowledge on a substance. This can be interpreted in such a way that knowledge on mixture effects or synergistic effects– if available – has to be considered and potentially communicated. However, no guidance is available, yet, on how to do this.

**2. Downstream users:** They are responsible to ensure their uses are covered by the exposure scenarios they receive. Otherwise, they have to make their own CSA and demonstrate safe use

or communicate upstream to have the use reassessed or to cease the use. If they place classified mixtures on the market or mixtures containing PBT/vPvB, they are obliged to communicate the conditions of safe use with the safety data sheet. In this they have to consider all information available to them.

Aggregated exposures:

- No explicit obligation to make an aggregated assessment in cases of use of the same substance in different products.
- However, it can be assumed that compliance check with exposure scenarios and assessment of safe use of a substance by a DU has to be taken into account the total amount of the substance which is used by the DU. This can result from different products with contain the same substance.<sup>24</sup>

In the REACH implementation project 3.5 the guidance document for downstream users has been developed (ECHA 2013a). The issue of aggregated exposures was thoroughly discussed. The representatives of the EU Commission and of industry agreed that the REACH text does not contain any legal requirement for the DU to aggregate the amounts of a substance if it is sourced from different suppliers. In contrast and although this does not seem logical, the DU is only required to check the coverage of an ES in relation to the specific substance or mixture it belongs to.

- There is no legal obligation to take into account used amounts of other DU.

Cumulative exposures:

- No formal obligation to make an cumulative assessment of mixtures with exposure estimation and quantitative risk characterisation
- No indicator for “safe use” equivalent to the indicator „RCR < 1“ for single substances.

**3. ECHA and Member State competent authorities:** They are responsible for dossier evaluations, substance evaluations and for the processes related to the authorisation and restriction of substances. This includes prioritising of substances and identification of substances of very high concern. Member States are also responsible for the enforcement of all REACH obligations in their territory.

Aggregated exposures:

- Substance evaluation/ identification of SVHC, proposal authorisation / restriction of substances: this includes assessment of aggregated exposures already with the current understanding of REACH.

Cumulative exposures:

- Cumulative exposure assessment and risk characterisation can be used as an option to show the need for further action on community wide level. This option has already been used by the competent authorities of Denmark in 2011. They proposed additional restrictions for four phthalates. It was based on the envisaged combined adverse effects of these substances on human health (for more details, see section 9.6.6).

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<sup>24</sup> This issue is to be further discussed in the project team, because there are different opinions concerning the understanding of the duty to assess aggregated exposures.

- Cumulative exposure assessment and risk characterisation can be used to demonstrate that a certain substance group needs further scrutiny and/or regulatory attention concerning their joint exposures and effects.

Within substance evaluation, member states can request additional information from registrants. This could include aspects of mixture assessment – for aggregated or combined exposures.

In chapter 2.5, different concepts for an assessment of technical mixtures under REACH are described in detail. In chapter 3 options for different actors to implement assessment of technical mixtures under REACH are analysed. This includes options to act for authorities.

## 1.8 Industrial Chemicals and other Substances in Environmental Mixtures

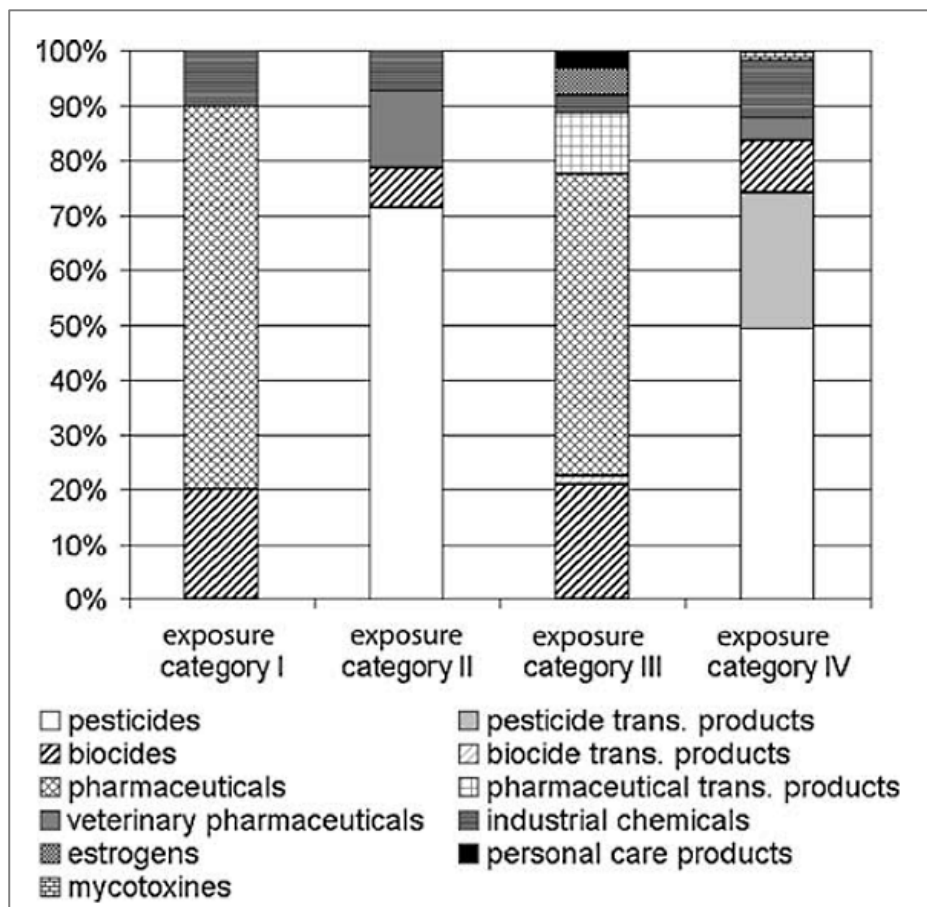
In this section the relevance of industrial substances (regulated under REACH) for environmental mixtures is discussed - in comparison to substances used in other types of mixtures, e.g. biocides and pesticides. The latter ones are subject to other legislations. This discussion provides a context for the priority of regulating substances in industrial chemicals as compared to other chemical mixtures. It influences recommendations for policy actions.

Environmental mixtures consist of various groups of substances. Industrial chemicals which have to be registered under REACH are only one of these groups. Götz et al. proposed a methodology to target aquatic microcontaminants for monitoring and for water pollution control. They start with a candidate list for aquatic micropollutants of 250 substances. These substances were listed in the Water Framework Directive, in the list of relevant substances for the river Rhine or had been measured in Swiss surface waters (Götz et al. 2009). The substances belong to the following groups: Biocides, pesticides, human and veterinary pharmaceuticals, estrogens and phytoestrogens, personal care products, industrial chemicals and metabolites. From a total of 250 substances 39 substances are used as industrial chemicals. (Environmental monitoring takes place in the framework of different regulations, e.g. the Water Framework Directive, OSPARCOM, HELCOM, the Convention on Long-Range Transboundary Air Pollution (CLRTAP). An overview on environmental monitoring activities and the use of these data for REACH has been prepared in a study for the German Environmental Agency (Gross et al. 2010)).

Götz et al. distinguish between industrial chemicals from point sources and from diffuse sources (Point sources: Additives, flame retardants, solvents, surfactants, anticorrosive/complexing agents, cooling and insulating liquids, plasticisers / diffuse sources: combustion products / formulation additives). The authors propose to group potential micropollutants in seven exposure categories with decreasing priority for water pollution control. Exposure category (EC) I substances are highly persistent chemicals that are continuously released into surface waters; EC II substances are highly persistent chemicals with a complex input dynamic. Rapidly degradable substances (EC VI) and unclassifiable substances (EC VII) have the lowest priority.

The following picture shows the distribution of different substance groups to the exposure categories I-IV.

Figure 8: Distribution of different classes of chemicals to the potentially relevant exposure categories for exposure categories I – IV. Source: Götz et al. 2010.25



The set of 250 substances contains only 39 “industrial chemicals”, seven of these are combustion products. The majority of the remaining 32 industrial chemicals belong to the exposure category IV (moderately persistent, periodic/complex input, 9 substances) and exposure category V (volatile and strongly sorbing, 19 substances), which have less priority for the environmental compartment water. (It should be noted that some of the substances analysed by Götz belong to several categories and can be used as industrial chemicals, too. E.g. PFOS and PFOA are listed as biocides in Exposure Category 1. As industrial chemicals they have to be registered under REACH; however PFOS is prohibited under the POPs regulation).

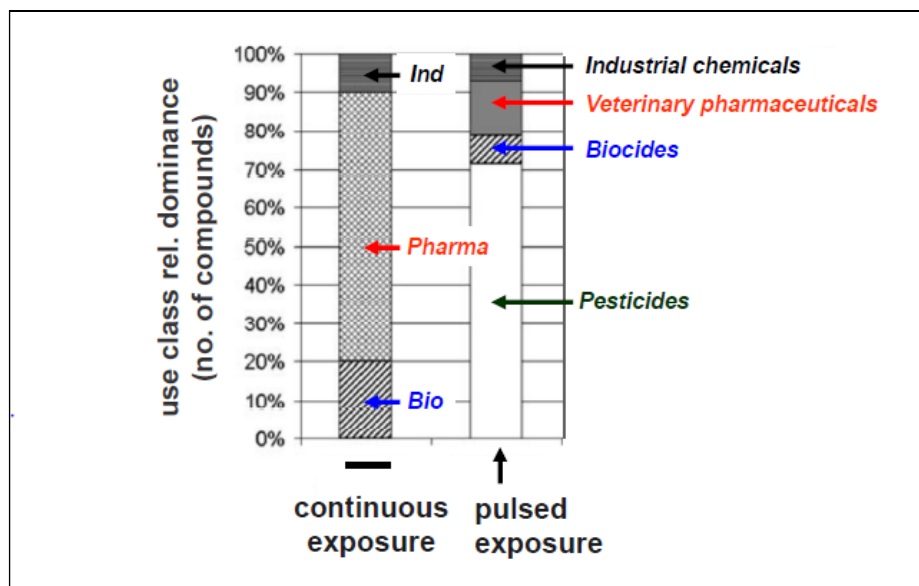
The data from Götz have been presented in a modified form by Porsbring (Porsbring 2011). The following picture shows that industrial chemicals have only a minor contribution to the total exposure, at least regarding the number of substances.

<sup>25</sup>

With kind permission from Springer Science+Business Media, Götz, C.W., Targeting aquatic microcontaminants for monitoring: exposure categorization and application to the Swiss situation, Environ Sci Pollut Res Int 2010, 18(2), 341-354



Figure 9: Contribution of different types of chemicals to the total number of chemicals in the analysis of Götz et al. 2010 (modified by: Porsbring 2011)



Similar results have been found in an analysis of more than 300 organic pollutants in large rivers in North Germany over a decade (Schäfer et al. 2011). It has been shown already in section 1.2.3 as an example for the analysis of a complex environmental mixture. The authors concluded that most of the substances responsible for the potential acute effects on aquatic organisms are currently not considered as priority substances in the European Union. Only 2 of 25 priority substances that have been measured occurred at levels that may be relevant in terms of toxicity for the selected test organisms (Schäfer et al. 2011).

## 1.9 Mixtures and European Legislations

Biocides, pesticides, pharmaceuticals and personal care products are regulated by specific legislation. In addition, protection of the quality of environmental compartments is an important objective of sectoral environmental laws and installation-related legislation such as the IPPC Directive / IED. Reduction of the total exposure of man and the environment due to complex environmental mixtures can only be achieved if all relevant groups of substances and the different types of pollution emitters are considered. Götz et al., 2010 proposes specific actions for the different exposure categories.

Kortenkamp et al. prepared an analysis of 21 European legal acts regarding aspects of mixture toxicity (Kortenkamp et al. 2009). It shows that current legislation does not properly take into account mixture toxicity aspects and risks from mixtures. Due to the sector and product focused structure of EU legislation with different assessment and risk management procedures each laws needs to be analysed separately to identify improvement options regarding addressing mixture toxicity and risks. It is not clear whether a horizontal framework legislation is required to overcome these challenges, but so far the political negotiations on this are not really reaching the surface. Moreover, The Danish EU Presidency mainly focuses on the 7th Environmental Action Programme as an instrument to advance the topic of mixtures in the future. This is likely to result into only a very general commitment by EU policy makers.

Four pieces of legislation have been identified as particular noteworthy regarding the assessment of mixtures among the 21 laws investigated in the state of the art assessment:

- REACH-Regulation (EC) No 1907/2006
- CLP-Regulation (EC) No 1272/2008
- Pesticide Residues Regulation (EC) No 396/2005
- Integrated pollution prevention and control (IPPC) – Directive 2008/1/EC.

With the exception of the Pesticide Residues Regulation, these legislations refer to industrial chemicals. In addition, the Water Framework Directive could address single industrial chemicals, if they are relevant for the quality of European Water Systems and if they are included in the Directive as priority pollutants.

The four regulations have different regulatory contexts and different purposes. This determines whether and to which extent they can be used as tools for the assessment of mixtures with regard to effects in the environment.

- REACH is the only legislation which addresses primarily the safe use of substances – as such, in (technical) mixtures and in articles. It is expected that more than 10.000 substances will be registered by the end of the third registration deadline in 2018. Chemical safety assessment of substances under REACH refers to the industrial, professional and private use of the substances. Registration is required only for substances – as defined under REACH (As described above, this definition includes isomeric mixtures, substances of unknown or variable composition and biological materials (UVCB) and multi-constituent substances (MCS)).
- The CLP regulation refers to the classification, labelling and packaging of substances and mixtures. It provides explicitly the framework for the classification of technical mixtures. However, this refers only to the assessment of the hazardous properties of the technical mixture with the objective of its classification. It does not include an exposure assessment and a risk characterization for the technical mixture.
- The Water Framework Directive (WFD) has the objective to ensure a high environmental quality of European water systems. It sets the obligation to reach environmental quality standards (EQS). It sets the focus on a limited number of 33 priority substances. It is under discussion to extend this list by further 15 substances. The assessment of the substances does not include mixture aspects at present. At least, possibilities to consider such effects have been discussed (Sydberg 2010). Consider the limited number of priority pollutants so far, it is unlikely that a reasonable fraction of relevant industrial chemicals can be included in this directive in the near future. Monitoring activities from the implementation of the WFD could be used as an important source of information to identify priority pollutants. Such priority pollutants could be one element in a prioritisation scheme for the assessment of technical and coincidental mixtures.
- The IPPC Directive aims to achieve a high level of protection of the environment taken as a whole. It refers to industrial activities with a high potential for pollution. These activities require a permit. Governing principle for all measures taken against pollution is the application of the best available techniques (BAT). Key instruments for pollution reduction are Emission limit values (ELV), which are based on the BAT. IPPC aims to reduce pollution to a technical minimum. Therefore substance specific hazard assessments and risk characterizations are not foreseen. ELVs are not restricted to single substances. They can be laid down for certain groups, families or categories of substances. Setting of the ELVs can include aspects of mixture toxicity, e.g. in the case of the Toxic Equivalence Factor approach for dioxins and furans. IPPC focusses on priority sectors, individual plants and sector specific processes and substances. There is no obligation to perform substance specific risk

assessments. Priority plants can perform whole effluent testing of their coincidental mixtures in order to document a low toxicity of their discharges.

Regarding accumulative exposure, a comparison of different legislation has been prepared by Gross et al. 2010.

Interfaces between REACH and sectoral environmental legislation have been analysed in several studies (e.g. Führ et al. 2010). Assessment of mixtures has not been in the focus of this analysis, yet. However, already regarding single substances it has been concluded that it is a major challenge to use existing interfaces between the legislation (e.g. to use PNECs as reference values for permits or to introduce REACH Annex XIV substances into the WFD). Recently, the European Commission published a study on the scope of REACH (Milieu 2012). The study looked at REACH and other EU legislation. In total 115 pieces of other EU legislation were considered. A closer interaction between REACH and the Water Framework Directive has been identified as one of 38 options to reinforce the coherence of the EU regulatory framework.

At least it is common understanding that REACH as the overarching substance-related legislation improves the quality of information on substance properties and exposure situations. This information could be used for sectoral legislations and plant related legislation such as IPPC. A discussion paper on this issue has been prepared by a working group of the German Federal Environmental Agency. It concluded that major efforts are needed to use existing interfaces between REACH and the other legislations.

## 1.10 Conclusions

Mixtures in the environment consist of different groups of substances. Industrial chemicals (which have to be registered under REACH) used in technical mixtures, build one of these groups. A reduction and minimisation of adverse effects of mixtures in the environment requires approaches which address the different groups of substances responsible for these effects. They are subject to different European legislations.

This report describes in the following concepts to assess technical mixtures under REACH (see chapter 2) – and options to act for different actors under REACH (see chapter 3). At present it is not clear which legislation or which combination of actions under different legislations offers the most effective way to reduce the adverse impact of mixtures, but it is likely to be a combination using several legal instruments. Therefore it is important to have similar activities focusing on mixtures and the WFD, on mixtures and the IPPC, and interfaces between legislations regarding assessment of mixtures.

## 2 Concepts for Environmental Risk Assessment of Mixtures and for Priority Setting

### Specific abbreviations used in this chapter

ACR	Acute to Chronic Ratio
AF	Assessment Factor
CA	Concentration Addition
CAG	Common Assessment Group; also used for “Cumulative Assessment Group” with identical meaning
CRA	Cumulative Risk Assessment
CRVTL	Chronic Reference Value specific for Trophic Level
ECHA	European Chemicals Agency
EPM	Equilibrium partitioning method
ETNCaq	Environmental Thresholds of No toxicological Concern for freshwater systems
HC5	Hazard Concentration 5: Concentration at which 5% of species are at risk
HI	Hazard Index, $HI = RQPEC/PNEC = \sum_{i=1}^n \frac{PEC_i}{PNEC_i} = \sum_{i=1}^n RCR_{,i}$
i	Index for chemicals contained in a mixture
IA	Independent Action
IF	Interaction Factor
Koc	Organic carbon normalized adsorption coefficient
MAF	Mixture Assessment Factor
MATS	Mixture assessment triggering substance(s)
MCR	Maximum Cumulative Ratio
MIAT	Mixture assessment team (A CEFIC team)
MoA	Mode of Action (identical to TMoA)
MoE	Margin of exposure
NOAEC/ NOAEL	“no observed adverse effect concentration / level”
PBPK Models	Pharmacokinetic based models
PEC	Predicted Environmental Concentration
PNEC	Predicted no Effect Concentration
POD	Point of Departure
QSARs	Quantitative structure activity relationships
RCR	Risk Characterization Ratio = $PEC_i/PNEC_i$
RCRTL	RCR for Trophic Level: $RCRTL = PEC_i/CRV_{i,TL}$

RQSTU (TL)	Risk Quotient from the Sum of Toxic Units for a Trophic Level: $RQSTU (TL) = (\sum_{i=1}^n \frac{PEC_i}{EC_{50} (TL)_i}) \times AF$
RQSTU	$RQSTU = MAX (RQSTU (TL))$ , TL = algae, aquatic invertebrates (inv.) and fish
SSD	Species Sensitivity Distribution
THI	Trophic Level Hazard Index: $THI = MAX (THITL)$ , TL = algae, aquatic invertebrates (inv.) and fish
THITL	Trophic Level Hazard Index for the specified Trophic Level: $THITL = \sum_{i=1}^n RCRTL,i = \sum_{i=1}^n \frac{PEC_i}{CRV_{i,TL}}$
TMoA	Toxic mode of action (identical to MoA)
TTC	Threshold of Toxicological Concern
TU	Toxic Unit

## 2.1 Introduction

This chapter describes concepts

- for hazard assessment, exposure assessment and risk assessment (related to the environment) of technical mixtures and
- for priority setting.

It includes in the beginning:

- a description of the **scientific “state of the art” of mixture toxicity** (section 2.2);
- a distinction between different **types of mixtures** (section 2.3);
- a detailed discussion of the **information provided under REACH** which could be the starting point for a mixture assessment (section 2.4).

Based on this, two types of concepts are described and discussed:

- **Concepts for the risk assessment of technical mixtures under REACH:** they aim to demonstrate the safe use of technical mixtures with regard to environmental effects (section 2.5).
- **Concepts for priority setting:** they are required to decide in which cases which of such mixture risk assessments should be applied and where to start if risk assessment of technical mixtures is integrated as a general principle into REACH (section 2.6).

It can be expected that the discussions at EU level will be an on-going, long-term process. It is therefore unlikely that the REACH review originally planned for 2012 (now postponed to 2013) will address specific points concerning any legal changes to REACH to address combination effects from chemical substances. Therefore we describe possibilities to use current REACH provisions and lay a greater emphasis on the risk of mixture effects. The proposed concepts refer to different actors under REACH. They differ in the degree of necessary changes and activities for their implementation.

The focus in this chapter is on the technical and scientific procedures for risk assessment of technical mixtures and for and priority setting, when to perform such risk assessments. Within this analysis, the actors involved and the regulatory conditions have been considered. (In the

next chapter 3, it is described and analysed in detail whether and how these concepts can be used by different actors under REACH).

## **2.2 Risk assessment of Mixtures: State of the Art**

This chapter documents the starting point for an environmental risk assessment of technical mixtures within the framework of REACH. It describes major recent scientific reviews and opinions from relevant institutions on this issue. However, this documentation is not meant to be an exhaustive and complete assessment of the current state of the art.

### **2.2.1 Main Conclusions from the “State of the Art report on Mixture Toxicity” (EC, 2009)**

#### **Relevant results**

In 2009, a “state of the art report on mixture toxicity” was published, which was prepared in behalf of the European Commission (DG Environment). This report covered four tasks, which were:

- analyzing scientific literature on mixture toxicity,
- analyzing EU risk assessment regimes relevant to mixture toxicity assessments,
- analyzing practical experiences in assessing mixture toxicity, approaches and methodologies used for this purpose in the EU,
- analyzing approaches (related to mixtures) to assess major competing economies of EU and international bodies.

This extensive report resulted in some relevant recommendations:

- It is reported from scientific research results that effects from mixtures are considerably more pronounced than the effects of each of its individual components (substances) and that environmental pollution is considerably aggravated by chemical mixtures. Therefore European guidelines for the assessment of chemical mixtures are recommended. Those should not only address human health but also environmental effects.
- Moreover, the legal mandate for mixture risk assessment in the European Union should be strengthened. This included the generation of know how to transfer scientific knowledge on mixture toxicity into appropriate regulatory approaches. The authors stress the promoting power from such a mandate in order to extend the knowledge of mixture effects and to improve the respective implementation.
- From the analysis of 21 Directives and regulations it is found that currently hazards and risks of substances (and sometimes products) are addressed in isolation. These pieces of legislation do not cover complex exposure situations from multiple substances. Therefore the authors recommend to explore options for the assessment of combined exposure within media and to extend legislation respectively. While some regulations like the Integrated Pollution Prevention and Control directive (IPPC) provide a basis for assessing mixtures of chemicals released from a definite source, those regulations would still not cover multiple sources.
- The recommendations include the application of concentration addition (CA) as a default assessment concept for mixture effects in tiered approaches. This conclusion is backed by the scientific research results as a conservative approach and would be compatible with similar recommendations from the International Programme on Chemical Safety (IPCS)

from the WHO and are in accordance with the Globally Harmonized System (GHS) for classification and labelling.

- It is recommended to generate data in a way, which they may be better applicable to mixture risk assessments (beyond and in addition to single substances assessments). The study design and reporting could be modified accordingly. As an example, the reporting of “benchmarks” at a uniform effect size level (e.g., with a benchmark response on 10%) is supported (instead of the more heterogeneous reporting of a “no observed adverse effect level” (NOAEL), which is erroneously sometimes regarded as a zero-effect level but is indeed a not clearly defined effect level).
- Further research needs are identified for better selection of priority mixtures and, for example, to understand determinants of synergistic effects.

### **Applicability for the current project**

The “state of the art report” (EC, 2009) provided most of the crucial data considered in the present report as proposed below. The results as presented in the “state of the art” report also influenced other work and opinions by various working groups and committees as referenced in sections 2.2.1 - 2.2.10. The report does not directly call for a change within REACH. However, with the request to implement European guidelines for the assessment of chemical mixtures this recommendation also has implications on the REACH regulation on chemicals. It is assumed that the information prepared and presented in chemical safety reports (CSR) on single substances under REACH

- should be compatible with further regulations addressing mixture effects,
- should provide the generated data in a way that they may also be used for mixture risk assessment, and
- should include mixture risk assessments as soon as there is sufficient clarification how to identify “priority mixtures”. One possibility for prioritisation would be on the basis of a causal relationship between marketing of a chemical and relevant contribution of this marketing to mixture effects.

The “state of the art report” calls for “concentration addition” as a default mixture assessment procedure. It also favours a tiered approach (to include advanced understanding of mixture effects where proportionate and the respective data are available) and it proposes to focus on “mixtures of concern”. All these recommendations are addressed in the present report. However, a clear definition on what is called a “mixture of concern” is not yet available. For the further discussion of this issue in different legal frameworks it would be helpful to have such a definition. Examples on “mixtures of concern” could enhance this step. Within the context of REACH, it is necessary to provide such a clear definition.

## **2.2.2 Main Conclusions from the EFSA-Project on Identification of Cumulative Assessment Groups of Pesticides (DTU, 2012)**

### **Relevant results**

An EFSA-report on the “identification of cumulative assessment groups of pesticides” prepared by the Technical University of Denmark (DTU) was published in early 2012 (DTU, 2012). The objective of the respective study was to identify common assessment groups (CAGs) for the human toxicological risk assessment of mixtures for pesticide active substances. In human toxicology, a CAG could be a group of substances which are assessed together with the

assumption of dose addition – because they affect the identical target organ or because they act via a similar mechanism of action.

The authors identified 4 levels of CAGs and assigned effect concentrations or no adverse effect concentrations of 224 active substances to each of these CAGs, if respective data were available. Levels for CAGs were structured from tier 1 (CA level 1: common assessment group at the target organ or tissue level) to tier 4 (CAG level 4 with an identified common mechanism of action). Level 4 was only reached for few substances and mechanisms because of lacking data and understanding for most of the substances/ mechanisms.

### **Applicability for the current project**

The DTU-project (DTU, 2012) contains valuable information and systematic work in order to classify pesticides (and other substances) with respect to their target organ toxicity. For pesticides this work provides information on the specific critical target organs and permits to use the NOAEL in the respective target organ instead of the generic “acceptable daily intake” (with no specific target organ assigned) for mixture risk assessment. This is an important improvement because, in a strict sense, dose additivity would only be justified, if the identical target organ is affected by all substances from a CAG within a mixture. Therefore those more specific target organ reference doses are needed for a higher tier dose addition mixture risk assessment. An even more qualified high tier assessment needs to consider CAGs on a “similar mode of action” - or even “similar mechanism of action” - level (CAG level 3 or 4). But these high tiers, as indicated, will usually not be reached.

As the DTU-project was concerned with human toxicology and only with pesticides, this project has only limited implications on the current project on ecotoxicological mixture effects and REACH-related substances. However, the basic idea to provide distinct information for the separate “target organs” may be transferred to the ecotoxicological assessment scenario. A common target organ in humans is, to some degree, similar to a common species in ecotoxicology. If mixture effects are discussed on the generic PNEC-level, it is “comparing apples and oranges” because toxicity data in fish and daphnia are mixed together and handled as if they were identical species. The background idea in the DTU-project, to combine only those substances in a CAG, which affect the identical target organ, corresponds to the idea in ecotoxicology to combine those substances to a CAG, which affect the identical species or – at least – which affect the identical trophic level (fish, daphnia, algae). At this CAG level we do not yet take account of the different sensitivity of the various species and response to different chemicals within a trophic level and we do not discriminate the mode of action which may or may not be identical for the various species at different trophic levels. At higher tiers one could try to combine data, where substances act via an identical mode of action to the identical species. However, as in human toxicology, there will not be sufficient data to realize such a high tier assessment.

### **2.2.3 Main Conclusions from an EFSA-Project on Mixtures of Substances with Dissimilar Mode of Action (Kortenkamp et al., 2012)**

#### **Relevant results**

This project (Kortenkamp et al., 2012) aimed to 1) summaries the state of the science on combined action of chemicals in food though dissimilar modes of action, an 2) to propose a science-based approach of performing the related cumulative risk assessment (CRA). The project progressed through six project tasks, cumulating to the respective report (task 6).



Task 1 was to collect and scrutinize the relevant scientific literature. Studies and reviews discussing mixture effects from mixtures with components (substances) assumed to be acting via dissimilar modes of action were collected and assessed and archived in a database called CRADIS.

Task 2 was to summarize and assess the state of science. With a focus on low dose effects the methodology of the existing studies was reviewed and the consequences were assessed. If study results are compared it turned out that the differences between “independent action” and “dose addition” effect predictions were usually small: they differed by less than one order of magnitude, even for mixtures with a high number of components. The data requirements in legislation on mixture effects were also analysed and documented.

Task 3 was to propose scientific criteria for establishing cumulative assessment groups (CAGs) of pesticides and other types of chemicals when dissimilar mode of action is a relevant mechanism leading to a common effect, in order to perform dietary risk assessment for regulatory purposes. Major problems to find demarcations of the term “dissimilar mode of action” were identified and discussed and the consequences for a strategy for grouping and mixture assessment were presented.

Task 4 was to assess the available approaches and methods for risk assessment of mixtures of pesticides and other chemicals in or on foods showing dissimilar mode of action. The approaches discussed by various bodies (U.S. EPA, EFSA, WHO/IPCS) were described and analysed. The use of tiered approaches in CRA was considered in detail and integrated into the final proposal.

Task 5 was to propose a science-based approach for performing cumulative risk assessment of chemicals in food acting through dissimilar modes of action. An approach was proposed that unifies the assessment of similarly and dissimilarly acting chemicals based on pragmatic use of dose addition. Therefore, distinctions on the mode of action were not included in lower tiers. According to this methodology, at higher tiers, and only if risks identified at lower tiers were deemed unacceptable, chemicals should be grouped together, if those evoke a common adverse outcome.

The overall conclusion of this project is that it is feasible and justified to utilize CRA methods also for combinations of dissimilarly acting substances. From this it is concluded that a unified approach for dealing with mixtures in regulatory practice is possible, irrespective of the (often presumed) mode of action.

### **Applicability for the current project**

Again, this EFSA project (Kortenkamp et al., 2012) is related to mixture effects to humans and is therefore of limited applicability to the current project on ecotoxicological effects of mixtures and the respective consequences under REACH. However, one of the main conclusions, which is the small difference between IA and CA assessment results was directly derived from ecotoxicological data as, in this case, human toxicological data were lacking. Therefore this important result may be used equally for the current project. Similarly, the principle idea of a tiered approach is not restricted to human toxicological risk assessments. Within the EFSA project it was not finally decided, in which situations such an assessment should be initiated. This could be the assessment of a single food item (“mixture risk assessment on the pesticide residues and contaminants in a salad crop”), it could be the assessment of a full meal including all other food items or it could be the assessment of the abstract food basket including, e.g., also drinking water. Because of these uncertainties the exposure scenario for the mixture effects was not specified in detail. It was, however, decided to restrict the assessment of

chemical mixtures taken up simultaneously. Therefore, there is not much to learn from the exposure assessment in the EFSA project. Finally, the situation in the current project and the EFSA project is very similar with regard to the fundamental data gaps. Lacking information on substance properties, modes of action, similarity or dissimilarity and questionable data on interaction in combination with an infinite number of possible mixture combinations is characteristic in both types of assessments.

## 2.2.4 Results from the ECETOC-Report (ECETOC, 2011)

### Relevant results

Recently ECETOC issued a “... guidance for assessing the impact of mixtures of chemicals in the aquatic environment” (ECETOC, 2011). As up to now literature guidance on practical assessment of mixture toxicity in risk assessment is scarce, the relevant aspects and ideas are summarized.

ECETOC finds that the most important theoretical concepts continue to be concentration addition (CA) and independent action (IA), whereas synergisms and antagonisms are only rarely observed and in respect to risk assessment according to ECETOC are of no major concern. Concentration addition is regarded as the default assumption in risk assessment. It is generally regarded as reliable, however conservative especially when applied for compounds of no common or unknown toxic mode of action (TMoA). This is because CA is believed to be strictly true only for chemicals acting via non-polar narcosis (baseline toxicity) and thus is applied for example in the hydrocarbon block method for petroleum substances. In contrast, chemicals exerting specific TMoA are likely to have threshold concentrations. Below these however they contribute only to baseline toxicity. For CA, concentrations of chemicals below their true no effect concentrations may cause toxic response when present as part of a mixture. This is not the case for IA (response addition). Because in most circumstances TMoA of mixture constituents are not known CA is applied as conservative default.

Based on the findings, described above, we conclude

- that adverse effects from environmental mixtures appear to be relevant,
- ECETOC reports on concepts of mixture toxicity, which are currently applied for example in the CLP regulation (EC 1272/2008) for environmental classification of mixtures (CA), for plant protection products (CA for the assessment of combined effects of several active substances or formulation toxicity; EFSA, 2009) and which are proposed in relation to the derivation of environmental quality standards (EQS) on behalf of the EU Water Framework Directive in TGD 27 (EC, 2011). Here, for mixtures like plant protection products or other intended technical mixtures of known and reasonable constant composition an optional derivation of EQS based on CA-concepts for the joint action of mixture components is allowed for and may be preferred case by case as an alternative to single substance assessment (or as a supplement). Proposed concepts are the toxic unit (TU) approach based on summing up the fractions of (predicted or measured) water concentrations (PEC) and PNEC (denominator), the hydrocarbons block method for petroleum substances based on CA and including application of non-testing methods for filling of data gaps as well as the toxic equivalency (TEQ) approach. The latter may be used for setting EQS in case of grouped substances exerting a similar mode of action and is used for example for PCDD/F and dioxin like - PCBs. The TEQ is defined as the sum of products of environmental concentration times TEF (toxic equivalency factor) for each compound of the group. The TEF for each compound

is calculated from the ratio of the particular PNEC and the PNEC of the compound of highest toxicity for a constituent belonging to the same group of substances (EC, 2011).

However, in the author's opinion, current risk assessment factors on the single substance level already cover combined action of pollutants to a certain extent due to their (postulated) inherent conservatism. They point out further that, in their view, the potential of prospective environmental risk assessment of mixtures (e.g. for mixture products or sewage treatment plant effluents) would be of very limited use. The information retrieved is valid only for the point of emission. Due to subsequent dilution effects and differential environmental fate and behaviour of the single mixture constituents, their environmental concentrations change and thus also PEC/PNEC ratios. For these reasons the ECETOC guidance focusses rather on retrospective assessment of mixture toxicity.

Retrospective evaluation of the potential environmental impact of chemical mixtures involves the qualitative and / or quantitative description of environmental deterioration as prerequisite for causal analysis. A suitable reference condition ideally not influenced by human activities has to be defined for comparison with the actual environmental state in question. Different methods are presented to this end and the reader is referred to the original publication for further details.

ECETOC discusses the "Direct Toxicity Analysis" (DTA) as one of the current approaches to address mixture effects. DTA gives a measure of total toxicity without necessity for single substance identification (whole sample tests with e.g. effluent, receiving water or sediment). The authors emphasize that even though DTA or other results may show the influence of chemicals on the ecosystem, other factors than chemicals may be dominating in causing ecological impact, e.g. ammonia, DOC or sediment deposition. To discern these, the Causal Analysis / Diagnosis Decision Information System (CADDIS, <http://www.epa.gov/caddis>) is discussed as hierarchic logical decision matrix developed by US EPA from multiple types of eco-epidemiological evidence with examples being accessible from the web page.

In the last section of the document whole ecosystem analysis concepts and examples for their application are presented. These so called eco-epidemiological studies gather a plethora of data like physico-chemical characteristics, water quality data, geographical position, drainage area and river reach slope, biota and chemistry. These data are integrated to determine relationships of biota and chemistry applying statistical analysis methods for attributing potential causality. In addition, the authors describe a concept integrating potential toxic effects caused by chemicals present in the local environment rather than trying to analyse the potential effect of single chemicals on species distribution and abundance. Based on Species Sensitivity Distributions (SSD) and the combination of CA and IA concepts of mixture toxicity the multi substance potentially affected fraction (msPAF) of species as a measure of "acute toxic pressure" is determined. For further details on SSD see de Zwart and Posthuma (2005).

### **Applicability for the current project**

The review of CA- and IA-models, their characteristics and applicability is in line with initial ideas for the current project of integrating aspects of mixture toxicology in the frame of REACH regulation. However, some opinions, like the statement that current assessment factors would be large enough to (partly) cover mixture effects, are not supported by the current state of knowledge on single substance low dose extrapolation (KEMI, 2010). A special aspect is the notion that concentration addition may be strictly true only for chemicals acting via nonpolar narcosis (baseline toxicity). In addition, chemicals exerting a specific TMOA are believed to have a certain threshold beyond which they will solely contribute to (unspecific) baseline toxicity.

However, these ideas, although plausible, have yet to be validated and transformed into quantitative substance specific data to be fully applicable. If at all, the respective information will only be available at higher tier risk assessments on mixtures and leads to (concentration dependent) nonlinear impacts. However, the conditions to implement this high tier approach are currently not provided with the information available under REACH.

In case of the species sensitivity distributions, de Zwart and Posthuma (2005) link several methodological elements: concentration addition for chemicals with similar TMOA and then applying response addition for these action groups in case of predicted effects. To enable similar approaches, data provided by REACH would have to be much more detailed in regard to concentration-effect relationships. A mathematical expression for the dose-response curve for each chemical would be needed.

## 2.2.5 Results from the KEMI-Report on Hazard and Risk Assessment of Chemical Mixtures under REACH (KEMI, 2010)

### Relevant results

The KEMI-report on „hazard and risk assessment of chemical mixtures under REACH“ (KEMI, 2010) comes much closer to the topic in question of the current project. The report summarises the “state of the art, gaps and options for improvements” as assessed by the authors.

The study starts from the observation, that exposure to “multi-component chemical mixtures” is the realistic standard exposure scenario for humans and environmental species. From scientific evidence it should be assumed that “joint toxicity of a chemical mixture is always higher than the individual toxic effect of even the most toxic compound present”. Therefore some acknowledgement of these mixture effects and protective measures is proposed. The authors regret that “REACH does not provide a mandate for considering the toxicity of so called ‘coincidental’ mixtures of industrial chemicals”. Therefore a difference to some other regulations is recognised where mixture effects are directly addressed (like the regulations on plant protection products). It is requested “to cut across the existing pieces of chemicals regulation” in order to regulate mixture effect consequences appropriately. For example, the Integrated Pollution and Prevention Control Directive (IPPC) and the Water Framework Directive (WFD) “might provide particularly valuable options for improved protection ... from risks from mixtures of chemicals”.

KEMI discusses two options to address mixture effects under REACH: 1) the use of a default “mixture assessment factor” (MAF), and 2) scenario specific cumulative risk assessments. To put those options into work, the authors regret “substantial knowledge gaps”. Especially knowledge on typical exposure scenarios involving REACH-chemicals as found to be missing. The authors find that knowledge about the (dis)similarity of the modes of toxic action of most components (substances) is scarce, or even absent. With the current “(eco) toxicological data that are generated or compiled during the registration of industrial chemicals with REACH, ... a case-by-case approach is certainly not possible”, where mechanism-driven case-by-case assessments are performed. Consequently, the authors support a default approach by concentration addition (CA) if a scenario specific risk assessment is to be performed. They refer to calculations which show only limited differences between CA and IA calculations and they argue that a full IA-approach is not justified because of the baseline unspecific, “narcotic” mode of action by most organic compounds, which justifies, in parts, some CA assumptions. “Especially the (eco) toxicity of some industrial chemicals that are registered within REACH can be expected to be explained to a good deal by such narcotic mode of action”.

Within the discussion on the mentioned MAF-approach it is pointed out

- that the current assessment factors used under REACH do not cover combination effects (“contrary to a popular belief”),
- that the appropriate factor could be linked to the typical number of substances (n) occurring in a mixture, because, for concentration addition, the (mathematically justified) MAF is equal or smaller than n in order to adequately account for such addition effects,
- that, more precisely, only those substances need to be accounted for, which contribute to a common ecotoxicological endpoint,
- that, as derived “from episodic findings”, only few major substances may contribute significantly to the mixture effects with much lesser contributions by the other constituents, which may argue for a somewhat smaller MAF.

The authors report a proposal in the Netherlands, where an assessment factor of 100 is applied to derive so-called “negligible concentrations”. This factor should also provide a safety margin for combined toxicity (It is not stated, where this factor is implemented into regulatory practice).

The authors finally provide six concluding recommendations:

1. an amendment to REACH should be incorporated similar to the one in the new PPP regulation explicitly addressing risks from mixtures and the respective protection goals
2. two options to take account of mixture effects should be considered, i.e. the MAF-approach and a cumulative risk assessment approach
3. existing guidelines for mixture effects should be studied and may be regarded as a good starting point to develop a guideline to address mixture effects for REACH on its own, but also “trans-sectoral strategies” to account for such effects
4. Specifically develop guidelines for ecotoxicological assessment of chemical mixtures, as those are not yet elaborated. Those guidelines could also be linked to the “Water framework directive” as an environmental media oriented piece of regulation.
5. Consider amendments or modifications of the CLP – directive to specifically address mixture effects for classification of environmental mixtures more adequately than currently established.
6. Analyse exposure scenarios under REACH (like “sectors of use”, “product categories”, “article categories”) to create and define typical exposure scenarios with respect to industrial chemicals usable for targeted mixture risk assessments.

### **Applicability for the current project**

The KEMI-report (KEMI, 2010) confirms many of the findings already discussed more generally in the reviews and opinions stated above (sections 2.2.1 - 2.2.4). It also confirms that, at present, the REACH regulation is not designed and not adapted to adequately address mixture effects. Respective amendments are outlined and requested.

The study focusses on “coincidental mixtures” without an intermediate consideration of other potential mixture effects which are more closely under control of the REACH registrant or downstream user (formulator or end-user), i.e., technical mixtures or discharge mixtures (at the point of entering the fresh water in the effluent of a sewage treatment plant). Possibly, some conclusions would have been modified, if this specific goal had been addressed in a more

targeted way. Scenario-specific cumulative risk assessments are mentioned, but feasibility to perform the respective risk assessment under REACH are not elaborated in detail.

The project report is very helpful in describing the various options to address mixture effects including the MAF-approach with its strength and weaknesses. The authors favor regulations which include REACH but also “cut across the existing pieces of chemicals legislation”. From an overall perspective, this is an important postulation in order to integrate the various sources which contribute to mixture effects. Those may be industrial chemicals, pharmaceuticals, pesticides or others, all entering identical media from multi-sources and possibly effect the health of environmental species.

## 2.2.6 CEFIC-Approach with the MIAT combined Decision Tree (Price and Han, 2012)

### Relevant results

In June 2012 a workshop on mixture effects was held by CEFIC in Brussels, Belgium. The “mixture effect assessment team” (MIAT) had developed a decision tree to decide on the relevance of human and environmental mixture effects. For this purpose, a calculation of the “maximum cumulative ratio” (MCR) is performed and combined with the WHO tiered approach (Meek et al., 2011), which is also supported by European Scientific Committee..

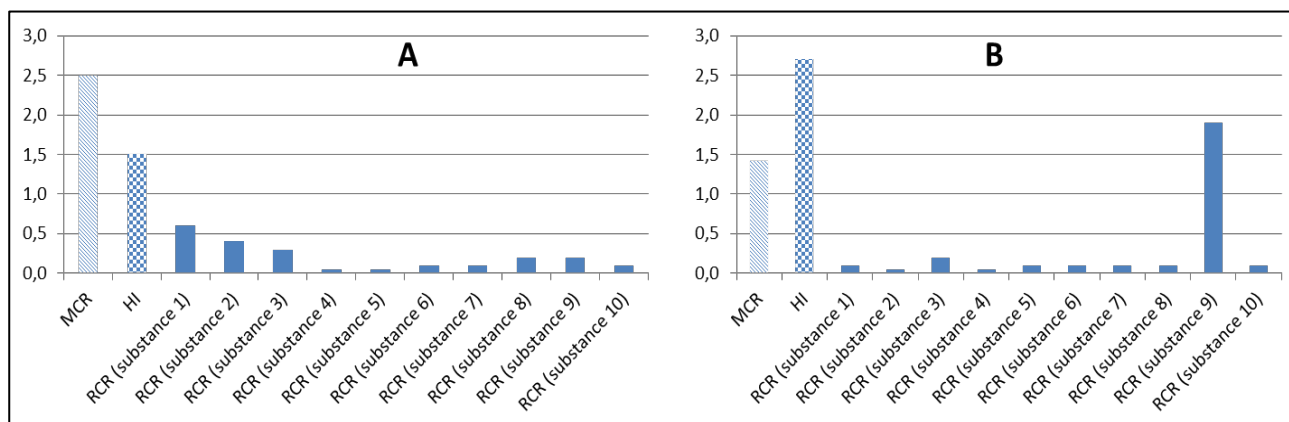
The MCR is defined as the calculated hazard index (HI) from a mixture divided by the maximum risk characterisation ratio (RCR) of the single substances within the mixture.

Using the terminology of the authors:

$$\text{MCR} = \frac{\text{Cumulative Toxicity}}{\text{Maximum Toxicity from One Chemical}}$$

MCR is not a measure of risk. Instead, it is regarded as a measure of the need for a combined risk assessment. Two examples may demonstrate the application of the MCR. Assume a Hazard Index of 1.5 for 10 substances within a mixture and the maximum RCR assigned to one of these 10 substances is 0.6. In this case the MCR is  $1.5/0.6 = 2.5$ . Then, assume another mixture with a hazard index of 2.7 and the maximum RCR assigned to one of these 10 substances is 1.9. In this case the MCR is  $2.7/1.9 = 1.4$ . Both situations are described in the study. The authors find that a mixture risk assessment would only be demanded in the first case (case A) with  $\text{MCR} > 2$ , whereas the probability of mixture effects are regarded to be low if MCR is  $< 2$  (case B).

**Figure 10:** Maximum Cumulative Ratio (MCR) and Hazard Index (HI), Examples with a MCR >2 indicating a relevant mixture effect (A) or non relevant mixture effect (B) (MCR < 2), for further explanation see text (source: Price and Han, 2012)



In addition, they found from statistical analysis of a large set of mixtures that, in many realistic cases, MCR is often close to 1 and in much less cases < 2.<sup>26</sup> In the next step, the authors discriminate 4 different outcomes of the MCR- and HI-calculations:

Group I: HI>1 and max RCR>1

Group II: HI<1

Group IIIA: HI>1 and max RCR < 1 and MCR < 2

Group IIIB: HI>1 and max RCR < 1 and MCR > 2

They suggest, that mixture assessment is not needed with Group I or II, is not important with Group IIIA and has to be considered with Group IIIB (HI>1 and max RCR < 1 and MCR > 2). In our example, Case B corresponds to Group I, and Case A corresponds to outcome Group IIIB.

The complete decision tree as proposed by CEFIC is shown in Figure 12. With 559 mixtures consisting of 222 substances with realistic exposure data for ecotoxicity they calculated the cloud of outcomes. Those are shown in Figure 13. The authors comment that only for 6% of 222 analytes the outcomes fell into group IIIB. Those exposures were driven by a small number of chemicals (four metals, two pharmaceuticals and a flame retardant in one set of data and three industrial chemicals, one herbicide and its degradation product, one pesticide, one pharmaceutical and one hormone in another set of substances). They propose to advance to higher tiers mixture assessments only in those cases.

### Applicability for the current project

The CEFIC project (Price and Han, 2012) is interesting with respect to a) the methodology (MCR as a tool to assess the relevance of possible mixture effects), and b) the postulated outcome, which indicates that mixture effects are not assumed to be relevant in many cases for existing

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For human toxicity they found even a smaller number of cases where they regarded mixture assessment as important. Often only few substances dominated the combined effect if HI was >1 Price, P.S.; Han, X. (2011); Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment; International Journal of Environmental Research and Public Health, 8, 2212-2225, ibid.

mixtures with realistic data (exposure and toxicity data at tier 1 level for toxicity information). Note, that the authors start their assessment with a conservative CA approach.

However, there are some relevant limitations in using these results for the current project with the present data available from REACH:

- It is assumed that measured data (as in the CEFIC project) significantly differ from the modelled low tier data, which would be provided as an enumerator in the  $RCR = PEC/PNEC$  ratio under REACH. Therefore, qualified information could only be expected and used with high tier PEC data (possibly, only with measured data). This limits the use of the MCR tool significantly.



Figure 11: Decision tree to decide for the relevance of mixture effects depending MCR (source: Price and Han, 2012)

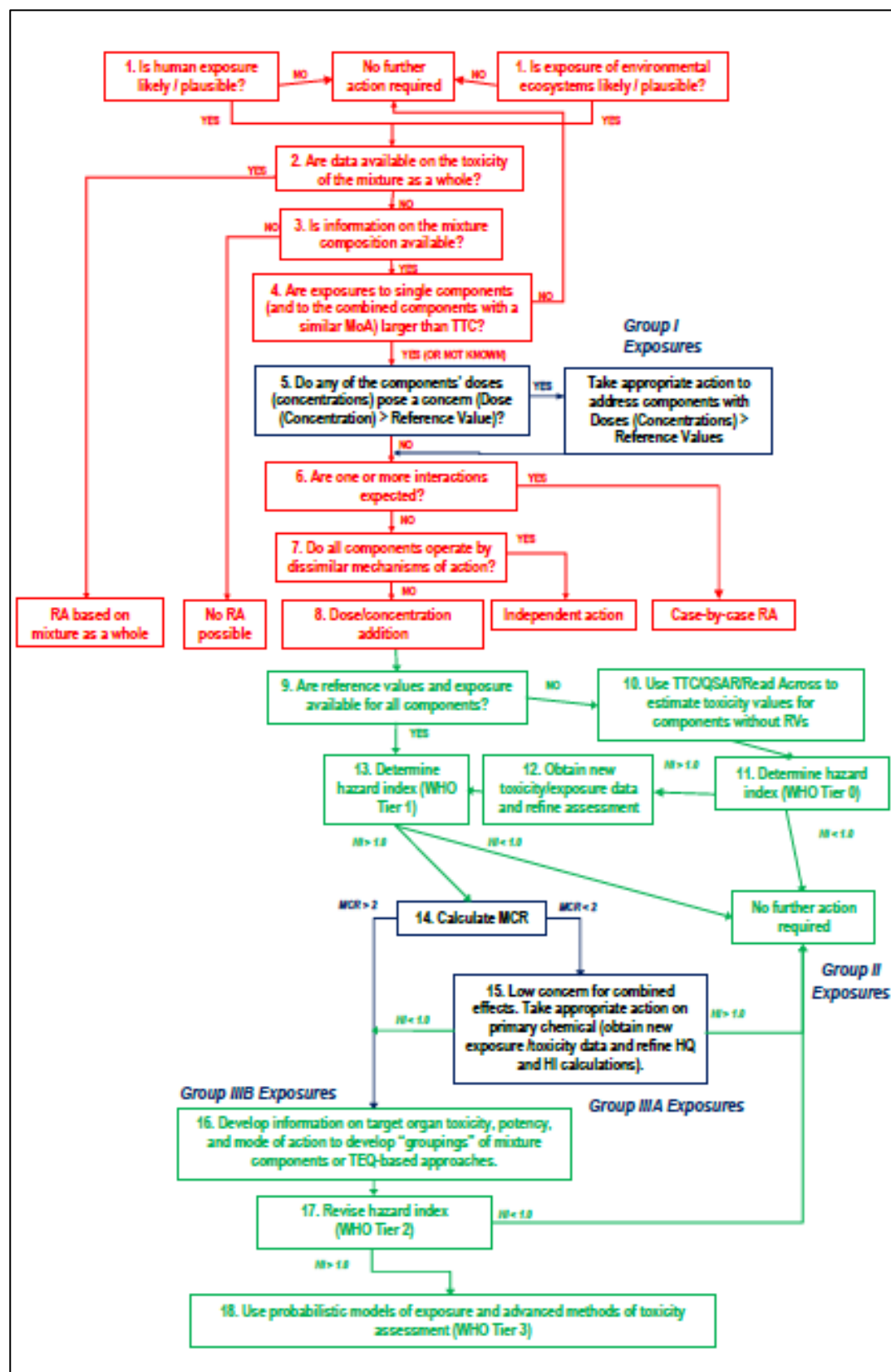
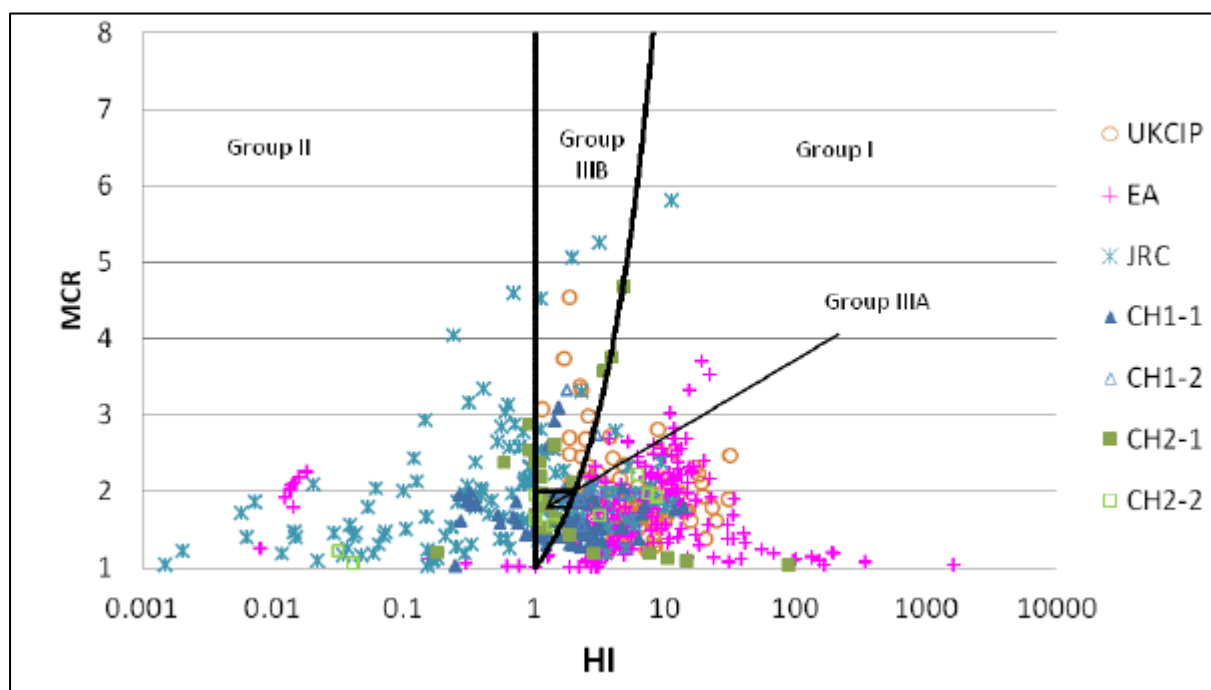


Figure 12: Distribution of MCR and HI with realistic example data in environmental risk assessments based on concentration addition (CA). Source: (Price and Han, 2012), different symbols (UKCIP, EA, JRC, CH...) correspond to different data sets.



- For small number of substances within a mixture categorization of outcomes (I, II, IIIA, and IIIB) may not be necessary because the calculations can be easily performed and analysed without this formalised procedure. However, for mixtures with a potentially large number of substances included (e.g., many discharge mixtures or environmental mixtures with identified substances based on monitoring data) the MCR tool may be very helpful.
- The statement, that the outcome of a small group IIIB (small number of mixtures where a higher tier mixture assessment is demanded) is representative has to be confirmed with more and qualified measured data. Principally, this would be an important result, because it would indicate that only in a limited number of cases industrial chemicals would lead to mixture effects if the concentration of the single substance (PEC) is below its own PNEC. This would limit the general relevance of mixture assessments in ecotoxicological risk assessments and its broad implementation.

However, the principles of MCR could also be used for a mixture assessment strategy within this project, e.g., as a simple and valuable cut off tool if qualified PEC data have to be analysed.

## 2.2.7 Results from the UFZ-project „Ökotoxische Kombinationswirkungen von Stoffgemischen“ (UBA, 2012b)

### Relevant results

The reported results below refer to draft project results presentations and an associated workshop: „Mixture Assessment in Biocidal Products Authorisation“, April, 24.- 25, 2012, Leipzig, UFZ, Germany (UBA, 2012a; b).

### **Project documents cover**

- The state of scientific knowledge on mixture toxicity (largely reported similarly in other respective recent reviews),
- Generic options for environmental risk assessment of mixtures (discussing the conditions, strength and weaknesses of CA, IA, whole mixture approaches and MAF),
- Environmental mixture toxicity assessment in the context of biocidal product authorization,
- Results from experimental studies on products and eluates.

As one element of the options to act the principle idea of a tiered approach was adopted. Based on sufficient evidence, in a second tier the possibility to assess mixture effects caused by IA was proposed. As explicated in an associated journal article (Backhaus and Faust, 2012) it is also proposed to include an intermediate tier, where the PNEC is substituted by a trophic level specific reference point (for fishes, daphnia or algae).

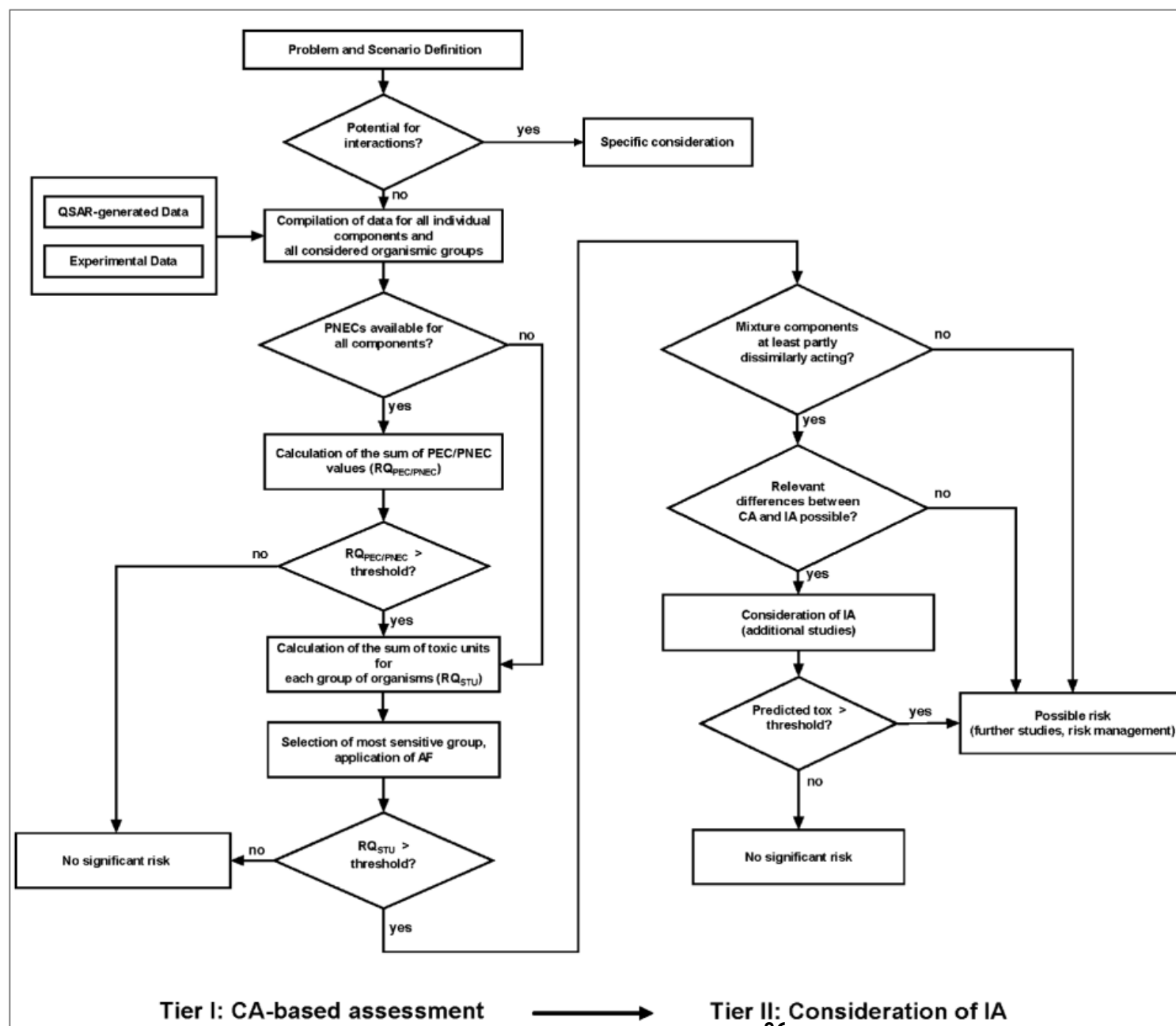


Figure 13: Tiered approach decision tree on concentration addition or independent action. (Note that a “threshold” in this decision tree would be identical to an index value of 1 (e.g., Hazard Index of 1) (source: (Backhaus and Faust, 2012))

In the workshop (UBA, 2012a) experiences and opinions from several member states authorities with mixture assessment in biocidal products authorization were presented. A special focus in this project and workshop was the discussion on three questions linked to the regulatory implementation of mixture risk assessment:

1. Can we introduce a tier between a PEC/PNEC summation and the summation of toxic units for defined endpoints?

No final answer was given to this question. However, the situation was described that there may be heterogeneous data from different trophic levels, species, endpoints, study design etc., which are to be harmonized before an appropriate “toxic unit”-approach for CA could be applied. There may be difficulties to identify the most sensitive species based on the given set of published data. There could be different ways to integrate an assessment factor (group assessment factor or on the single species data?) and there are questions how to employ extrapolation techniques (e.g., QSAR, acute to chronic modelling) to derive proxies for lacking data in a toxic unit approach.

2. What are “relevant substances”?

The question was closely linked to the area of applications (biocides) but extended beyond. It was confirmed that mixture assessment cannot be restricted to active substances of biocidal products only. Relevance relates to effects to non-target organisms in environmental risk assessment and not to the purpose of the products use. In case of lack or insufficiency of data product testing was proposed. The current definition of “substance of concern” as used in the Biocidal Products Directive may have to be extended for the purpose of mixture assessment.

3. Purpose and application of (additional) interaction factors (IF)?

The use of an additional IF could address uncertainties linked to the use of an additivity approach. Specifically, the possibility that synergism may not be fully excluded. Other sources of uncertainty were identified: model errors, mixture effects after sequential exposure (in addition to simultaneous exposure), additional effective substances, left out from mixture considerations (substances not considered as relevant substances, e.g., due to lack of data, but significantly contributing to mixture effects). Different scenarios to include or exclude an IF were discussed, e.g. default procedure, linked to product-type, or case-by-case considerations. There was no agreement on the use of an additional IF as originally proposed by Germany.

### **Applicability for the current project**

The results from the UFZ-Project (UBA, 2012a; b) are only partially applicable to the current project as the legal background (biocides, pesticides) is somewhat different from REACH. The definition of the mixtures to be looked at and the exposure situation differs from the scenario to be addressed under REACH. Usually, for the active ingredient of pesticides and biocides a more detailed (eco-) toxicological profile is publicly available, the most relevant exposure for pesticides is not via sewage treatment plants and the product (mixture) is subject to a distinct assessment of its own. The exposure assessment software differs from the one proposed under REACH. However, in the accompanying journal article (Backhaus and Faust, 2012) a proposal is presented which is very similarly discussed below as a higher tier assessment. The principles of a tiered approach are confirmed with CA as a low tier default procedure. The basic idea that all substances, if present in sufficient concentration in relation to their effect reference point in a mixture, may contribute significantly to mixture effects was also stressed at the Leipzig workshop on the UFZ project. Thus, not only those substances are relevant, which are defined as relevant due to their intrinsic properties (e.g. not only substances classified as environmental

harmful or substances assessed as “SVHC”). Finally, the discussion on the “interaction factor” (IF) is helpful to acknowledge the remaining uncertainties, which means, that CA calculations are not “worst case”- assessments, if such IF are not included in the assessment procedure.

## 2.2.8 Conclusions by EU Committees (SCHER/SCENIHR/SCCS, 2012)

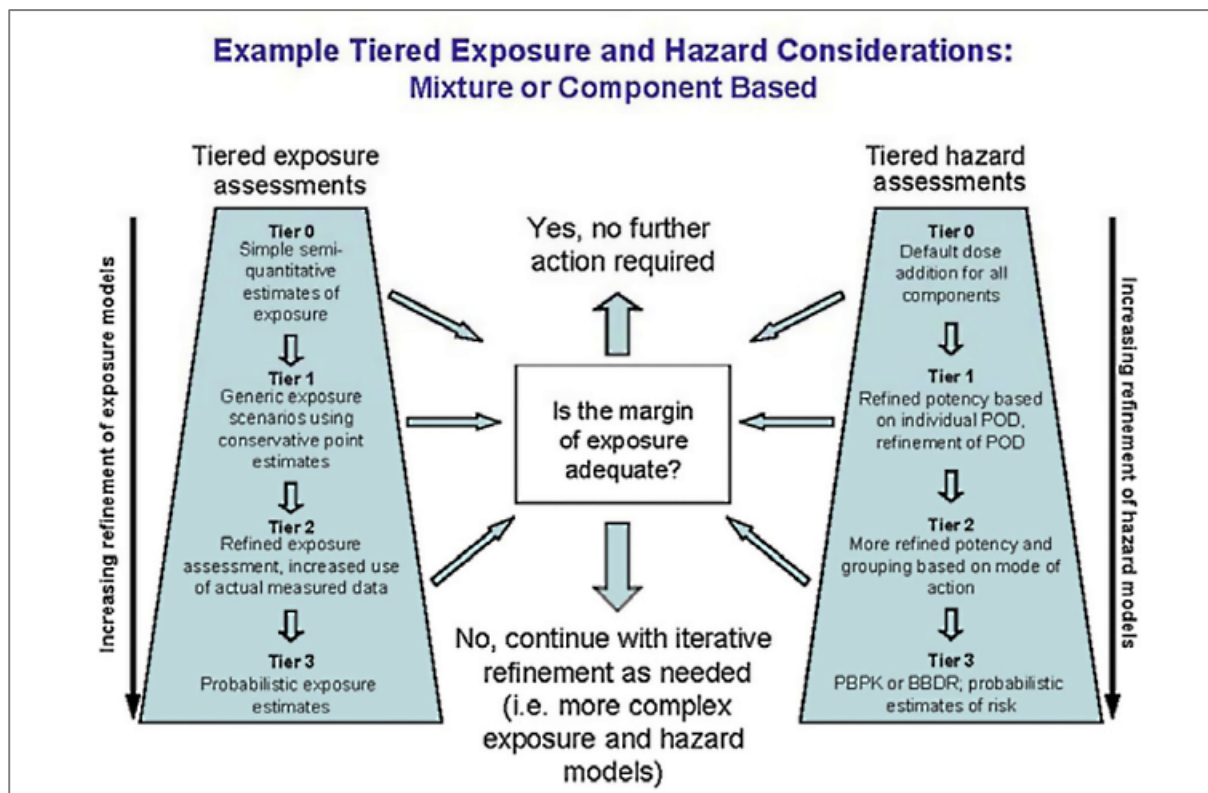
### Relevant results

In 2012 scientific committees of the EU (SCHER, SCENIHR and SCCS) published a consensus opinion on “toxicity and assessment of chemical mixtures” (SCHER/SCENIHR/SCCS, 2012). These committees concluded:

- under certain conditions, chemicals will act jointly in a way that the overall level of toxicity is affected.
- Chemicals with common modes of action will act jointly to produce combination effects that are larger than the effects of each mixture component applied singly. These effects can be described by dose/ concentration addition.
- For chemicals with different modes of action (independently acting), no robust evidence is available that exposure to a mixture of such substances is of health or environmental concern if the individual chemicals are present at or below their zero-effect levels.
- Interactions (including antagonism, potentiation, and synergies) usually occur at medium or high dose levels (relative to the lowest effect levels). At low exposure levels, interactions are either unlikely to occur or are toxicologically insignificant.
- In view of the almost infinite number of possible combinations of chemicals to which humans and environmental species are exposed, some form of initial filter to allow a focus on mixtures of potential concern is necessary.
- With regard to the assessment of chemical mixtures, a major knowledge gap at the present time is the lack of exposure information and the rather limited number of chemicals for which there is sufficient information on their mode of action. Currently, there is neither an agreed inventory of modes of action, nor a defined set of criteria how to characterize or predict a mode of action for data-poor chemicals.
- If no mode of action information is available, the dose/concentration addition method should be preferred over the independent action approach. Prediction of possible interaction requires expert judgement and hence needs to be considered on a case-by-case basis.

The authors support a tiered approach for mixture risk assessment and refer to the methodology as discussed at an earlier WHO-workshop and initially specified by Meek et al. (2011).

Figure 14: Tiered Approach for mixture effects according to a proposal from WHO (source: Meek et al., 2011)



With regard to the “almost infinite number of possible combinations of chemicals” the committees propose to focus on mixtures of potential concern. Specifically, they suggest to consider (SCHER/SCENIHR/SCCS, 2012):

- human and/or environmental exposure at significant levels (e.g., close to the PNEC for several components),
- chemicals that are produced and/or marketed as multi-constituent substances or commercial mixtures with several components and/or active ingredients and/or substances of concern,
- potential serious adverse effects of one or more chemicals at the likely exposure levels,
- likelihood of frequent or large scale exposure of the human population or the environment,
- persistence of chemicals in the body and/or in the environment. High persistence/bioaccumulation would be a property of importance,
- known information of potential interaction at levels of human and environmental exposure,
- predictive information that chemicals act similarly such as (quantitative) structure activity relationships and structural alerts.
- particular attention should be paid to mixtures for which one or more components are assumed to have no threshold for its effects such as genotoxic carcinogens; a MOE or a lifetime cancer risk approach could be applied.

These conclusions and proposals for priority setting were adopted by the European commission in 2012 in a communication on the combination effects of chemicals and were linked to a list of operational follow-ups (EC, 2012a).

### **Applicability for the current project**

The scientific committees provide information which is, in part, helpful for priorities and implementation strategies to address mixture effects under REACH. Specifically, we refer to the following conclusions:

- The committees confirm our understanding that the PNEC is not necessarily a zero effect level. Specifically it is stated “For ecological effects, the exposure to mixtures of dissimilarly acting substances at low...concentrations should be considered as a possible concern, even if all substances are below the individual PNECs.” (SCHER/SCENIHR/SCCS, 2012)
- They support a concentration addition as a plausible default approach in ecotoxicological mixture risk assessment.
- The committees support the use of a PEC/PNEC ratio as a first tier approach, even though this would not be the appropriate aggregation rule for a higher tier mixture risk assessment.
- The committees propose a group uncertainty factor in combination with a “toxic unit” reference point for higher tier assessments instead of using the PNEC. However, as discussed in section 2.5.2, this proposal by the committees has to be adapted to the data gaps and available substitute data generation under REACH and cannot be directly applied in our project.
- The committees propose cut off levels like the “threshold of toxicological concern” (TTC) for inclusion/ exclusion of substances into mixture effect considerations.
- The committees confirm that, currently, the data are insufficient to generally and systematically assign a specific “mode of action” (MoA) to a substance and to group substances according to their similarity with regard to this MoA.
- The committees cite study results which state that, assuming concentration additivity, only few substances dominate the mixture effect even in cases with many components within a mixture (Price and Han, 2012; Price and Han, 2011). It has to be noted, that this conclusion is claimed for human and environmental risk assessments on mixtures, but is more pronounced for mixture effects to humans.
- For priority setting, the committees favour approaches where an observed high PEC/PNEC ratio is a relevant selection criterion.
- Furthermore, the committees favour the search for “typical mixtures” from production, similarity in chemical structure and occurrence data as priority criteria.

These very important results are taken up below in our proposals to address mixture effects under REACH.



## 2.2.9 Main Conclusions from the Project UBA 360 01 058 (2011) on aggregated Exposure

### Relevant results

The ECHA Guidance Documents R.12 to R.18 include detailed provisions on how to conduct an exposure assessment as part of the Chemical Safety Report. The guidance documents, however, only restrictedly address the consideration of a substance's emissions into the environment, if the local releases from various uses of the same substance result in an aggregated exposure. In a situation where a chemical has a number of applications in one site, it may however occur that the emissions of several uses which only have a low risk if considered separately will sum up and cause an unacceptable risk to the environment.

Against this background, the study elaborated details on aggregated risk assessment according to the REACH Regulation.

Besides the definition of the key terminology, guidelines on aggregated exposure assessment already laid down in other legal regulations have been evaluated and their transferability to the environmental exposure assessment according to REACH has been investigated. Moreover, the fields of application for which an aggregated exposure assessment might be relevant have been worked out. A distinction was made between cases where the responsibility for an aggregated exposure assessment falls into the hands of the registrant as part of the Chemical Safety Report and other cases, where the responsibility lays with the downstream users (DU) or the Member State Competent Authorities (MS-CA).

Initial proposals have been elaborated for a technical implementation of the aggregated exposure assessment of chemicals as part of the preparation and evaluation of chemical dossiers by the registrant and the MS-CA, respectively, and as part of the responsibility of the DU.

### Applicability to the current project

The results have been used to describe options to act for final downstream users on aggregated exposures (sections 2.6.5 and 3.6.8).

## 2.2.10 Main Conclusions from the Project UBA FKZ 3710 63 403 (2012) on DPD+

### Relevant results

The DPD+ method,<sup>27</sup> named to refer its foundation on the principles of classifying mixtures defined in the Dangerous Properties Directive (DPD), was developed by CEFIC to facilitate the consolidation of information from exposure scenarios of substances used in on mixtures by their formulators.

The method's core is the derivation of so called lead substances indicators, which are calculated based on a substance's classification and its concentration in the mixture, for which

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<sup>27</sup> CEFIC: REACH: Exposure scenarios for preparations - Methodology for the identification of substances that represent the dominant risks to human health and/or the environment and the drivers for risk management measures, June 2009. Available at: [http://www.cefic.org/Documents/IndustrySupport/ES\\_for-preparations-DPD+methodology.pdf](http://www.cefic.org/Documents/IndustrySupport/ES_for-preparations-DPD+methodology.pdf)

information is developed. Only the information from the exposure scenarios of the lead substances is transferred to the safety data sheet (or an annexed ES), thereby reducing the amount of information to be assessed and forwarded.

A study commissioned by the German Environment Agency<sup>28</sup> analysed if environmental risks could be overlooked and / or risk management measures necessary to avoid risks would not be communicated, if the method were applied by the formulators.

Among others, it was concluded that

- in the consolidation of RMMs the substances' mobility needs to be considered in order to include all relevant emission pathways to the environment
- the efficiency of RMMs may considerably differ for substances of different groups (organic, inorganic, metals etc.) and hence, RMMs controlling risks for the lead substance may not be (sufficiently) effective for components in the mixture
- the classification system with distinct steps between e.g. the category R50 and R51 can distort the relevance of substances in a mixture (LC50 of 0.99 mg/l leads to R50; LC50 of 1.01 to R51) and hence the correct selection of a lead substance
- the air pathway is insufficiently addressed, due to a lack of respective classification categories

For the environment, the DPD+-method does not take mixture toxicity aspects into account, because only one of the substances in the mixture is selected to determine the risk management measures for the environment.

There is no specific guidance provided in how the information from a substance exposure scenario is transferred to the safety data sheet (or annex) of a mixture. However, CEFIC recommends “consistency checking” at the end of the process.

### **Applicability to the current project**

The results of the evaluation of the DPD+ method are not relevant for this project.

## **2.2.11 Conclusions: Key Findings from other Projects – Consequences for this Project**

For our proposal of an approach for the ecotoxicological assessment of mixture effects we conclude on some key findings presented in sections 2.2.1 to 2.2.10. They – to a large degree – summarise the current state of the art. These conclusions are specified for surface water as environmental compartment and have to be adapted or extended, if other environmental compartments are looked at:

- In case of similarly acting substances concentration addition (CA) may reasonably be assumed as principle mixture effect, also to be assumed in low concentrations below single substances' PNEC

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<sup>28</sup> Consolidation of information on mixtures under REACH – Analysis of the DPD+-Method (FKZ 3710 63 403). The report is not published yet but a draft executive summary is available at: [http://www.reach-hamburg.de/fileadmin/user\\_upload/dokumentationen/Materialien/4\\_5\\_3\\_Kommunikation\\_in\\_der\\_Lieferkette/120430\\_Mixtures\\_under\\_REACH\\_Exec\\_Summary.pdf](http://www.reach-hamburg.de/fileadmin/user_upload/dokumentationen/Materialien/4_5_3_Kommunikation_in_der_Lieferkette/120430_Mixtures_under_REACH_Exec_Summary.pdf)

- In case of dissimilarly acting substances concentration addition is a conservative approach. With very low exposures the assumption of independent action (IA) may be more appropriate.
- There is no clear threshold for mixture effects from independently acting substances at single substances PNEC-level or below. Therefore, IA may also be a relevant mixture effect below the single substances' PNEC.
- The dose response data (dose-response curve) for single substances in the various species is rarely known apart from single distinct effect are levels like EC<sub>50</sub>. Therefore, calculations based on IA are not generally feasible as a routine regulatory approach.
- Differences between mixture effect sizes calculated according to the CA approach in comparison to those calculated with the IA approach are usually small, if a) those are calculated at exposure levels above single substances' effect thresholds, b) the number of substances within the mixture is limited.
- Synergistic action within a mixture is rarely observed at effect levels close to single substances' PNEC. If it is observed the extent is limited with regard to the quantitative consequences on the mixture effect size. There may, however, be exemptions with relevant synergism, e.g. under the influence of metal compounds. No general quantitative conclusions may currently be derived for integration such synergistic influences.
- Also, antagonism is rarely observed at low exposure concentrations. There is no focus on potential antagonisms as those should usually not be taken into account within a precautionary regulatory framework for mixture effect assessment.
- The distinction between similarly and dissimilarly acting substances is not feasible in most cases because of a) limited information on the respective mode of action for the single substances, b) the complexity of calculations necessary to cover all pairwise or multiple similarities and dissimilarities within multi-substances mixtures in various concentrations and under further environmental exposure conditions, c) complexity may even expand because "partially similar" / "very similar" and "slightly similar" differentiations may have to be discriminated.
- Therefore, only exceptionally defined substance combinations may be taken as a "cumulative assessment group" (CAG). This situation may deviate somewhat from pesticides' mixture assessment with more defined parameters and more detailed information within this regulatory area compared to industrial chemicals. If, however, CAGs may be defined, those are of interest, because higher quality assessments may be possible for such CAGs and substances within a CAG.
- The use of PNECs as reference to build up "risk characterization ratios" (RCR) as elements of indices for mixture effects is a rather crude approach. It is applicable for screening assessments at low tier hazard assessment level. It cannot be used for refined assessments because potency information from one trophic level is transferred to other trophic levels without adaptations. Similarly, in human toxicology the "acceptable daily intake" (ADI) would not be an adequate denominator in refined mixture risk assessments, where specific organ toxicity thresholds may be more appropriate to reflect an impact on a common target.
- Therefore, if possible, effect potency indicators for the single substances within the mixture should be built up on identical trophic levels (algae or daphnids or fish, respectively).
- Effect potency indicators should be built on comparable effect information for all elements of an indicator. Those should be either acute or chronic effects, either "no effect levels" or

“EC<sub>10</sub>” or “EC<sub>50</sub>” (or “LC<sub>50</sub>”, “IC<sub>50</sub>”, respectively) or extrapolated values derived from are these effect levels. These would be PNECs (acknowledging the limitations mentioned above) or similarly derived extrapolated reference values (see below for such a suggested reference value: CRV<sub>TL</sub>). A “toxic unit”-approach (TU) usually uses such comparable effect potency information. However, possible limitations to use this reference point are to be discussed within the data provided and assessments performed under REACH.

- Quantitative CA or IA approaches are categorized as “component based approaches” (Backhaus et al. 2012) given that all relevant components (substances) within a mixture to be assessed are known and quantitative information is available on substances’ toxicity (PNEC and/or effect levels) and on exposure (modelled/ estimated PEC or measured effect concentrations). Component based approaches are only feasible if this information or if suitable defaults instead are available. For coincidental mixtures or environmental mixtures, in most cases not all relevant substances are known with their respective concentrations, unless appropriate monitoring data are available. Therefore component based approaches may not be feasible for coincidental mixtures or environmental mixtures. They may be feasible for technical mixtures and mixtures discharged from a single industrial unit.
- Mixture assessment factors (MAFs) are sometimes proposed if a components’ approach is not feasible. A MAF is used as an additional assessment factor to calculate a PNEC for all those single substances known to be present within a mixture. However, as the appropriate size of a MAF depends on the number of components within the mixture, there is a high uncertainty about the appropriate size of a MAF.
- Alternatively to using a MAF, whole mixture approaches / whole effluent approaches are proposed to assess effects of mixtures with (partly) unknown substances. This assessment includes testing of the complete technical mixture/ discharge mixture/ coincidental mixture or environmental mixture. Because of infinity of resulting potential mixtures this approach would not be feasible as a routine regulatory procedure to assess mixture toxicity. It may, however, be very helpful a) to validate CA or IA assumptions or interactive behaviour (synergism/ antagonism) for specific mixtures with known substances and b) it may be helpful to compare such assessments with known substances with the additional influence by unknown further substances within a mixture, and c) it may be useful for constant immission scenarios, where (known and unknown) substances are present in stable compositions in environmental media (permitting a representative result from whole effluent tests).
- Substances with a high exposure concentration compared to their respective single substance PNEC (or other ecotoxicological reference concentrations) – i.e., RCR - are of high priority for mixture risk assessment. Similarly, persistence and bioaccumulation may be priority criteria. However, priority setting based only on some hazard properties (like H400; “very toxic to aquatic life”) may be less meaningful if accompanied with very low exposure concentrations (low RCR).
- Analysis of environmental mixtures has suggested that statistically, often only few substances within a mixture dominate the resulting mixture effect, whereas equal distribution (many substances with similar contributions to a mixture effect) would be the exemption. This result would be important, however, it has to be confirmed with a larger set of analysed mixtures, and it may not be equally justified for discharge or technical mixtures (as discriminated from environmental mixtures).

- Current data presentation and data communication as established under REACH and as demanded by guidance documents are not fully appropriate, if mixture effects are to be addressed.
- In addition to changes in reporting and communication within REACH additional strategies are required which may refer to other regulations. Especially, “trans-sectoral approaches” may be required, which cover substances present in a mixture but regulated elsewhere (e.g., pharmaceuticals, pesticides in combination with substances regulated under REACH).
- Currently, most approaches emphasize the need for priority setting. However, there are no specific and detailed concepts available how “priority mixtures” or “critical mixtures” are to be selected and discriminated.

## 2.3 Types of Mixtures to look at under a REACH Regulatory Perspective

Different types of mixtures (technical mixture, discharge mixtures, coincidental mixtures and environmental mixtures) have been defined and explained in chapter 1.2 of this report. For the assessment of options to act under REACH, we will mainly focus on **technical mixtures**.

Technical mixtures are prioritized in this project because the related actor under REACH (manufacturer or importer of a substance, formulator of a technical mixture or final downstream user who uses a technical mixture) may be identified more easily. The discharger of a technical mixture and/or the suppliers of it (manufacturers/ formulators) may, possibly, be regarded as directly responsible for potential mixture effects. The link between mixture effects in the case of coincidental and environmental mixtures is much more indirect and responsibilities may not be easily attributed to a REACH actor. In principle, the approach under REACH may be extended to discharge mixtures by combining the data from several technical mixtures and single substances, all of which are discharged from the identical industrial unit. This extension would just be a matter of data availability, but it has to be handled according to the same methodology as for technical mixtures. Therefore the assessment of discharge mixtures is also covered by the methodology used, but is not addressed in detail, below.

Looking at discharge mixtures the discharger may also be found responsible for the particular case, where aggregated exposure to single substances occurs, because a multitude of single substances and mixtures is discharged to the identical sewage plant. Therefore this special problem is briefly addressed in the scenarios discussed below.

Note, that the scenario where we look at technical mixtures or discharge mixtures is identical to the spot (effluent closely after the sewage treatment plant) where the PEC (freshwater) is defined for a single substance assessment currently performed under REACH. Therefore the principle parameters used for the PEC calculation may directly be used also for these mixture assessments. Also note, that usually at this spot in the effluent of a sewage treatment plant the calculated PEC may not easily be confirmed by analytical measurements / monitoring, because in most cases other dischargers also contribute to the real concentrations of substances of the coincidental mixture at this spot.

### Conclusions on type of mixtures

Based on these key elements to work with as derived from the state of the art, we return to define the most relevant type of mixture risk assessment under REACH. From the viewpoint of societal priority, environmental mixtures and coincidental mixtures are of key importance, as they represent substances and mixtures in combinations and concentrations, which really effect environmental species. However, considering the responsibilities and available information for

the actors under REACH, we provide a methodology to assess technical (and discharge) mixtures. It is understood that the discharges of technical mixtures and single substances are the main drivers of mixture effects observed in coincidental and environmental mixtures. Therefore, it would be worth pursuing approaches that link technical mixture risk assessment to environmental mixture risk assessment. The local point of assessment of mixtures in fresh water under REACH should be identical to the current assessment point (entering freshwater after the sewage treatment plant with limited dilution, where substances of the technical mixture are already part of a coincidental mixture).

## 2.4 Type of Data and Availability of Data currently provided under REACH for Assessments of Technical Mixtures

In this section, the availability and quality of the following types of data for single substances under REACH are described:

- PNECs,
- data on ecotoxicological properties,
- data on physicochemical properties
- data on fate properties,
- data on PBT properties and
- exposure data.

The possibilities to use these data for the assessment of technical mixtures under REACH are analysed.

(The obligations and the extent to address mixture risk assessments under REACH for the different stakeholder are described in this report in section 1.71.7 and in chapter 3.2 and are not discussed here again).

In science, there may be interesting ideas to address mixture effects which are reaching too far compared with the data available under REACH. Therefore, in this section 2.4 we analyse the current data provided and those possibly needed. However, we do not call for fundamental changes in data generation far beyond current high quality standards.

### 2.4.1 Toxicological Data: Quality of the PNEC

In a Chemical Safety Report (CSR) under REACH a “predicted no effect concentration” (PNEC) is derived and provided for risk characterisation in the disseminated registration document. This reference point is a crucial benchmark, because “safe use” of the single substances with regard to environmental effects is described by comparison with the PNEC. Moreover, concentration additivity models for mixtures are often based on the PNEC as the reference point.

In addition, no response additivity in mixture effects would scientifically be justified, if exposures were below a “no effect concentration”, which, by first glance, may be the PNEC. However, this latter link between a PNEC and a “zero effect concentration” has to be questioned:

- Per definition, ecotoxicity does not aim to protect each individual organism, rather structure and function of ecosystems should be protected and thus impacts on organisms must be restricted to prevent long term changes of population size and community

structure. In this context the PNEC is defined, which means that it is not a true zero effect level (SCHER/SCENIHR/SCCS, 2012).

- The NOEC applied most commonly as a “point of departure” (POD) is indeed an effect concentration with considerable uncertainty in regard of particular effect size. Applied assessment factors (AFs) do not account for higher effect levels potentially “hidden” in the NOEC, rendering the PNEC a potential (low) effect concentration.
- Assessment factors commonly applied to cover uncertainty associated with intra- and inter-laboratory variation, intra- and interspecies variations (biological variation), short- to long-term toxicity extrapolation, and laboratory data to field impact extrapolation are mostly convenience based and lack theoretical foundation. Meanwhile the size of variability for certain aspects (e.g. (Ahlers et al., 2006; Chapman et al., 1998; Raimondo et al., 2007), interspecies variability (Chapman et al., 1998; Slooff et al., 1986)) was quantified for subsets of chemical-species combinations and found to be often not sufficiently covered by the AFs usually applied. This renders the resulting PNECs with considerable uncertainty regarding their protective value for ecosystems. Calow and Forbes (2003) therefore stipulate ecosystem monitoring to detect possible adverse effects due to uncertainties in risk assessment not sufficiently covered by AFs.
- Sublethal endpoints are most often not or insufficiently assessed in ecotoxicity tests. Thus effects are overlooked which might lead to a decrease in population density (e.g. Hammers-Wirtz and Ratte, 2000) or might otherwise be of relevance in the context of other stressors and mixture toxicity.

This leads to the conclusion that the PNEC indeed is usually an effect concentration in many cases (for several chemical-species combinations) rather than a zero effect level. Therefore, also at concentrations below the PNEC some effects may still occur. This, however, means for chemical mixtures that an assessment of at least independent action (IA) is mandatory. As ecotoxicity data are often insufficient to apply the model of response addition (independent action), concentration addition may be assumed as a conservative default approach to predict possible mixture effects.

A more detailed analysis of the quality of a PNEC is provided in Annex 5 (section 9.5).

## 2.4.2 Data on Eotoxicity of single Substances – Data available under REACH or to be derived

### 2.4.2.1 Ecotoxicity: Available Data under REACH

Data requirements under REACH in general depend on the tonnage level. The higher the production volume, the more data are requested and this also holds true for ecotoxicity data. Moreover, at 10 t per year and above a chemical safety report has to be prepared and concomitantly PNECs have to be derived. For chemicals below this production level, no PNEC will be available in the REACH dissemination database of ECHA. The aquatic ecotoxicity data requested by REACH are summarized in Table 7. There are, however, exceptions from the rules. Data needs are reduced for certain application forms (e.g. intermediates, chemicals required for research, exposure can be excluded) and dependent on intrinsic properties of chemicals (e.g. compounds highly insoluble in water).

Table 7: Minimum Data Requirements under REACH for aquatic ecotoxicity<sup>29</sup>

1-10 t/year	⚡ 10-100 t/year, data additionally required	⚡ 100 t/year, data additionally required
Short term toxicity Daphnia (EC <sub>50</sub> )		Long term toxicity Daphnia (NOEC, LOEC, possibly EC <sub>10</sub> )
Growth inhibition aquatic plants (algae preferred, EC <sub>50</sub> , EC <sub>10</sub> /NOEC)		OR (only if fish is likely to be especially sensitive species)
--	Short term toxicity fish (LC <sub>50</sub> )	Long term toxicity fish (NOEC, LOEC and/or EC <sub>x</sub> )
--	PNEC <sub>aquatic</sub>	PNEC <sub>aquatic</sub>

#### 2.4.2.2 Ecotoxicity: Derived Data, PNECs

As PNECs are needed for the supposed first tier assessment of mixture toxicity (see section 2.5.2) these must be derived if not already provided by REACH. Normally, this should only be the case for substances below 10 t/year. The methodology is described in REACH Guidance on Information Requirements and Chemical Safety Assessment R.10 and roughly summarized in Table 8.

Table 8: Assessment factors to derive PNEC (aquatic): Table taken from REACH Guidance on Information Requirements and Chemical Safety Assessment, section R.107, simplified. For full details see original publication.

Available data	Assessment factor
At least one short-term L(E)C <sub>50</sub> from each of three trophic levels (fish, invertebrates (preferred Daphnia) and algae)	1000 on lowest L(E)C <sub>50</sub>
One long-term EC <sub>10</sub> or NOEC (either fish or Daphnia)	100 on EC <sub>10</sub> / NOEC if generated for most sensitive trophic level
Two long-term results (e.g. EC <sub>10</sub> or NOECs) from species representing two trophic levels (fish and/or Daphnia and/or algae)	50 on lowest of long-term results if these were generated for most sensitive trophic levels
Long-term results (e.g. EC <sub>10</sub> or NOECs) from at least three species (normally fish, Daphnia and algae) representing three trophic levels	10 on lowest of long-term results
Species sensitivity distribution (SSD) method	5-1 (to be fully justified case by case)
Field data or model ecosystems	Reviewed on a case by case basis

Therefore, to derive a PNEC a minimal dataset of acute toxicity results for three trophic levels (fish, daphnids and algae) are needed. Below 10 t/year, however, often only data on daphnids and algae will be available. We suggest using QSAR estimation software ECOSAR of US EPA EPI Suite TM package to derive acute data on fish toxicity in such cases (96 hours value) as far as organic compounds are concerned. ECOSAR often suggests several possible chemical classes with differing effect concentrations. As a conservative estimate the class resulting in the lowest

<sup>29</sup> We only discuss information related to PNEC in freshwater. PNEC for the marine environment is excluded from discussions in this project. For further information on data availability see Annex 2 (section 9.2) of this report.



effect level should be chosen unless one can provide good arguments to choose another class. The PNEC is derived by applying a factor of 1000 on this value. ECOSAR estimation is based on baseline toxicity with some refinement by introducing distinct regression functions for several chemical classes besides “neutral organics”. To choose this approach is justified by the following reasoning:

For chemicals with excess toxicity (i.e. exerting specific mechanisms of toxic action), threshold levels are likely. Below these levels they are believed to contribute only to baseline toxicity (ECETOC, 2011). Environmentally relevant concentrations will be in most cases low and therefore often below threshold levels for chemicals with specific TMOAs. Therefore, estimated values by ECOSAR may yield a reasonable approximation in most cases.

#### 2.4.2.3 Close of Data Gaps: TTC Assessment

An alternative approach to bridge data gaps could be the TTC-analogue approach (TTC: threshold of toxicological concern) for ecotoxicity, the ETNCaq. The relevant ETNCaq according to chemical mode of action could be chosen as an equivalent to a PNEC. In this case, no further extrapolation is needed. For further details on the background, the methodology as well as strength and weaknesses of the TTC-approach we refer to the literature (de Wolf et al., 2005; Sokull-Klüttgen, 2007; Vaes et al., 1998; Verhaar et al., 1992).

#### 2.4.2.4 Conclusions: Availability of Ecotoxicity Data

If a substance is registered under REACH, usually a minimum set of data related to the environmental health characteristics is available. In the IUCLID5 document (disseminated data) PNECs for all media (including aqua (freshwater)) are provided. This information is also transferred to safety data sheets (SDS) and therefore usually is available to downstream users (formulators of mixtures and final downstream users).

However, there are relevant gaps and exemptions where PNECs currently are not published and not available in the SDS. In these cases, calculations of RCR (and resulting calculations of mixture risk indices like Hazard Index or others) are currently not immediately possible for the respective substance. Therefore, already simple “concentration addition” screening calculations are hampered as relevant data for the single substances are not prepared accordingly.

Some of these restrictions could be compensated,

- by a more extensive interpretation of existing REACH obligations,
- by extension of obligations under REACH,
- by data generation by the mixture risk assessor.

By pointing to QSAR approaches from ECOSAR and/or TTC, we conclude that lacking PNEC data usually do not totally prevent the modelling or derivation of these data. For a higher tier qualified assessment this data generation is essential. The derivation of all PNECs only based on structural alerts and/or original experimental toxicity data and the proper application of assessment factors (where needed) requires knowledge and exercise and may usually not be performed by end-users. It is a time-consuming and complex task even for manufacturers, importers or formulators of chemicals.

If a PNEC is provided, we still have to keep in mind that this reference point is derived from heterogeneous data (acute and chronic, modelled and tested) according to an extrapolation procedure with relevant uncertainties. Therefore, the respective uncertainties are inherent also to RCRs included in mixture effect hazard indices. More sophisticated reference values like

those derived from “species sensitivity distributions” (SSD) may usually not be expected and may not be readily calculated due to the lack of data.

As indicated above, the provision of PNECs would not be sufficient to perform a higher tier assessment of mixture effects. For such a higher tier assessment reference points for the single trophic level would be needed. Within the currently disseminated data in IUCLID (but not in the SDS) we can find information of effect levels (EC<sub>10</sub>, EC<sub>50</sub>, LC<sub>50</sub> etc.) for these single trophic levels. These data are not forwarded with the SDS to the downstream user. Moreover, this information is currently not prepared in a way that enables non-professionals to adequately interpret these data:

- often acute and chronic data are to be integrated and scaled to an identical duration reference point by somewhat sophisticated extrapolation procedures,
- some of the study reports provide conflicting data without advice how to select the most suitable data for trophic level specific reference information,
- some of the data are from nonstandard tests with additional interpretation necessary,
- some test results have to be transformed prior to further use, for example: if various tests were performed and documented at different pH values, the results may need corrective calculations, if pH directly or indirectly influences effect levels,
- some results may be provided only as limit tests (toxic effects > x mg/l), without guidance to use this information quantitatively,
- some toxicity data are just linked to solubility properties, which may not easily be handled for quantitative assessments,
- instead of EC<sub>10</sub> or EC<sub>50</sub>, unusual effect levels may be provided, such as EC<sub>0</sub> or EC<sub>100</sub> or NOELs, which need further guidance for appropriate transformation into a reference point.

We conclude that these higher tier calculations of qualified trophic level reference points may not be performed by end-users and may only exceptionally be performed by formulators. In this case, intensive support by the registrant is essential. Usually, only the registrant himself may be able to prepare this information on substance properties. Moreover, for a harmonized procedure specific guidance would be necessary how to extract, assess and quantify trophic level specific toxicity data from the data available under REACH or from supplemental assessment procedures to be defined. This guidance has to include default procedures to handle data gaps. Considerable activities therefore are necessary to achieve this higher tier level to generate ecotoxicological data more appropriate for mixture assessments. In section 2.5.2 we propose a procedure how to a PNEC may be derived if no appropriate data are available.

## 2.4.3 Data on Physicochemical and Fate Properties relevant for Ecotoxicological Risk Assessment for single Substances

### 2.4.3.1 Data on PBT properties for single Substances

PBT properties of substances are defined in REACH Annex XIII and summarized in Table 9. column 2. Frequently, however, the actual data basis is inappropriate for application of these criteria and screening criteria from REACH guidance documents may be applied (column 3 of Table 9).

Table 9: Summary of PBT-criteria according to REACH Annex XIII and screening criteria according to REACH guidance documents

Property	Criterion according to REACH Annex XIII	Screening-criterion according to guidance
Persistence	T½ fresh water > 40 d T½ sediment (freshwater) > 120 d T½ soil > 120 d	Not readily biodegradable and/or Not inherently biodegradable and/or Not degradable by physicochemical processes (e.g. hydrolysis)
Bioaccumulation	Bio-concentration factor (BCF) > 2000	Log Pow > 4.5
Toxicity	Long term NOEC < 0.01 mg/L OR CM cat. 1 or 2, R cat. 1, 2, or 3 OR T, R48, or Xn, R48 according to 67/548/EWG	EC50 / LC50 (alga, daphnia or fish) < 0.1 mg/L: T presumably fulfilled < 0.01 mg/L: T definitely fulfilled

A PBT-assessment has to be performed under REACH for all registered substances ≥ 10 t/a as part of the chemical safety assessment.

Experimental data in relation to physicochemical properties and environmental fate with relevance for B and P, which may be expected to be available under REACH legislation depending upon tonnage, are summarized in Table 10.

Table 10: Requirements on experimental data in relation to bioaccumulation and persistence according to REACH and REACH guidance documents

Property / data type	1-10 t/a	✦ 10-100 t/a	✦ 100 t/a
Ready biodegradability, screening tests	For all organic compounds		
Hydrolysis as a function of pH	--	For all compounds, but not required for readily biodegradable or highly insoluble compounds	
Biotic degradation, simulation testing	--	--	Dependent on the outcome of the chemical safety assessment (not required for readily biodegradable substances): Surface water Soil* Sediment*
Log Kow (octanol-water partition coefficient)	For all organic compounds		
Bioaccumulation, aquatic	--	--	A bioconcentration factor has to be determined. Not necessary for compounds with a log Kow <3 or compounds with a low likelihood for crossing of biological membranes. According to REACH guidance R7C, QSAR may be applied instead under certain conditions.

\* if substance shows high adsorption

## Data on Persistence

Degradation half-lives may be directly determined from simulation studies for substances >100 t/a. Such studies, however, are only required under certain conditions only and will often not be available.

Studies on ready biodegradability will be available for all organic substances above 1 t/a. Readily biodegradable substances are certainly not persistent and in absence of other data substances not fulfilling this criterion may be regarded as persistent as a worst case scenario. Frequently, however, substances may not be readily biodegradable (OECD 301 and 310), but nonetheless ultimately biodegradable under less stringent conditions. In addition, studies on inherent biodegradability (often performed prior to REACH) may be available (OECD 302) and inherent biodegradability may also be deduced from studies on ready biodegradability, in which the requirements of the guidelines were missed, but results are close to the threshold levels.

Furthermore, following the REACH guidance documents for P criterion (ECHA, 2008b) QSAR may be applied: A pairwise combination of the results of three of the BIOWIN programmes of US-EPA's EPI Suite is proposed to assess persistence. One combination indicating persistence is sufficient for a positive screen on P.

Additionally, and sometimes relevant for inorganic compounds, data on hydrolysis as a function of pH may be available (OECD 111). However, only primary degradation is assessed and fate of degradation products must be separately followed.

To exclude the assessment as “very persistent” (vP) for poorly degradable compounds ( $T_{1/2} > 60$  days for fresh- and seawater or  $> 180$  days for sediment and soil), generally simulation tests will be necessary.

## Data on Bioaccumulation and Bioconcentration

Experimentally determined data on bioconcentration are only required for compounds  $\geq 100$  t/a and only under certain conditions, most importantly  $\log K_{ow} \geq 3$  (for details see Table 10). In all other cases, a screening assessment based on  $\log K_{ow}$  is performed with the cut-off criterion of  $\log K_{ow} > 4.5$  for fulfilment of the B criterion.

To exclude the assessment as “very bioaccumulative” (vB,  $BCF > 5000$ ) for compounds with  $\log K_{ow}$  values above 4.5, tests on bioconcentration (usually in fish) will generally be necessary. Under certain conditions, QSAR may be applied to estimate BCF from  $K_{ow}$  and possibly additional descriptors (ECHA, 2008a).

All the individual data referred to above are available to the public, i.e. they are contained in the disseminated dossiers available on ECHA CHEM. The main problem in this context is the fact that many different studies with sometimes different (and even contradictory) results may exist for the same endpoint. These data will generally be discussed – and the value taken for the chemical safety assessment identified – in the CSR, which, however, is not available to the public.

The most relevant value may be derived from the disseminated dossier on the basis of flags and reliability scores assigned, but this is only a work around for stakeholders having no access to the CSR.

This problem will be resolved for future PBT/vPvB assessments. With the release of IUCLID version 5.4, the PBT/vPvB assessment is now part of IUCLID (section 2.3) and will be disseminated. According to ECHA,<sup>30</sup> both the endpoint study records and the endpoint summary of the PBT/vPvB assessment results will be disseminated, unless they are claimed confidential. More specifically, the technical annex to the Data Submission Manual 15 describes that the detailed information and justifications in all fields will be disseminated (unless claimed confidential).<sup>31</sup> As a consequence, future disseminated dossiers on ECHA CHEM will usually contain a transparent PBT/vPvB assessment.

#### 2.4.3.2 Availability of Data on Physicochemical Properties depending on Tonnage

Most of the physicochemical properties are information requirements according to REACH Annex VII, i.e. they already have to be provided for substances manufactured or imported in quantities of one tonne or more. This applies to important parameters such as the vapour pressure, water solubility and the partition coefficient n-octanol water (log Pow).

There are only three additional information requirements for substances manufactured/imported above 100 t/a, namely data on the dissociation constant, the viscosity as well as the stability in organic solvents and identity of relevant degradation products, which, however, is only required if stability is considered to be critical.

#### 2.4.3.3 Availability of Data on Physicochemical Properties depending on Type of Substances

As a matter of principle, the information requirements for physicochemical properties depend on the physical state of the substance. For example, the particle size distribution does not need to be provided for liquids. In addition, some parameters are not required if their measurement is not feasible or does not make any sense. Thus, the log Pow is not required for inorganic substances.

It must be noted that results for one parameter might well lead to a situation in which another parameter does not need to be measured. Again, there is a rationale behind this and in fact extensive testing strategies have been developed to avoid unnecessary testing (ECHA, 2012a). For example, data on the surface tension are not required for substances with water solubility below 1 mg/L.

#### 2.4.3.4 Availability of Data on physicochemical Properties depending on Use Parameters

Basically, the information requirements for physicochemical properties do not depend on the use parameters. One notable exception are isolated intermediates, for which only available data need to be reported if they are manufactured and used under strictly controlled conditions (see REACH Articles 17 and 18).

#### 2.4.3.5 Availability of Data on physicochemical Properties depending on Substance Classification

This is generally not relevant. However, if a substance is classified for specific physicochemical hazards, data on this property will be available and have an impact on the information requirements. For example, if a solid substance has explosive or pyrophoric properties, no testing of flammability should be performed (which, in fact, could be quite dangerous).

<sup>30</sup> See [http://echa.europa.eu/documents/10162/13651/questions\\_and\\_answers\\_sds\\_info\\_dissemination\\_en.pdf](http://echa.europa.eu/documents/10162/13651/questions_and_answers_sds_info_dissemination_en.pdf)

<sup>31</sup> See [http://echa.europa.eu/documents/10162/13653/dsm\\_15\\_dissemination\\_annex\\_1-3\\_en.pdf](http://echa.europa.eu/documents/10162/13653/dsm_15_dissemination_annex_1-3_en.pdf)

However, these provisions are independent of the classification and just refer to the properties as such (similar to “type of substances” above).

#### **2.4.3.6 Direct Availability of Data on Physicochemical Properties to Downstream Users (SDS or Registration IUCLID file)**

The data required under the respective tonnage band will be available in the disseminated dossier available on the ECHA website. However, some details may be missing in this public version. For example, the more detailed justification for data waiving is not displayed, making it difficult to assess the rationale behind the waiving decision.

Most of the physicochemical parameters representing information requirement are also required in the safety data sheet according to REACH Annex II for the downstream user. Exceptions relate to endpoints, such as surface tension, which are not specifically mentioned in REACH Annex II and therefore do not have to be reported in the SDS. Conversely, REACH Annex II requires properties to be reported in the safety data sheet, which are not information requirements under REACH annexes VII-X. This, for example, applies to the vapour density.

It should be noted that the information reported in safety data sheets for mixtures normally does not necessarily differentiate between single components and could be missing for single components, either because the properties are tested for the mixture as such or the information on individual components is “left out” because it is regarded as not relevant.

#### **2.4.3.7 Indirect Availability of Data on physicochemical Properties to Downstream Users (after further Calculations (which may need Assistance))**

There are some cases, where data presented in the disseminated dossier can be converted. For example, if the vapour pressure at a temperature other than 20-25°C is required (e.g. for high temperature processes in occupational exposure assessment), it may be calculated from the data in the disseminated dossier, provided that details on the regression equation (Antoine constants<sup>32</sup> in this case) are included in IUCLID fields displayed in the disseminated dossier.

#### **2.4.3.8 Availability of Data on physicochemical Properties to the Registrant or to Authorities (CA, ECHA), but usually not the Public**

Additional details are generally available to authorities based on the information provided by registrants. This particularly applies to all authorities that have access to the Chemical Safety Report (CSR) and the full IUCLID file (i.e. not just the disseminated version on ECHA CHEM), which typically contain a detailed description and discussion of all relevant data. For example, waiving justifications become more apparent and the background of the individual data is more detailed. In particular, if several data exist for a single endpoint, these will be discussed in the context of the CSR and the value finally used for the chemical safety assessment will be identified. In the disseminated dossier, in contrast, these values exist side-by-side and the more valid data can only be separated from less valid data on the basis of the purpose flags (key study vs. supporting study) and reliability assigned by registrants.

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<sup>32</sup> The Antoine equation is a vapour pressure equation and describes the relation between vapour pressure and temperature for pure components. Resulting numbers are tabled as Antoine constants.

#### 2.4.3.9 Quality of available Data on physicochemical Properties

The quality of the physicochemical data reported by registrants – like any other endpoint data in IUCLID – is directly accessible from the information provided in the disseminated dossier. Important elements in the dossiers for a quality assessment are e.g.:

- Purpose flag: key study
- Study result type: experimental result
- Reliability: 1 (reliable without restrictions) or 2 (reliable with restrictions)
- Test guideline followed
- GLP compliance (although not a priority for older physicochemical data)

All these elements are publicly available and can be assessed straight away. A more in depth evaluation of physicochemical data may in some cases identify conflicting values or uncertainties. These may have been discussed in the CSR and could thus be clarified by authorities, but these discussions are not publicly available. In some cases, a physicochemical property might have data of identical quality (experimental key studies performed according to guideline with identical reliability). In these cases, the information provided in the disseminated dossier is not sufficient to identify the final value taken for the chemical safety assessment. Again, such information is only contained in the CSR. These cases, however, are probably quite rare.

#### 2.4.3.10 Conclusions: Availability and quality of Data on Physicochemical Properties

Data on many basic physicochemical properties are available publicly in the disseminated dossiers on ECHA CHEM and the quality of the data can generally be assessed. Non-disseminated information may provide additional background, but access is usually restricted to authorities. Data on other properties (e.g. removal rate, in STP) are usually only available if an exposure estimation and risk characterisation (Ch. 9 and 10 of the CSR) is performed for environmental exposure. While these properties relate to environmental fate, they are often estimated on the basis of physicochemical data (e.g. Log K<sub>ow</sub> and Henry constant). Derived data such as the removal rate in the STP are not available to the public. The same basically applies to the underlying data of the PBT/vPvB-assessment. However, the full PBT-/vPvB-assessment (only recently included in IUCLID 5.4, section 3.7.1, see technical annex to the Data Submission Manual 15,<sup>33</sup> will be disseminated in the future (unless claimed confidential) and therefore considerably increase publicly available information on these properties.

#### 2.4.4 Exposure Data for Single Substances

Environmental exposure estimation under REACH generally follows the same principles as under previous legislation, i.e. the TGD (EC, 2003). The tonnage assigned to a specific use and the release fraction associated with that use are the two most important single input values in determining the amount of substance released. At the next level of an environmental exposure assessment, partitioning and degradation are considered, which depend on the physicochemical properties as well as on the biodegradation data of the substance. While the latter are intrinsic properties of the substance, the tonnage for an identified use will be

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See [http://echa.europa.eu/documents/10162/13653/dsm\\_15\\_dissemination\\_annex\\_1-3\\_en.pdf](http://echa.europa.eu/documents/10162/13653/dsm_15_dissemination_annex_1-3_en.pdf)

assigned by registrants. Similarly, the release fraction (at least at the tier 1 level) is set by the use descriptor for the specific use, i.e. either ERCs (Environmental Release Categories) or spERC (specific ERCs), assigned by the registrant. Descriptor-derived release fractions may be changed due to additional sector-specific information from exchanges between registrants and downstream users at a higher tier level.

Most generally, data on environmental exposure are only available, if

- a chemical safety assessment (and a CSR) is required, i.e. for substances manufactured/imported at tonnages of 10 t/a and above (excluding intermediates under strictly controlled conditions),
- exposure estimation and risk characterisation are required, i.e. if the substance is classified for at least one hazard (this applies to most, but not all hazards, see REACH Article 14(4) or if it is a PBT/vPvB substance) and
- the environment is considered to be within the scope of exposure estimation and risk characterisation; most generally, this means that the substance is either classified for environmental hazards or presents “non-classified hazards” to at least one of environmental compartments. In the December 2011 version of the respective ECHA Guidance (ECHA, 2011), “non-classified hazards” are basically indicated if a PNEC has been derived for at least one environmental compartment.

This latter point is of particular interest. Prior to this ECHA Guidance, there was some room for interpretation in relation to the scope of exposure estimation and risk characterisation, with the consequence that environmental exposure estimation was sometimes not performed when a substance was only classified for its human health or physicochemical hazards, even though a PNEC was derived. The new Guidance basically means that a substance classified solely e.g. as a skin irritant should have an environmental exposure estimation and risk characterisation, if a PNEC was derived and a “non-classified hazard” is thus indicated.

But even after publication of this Guidance, the Guidance interpretation in relation to “non-classified hazards” may be questioned by some registrants and time will tell, whether the strict Guidance requirements will be met. As a consequence, for a number of substances PECs will not be available for a mixture assessment.

Substance evaluations, restriction proposals and proposals for inclusions of substances on Annex XIV as well as respective authorisation applications may be sources of information on environmental exposures of substances, which are registered below 10 t/a as these procedures have no lower tonnage threshold. However, these procedures will be applied to a limited number of substances.

#### **2.4.4.1 Availability of Exposure Data depending on Tonnage**

Requested reporting on exposure is identical for all substances manufactured/imported at or above 10 t/a (except intermediates under strictly controlled conditions) – see above. Note that for substances between 1 and 10 t/a (i.e. those substance not requiring a CSR and, therefore also do not require exposure estimation) REACH Article 10 requires exposure information to be submitted as part of the technical dossier. This, however, only includes qualitative information described in more detail under section 6 of REACH Annex VI.

#### **2.4.4.2 Availability of Exposure Data depending on Substance Classification**

Exposure information will generally only be available for classified (or PBT/vPvB) substances – see above.



#### 2.4.4.3 Availability of Exposure Data to Downstream Users (SDS or Registration IUCLID File)

There is a fundamental difference between the public and downstream users. Only the latter will have access to SDS of their products and the information included in the SDS (see below).

The general public has access to very little information related to exposure, such as (REACH Article 119):

- physicochemical data concerning the substance and on pathways and environmental fate,
- guidance on safe use,
- the total tonnage band (i.e. 1 to 10 tonnes, 10 to 100 tonnes, 100 to 1 000 tonnes or over 1 000 tonnes) within which a particular substance has been registered as well as
- information other than that listed in paragraph 1, contained in the safety data sheet.

It is clear that no results of the exposure estimation and risk characterisation are disseminated to the general public.

The downstream user, in contrast, has access to the SDS. Information on exposure estimation and risk characterisation may or may not be included in the SDS as such. They are required to be contained in the exposure scenarios annexed to the substance SDS (some registrants offer online access to these exposure scenarios rather than printing them).

REACH Annex II (Requirements for the compilation of safety data sheets), however, provides no information, which type of information the registrant should include in the exposure scenarios annexed to the SDS. Similarly, ECHA's "Guidance on the compilation of safety data sheets" does not detail the kind of information to be included in the annexed exposure scenarios. Rather, some limited hints can be found in the "Guidance on information requirements and chemical safety assessment: Exposure Scenario Format". According to this Guidance, the exposure scenario for communication (i.e. the ones annexed to an e-SDS) should contain

*"estimation of exposure and risk characterisation ratios (for all route of exposure for consumer and all compartment for the environment) resulting from the conditions described above (entries 2.1 and 2.2) and the substance properties; make reference to the exposure assessment method applied (specify for the routes if relevant); Alternatively: Include a link to a website from where the information described above can be retrieved."*

No further details are provided, but it is simply stated that

*"the registrant will need to make the following choices:*

*Which information from the CSR-ES to communicate down the supply chain? [...]*

*Which information from exposure estimation (section 9.x.2 of CSR) and risk characterisation (section 10.x of CSR) to communicate to the downstream user [...]?"*

As a consequence of these statements, different registrants may decide on different levels of detail. For example, some registrants may decide to pass down only limited pieces of information, while others may simply include the entire ES of the CSR. The choice will ultimately have an impact on the options available to the downstream user and any potential mixture assessment.

For example, if information on STP discharge and river flow rates (which together determine the dilution factor for the freshwater compartment) are lacking, the downstream user is prevented from scaling according to site-specific data for these parameters. While in theory, the effectiveness (or, more exactly, the removal rate) of the STP is an important figure, it is probably the one the downstream user is most often unable to verify. In contrast, the river flow

and STP discharge rates are comparatively easily accessible in many cases, partly because they are also subject to wastewater regulations. The same applies to lacking information in relation to the amount used locally and/or the number of release days. For example, release rates (in kg/d) are sometimes provided, which may be difficult to convert to amounts used depending on the overall level of detail provided. Such lacking or only indirect information is all the more a pity, since much effort has been put in the development of scaling tools to be used by downstream users (see e.g. [http://www.reach-info.de/scaling\\_unter\\_reach.htm](http://www.reach-info.de/scaling_unter_reach.htm)). In addition, ECHA advice to downstream users is also based on the assumption that information such as the amount used is communicated from the registrant to the downstream user.<sup>34</sup>

As a consequence of these problems, industry and ECHA have tried to develop some guidance as to what to communicate in an ES.<sup>35</sup> The amount used and the capacity/dilution capacity of the STP is specifically mentioned (at least for industrial uses), but some of the other information is described more in general terms (“describe conditions of use at the site driving the release”). Yet another set of data are not specifically mentioned in this document (e.g. PECs and RCRs), but are probably meant to be included in the more general descriptions (since they are also mentioned in the respective Guidance, see above).

It would be helpful if stakeholders developed a more specific description of the type of information to be included in the ES for communication and if these would be included in ECHA Guidance documents. A proposal (at least) for industrial uses – which meet the requirements to allow scaling – is shown in the following Table 11.

Table 11: Proposal for the type of information to be included in ES for communication

Input/assumptions	Comment
Exposure assessment tool used	Alternatively: measured data
ERC	If applied: spERC
Operational conditions determining emissions	Needed for DU to check coverage of his use; not necessary for mixture assessment
Amounts used locally (kg/d)	May be given as MSPERC or MSAFE
No. of emission/release days	
RMMs assumed to be in place when determining the release factors	Needed for DU to check coverage of his use; not necessary for mixture assessment
Receiving surface water flow rate (m <sup>3</sup> /d)	Resulting dilution factor would also be helpful
Discharge rate of STP (m <sup>3</sup> /d)	
STP (yes/no)	
Removal rate in STP (%)	
Results	
Local release rate (kg/d)	
Local PEC (mg/L)	
RCR	

<sup>34</sup> See e.g. ECHA’s Practical Guide 13:  
[http://echa.europa.eu/documents/10162/13655/du\\_practical\\_guide\\_13\\_en.pdf](http://echa.europa.eu/documents/10162/13655/du_practical_guide_13_en.pdf)

<sup>35</sup> [http://echa.europa.eu/documents/10162/3516339/ENES2\\_report\\_en.pdf](http://echa.europa.eu/documents/10162/3516339/ENES2_report_en.pdf)

With this information available, a basic mixture assessment would also be possible.

#### **2.4.4.4 Availability of Exposure Data to the Registrant or to Authorities (CA, ECHA), but usually not to the Public**

Registrants and authorities will have access to the CSRs and therefore to all data relevant for the exposure assessment. In contrast, no information on the exposure assessment will be available to the public. This difference is not specific to the environmental assessment, but relates to all impact areas aspects. The provisions of REACH in relation to the dissemination of data to the public are essentially hazard-based and not risk-based. As a consequence, the disseminated dossiers contain no information on the exposure assessment or the risk characterisation.

The differences between information available to registrants/authorities, but not to the downstream user, have already been described above under headline: “Availability to downstream users”.

#### **2.4.4.5 Quality of Available Exposure Data**

Within the 5 Years Update of the REACH Baseline Study (Eurostat, 2009), a considerably better quality of the data for environmental exposure estimation was observed in registration dossiers compared to the baseline evaluation prior to REACH (EUROSTAT, 2012). This evaluation was based on 62 randomly selected HPV chemicals and SVHCs. The increased quality is e.g. due to the increased availability of measured key input parameters compared to modelled ones at baseline. The result testifies to the effort put into environmental exposure assessments in the registration dossiers, but does not constitute an analysis of the data quality within the dossiers as such.

An assessment of the quality of available data faces the fundamental problem that quality criteria – while available for measured data in the Guidance on Environmental Exposure Estimation (ECHA, 2012b) – are lacking for modelled data, which is the predominant case. Key values entering environmental exposure estimation, e.g. the tonnage assumed per use/exposure scenario, is not assigned any quality rating whatsoever and is difficult to check, even for authorities. So, while the ECHA Guidance (ECHA, 2012b) repeatedly notes that these data must be reliable, a “reliability rating” (which needs to be assigned to every single study in IUCLID sections 4-7) for the most central input values for exposure estimation in general is not required under REACH.

This general problem notwithstanding, the quality of exposure-related information can be analysed to a certain extent. For example, tonnage information can be subjected to simple plausibility checks (e.g. is the formulated tonnage higher than the manufacture/imported tonnage?). Similarly, obvious discrepancies between use description and assigned ERCs may be identified (e.g. if and industrial ERC is assigned to a consumer use). Finally, local PECs for STP and freshwater may be checked manually based on the information provided in the CSR (more difficult for other compartments, e.g. due to partitioning). Transparent documentation of relevant input values and important interim results, e.g. as an annex to the CSR, can also be considered as a quality criterion for environmental exposure estimation.

Since details of the exposure estimation are only available in the CSR, such an analysis of the quality is currently only possible for authorities.

A new section 3.7.1 (exposure scenarios and local assessment) has been introduced in IUCLID version 5.4. Detailed information on the entire exposure assessment will be entered in this section in the future. However, according to the technical annex to the Data Submission

Manual 15,<sup>36</sup> this information will not be disseminated before the 2013 registration deadline and further “information on how this section will be disseminated after the deadline will be made available in due time”.

#### **2.4.4.6 Range of Exposure Data (Measured Data vs. Modelled Data)**

The ECHA Guidance on Environmental Exposure Estimation (ECHA, 2012b) briefly discusses PECs derived from measured vs. those based on modelled data as well as possible reasons for discrepancies between the two. If the modelled PEC is considerably higher than the one derived from measured data, this may indicate that elimination processes were not considered in the modelling or that the model was not suitable to “simulate the real environmental conditions”. However, the authors also noted that this may also indicate that the measured values only reflect the (regional) background and do not adequately represent the local situation.

Modelled PECs may sometimes be orders of magnitude higher than those derived from measured data even in the STP effluent (thus clearly not only covering the regional background). This would indicate that ERC- and even spERC-based modelled PECs are clearly a (reasonable?) worst case values not supported by field data. However, due to the limited number of observations, this remains speculative. A more systematic analysis of CSRs containing both modelled and measured data in order to identify any possible systematic pattern would clearly be helpful in the future.

#### **2.4.4.7 Exposure Data: Example for a Tiered Exposure Assessment (Leather Industry)**

Within this project, the authors calculated PECs for some example substances used in the leather industry using realistic data and found that differences in the calculated PECs may vary over three orders of magnitude from a tier 0 (worst case) to a higher tier scenario, where operational conditions, more realistic assumptions on the water flow and “state of the art” risk management measures were included (see Annex 5; section 9.5).

The following Table 12 demonstrates the range of PECs derived for glutaraldehyde, a substance which is used in leather tanning.

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<sup>36</sup> See [http://echa.europa.eu/documents/10162/13653/dsm\\_15\\_dissemination\\_annex\\_1-3\\_en.pdf](http://echa.europa.eu/documents/10162/13653/dsm_15_dissemination_annex_1-3_en.pdf)

**Table 12:** Example (glutaraldehyde, use in leather tanneries): Range of possible exposure estimates (PEC) based on different levels of information; exposure tiers may be defined differently from this example

Tier	PEC	Parameters/ assumptions (calculated with ECETOC TRA)
Tier 0	934 ↔g/l	100% discharge, usage 150 kg/d; no further exposure determining OCs (e. g. fixation), no RMMs; default STP discharge and river flow rates (dilution factor 10)
Tier 1	467 ↔g/l	ERC-based; ERC 5; 50% release fraction, no further OCs, or RMMs; default STP discharge and river flow rates
Tier 2a	280 ↔g/l	spERC-based; high release; release fraction 30% instead of 50% (ERC); no further OCs, or RMMs; default STP discharge and river flow rates
Tier 2b	46.7 ↔g/l	spERC-based; low release; release fraction 5% instead of 50% (ERC); no further OCs, or RMMs; default STP discharge and river flow rates
Tier 3	93.4 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90% no further RMMs; default STP discharge and river flow rates
Tier 4	9,34 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90% no further RMMs; river flow rate increased, resulting in a 10-times higher dilution
Tier 5	0,467 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90%; removal/ reaction in wastewater streams 95%; river flow rate increased (identical to tier 4)
Tier 6	?	Measured data if qualified and if they may be attributed to a single technical mixture or to a discharge mixture (not available for this example)

Additional knowledge contributed by the tannery (end-user) is used to further reduce the PEC in a tier 5 assessment, where specific (“real”) parameters on the STP and river flow rate are added. Finally, a refinement of the PEC estimate with reliable measured data is possible. In some cases, only limited measured data are available, which are not reliable as such, but can be used to support modelling approaches.

Note, that registrants could usually only proceed until tier 2 (a or b). Information contributed in tier 3 to 5 may only be contributed by the formulator or the end-user. Access for the formulator may also be restricted. For example, the 95% reduction of the substance in tier 5 assumes that there always is a mix with a simultaneous alkaline stream from the water workshop which contains relevant amounts of proteins to remove glutaraldehyde quantitatively. For tanneries, this is common practice and described in the BAT document. Therefore, the formulator can assume this procedure for his customers. This kind of sector-specific end-user information is necessary for the tier 5 (and 6) calculations. Otherwise the estimated PEC (at tier 4 level) deviates by a factor of up to 20 from an exposure concentration, which resembles more closely the “real” contribution of this substance to freshwater concentrations.

In the case study, elaborated exposure scenarios based on a detailed exchange between end-users and formulators have been the starting point. Therefore the higher tier estimations have been possible. We question that such specific information is available for many sectors.

#### 2.4.4.8 Conclusions: Exposure Data

Qualified data on exposure such as meaningful predicted environmental concentrations (PEC) for all relevant substances within a technical mixture have to be available in order to calculate risk characterization ratios (RCR) for single substances and thus to provide the necessary input for mixture risk assessment. PEC, RCR and (assumed or safe) tonnage (given as M(use), M(safe)) may be reported in safety data sheets as found in several recently published SDS. However, this

key information for exposure assessment is not always available to downstream users as may be shown by other recent SDS, including those for registered substances. The situation is different also for mixtures, where the exposure and risk assessment information may be provided only for some of the components for which a CSR was provided.

Moreover, PEC, M(use) or M(safe) are not always calculated, because environmental exposure assessment is e.g. not performed under REACH in the following cases:

- a chemical safety assessment (and a CSR) is not required, i.e. for substances manufactured/imported at tonnages of <10 t/a,
- exposure estimation and risk characterisation are not required, i.e. if the substance is not classified and is not a PBT/vPvB substance.

Most data for exposure calculations (e. g., tonnage for a specific use) are currently only available to REACH registrants and authorities, although this may change after the 2013 registration deadline because of extended reporting obligations.<sup>37</sup> Only registrants have currently access to the exposure assessment section of the CSR (section 9). Tonnages attributed to the specific identified uses are only reported in section 9 and are not disseminated.

Quality and exactness of the calculated PEC compared to the “real” exposure concentration in the STP effluent depend on two conditions:

- The minimum information necessary to achieve a single substance’ RCR of less than 1,
- The information available and retrieved by the registrant on use and discharge parameters for all dischargers within the life cycle of a substance (where the registrant may be assisted by the downstream user like the formulator or by branch-specific data generation from industrial associations).

By most registrants PECs are currently interpreted as upper bound exposure levels to ensure safe use of a single substance for all stages of the life cycle and for all respective uses.

Another factor of uncertainty and possible deviations from reality and calculated PEC is the number of release times/ year. In PEC calculations default assumptions are used for this parameter. In reality, the RCR and therefore any calculated mixture assessment indices may considerably vary depending of the release rates assumed.

Currently under REACH there only are economic incentives to calculate and to report PECs which are close to real exposure concentrations. If high usage is intended and M(safe) is low, the registrant or the formulator are interested to include more data on real RMM, on the release times, more specific sewage treatment plant characteristics or more data on the river flow characteristics. As mixture risk assessment is not regarded as obligatory part of a substances registration, there is no reason to calculate something else than an upper bound of exposure using generic instead of specific local data. This background situation leads to great biases in RCR calculations (and, thus, in resulting mixture risk assessment indices). As shown by the example, the increase in quality of exposure data may need complex, laborious and costly further calculations and specific knowledge, which is currently not available to the registrant and only to a limited extent to the formulator. It may well be that, in many situations, the currently available or (after some adaptations) achievable level of information is sufficiently

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See [http://echa.europa.eu/documents/10162/13653/dsm\\_15\\_dissemination\\_annex\\_1-3\\_en.pdf](http://echa.europa.eu/documents/10162/13653/dsm_15_dissemination_annex_1-3_en.pdf)

qualified to demonstrate the safe use of a mixture with regard to the environment ( $HI < 1$ ). This, however, should be interpreted cautiously and is not necessarily identical to a true size of risk.

## 2.4.5 Toxicological Data on Mixtures and Exposure Data on Mixtures

Usually, there are no toxicological data available on mixtures under REACH. Only in case of multi-constituent substances and complex reaction products or substances of unknown or variable composition (UVCB) the mixture is tested itself and respective data may be directly available in the CSR. The REACH guidance, however, also allows the use of other methodological approaches based, e.g. on concentration additivity or independent action (“component based approaches”) for predicting the overall risk based on information on the individual components of ‘complex substances’ (see also chapter 2.2 and section 2.2.8 (SCHER/SCENIHR/SCCS, 2012)).

Except of the data on complex mixtures/ UVCB no exposure data may usually be expected on mixtures currently under REACH.

## 2.4.6 Data on other environmental Compartments (Sediment, Soil, Air)

In principle, all proposed tiers of mixture assessment are applicable also to compartments sediment and soil. However, data availability is much more restricted for both compartments and especially for sediment available test guidelines are essentially restricted on primary consumers (like herbivores) or decomposers (organisms that break down the remains of plants and animals). Therefore the concept of three trophic levels must be modified for sediment in that rather species should cover different taxonomic groups, habitats and feeding modes. As most often no data on sediment toxicity are available and acute exposure is of less relevance for sediment organisms than for freshwater organisms, PNEC sediment is most often derived applying the so called equilibrium partitioning method (EPM). Input parameters are the PNEC for freshwater organisms, the partitioning coefficient suspended matter water (which itself may be calculated from the organic carbon normalized adsorption coefficient and standard assumptions) and the bulk density of wet suspended matter (standard assumptions). Under REACH, this method is accepted and supported by experimental data for sediment, for highly adsorptive substances however, the ratio  $PEC/PNEC$  EPM must however be multiplied by a safety factor. As most sediment dwelling organisms are invertebrates and algae may only be found on the surface of sediments, application of EPM on CRVTl-freshwater<sup>38</sup> for separate assessment of trophic levels would be possible but not reasonable due to the large differences in regard to taxonomic groups and their food web found in the sediment. With long term tests for species representing different living and feeding conditions assessment factors are 100, 50 and 10 for one, two or three organisms tested, independently from available acute test data. Without clearly defined trophic levels tested and acute test results not routinely present in contrast to the freshwater compartment, the assessment scheme proposed for the latter based on separate assessment of trophic levels using CRVTl instead of PNEC may not be transferred 1:1 to the sediment compartment.

A similar conclusion is true for soil. Also for soil EPM is applied, however in most cases under REACH not accepted unsupported by experimental data for soil organism (but often one acute or chronic test result supporting EPM is deemed to be sufficient). Trophic levels are more

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<sup>38</sup> Chronic reference value (specific for trophic level (see section 2.5.2))

clearly defined (detritors = decomposers: soil microorganisms; heterotrophs = consumers, e.g. earthworm; primary producers: higher plant species). Therefore, also for soil one chronic test result may be available unsupported by acute tests for the other trophic levels, thus precluding 1:1-transfer of CRVT approach from freshwater compartment to soil.

In conclusion, to refine the mixture approach for sediment and soil analogous to tier 2 for freshwater, new concepts have to be developed. The similar holds true for tier 3 assessments, as currently no generally accepted QSARs are available for prediction of narcotic toxicity to sediment or even soil organisms.

Environmental exposure estimation under REACH generally also involves compartments other than freshwater. In particular, the STP, marine water as well as sediments (both freshwater and marine water) and soil are considered in exposure estimation and risk characterisation, i.e. PECs as well as RCRs are usually derived for these compartments. In addition, two other PECs are calculated (depending on the software used, these results are more or less directly accessible). First, while a PEC air is also calculated, this is not compared with a respective PNEC, since a PNEC for air is usually not available. Rather, PEC air is used in estimation of human inhalation exposure via the environment (and deposition fluxes are also calculated as an input for the calculation of PEC soil). Second, a PEC for groundwater is also calculated, which is used in indirect human exposure via drinking water.

These remarks do not provide specific approaches for mixture assessment under REACH in other compartments but freshwater. A more detailed analysis is beyond the scope of this project.

## 2.4.7 Discussion and Conclusions: Data availability under REACH

Data as currently provided under REACH may be sufficient to calculate mixture risks for technical mixtures according to the principles of “concentration addition” for the compartment of fresh water (assessed in the effluent of the STP). However, these calculations will usually be limited in quality.

More specifically, we conclude on the availability and quality of ecotoxicity and exposure data under REACH and the meaning of the resulting calculated mixture risk:

### a) ecotoxicity data for hazard assessment of technical mixtures

- PNECs will usually be reported, but may only be regarded as a screening type denominator for calculation of mixture effects.
- Ecotoxicologically adequate data for higher tier hazard assessments are often generated, but are not available for downstream users. Also, for manufacturers or importers those data may not easily be used and adequately transformed to perform higher tier mixture hazard assessments, because study results have to be interpreted with respect to their ecotoxicological meaning and adequate assessment factors have to be applied in non-routine extrapolations.
- Further limitations exist, where no SDS is provided or less ecotoxicity data are generated, e.g., in case of substances marketed in low tonnages.
- However, documentation of ecotoxicological effects could be improved without change of the principal obligations under REACH by several modifications, which are rather easily accomplished. For example, the key experimental study to be used in case of a single trophic level assessment could be marked in the CSR and provided



for refined assessments. Details of such modifications in documentation and reporting should be elaborated and integrated in a “guidance document”.

b) data for exposure assessment of technical mixtures

- Reporting obligations with regard to exposure under REACH are not designed to provide real local discharge concentrations, and are of variable quality and precision. For a single substance assessment according to the current procedures they may reflect upper bound exposure concentrations and do not necessarily take into account real discharge amounts, local risk management activities, STP and water flow rate data. Instead they may use generic, “normalised”, “typical” or “default” parameters, which need adjustments for higher tier exposure assessments of mixture effects.
- Moreover, currently available guidance under REACH for exposure assessment does not guarantee the reporting of all parameters needed for mixture exposure assessments by the downstream user.
- Finally, existing exposure data, available to manufacturers, formulators or end-users or generated by the well-known modelling devices (like TRA, EUSES, CESAR) are sufficient to proceed to higher tier exposure assessments, if communication along the supply chain is improved and if reporting demands necessary for such refined PEC data are more precisely stated. Again, details have to be elaborated and need to be accompanied by a suitable “guidance document”.

c) Interpretation of resulting data from risk assessment of technical mixtures

- It may well be that, in many situations, the currently available or (after some adaptations) achievable level of information is sufficiently qualified to demonstrate the safe use of a technical mixture with regard to the environment ( $HI < 1$ ). This, however, should be interpreted cautiously and is not necessarily identical to a true size of risk.
- Equally, because of the limitations in data quality with respect to their use in mixture risk assessment, a resulting “hazard index” above one ( $HI > 1$ ) at a medium tier assessment will not necessarily mean that there is a definite appreciable risk for the environment.
- For mixture risk assessments at highest tiers (tier 3 and above for hazard assessment; tier 4 and above for exposure assessment; tier 3 and above for risk assessment; see section 2.5.2 for definition of tiers) the usually available data under REACH today may not be sufficient and major changes in data generation, reporting and analysis would be necessary in combination with major changes in regulatory prescriptions.

## 2.4.8 Summary of chapters 2.1 – 2.4

In this chapter we focused on six topics:

1. Report and discuss the scientific background (state of the art) on mixture effects assessment,
2. define and restrict mixture risk assessment within this project to technical mixtures (and, possibly, discharge mixtures) with potential effects to environmental species (fresh water compartment),
3. report and discuss the data input as provided currently under REACH to perform mixture risk assessments, including some considerations on supplemental expert systems to fill in current gaps in REACH provided information,
4. propose, describe and discuss methodologies to perform a mixture risk assessment under REACH,
5. consider priority setting strategies, as a full routine mixture risk assessment for all discharged mixtures is considered as not proportionate, and
6. describe two approaches for priority setting by formulators and end-users (tiered approach for MATS/priority mixtures and assessment of aggregated exposures).
7. The scientific background (state of the art) leads to some key elements of the subsequent methodology proposed. The most relevant findings are listed below:
  - Concentration addition (CA) may reasonably be assumed as principle mixture effect, also to be assumed in low concentrations below single substances' PNEC, and may be used for similarly acting and (as a conservative default) for dissimilarly acting substances.
  - The dose response data (dose-response curve) for single substances in the various species is rarely known apart from single distinct effect levels like EC<sub>50</sub>. Therefore, calculations based on independent action (IA) are not generally feasible as a routine regulatory approach.
  - Synergistic action within a mixture is rarely observed at effect levels close to single substances' PNEC. If it is observed the extent is limited with regard to the quantitative consequences on the mixture effect size. There may, however, be exemptions with relevant synergism, e.g. under the influence are of metal compounds. No general quantitative conclusions may currently be derived for integration of such synergistic influences.
  - The distinction between similarly and dissimilarly acting substances is not feasible in most cases because of a) limited information on the respective mode of action for the single substances, b) the complexity of calculations necessary to cover all pairwise or multiple similarities and dissimilarities within multi-substances mixtures in various concentrations and under further environmental exposure conditions, c) complexity may even expand because "partially similar" / "very similar" and "slightly similar" differentiations may have to be discriminated.
  - The use of PNECs as reference to build up "risk characterization ratios" (RCR) as elements of indices for mixture effects is a rather crude approach. It is applicable for screening assessments at low tier hazard assessment level. It cannot be used for refined assessment because potency information from one trophic level is transferred to other trophic levels without adaptations. Therefore, if possible, effect potency indicators for the single substances within the mixture should be built up on identical trophic levels (algae or daphnids or fish, respectively).

- Generally, all assessment strategies are built on “tiered approaches” with increasing quality demanded for the respective assessment parameters in order to proceed to higher tiers. There are no tiered approaches linked to mixture risk assessment under REACH yet.
- Mixture assessment factors (MAFs) are sometimes proposed if a component approach is not feasible. A MAF is used as an additional assessment factor to calculate a PNEC for all those single substances known to be present within a mixture. However, as the appropriate size of a MAF depends on the number of components within the mixture, there is a high uncertainty about the appropriate size of a MAF.
- Alternatively to using a MAF, whole mixture approaches / whole effluent approaches are proposed to assess effects of mixtures with (partly) unknown substances. This assessment includes testing of the complete technical mixture/ discharge mixture/ coincidental mixture or environmental mixture. Because of infinity of resulting potential mixtures this approach would not be feasible as a routine regulatory procedure to assess mixture toxicity. It may be very helpful as a supplemental approach.
- Substances with a high exposure concentration compared to their respective single substance PNEC (or other ecotoxicological reference concentrations) – i.e., RCR - are of high priority for mixture risk assessment.
- Analysis of environmental mixtures has suggested that statistically, often only few substances within a mixture dominate the resulting mixture effect, whereas equal distribution (many substances with similar contributions to a mixture effect) could be the exemption. This observation should be validated in future.
- Currently, most approaches emphasize the need for priority setting. However, there are no specific and detailed concepts yet available how “priority mixtures” or “critical mixtures” are to be selected and discriminated.

Based on these key elements to work with as derived from the state of the art, we return to define the most relevant type of mixture risk assessment under REACH. From the viewpoint of societal priority, environmental mixtures and coincidental mixtures are of key importance, as they represent substances and mixtures in combinations and concentrations, which really effect environmental species. However, considering the responsibilities and available information for the actors under REACH, we provide a methodology to assess technical (and discharge) mixtures. It is understood that the discharges of technical mixtures and single substances are the main drivers of mixture effects observed in coincidental and environmental mixtures. Therefore, it would be worth pursuing approaches that link technical mixture risk assessment to environmental mixture risk assessment. The local point of assessment of mixtures in fresh water under REACH should be identical to the current assessment point (entering freshwater after the sewage treatment plant with limited dilution, where substances of the technical mixture are already part of a coincidental mixture).

Chapter 2 describes the information available under REACH to perform such a mixture risk assessment for technical mixtures. Usually, with the information disseminated in the registration document, low tier mixture risk assessments may be performed. However,

- some relevant data gaps have to be accepted, leading to uncertainties of the assessment result,
- the use of single expert systems to supplement lacking data should be considered to improve the assessment results, even for low tier assessments,

- proceeding to higher tiers may currently be difficult or sometimes even impossible, limiting the chance to generate meaningful assessment outputs,
- with some modifications in reporting and communication (additional guidance under REACH specifically relating to mixture assessment needs) generation of meaningful results could be considerably improved.

In this section of chapter 2 examples are provided how to improve assessment results by better reporting or expert systems. For example, low tier exposure assessments may provide “predicted exposure concentrations” (PEC) orders of magnitude beyond the *real* discharge PEC, because generic assumptions are currently used under REACH and no local specific discharge parameters enter the calculation. In addition, there are limitations in the availability of adequate local exposure data to formulators or manufacturers/ importers and, thus, proceeding to high tier exposure assessments (within mixture risk assessments) may be hampered.

## 2.5 Concepts for Risk Assessment of technical Mixtures under REACH

### 2.5.1 Introduction

This section describes a number of possible concepts for future risk assessments of technical mixtures under REACH. (Concepts for priority setting are described in section 2.6).

The concepts are based on

- the scientific state of the science on mixture effects and existing methodologies discussed to address this problem (section 2.2)
- the specification of mixture types to be looked at (section 2.3), and
- the background conditions provided by the regulatory framework of REACH (section 2.4).

The concepts differ with the degree of necessary changes in the REACH regulation and / or their guidance and activities (additional reporting, different complexity of scientific input) for their implementation. Also, the primary actors capable and responsible for implementation may differ.

Several regulatory approaches can be considered by national authorities to take account of risks from technical mixtures based on the current instruments provided by REACH. Specifically, risks from mixtures may be addressed in combination with the fundamental REACH processes of substance evaluation, authorisation and restriction. The respective options to act for specific actors are discussed in chapter 3 of this report.

Below, we discuss concepts to perform risk assessments of technical mixtures and to integrate mixture risk assessment as a general principle into REACH substance registration, risk management, and control. However, it is acknowledged that these concepts have to consider the availability of data, the uncertainty of the results, and proportionality (benefits, efforts) of requested activities.

Three concepts are discussed in the following sections:<sup>39</sup>

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<sup>39</sup> As described in section 2.3 the concepts are related to technical mixtures. However, the procedure may easily be adapted for risk assessment of discharge mixtures, if the substances within the discharge mixture are known. In this case more substances usually have to be included and, because of possible aggregated

- A Tiered Approach for Risk Assessment of Technical Mixtures (section 2.5.2)
- Mixture Assessment Factors (MAFs) (section 2.5.3)
- “Whole Mixture” Test Approach (section 2.5.4).

These concepts are characterised below, advantages and weaknesses are discussed, and the areas of potential application and actors are specified. Not all of these concepts are elaborated in detail at the current state of discussion because they are not regarded as equally suitable approaches or they may need further research input beyond the scope of this report before they can be discussed for implementation. Some concepts are not considered to be alternatives but they may be combined or implemented simultaneously.

## **2.5.2 Tiered Approach for Risk Assessment of Technical Mixtures**

The idea to follow a tiered approach in mixture risk assessment has repeatedly been proposed before (Kortenkamp et al., 2012; Meek et al., 2011; UBA, 2012b) (see, e.g., sections 2.2.1 - 2.2.3, 2.2.7). However, in the project 4M the general concept has been transformed to the specific conditions of the regulatory framework of REACH and potential environmental effects of technical mixtures. The tiered approach allows the risk assessment of technical mixtures consisting of known substances.

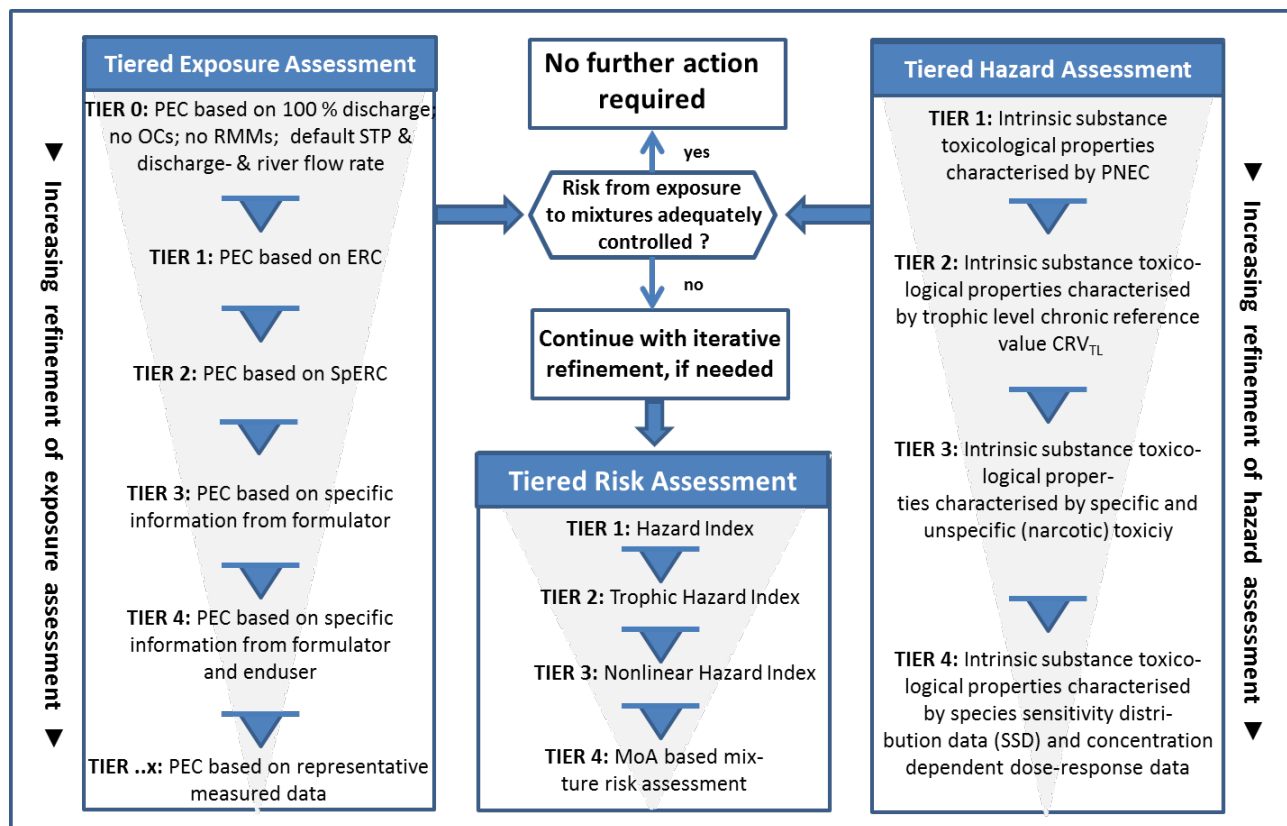
### **2.5.2.1 In a Nutshell: The Tiered Approach for Risk Assessment of Technical Mixtures**

Figure 16 shows the structure of the tiered approach for the risk assessment of technical mixtures under REACH, developed in the project 4M.

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exposure to identical substances within the discharge mixture, the calculations include some crosschecking on substance identity.

Figure 15: Schematic presentation of a tiered approach for assessment of technical mixtures under REACH<sup>40</sup> (source: adapted from Meek et al. (2011),<sup>41</sup> modified and specified for REACH)



This tiered approach consists of three components:

- a tiered exposure assessment (left column),
- a tiered hazard assessment (right column) and
- a tiered risk assessment (central part). As usual, the resulting risk is calculated as quotient of the figures from the exposure assessment and the hazard assessment.

Which type of data are used for the different tiers? What indicators result from the assessments? What are the differences between the tiers?

At tier 1, concentration addition is applied in its simplest form. As for the chemical safety assessment of single substances, for each substance in the mixture risk characterisation ratios are calculated. For this purpose, PECs and PNECs are used. The ratios of the substances are summed up. The result of this addition is most commonly called “Hazard Index” HI for the technical mixture.<sup>42</sup>

$$HI = \sum_{i=1}^n \frac{PEC_i}{PNEC_i}$$

<sup>40</sup> Note that numbering of tiers is flexible and not necessarily identical to tiers as used in similar schemes.

<sup>41</sup> This figure only demonstrates the principle factors and hierarchies schematically. For a final guidance, numbering and assigned definitions may have to be adopted.

<sup>42</sup> The term “hazard index” is somewhat confusing: it really describes risks instead of hazards.

If the Hazard Index of the technical mixture is below 1, no risk from mixture effects is expected. This approach is relatively simple. However it may overestimate the risk to a certain extent. This is because predicted environmental concentrations often overestimate the real exposure situation. In addition, the PNEC as a single value must be protective for all three trophic levels – for algae, daphnia and fish. Species specific toxicity data (e.g. chronic toxicity values for fish) are not evaluated specifically at this tier.

At **tier 2**, the assessment is refined. The proposed refinements of exposure tiers are identical to the tiered exposure assessment of a substance during chemical safety assessment (e.g. use of specific Environmental Release Categories).

On the hazard side, a new element is introduced. PNECs are no longer used. They are replaced by so-called “chronic reference values” (CRVs). These values are based on species-specific ecotoxicity data.

For each trophic level such a reference value is calculated for the substances of the mixture. Risk characterisation ratios for the substances are calculated using these reference values. They are added up to calculate a hazard index for the mixture - for each trophic level.

Finally, the highest of these hazard indexes is chosen to characterise the risk posed by the mixture. This index is called “**trophic level hazard index**” THI. It is directly comparable to Hazard Index HI at tier 1 – but specific to a trophic level.

At tier 2, the resulting risk quotient – the trophic level hazard index HI – will be usually lower than the risk quotient calculated at tier 1, based on PNECs. According to theoretical considerations, the reduction will have an upper limit of maximally a factor of 3.

The approach described here for tier 2 enables one to take out the best of given data under REACH. It is equally conservative compared to PNEC derivation under REACH. It avoids overestimation of mixture ecotoxicity at least to some degree due to the separate assessment of each trophic level.

At **tier 3** and **tier 4**, even more sophisticated elements are introduced on the hazard side.

- At tier 3 a differentiation between specific and unspecific (narcotic) toxicity is proposed for the substances of the mixture (this can result in derivations of the risk characterisation ratios from additivity).
- At tier 4, knowledge on the “mode of action” of substances in the mixture can be incorporated in the assessment.

For tier 1 – 3 of the hazard assessment, concentration addition is assumed as the basic principle for emerging mixture effects. In the fourth tier, independent action (IA) and more sophisticated information may be used for mixture risk quantifications.

However, already tier 2 of the hazard assessment requires expert knowledge. This is even more the case for hazard assessments at tier 3 and tier 4. In addition, it is not feasible to realise a hazard assessment at tier 3 and 4 with the set of data usually generated (and published) under REACH.

In the following sections, more details of this tiered approach for the assessment of technical mixtures are given.

#### **2.5.2.2 Details on the Tiered Approach for Assessment of Technical Mixtures**

The tiered approach offers several options for refinement – related to the hazard assessment, the exposure assessment and the resulting risk assessment. By stepping from a lower tier to a

higher tier, data requirements on the one side and quality of the resulting output on the other side increase (Data requirements and quality of available data are discussed in detail in section 2.4 of this report).

Because of the lower data quality, lower tiers are associated with higher risk estimates (to be precise: higher hazard, higher exposure, or higher risk estimates, respectively). Thus, the proposed approach is conservative. However, improved quality will permit less cautious risk estimates. Frequently, high tiers may not be reachable because there is a lack of generated or published appropriate data. In order to avoid unnecessary efforts, the progression to higher tiers will be stopped as soon as the risk from exposure to mixtures is sufficiently controlled. This criterion may, e.g., be fulfilled, if the “hazard index” (HI) falls below a value of 1 (the hazard index (HI) is defined as sum of the risk characterisation ratios of the substances in the mixture).

However, depending on the risk assessment tier, other indices are used to describe what is regarded as “risk that is sufficiently controlled”. Actually, the exact definition of a tolerated risk, where no regulatory action is needed, has not yet been clearly defined and is up to further discussion.

The risk assessor may not always have to start with a low quality information, i.e., with a low tier on either hazard or exposure data. If he is supplied with high quality input, he can start at a high tier level. However, note that a “tier 1”-hazard index could comprise superior exposure data and is still called a tier 1 risk assessment, if only low tier (limited quality) hazard data (PNEC) are available. From practical experiences it is concluded that one may more easily step forward with improving the quality of exposure data whereas the improvement of hazard data may be more difficult.

Figure 16 above showed the structure of the tiered approach. As already mentioned above, the first three tiers for a risk assessment of mixtures in this proposal are based on the principle of “concentration addition” (CA). This is in line with the current understanding of the most appropriate procedure to approximate mixture effects with limited data quality and is regarded as a conservative approach (EC 2009, State of the Art Report on Mixture Toxicity). In the fourth tier (which may, in fact, comprise a number of more differentiated sub-tiers) more sophisticated information on “species sensitivity distributions” and a more specific definition of “common assessment groups” (CAGs) and “mode of action” may be used for mixture risk quantifications.

**Exposure tiers** start with the baseline set of data available to the registrant (manufacturer or importer of the substances in the mixture). At higher exposure tiers the appropriate data will usually not be accessible to the registrant. For mixture risk assessment of technical mixtures the formulator is informed on most parameters for his formulated product. He may, however, need some additional information by the manufacturer / importer, in order to be able to step to higher hazard tiers. The formulator also is in better contact with the following downstream user or end-user. Therefore, he may – to some degree – be able to modify discharge data and specific risk management measures from identified uses for his mixture. However, he will probably still use generic instead of specific local information on the sewage treatment plant parameters and the river flow rates. Therefore there often are limitations to proceed up to highest exposure tiers. The formulator should report the results of his assessment “up the supply chain” to the respective substance manufacturers / importers to inform them on the safe use of their substances in technical mixtures.

**Focus on technical mixtures.** It is not a realistic scenario to assign mixture risk assessment tasks as routine obligation to formulator or downstream user. Therefore, the tiered approach – as proposed above – will primarily be used for technical mixtures and in fewer cases for



discharge mixtures, although the principle procedure is feasible for both types of mixtures, if all relevant substances within the mixture are known to the respective risk assessor in the supply chain.

**PEC/PNEC ratio as starting point.** Basically, all mixtures discharged into the environment and all substances within a mixture are regarded as possible candidates for a mixture assessment. They all may contribute to mixture risks. Assuming that we want to avoid all types of adverse effects to environmental species with similar rigor, the most important critical parameter for mixture risk assessment is the ratio between exposure to the substances (concentration in the environment, derived from monitoring or calculated as Predicted Environmental Concentration (PEC)) and the substance specific reference point characterizing its ecotoxic potency (e.g., it's predicted No Effect Concentration (PNEC)).

**Modifications of the approach.** This basic starting point (PEC/PNEC ratio) may be modified to some degree:

- If we argue that some types of adverse effects are of higher public concern than others we have to take account of this **societal differentiation**.
- If we find that some **minimum contribution** to mixture effects may be neglected because of analytical problems (below detection limits), or the uncertainty of its factual contribution, we may establish a respective **“cut-off”**.
- If we accept that some substances may be exempted from an assessment, because, e.g., the **substance is not classified** according to current classification and labelling regulations, we, therefore, can withdraw this substance from a mixture assessment. This, however, would include the acceptance of the uncertainties of (incomplete or misleading non-) classifications.
- If we feel concern that current exposure data are not representative, we may also take into account some **“indirect” parameters of relevance** like the “persistence” or “bioaccumulation” properties.

The following section describes how the different tiers of the hazard assessment and the risk assessment work (section 2.5.2.3). The tiers for the exposure assessment are explained in section 2.5.2.4.

### 2.5.2.3 The Tiered Approach: Hazard Tiers and Risk Tiers

#### Step 1: TIER 1 Hazard Assessment (Calculation of a Hazard Index HI )

As a first tier assessment of risks from mixtures the concentration addition model is applied in the simplest way: Predicted environmental concentrations (PEC) for all chemicals determined in the mixture are compared to their respective Predicted No Effect Concentrations (PNECs) being most often readily available from single substance risk assessments. This yields PEC/PNEC-ratios (Risk Characterization Ratios, RCR) and these are summed up (Backhaus and Faust, 2012). Although the term Hazard Index (HI) is somewhat confusing (as it really describes risk instead of hazard) HI will be used in this report in accordance to the most common current terminology:

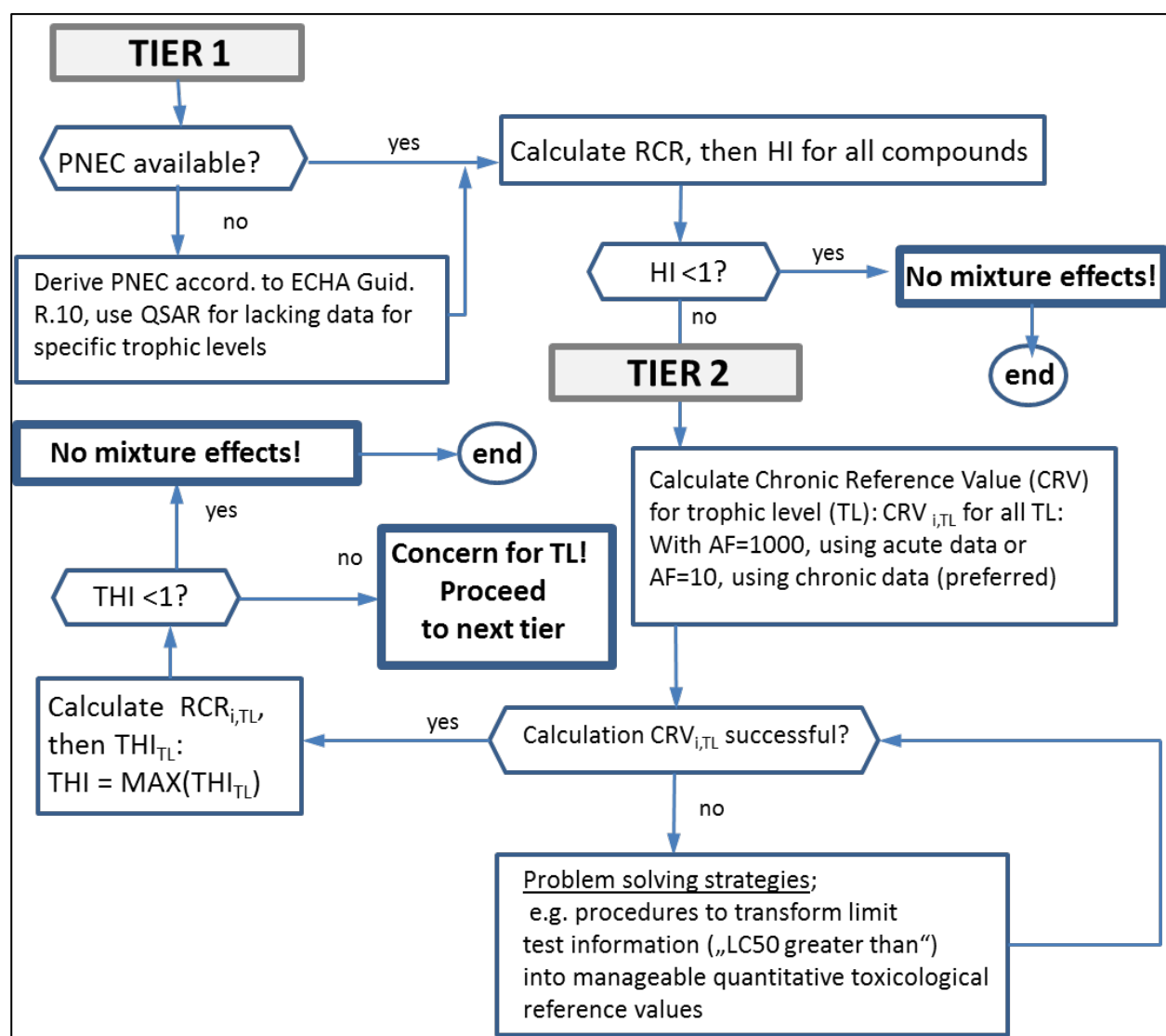
$$HI = \sum_{i=1}^n \frac{PEC_i}{PNEC_i} \quad (1)$$

If HI is below 1, no risk from mixture effects is expected. This approach is relatively simple as no species specific toxicity results have to be retrieved and evaluated. However it may overestimate the risk to a certain extent. This is because the PNEC as a single value must be

protective for all three trophic levels. As such, the respective assessment factor chosen according to the methodology outlined above and detailed in REACH Guidance R.10 are applied on the lowest result of three trophic levels.

Figure 17 describes the decision flow to move from tier 1 to tier 2, if HI is larger than 1. It should be noted, however, that – within tier 1 – it may be possible to increase the quality of the exposure information (see below for exposure tiers). This could mean a realistic chance to achieve a lower HI, without the need to enter a tier 2 assessment (calculation of a trophic hazard index).

Figure 16: Decision flow to move from tier 1 to tier 2 risk assessment. See Annex 5 for an example application. (source: own illustration)



## Step 2: TIER 2 Hazard and Risk Assessment (Calculation of a Trophic Hazard Index THI)

Because of the possible overestimation of risk by the HI-approach, second tier assessment is recommended if  $HI \geq 1$ .

Following Backhaus and Faust (2012), the risk quotient (RQ) based on the sum of toxic units (STU) is derived for each trophic level (TL) separately (i.e. algae, daphnids and fish) by summing

up fractions of PEC and effect concentration for each substance contained in the mixture and finally multiplying this sum with the relevant AF (1000 in case of acute studies):

$$RQ_{STU} (TL) = \left( \sum_{i=1}^n \frac{PEC_i}{EC_{50} (TL)_i} \right) \times AF \quad (2)$$

Then the highest RQSTU of the three trophic levels is taken:

$$RQ_{STU} = \text{MAX} (RQ_{STU} (TL)), TL = \text{algae, aquatic invertebrates (inv.) and fish} \quad (3)$$

Using this method, a high risk quotient for substance x for daphnids due to high toxicity towards daphnids will only contribute to RQSTU (daphnids) whereas the contribution to the other trophic level RQSTU will be less if toxicity towards these is less pronounced for this chemical – in contrast to the PNEC-method where by using the PNEC implicitly for each chemical only the highest risk quotient from three trophic levels is chosen and summed up. Assessing mixture toxicity by concentration addition using this outlined RQSTU-approach in contrast to the earlier described HI-approach based on PNECs, assessing three trophic levels the resulting RQ will be usually lower however with an upper limit of maximally a factor of 3. This was the result of theoretical considerations (Backhaus and Faust, 2012).

We suggest changing this methodology (RQSTU-approach) to enable the use for heterogeneous data, which are provided in REACH registration documents (acute and chronic data, data gaps, and difficult substances). This demands first of all a decision on what time frame the mixture toxicity assessment is directed – long term exposure or rather short term peak exposures with certain mixtures. PNECs, as supposed to be used in the first tier assessment, are derived in respect to long term (chronic) exposure. For mixture assessment of industrial chemicals, this may in fact be the more relevant scenario compared to acute peak exposures which are especially important in case of e.g. plant protection products. Therefore the following proposal is aimed at chronic mixture toxicity assessment, while an analogous approach may target intermittent release scenarios.

As described above RCR would be calculated, however the denominator of the RCR for each chemical would be a RQSTU or chronic reference value (CRV<sub>TL</sub>) specific for the trophic level (TL) based either on a chronic NOEC or chronic EC<sub>10</sub> or – if chronic data are not available for the relevant trophic level – an acute effect concentration / lethal concentration (EC<sub>50</sub> / LC<sub>50</sub>) extrapolated by an appropriate assessment factor to account for long term exposure. Thus, for each trophic level a separate RCR<sub>TL</sub> is calculated. From these a hazard index specific for each trophic level is derived, the THI<sub>TL</sub>:

$$THI_{TL} = \sum_{i=1}^n RCR_{TL,i} = \sum_{i=1}^n \frac{PEC_i}{CRV_{TL,i}} \quad (4)$$

THI is then defined as the highest THI<sub>TL</sub> of three trophic levels:

$$THI = \text{MAX} (THI_{TL}), TL = \text{algae, aquatic invertebrates (inv.) and fish} \quad (5)$$

THI is directly comparable to the HI based on PNECs but specific to a trophic level.

For PNEC derivation according to REACH Guidance R.10, for chronic data alone (all three trophic levels at least) an AF of 10 is applied on the lowest long term results (NOEC or EC<sub>10</sub>) to account for several uncertainties, first of all the extrapolation from single species laboratory tests to multispecies communities in the environment. In contrast, for acute data alone covering at least the three trophic levels additionally a factor of 100 for acute to chronic extrapolation is necessary, yielding in total a factor of 1000 on the lowest acute L(E)C<sub>50</sub>. Because with the PNEC one concentration must be protective for all three trophic levels, in case of mixed results AF of 100 (10 x 10) is recommended in case of one and AF of 50 (5 x 10) in case of two long term results (in addition to acute results covering the three trophic levels) to

account for the uncertainty of available chronic data being sufficiently protective for the trophic levels without chronic data.

This means that for PNEC derivation data on the three trophic levels cannot be assessed independently for selection of the appropriate AF. In this respect, the THI-approach is different, as each trophic level is assessed separately and the one trophic level especially at risk for a certain mixture is chosen as the relevant one (i.e. the highest of three  $THI_{TL}$  is selected). This is supported by statistical data analysis regarding the question if there is interdependence between acute to chronic ratios (ACR) determined for a chemical for one trophic level and the ACR determined for one of the two other trophic levels. Different authors analysing different data sets found no correlation (Ahlers et al., 2006; Raimondo et al., 2007). If acute to chronic ratios for one trophic level are independent from the others, independent acute to chronic extrapolation is justified. For the acute to chronic extrapolation (ACR) and other uncertainties (e.g. single species- to multi species-extrapolation) within the second tier-approach based on THI-concept we thus recommend the following values for  $AFA_{CR}$  and  $AF_{other}$  to derive  $CRV_{TL}$ -values:

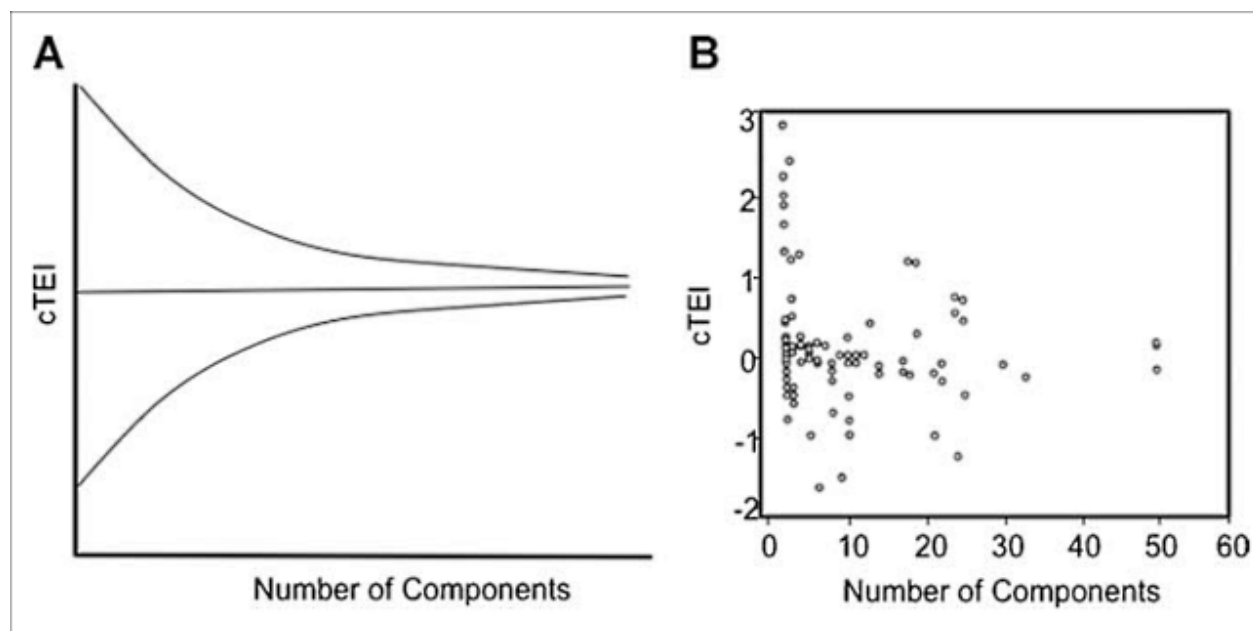
- Algae, Daphnids or fish acute ( $E(L)C_{50}$ ):  $AFA_{CR}$  100,  $AF_{other}$  10
- Algae (72 hours) NOEC or  $EC_{10}$ :  $AFA_{CR}$  1 (studies with algae may be regarded at the same time as acute - taking the  $EC_{50}$  - and chronic - taking NOEC or  $EC_{10}$  - as 72 hours cover several generations),  $AF_{other}$  10
- Chronic results on fish or daphnids:  $AFA_{CR}$  1,  $AF_{other}$  10

This approach enables one to take out the best of given data under REACH and – while being equally conservative compared to PNEC derivation under REACH – avoids overestimation of mixture toxicity at least to some degree due to separate assessment of each trophic level. In the further sections out of simplicity reasons global AFs of 10 or 1000 cover  $AFA_{CR}$  (1 or 100) as well as  $AF_{other}$  (10) applied to account for further uncertainties.

### Step 3: TIER 3 Hazard Assessment (Calculation of a Nonlinear Hazard Index)

In larger receiving waters there may be sometimes the problem of a multitude of organic chemical substances being present in only low concentrations. The mechanistically based funnel hypothesis developed by Warne and Hawker (1995) states for equitoxic mixtures of mainly narcotic chemicals that the higher the number of components present in the respective mixture the lower the deviation from additivity will be while at the same time each single chemical is present in increasingly lower concentration (equitoxic mixture; see Figure 18 A, where in a funnel-like shape a mixture toxicity is approached which would be expected from additivity). The hypothesis was validated on 104 equitoxic mixtures composed of 182 different chemicals including some pesticides with lower than 10 to maximally 50 components. For mixtures composed of 10 to about 30 components, deviation from additivity decreased in a funnel-like shape (Figure 18 B) as predicted according to the funnel hypothesis, i.e. while at lower than 10 components toxicity of mixtures was frequently up to about 4 times higher (synergism) or up to about three times lower (antagonism) than expected from additivity, for mixtures with numbers of components close to 30 or 50 essentially additivity was observed ( $cTEI = 0$ ).

Figure 17: Mixture toxicity depending on the number of components of an equitoxic mixture (A) as predicted by the funnel hypothesis of Warne and Hawker (1995) and (B) as observed evaluating 104 equitoxic mixtures composed of 182 different chemicals. Mixture toxicity obeys concentration addition for cTEI (corrected toxicity enhancement index) of 0 and is 2 and three times higher (or lower) than expected from concentration addition for cTEI of 1 and 2 (or -1 and -2), respectively. Reprinted from Warne and Hawker (1995).



Building on this and adding that chemicals with a particular mechanism of toxic action will contribute solely to baseline toxicity if present below their threshold of specific toxic action, Dyer et al. (2011) propose a pragmatic classification of chemicals: All compounds present below 1/30th of their acute lethal toxicity threshold should be assumed to exert their toxicity by narcosis, independent of their respective mechanism of toxic action. 1/30th was chosen on the basis of the results from Warne and Hawker (1995), where additivity was observed for equitoxic mixtures of around 30 and more components.

As such, it might be possible to develop an approach based on grouping of those organic chemicals in the mixture present at lower than some fraction (e.g., 1/30th) of their effect level. These would be supposed to act by narcosis only and thus prediction of their narcotic effect concentrations using ECOSAR and choosing the ECOSAR class neutral organics would mirror their respective potency at concentrations below the threshold of specific toxic action. With application of the concentration addition model and differentiating for substances with exposure concentrations below some cut-off fraction, the mixture toxicity of this group of substances could possibly be approached in a reasonable manner and more specifically than proposed in lower tiers. The reference value would be determined from the narcotic properties in low concentrations, and from specific toxicity in higher concentrations. This means a nonlinear (hockey stick type) increase of the RCR of the single substances within the mixture depending on their concentration.

This possible “tier 3 approach” is not further refined in this report but might be elaborated in future. Moreover, the scientific background of a) the funnel hypothesis and b) of a fixed fraction of the lethal toxicity (e.g., 1/30th) being defined as a threshold for specific toxicity, may not yet be sufficiently validated and may need further differentiations and modifications before implementing it as a routine tier 3 assessment.

Similarly to tier 2 improvements, the consequences of such a higher tier assessment may be limited:

- If only few substances dominate ecotoxicological mixture effects (Price and Han, 2012), the overall contribution of the many substances with low RCR may not be decisive.
- The difference between an IA-assessment and a CA-assessment is already described as rather small. Therefore the differences between these two types of CA- assessments may even be somewhat smaller.

It is assumed that the data quality will rarely be sufficient to reach a tier 3 mixture hazard assessment level.

#### **Step 4: TIER 4 Hazard Assessment (MoA based Mixture Risk Assessment)**

For tiers 1 to 3 we assumed concentration addition as the basic principle for the emerging mixture effects. If better data were available, it would – in principle – be advised to proceed to higher tiers, where improved knowledge on the “mode of action” (MoA; or even the “mechanism of action”) is incorporated in the calculation. Even if called a tier 4 assessment, there may be several further steps (tiers 4, 5....and more) to include expert knowledge on the hazard characterisation of the single substances within the mixture and the type on combination effects, which may then deviate from concentration addition and include independent action (IA) or more complicated interactions. To integrate IA into mixture risk assessment the dose response on the effects of the single substances has to be known, which rarely is the case. This dose response may differ for the various trophic levels or – even more specific – for the different species within a trophic level. At these tier levels, species sensitivity distributions (SSD) would be incorporated. Aggregation rules become increasingly complicated and data are usually missing. Realisation with the usual set of data generated and published under REACH is not feasible. Therefore this high tier approach is not elaborated in this project and may only be realised for some rare defined sets of substances in exceptional cases. However, extensive work has been performed to accomplish such high quality risk assessments in scientific studies on mixture effects (de Zwart and Posthuma, 2005; Posthuma and de Zwart, 2006; Posthuma and Suter, 2011).

#### **Tiered Approach, Hazard Assessment: Problems Associated with “Difficult Compounds” or Data Gaps**

An example for the application of the tiered approach is described in Annex 5 (section 9.5). It gives a discussion of some of problems as observed realistic safety data sheets. In addition, a hazard index (HI; tier 1) and a trophic hazard index (THI; tier 2) are calculated for an example set of data, to demonstrate the reduction of the reported risk due to the refined assessments (see section 9.5).

#### **Tiered Approach, Hazard Assessment: Module “Typical Enhancers in CA Assessments”**

While the tiered approach, in the lower tiers, is based on concentration addition assumptions, this does not preclude that some nonlinear elements could be included in a risk assessment on mixtures under REACH.

There are indications that, for example, metals – if present in a mixture – may lead to more complicated interactions, which could mean, e.g., synergistic effects. Moreover, the overall effect of a mixture may be enhanced (or reduced) by some solvent or complexing agent. Details are not available to include this knowledge at a well-founded scientifically satisfying level into risk assessment of mixtures.

However, a simple multiplier may principally be thought of, which may be linked

- to some single substances within the mixture to increase their relative weight,
- to some set of substances sufficiently characterised to assign an enhancement factor to that group, or
- to the full mixture, similarly to a “safety factor”, to cover more than additive effects or to address other uncertainties.

This factor would be similarly defined as the “interaction factor” IF as it currently discussed for biocidal mixtures (UBA, 2012a); see section 2.2.7 for details. This principle option, however, is not further elaborated in this tiered approach due to limited data which substances should generally be regarded as enhancers, if they occur in a mixture.

### **Tiered Approach, Hazard Assessment: Conclusions for Mixture Hazard Assessment and Demands on Data Dissemination under REACH for Toxicity Data**

In conclusion, as PNECs are in most cases readily accessed via the REACH dissemination database on properties of chemicals from ECHA, a first tier assessment based on summation of RCRs (PEC/PNEC-ratios) for all compounds present in the mixture is straight forward. If the resulting HI is equal to or smaller than one, mixture toxicity may most probably be neglected. If it is larger than one, the THI has to be determined as a less conservative and more sophisticated assessment. If it is again larger than 1, mitigation of risk by a more sophisticated exposure assessment or a reduction of exposure is mandatory whereas a higher tier assessment of mixture toxicity would afford further knowledge of TMoA and / or species at risk for the substances contained in the mixture.

Following this concept, often beyond the PNEC-based tier 1-assessment original effects data have to be evaluated by the downstream user applying the proposed tier 2-assessment scheme of mixture toxicity. Thus, to enable the assessor to choose the more appropriate data, several improvements under REACH in data processing would be essential:

- In case of several studies to choose from: It should be made clear in the form of an endpoint summary (currently not accessible via the dissemination database of ECHA) which of these studies the most relevant would be.
- In case of weight of evidence (WoE): The WoE-conclusion must be readily accessible and a clear conclusion on the effect-concentration regarded as relevant for the given endpoint is essential.
- In case of substances poorly soluble in water or instable in water or where an pH dependent solubility difference is observed, each effect concentration defined as most relevant for a given endpoint should be discussed against the physicochemical properties of the compound and clear conclusions in respect to the effect concentration be drawn: If for example an emulsion has been tested and a LC50 fish determined far above the solubility limit, toxicity caused by physicochemical effects (impairment of gill respiration) is very likely. If no toxicity was observed at lower concentrations, should this value rather be treated like an LC0 at the concentration of the saturated solution?
- The similar holds true for substances prone to hydrolysis in water: In endpoint summaries it has to be made clear what the toxic agent is, to what extent it is formed and how the nominal concentration can be traced back if only measured values for hydrolysis products are given and effect concentrations relate to the measured value only.

- In case of metal compounds where the metal ion is the toxic agent per se, in accessible endpoint summaries all determined effect concentrations should be normalized to the metal ion concentration to enable comparison of results from different studies.

We conclude that a tier 1 mixture hazard assessment is, in most cases, a procedure, which may be introduced without major changes under REACH and is easily accomplished. Because of imprecise toxicological reference points this tier 1 assessment with the resulting HI tends to overestimate mixture effects. In order to get a more precise mixture hazard assessment under the assumption of CA, the assessor has to proceed to tier 2 (or strive for better exposure information; see below). To enter a tier 2 assessment is much more demanding and may usually not be performed by end-users or even formulators. This information will only reasonably be assessed by the manufacturer or importer of a substance. Only, if reporting with the SDS or information availability in ECHA CHEM is considerably extended and improved, DU may possibly be enabled to step forward to a tier 2 assessment. A tier 3 mixture hazard assessment would, again, only be realised by a manufacturer or importer of the substances within a mixture. These limitations may not be decisive, because a progression from tier 1 to tier 2 or 3 in toxicological tiers will, in any case, usually be less effective than improving exposure information. However, there may be situations where it is indicated to proceed to a higher tier in hazard assessment.

#### 2.5.2.4 The Tiered Assessment: Tiers for Exposure Assessment

The various degrees of accuracy for exposure estimates under REACH were already described above. In essence, the REACH chemical safety assessment for registration is not focusing to provide exact exposure estimates, but to provide information on conditions of use (based on estimated exposure concentrations) that ensure there is no adverse effects to environmental species. Therefore, reported PECs are in many cases “upper bound type” data.

The identification of conditions of safe use for a single substance may already require a higher tier exposure assessment, which comes closer to reality (i.e. PECs more closely linked to concentrations which could be validated by measurements).

Therefore, some tiers may be defined, e.g.

Table 13: Tiers for exposure assessment of technical mixtures under REACH. Source: own compilation.

Tier	Assumptions made / Data used for the calculations
Tier 0	100% discharge, no OCs, no RMMs; default STP discharge and river flow rates
Tier 1	ERC-based; no further OCs, or RMMs; default STP discharge and river flow rates
Tier 2	spERC-based, potentially including integrated RMMs and/or options to iterate using specific RMMs for the sector; default STP discharge and river flow rates
Tier 3	Calculated with specific information by the formulator: OC specified ; no further RMMs; default STP discharge and river flow rates
Tier 4	Calculated with specific information by the formulator: OC and most RMM specified; river flow rate increased
Tier 5	Calculated with specific information by the formulator: OC specified; removal/ reaction in wastewater streams specified; river flow rate increased
Tier 6	Qualified measured data

In practise, tier 0 is a somewhat unrealistic worst case and would rarely be the starting point. Some steps are usually combined or modified and the real number of tiers therefore is changed. There is not fixed assignment of exposure detail characteristics to a defined tier.



Note, that often high differences in PEC quantification can be expected when proceeding from a low to a high tier (see section 2.4.4.6). The availability of specific qualified discharge data is usually much better for DU (formulators and - often even with increasing details – final downstream users), whereas higher ecotoxicological tiers could more easily be reached by manufacturers or importers of the substance.

#### 2.5.2.5 Conclusions: the Tiered Approach for Risk Assessment of Technical Mixtures

The proposed tiered mixture risk assessment assuming CA may, in principle, be a conservative but adequate way to address mixture effects from technical mixtures or discharge mixtures with known composition. It can be a laborious exercise with results showing high uncertainty and, probably, overestimated risks at low tiers, if the data for the single substances do not reflect real exposures situations. This may be the case as REACH provides generic exposure scenarios and normally no real local exposure estimates. Thus, an RCR with some generic PEC may be conservative but often feasible, but this generic PEC possibly may not always be meaningful if used for all substances in a mixture risk assessment approach. Stepping forward to higher tiers increases predictive quality, but also increases necessary resources and therefore may not be suitable as a routine procedure.

There are clear limitations in feasibility to accomplish a high tier mixture hazard assessment for a downstream user taking into account the current practise in data assessment and public availability under REACH, and there are clear limitations in feasibility to accomplish a high tier mixture exposure assessment for a manufacturer or importer, as he may have no access to the exact local parameters of exposure of some far away downstream user.

Also, for regulatory institutions who want to perform a mixture risk assessment, it may be complicated to get access to realistic and representative exposure data. As regulatory bodies may have access to original CSR data, they may be more successful to accomplish higher hazard assessment tiers. Moreover, regulatory bodies may have better access to exposure data from monitoring activities apart from REACH. They could be used for the mixture assessment.

Acknowledging that it is much easier to reach higher exposure assessment tiers for downstream users and that this often leads to a significant increase in quality of the mixture assessment, we expect the most meaningful information, if a downstream user is the priority user of this type of mixture assessment approach. Such a downstream user would most probably be the formulator of a mixture, who has most necessary information of the products composition and may be close enough to the end-user, in order to judge on the exposure parameters with sufficient quality. This may be especially true for technical mixtures, but not to the same degree for discharge mixtures. Even if the highest tiers were reached, the mixture assessments are still regarded as “worst case” scenario providing sufficient safety, if a hazard index close to 1 is maintained.

In combination with other concepts the tiered approach may be restricted to specific situations under which it has to be performed and is not necessarily a routine procedure for all technical mixtures which are marketed. However, there may be specific cases where also manufacturers or importers or end-users are asked to perform exhaustive tiered mixture assessments.

In the following sections, two further concepts are described which could be applied for the assessment of technical mixtures: the approach of “Mixture Assessment Factors” (MAF) (section 2.5.3) and the testing of the whole mixture (section 2.5.4).

### 2.5.3 Mixture Assessment Factors

For regulatory handling of mixture effects there are proposals to apply a “mixture assessment factor” (MAF) to the single substances (see, e.g., section 2.2.5). Other assessment factors, as currently used under REACH to calculate reference points (like the PNEC) for the single substances, do not cover the possible influences of co-exposures. This would mean an additional “safety factor” to take account of simultaneous exposure to multiple substances. Therefore the use of a MAF means a reduced value for a PNEC or the MAF could equally be interpreted as a separate multiplier extending the formula to calculate an RCR:

$$\text{RCR} = \text{PEC} / \text{MAF} \times \text{PNEC} < 1 (!)$$

for all (known) substances within a mixture (for higher tiers the MAF would be included accordingly to other indices).

However, MAFs are a rather imprecise way to handle risks from mixtures,

- as they do not take into account of the specific data on the substances present in the assessed mixture (the factor does not vary depending on the concentration and the identity of the substances in a specific mixture),
- the appropriate size of a MAF to correspond to assumed concentration additivity depends on the size of the mixture (number of included substances), for which it is used.

As the specific data on the substances in the assessed mixture are not looked at, the MAF is often proposed in the case that not all of the relevant ingredients of the assessed mixture are known. This will be the case for environmental mixtures or other coincidental mixtures, where the establishment of MAFs is a very notable proposal.

The appropriate size of the MAF could be linked to the typical number of substances (n) occurring in a mixture, because, for concentration addition, the (mathematically justified) MAF is equal or smaller than n in order to adequately account for such addition effects. Note that, more precisely, only those substances need to be accounted for, which contribute to a common ecotoxicological endpoint (e.g., only those substances need to be considered which are toxic to fish). As derived “from episodic findings”, some authors (Price et al., 2010; Price and Han, 2011) argue that only few major substances may contribute significantly to the mixture effects with much lesser contributions by the other constituents, which may argue for a somewhat smaller MAF compared to the full number of constituents of the mixture. KEMI (2010) report a proposal in the Netherlands, where an assessment factor of 100 is applied to derive so-called “negligible concentrations”. This factor should also provide a safety margin for combined toxicity (It is not stated, where this factor is implemented into regulatory practice).

The advantage of the MAF-approach is the easy handling, once the size is fixed. The overall application would usually provide a relevant margin of safety to significantly reduce concerns from mixture effects. However, the scientific justification of the size of this factor is poor in case of mixtures with flexible size. Very often a factor of 10 is proposed as a minimum yet relevant quantification for a MAF.

For the general use of such a factor under REACH the consequences would be too far reaching, as all discharges into the environment would have to be reduced to an RCR of, e.g., 0.1. This may be regarded as not proportionate without further substance specific justification. A more targeted use of the MAF could be considered: this may be realised in other regulatory frameworks (provision of selected quality standards which include the mixture assessment factor for selected substances) or it may be possible under REACH, if criteria are provided, for which substances a MAF assignment is proportionate.

## 2.5.4 Testing of the Whole Mixture

The „whole mixture approach“ is the most exact way to describe the environmental effects of a mixture. No assumptions on *concentration addition*, *independent action* or interactions like *synergism* or *antagonism* are necessary and the substances in the mixture do not have to be identified. Depending on the test system, however, other uncertainties may remain. This can be the need for *time extrapolation* (if only short term whole mixture testing is performed), extrapolations *from high to lower concentrations* and the uncertainties whether *other test species* would react identically.

The essential problem of the “whole mixture approach” is that the results may not always be valid any more if major constituents of the mixture change (other substances, additional or fewer substances, and/or other relative concentrations of the substances within the mixture). Because of the infinity of possible mixtures in the environment and the impossibility to test all potential combinations, the whole mixture approach is no *stand-alone* procedure for mixture risk assessment. It may, however, be relevant,

- if a modelled mixture assessment is questioned, e. g. in case... and therefore a validation for this specific situation is wanted,
- if a largely invariable (technical or) discharge mixture has to be assessed, or
- if a typical priority mixture is found (e.g., by monitoring or other means; see section 2.6.2.3) and it is intended to assign quantitative risk figures to this typical mixture. This assignment would only be meaningful, if it may reasonably be assumed that this typical mixture will react similarly even if co-exposed with further substances and if changing relative amounts of the constituents would not invalidate the principle outcome of the whole mixture test results for this specific typical mixture.

## 2.5.5 Conclusions: Concepts for the Risk Assessment of Technical Mixtures under REACH

Three principle methods are described above to perform a mixture risk assessment under REACH.

- The tiered approach is a component based methodology, suitable for mixtures with known substances contained. The method may therefore be used for technical mixtures and discharge mixtures. Because of the provided tiers it is adapted to variable data availability. In the lower tiers it is based on concentration addition, which is a plausible default assumption for mixture risk assessment. The use of this method needs more data, is more time-consuming and laborious compared to the MAF-approach and the results may be of less quality compared to the whole mixture test approach. Necessary information to proceed to higher tiers is not distributed equally to all involved actors along the supply chain. Therefore, a qualified tiered approach will need advanced communication and reporting.
- The MAF-approach is easily handled and may be regarded as a very conservative method to account for potential mixture effect, depending on the size (safety factor) of the selected MAF. With the appropriate size, it may be justified as an approximation method to concentration addition. It is not suitable for coincidental mixtures or environmental mixtures with many unknown substances included. Application is easy and data requirements are low. However, this approach still may not be used by a manufacturer/importer under REACH, if he is not well informed on the composition of the mixture to be assessed. The quality of the mixture risk assessment result will usually be the lowest compared with the other mentioned methods.

- The Whole Mixture Test approach provides the most adequate quantification of a mixture effect, if it is performed with a mixture which is representative for the required assessment scenario, and if it is performed according to adequate testing conditions (duration, tested species, appropriate conditions of the medium, dilution factors). Therefore this method is, in principle, suitable for all types of mixtures including coincidental mixtures and environmental mixtures, especially if not all substances within the mixture are known. It is not adequate if the composition of the mixtures to be assessed is highly variable. In case of changing mixture compositions the method may be overly complex and costly to cover the various resulting alternatives which are to be assessed. Therefore it may not be used as a routine method under REACH to assess, e.g., the mixture effects caused by the discharge of a large portfolio of mixtures by a formulator. Generally, it may best be performed and interpreted by the discharger of a mixture. For coincidental mixtures and environmental mixtures, this method may also be very helpful for an authority mixture risk assessment.

All these methods may also be combined for a mixture risk assessment under REACH in practice, namely for mixture risk assessment of technical mixtures. For example, for more routine-type assessments the tiered approach could be applied. For some substances an additional (MAF-type) safety factor could be foreseen, in order to account for its contributions to potential mixture effects and in special cases, where the quality of the tiered approach is not sufficient and priority appears to be high, mixture effects can be assessed by targeted whole mixture testing.

**Further conclusions regarding the tiered approach:** Based on the scientific background, the focus to assess technical mixtures and conditions for data availability, the general concept of a tiered approach has been specified and adapted to the mixture risk assessment scenario under REACH.

Mixture risk assessment is structured into a hazard assessment part, an exposure assessment part and a risk assessment part, using the outcome of the former two assessments (hazard and exposure) to calculate some risk figure in the risk assessment part. In **lower tiers** risk figures would be calculated assuming concentration additivity. Within the hazard assessment, in the lowest tiers the PNEC is used. However, strategies are mentioned how to handle a scenario where the PNEC is not provided.

In **higher tiers**, it is proposed to generate trophic level chronic reference doses and to calculate trophic hazard ratios, also based on concentration addition. Possibly even higher hazard assessment tiers are outlined but not discussed in detail, because too many data are lacking and procedures are too complex to implement such high tier hazard assessment as elements of a REACH guidance.

For **exposure assessment**, it is regarded easier to achieve high tier PEC estimates compared to high tier hazard estimates. A hazard index or trophic hazard index below 1 provides a sufficient margin of safety to protect from potential mixture effects because of the conservative character of the calculated figure.

There is considerable uncertainty on the consequences of a **hazard index exceeding 1** and a subordinate discussion should provide criteria, at which tier the uncertainty of the results is regarded insignificant compared to concern shown by the calculated figure and at which tier the respective result would be taken to lead to regulatory action (c.f. also the discussion in section 3.2.5).

In addition to a detailed presentation of this tiered approach, advantages and limitations of an approach using “mixture assessment factors” (MAF) and/or applying a “whole mixture test” for the mixture risk assessment are discussed (sections 2.5.3 and 2.5.4). It is noted that these

methods could be relevant as supplemental information, but are not adequate as a single assessment method for technical mixtures.

## 2.6 Concepts for Priority Setting

### 2.6.1 Introduction

Risk assessment may not be performed under REACH as a routine procedure, wherever a technical mixture is discharged, as efforts were not proportionate. Therefore, **criteria and concepts for priority setting** are required to decide

- in which cases risk assessments of technical mixtures should be performed and
- where to start if risk assessment of technical mixtures is integrated as a general principle into REACH.

In this section we describe two different concepts for priority setting:

- Nomination of “**Mixture Assessment Triggering Substances**” (**MATS**). These substances initiate (trigger) in a general approach risk assessments of technical mixtures which contain such substances. They indicate that a technical mixture requires an assessment which goes beyond the isolated assessment of the substances of the mixture themselves.
- Identification of “**priority mixtures**”. These mixtures have specific properties which increases the likelihood of mixture effects. Therefore priority mixtures need an additional assessment of mixture effects. In this report, focus is set on possibilities to identify priority **technical** mixtures.

The two concepts have different starting points. The concept of MATS aims to identify substances (such as the priority substances of the Water Framework Directive), which occur already in relevant concentrations in **real environmental mixtures**. This has two consequences:

- Further discharges of these substances should be avoided.
- The likelihood of mixture effects with other substances increases, because the risk characterisation ratios for these substances alone are already close to 1 or above 1.

If a technical mixture contains such a mixture assessment triggering substance, it has to be demonstrated that the use of this technical mixture

- does not result in an relevant additional occurrence of this substance in the environment;
- does not cause a concern of mixture effects in the environment.

Therefore for technical mixtures which contains a MATS a mixture risk assessment has to be performed.<sup>43</sup> The concept of MATS uses information from environmental data to set priorities for the assessment of technical mixtures.

The concept of “**Priority mixtures**” has as starting point information about **technical mixtures**. Priority mixtures show specific properties of their substances or have specific uses

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<sup>43</sup> For these technical mixtures it is not sufficient only to show that the intended uses lead to risk characterisation ratios below 1, as for technical mixtures which do not contain a MATS.

which increase the likelihood of mixture effects. Therefore these technical mixtures require an additional assessment whether such effects could take place or not.

The concept of **MATS** is described in section 2.6.2.

The concept of **priority mixtures** is described section 2.6.3

In addition, we describe how formulators and end-users could set priorities, related to **combined exposures** (see section 2.6.4) and related to **aggregated exposures** (section 2.6.5).

## 2.6.2 “Mixture Assessment Triggering Substances” (MATS)

One trigger for an additional assessment of technical mixtures could be that the mixture contains substances of specific concern. This means: substances which indicate that the mixture requires an assessment which goes beyond the isolated assessment of the substances themselves. In the following, we call such a substance a “Mixture Assessment Triggering Substance” (MATS).

### 2.6.2.1 Characteristics of MATS

A MATS is a substance which causes concern, because it already occurs in relevant concentrations in the environment in relation to its inherent ecotoxicity. This proposal foresees that in most cases Mixture Assessment Triggering Substances are nominated and selected by a regulatory decision from authorities. MATS will usually be identified on a macroscopic (possibly national) and not on a local level.

A “relevant occurrence” may be defined as an ubiquitary occurrence with an RCR close to 1 in many locations. Examples for such substances are the priority substances of the Water Framework Directive (e.g. mercury, 4-nonylphenol, PFOS). A more precise quantification of what is meant by “close to 1” is open for discussion with regulatory experts and is not fixed in our proposal. However, for illustration and in order to work with quantitative figures, we suggest a starting point of  $RCR \geq 0.8$  as key criterion for “relevant occurrence”. The PEC in this RCR is derived from representative monitoring or other high quality exposure data (see Figure 16).

If a technical mixture, discharged by any actor within the supply chain under REACH, contains a MATS, a mixture risk assessment has to be performed in order to demonstrate that no relevant additional occurrence of the MATS causes a concern of mixture effects in the environment.

“Relevant *additional* occurrence” may be defined as a significant increase to background occurrence. A more precise quantification of what is meant by “significant increase” is open for discussion with regulatory experts and not fixed in our proposal. However, for illustration and in order to work with quantitative figures, we suggest a starting point of  $RCR \geq 0.1$  (calculated local above regional background) as key criterion for “relevant additional occurrence”.

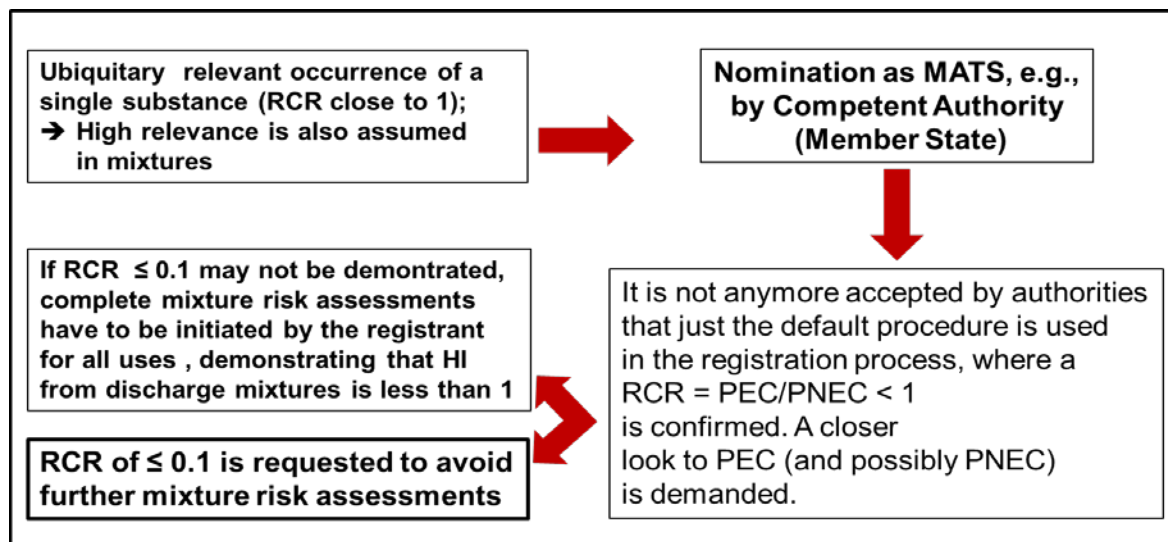
The relevant occurrence implies a higher probability of mixture effects if other substances are also present in the respective environmental medium. Because of this relevant occurrence, further discharges of a MATS into the environment should a) be carefully controlled for and b) lead to a thorough mixture risk assessment, if - after careful control of further discharges - calculations still indicate *relevant additional occurrence*.

In order to calculate an RCR, the (modelled or measured) exposure concentration is divided by the PNEC, with the PNEC usually provided by the substances’ registrant in the CSR or in the safety data sheet. For the default procedure, limitations in quality of some derived PNEC are

not accounted for. If no PNEC exists, these may be derived or estimated (by approaches discussed in section 2.5.2 of this report).

Figure 19 illustrates the principle function of MATS for manufacturers or importers of chemicals.

Figure 18 : Nomination of MATS and the principle function of MATS for registrants under REACH in this concept to integrate mixture risk assessment into REACH regulation (source: own illustration)



As proposed above, the regulatory consequences of an identified MATS could be far reaching depending on the agreed function which would be up for discussion for policymakers: either no relevant additional occurrence is ensured for a specific discharge assessment (i.e., with the chosen figures:  $RCR < 0.1$ ) or a possibly laborious, complex and costly thorough mixture risk assessment has to be performed. Therefore, MATS have to be selected carefully with an adequate sense of proportion based on qualified data.

“Relevant occurrence” may not merely be defined by the  $RCR \geq 0.8$  as only criterion. Other properties (like the type of adverse effect) may also be considered as influencing the selection as a MATS. In addition the frequency and distribution of such an observed RCR in monitoring programmes or in chemicals safety assessments will probably be an additional parameter to be accounted for. Whether a substance appears in high concentrations occasionally, regularly, regionally or ubiquitary, has to be considered.

Similarly to priority mixtures (see section 2.6.3), other criteria like amounts and types of uses, substance properties like bioaccumulation or persistence may be included in selecting a MATS. Also, specific toxicity characteristics (e.g., endocrine disruption), could contribute to selecting a substance as MATS. If, in addition, a MATS is a known enhancer of effects within mixtures leading to synergistic effects, this could be addressed by a modified calculation of the hazard index (see section 2.5.2).

Mixture assessments may also be initiated, if a single substance occurs frequently, which is a lead substance, representing a group of substances (like “benzo(a)pyrene as proxy for polycyclic aromatic hydrocarbons), a substance of unknown or variable composition (UVCB) or a mixture. In this case, the lead substance may equally be nominated as a MATS with similar consequences as if it were a substance representing just itself.

### 2.6.2.2 Consequence of MATS: tiered risk assessment of technical mixtures

If the RCR of each of the intended uses of a MATS is not  $\leq 0.1$ , this triggers a mixture risk assessment of technical mixtures containing this MATS, possibly at a high tier level. The principles of a tiered approach are presented in section 2.5.2. This mixture risk assessment usually can best be carried out by the formulator of a mixture. However, he will need highly qualified data from downstream users (including the end-user) and upstream actors (manufacturer/ importer; mainly for substance inherent properties) to demonstrate that a risk is sufficiently controlled for.

This calculation needs major efforts and favourable results may only be achieved after high tier assessments and extensive search for critical users with critical discharges. It will be helpful to demand RCRs as low as possible in the SDS, in order to increase the probability that high tier mixture risk assessments will be successful. It is proposed, that PEC reporting comes closer to more precise exposure estimates instead of “upper bounds” and to prepare substance specific toxicity data more appropriately to proceed to higher tiers in mixture hazard assessment.

Feedback from reporting (see above) communicated between regulatory authorities and manufacturers of MATS may assist in finding also hidden dischargers, i.e., dischargers where information on technical mixtures still indicates safe use, but – because of multiproduct uses and combined discharges – the summed up discharge tonnage leads to critical mixture risks.

### 2.6.2.3 How to find MATS?

The registrant will usually generate RCR which do not (or not sufficiently) correlate to existing concentrations in environmental mixtures, i.e. realistic “RCR” calculated from representative exposure concentrations. Therefore, external institutions usually should generate the data and candidates to select a MATS. However, hazard data as proposed by the registrant are used to calculate this (externally derived) RCR.

As indicated above, selection of a substance as MATS may have relevant consequences for the registrant of this substance. Therefore the nomination of a MATS should be initiated either by member states competent authorities or by ECHA. Member state activities could better account for the specific national exposure data, e.g. from monitoring programs und could possibly integrate the follow up (i.e., mixture risk assessment or control of compliance with the reduced RCR) into the “substance evaluation” program. The selection of the appropriate administrative body to nominate MATS is not further discussed in this project. There may be circumstances where MATS may also be identified by the registrant, for example, if clear criteria for MATS nomination are laid down in addition to the representative exposure data (e.g. from monitoring).

As an additional module under REACH, the nomination of MATS should start with a limited number of very high priority substances. Those nominees should be chosen from the most representative monitoring programs, and the highest frequencies with findings that cause major concern. Because of the mentioned relevant implications, the registrant of this nominee should have the right to show that a MATS’ nomination is not justified. It may be argued that such well known problematic substances are often already covered by current environmental risk reduction and risk control programs and that a further reduction to lower RCR may not be easily accomplished. However, if the current monitoring programs identify problematic substances by their high RCR (close to 1), then these problematic substances will undoubtedly be relevant for the potential occurrence of mixture effects and therefore are highly relevant as MATS. Therefore, those substances are a qualified starting point. Moreover, there probably are



a number of other problematic industrial chemicals with a high RCR not yet recognized and addressed by current environmental control programs.

It is sometimes suggested that SVHC should receive additional high priority to be selected for mixture assessments. Others argue that substances with a classification as an environmental hazard should be prioritized. We question that these properties should be key criteria for selecting MATS. For mixture effects, concentration additivity is assumed. Therefore, a RCR close to 1 is a more important selection criterion. A substance, which is classified as environmentally hazardous will not contribute much to mixture effects if present in the environment with a small fraction of the PNEC (small RCR). The same is true for SVHC. In addition, for SVHC from the candidate list already other regulatory provisions currently should lead to exposure reduction and trends for smaller RCRs. There may be some supportive criteria to select SVHC or environmentally hazardous substances as MATS, but this should not be a major prioritizing issue.

Monitoring data can be a good starting point for selecting MATS. Monitoring including additional experimental and analytical data to provide a validated RCR, would equally be the most adequate response by the industrial registrant to reject a nominee for MATS. Another proposal within this project is to allow for modelled data to justify a MATS nomination. However, only very high quality modelling results should be considered as alternative procedure for a MATS nomination. Possibly, such data may be generated in the course of member state substance evaluations or other regulatory measures. Furthermore, reporting from downstream users may reveal the repeated occurrence of specific substances. Such a reporting may be an additional tool to find MATS nominees and may be a substitute to monitoring as a finding tool for MATS (see below, section 2.6.6 and section 2.6.6.2). Other modelling approaches for possible MATS nomination are not further elaborated within this report.

#### 2.6.2.4 Discussion about MATS

The proposal to use MATS as a starting point for risk reduction due to exposure to mixtures has several strong advantages:

- It provides a single substance starting point which is an approach in accordance with the basic philosophy of REACH,
- by the request to ensure a  $RCR < 0.1$  for MATS, activities (risk assessment and establishing of risk reduction measures) are linked to the manufacturer or importer of a substance and the formulator and therefore to the responsible actors under REACH, reducing the main consequences to national authorities or end-users unable to cope with the problem (however, the identification and nomination of MATS candidates and MATS would be assigned to competent authorities, as only those may possess the necessary information on multisource priority substances and typical mixtures),
- the downstream user (the formulator) is only requested to actively engage, if the manufacturer/ importer is not able to guarantee generally for the respective use, that the  $RCR < 0.1$  will be met.
- Via MATS a link is established between a real concern (the environmental risk from environmental mixtures) and the origin of this concern (i.e., the discharged technical mixture) or between the anonymised potential environmental consequences and the identifiable causative REACH-actor, respectively. MATS are selected from their ubiquitary relevance and therefore represent those substances with a generally accepted high priority because of their environmental effects, substance properties, use characteristics as single

substances and within mixtures. This selection is linked to environmental mixture risks and therefore brings forward a harmonized procedure for mixture risk assessment for either environmental or coincidental or discharge or technical mixtures.

- Even though the ubiquitary scale is used, MATS may be selected on a national or even regional level. Differences in background level may lead to different consequences. This differentiation of the MATS concept is not equally elaborated yet, but is principally feasible and may be used to ask for different consequences for mixtures e. g. discharged in northern Germany or southern Sicily.
- The request to show compliance with an RCR of 0.1 in order to avoid further mixture risk assessment is in accordance with a MAF- approach, where an additional safety factor is applied related to the possibility of mixture effects. The size of this MAF is modest, as it would be adequate for mixtures with 10 substances to prevent concentration additivity effects.
- However, the factor 10 does not need to be regarded just as a safety factor (MAF). It may also be seen as the request to perform a better founded higher tier exposure assessment for critical substances, which does not end to show a RCR of  $< 1$ . Therefore this request supports that reported PEC more closely resemble the “real” estimated exposure and not upper bounds.
- This indirect pressure potentially extends to other PEC reportings: in order to avoid nominations as future MATS, a more realistic reporting of real exposures as PECs is encouraged. Some more accurateness in exposure assessment may pay off, when it comes to HI calculations. Similarly precautionary application of additional exposure reduction measures will result in reduced PECs if shown in the calculations and is equally advantageous.
- With MATS, this process of mixture assessment under REACH is introduced slowly and therefore will take account of other REACH obligations which also have to be carried out in near future (this argument is not intended to slow down other initiatives to activate mixture risk assessment under REACH as soon as possible; for example, proposals as presented in chapter 4.2 could be started, and activities to identify “priority mixtures” could be increased without delay).

The weaknesses of the MATS approach are:

- The process via MATS is a reactive instead of an (pro)active one. This means that relevant environmental contaminations have to exist instead of being just expected and are be evidenced by monitoring in order to nominate the first set of MATS.
- If a manufacturer or importer reports a low PEC and hence a low RCR ( $< 0.1$ ) for a MATS, there will usually be no calculation of mixture risks for a mixture containing this MATS.
- There may be differences in priority on a local scale or on a more regional, national or even European scale. MATS are derived from a macroscopic starting point. This may violate priorities at the local or regional level.
- The well-known critical substances in existing monitoring programs are probably already regulated elsewhere. Therefore it may be complicated to further reduce their concentration to a RCR of 0.1. This means that more complete mixture assessments will often be needed for the first well known MATS.

Some of the mentioned disadvantages may be compensated by the supportive measures to be seen in combination with MATS as an integrated concept:

- The slow and reactive process to find MATS may be supplemented by the systematic search for further priority substances and/or “priority mixtures” (section 2.6.3), which enables the actors to nominate more candidates at an earlier stage for further MATS.
- The contradictions between local and ubiquitary priorities may not be solved, but may be reduced due to the flexibility of the specific MATS approach put into practice.
- Currently there are only few adequate monitoring programs to address industrial chemicals. Most of them are related to pesticides, biocides, or pharmaceuticals. With appropriately designed monitoring programs it is assumed that, in near future, qualified data on industrial chemicals become available as additional MATS nominees.

### 2.6.3 Priority Mixtures

There is a huge amount of technical mixtures placed on the market by formulators. What are the technical mixtures which should be assessed first?

The identification of „priority mixtures“ has been proposed from different actors as a possible first step to implement mixture assessment. In the following sections several possibilities to define and to find such priority mixtures are described. Starting point for priority mixtures are the technical mixtures (contrary to the MATS approach described above, which starts with the identification of specific triggering substances in environmental mixtures).

#### 2.6.3.1 What are “priority mixtures”?

The term “priority mixtures” is frequently used, but criteria which determine priority are usually not provided. In fact, a similar term, called “mixtures of concern” is yet to be defined (SCHER/SCENIHR/SCCS, 2012).

In the following we propose to call a mixture a “priority mixture” in five cases:

- There is a high probability that a “**hazard index**” of 1 will be exceeded (assuming concentration additivity).
- There is a high probability that – due to exposure to this mixture – certain **adverse effects**, which themselves are prioritised, may occur.
- The type of use of a mixture implies a **high probability of a combined exposure** of the environment to the substances in the mixture (e.g. use of or contamination from mixtures on soils.)
- There is a higher probability that **concentration additivity** as a mixture effect occurs (in comparison, where concentration additivity is just a conservative default, without explicit support from the specific similarity properties of the ingredients), or
- there is a higher probability that **synergistic effects** as a mixture effect occur (in comparison to the usual additivity default assumption).

Up to now, a systematic identification of priority mixtures did not take place. The five cases above describe more principles than give actual examples. In the following, criteria are described which could help to find priority mixtures.

#### 2.6.3.2 Criteria for priority mixtures

If the composition of a technical mixture is known, the following criteria can help to decide whether the mixture should be assessed for mixture effects:

- Relevant occurrence of one or more substances of the mixture in the environment
- Specific critical properties of one or more substances of the mixture
- Critical use characteristics of the mixture
- Critical combinations of substances in the mixture
- Closely related substances in the mixture, which occur frequently together

**Relevant occurrence of one or more substances of the mixture in the environment.** A technical mixture becomes a “priority mixture”, if it contains one or more substances which already pose a comparably high risk to the environment. Prioritisation criterion would be the risk characterisation ratio (PEC/PNEC). Environmental concentrations should be derived from monitoring data, because of the uncertainties of modelled PEC values. Substances with “relevant occurrence” could be identified as MATS, as described above. For more details on “relevance occurrence”, see section 2.6.2.1. (As discussed above and in section 2.6.6.1, it has to be considered, that only for a limited number of substances robust monitoring data are available).

**Specific critical properties of one or more substances of the mixture.** Specific substance properties could increase the concern for mixture effects. If a technical mixture contains such substances, the mixture could be prioritised for mixture assessment. Substance properties are not regarded as “stand-alone” criteria for priority setting. However, they can increase another concern, e.g. from relevant occurrence.

- Persistence and bioaccumulation are likely to increase the likelihood of mixture risks because they indicate a prolonged exposure time (persistence) and the long-term presence in biota (bioaccumulation) and hence an increased likelihood of simultaneous internal exposures.
- Substances with properties affecting general biological functions, such as increasing the bioavailability of substances or enhancing uptake through biological membranes could be regarded as “general synergists”.<sup>44</sup> These substances would increase the priority for mixture assessment as they generally increase the likelihood and the levels of combined exposures due to their general influence on biological systems.
- Endocrine disrupting chemicals, which lead to longterm effects on population level, and substances with properties indicating synergistic activity related to general biological functions.

These properties (and/or combinations of them) may be useful elements to set priorities which technical mixtures should be assessed with priority.

If certain substance properties were selected as complementary prioritisation criteria, industry could check whether or not “their” substances fulfil these criteria and act accordingly. As mentioned above, these criteria are only complementary criteria. It should be checked whether these substances fulfil in addition one or more of the other criteria described here (e.g. relevant occurrence). Proposals for the application of these criteria for priority setting by registrants, formulators and downstream users are made in chapter 4.2).

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<sup>44</sup> Normally, synergists are defined only in combinations with other substances and hence, this is not a substance – related criterion but addresses mixtures. However, some general synergistic actions have been identified e.g. for metals (increased substance uptake) or tensides (alteration of bioavailability).

**Critical use characteristics of the mixture.** Assessment could focus on cases where mixture risks are particularly likely due to specific use characteristics. If technical mixtures are used in the open environment, combined exposure is likely. An example are chainsaw oils for tree felling. Substances in these mixtures jointly drop to the soil. They don't quickly partition and don't move separately to other compartments. Therefore formulators of the chain oil could perform a tiered approach mixture risk assessment according to section 2.5.2.

The conditions which would make the use of a mixture such a “critical use” could be established based on existing studies, expert judgement and other information.<sup>45</sup>

**Critical combinations of substances in the mixture.** Specific combinations of substances (e.g. specific metals together with specific organic substances) are known to enhance mixture effects. In these combinations, mixture effects exceeding additivity have been shown. Assessment could focus on technical mixtures which contain such “critical combinations” of substances that are known to cause mixture risks.

**Existing studies from mixture toxicology could be used as starting point to identify these “critical combinations”.** Sector knowledge and mixture data bases could be used to screen which technical mixtures contain such critical combinations.<sup>46</sup>

**Closely related substances in the mixture, which occur frequently together.** Under REACH, substances which are closely related (e.g. a homologue series of saturated hydrocarbons) can be registered in groups.<sup>47</sup> For registration, read-across can be applied to close data gaps for substances within such a group.

ECHA's IR/CSA guidance already indicated that for such closely related substances a priority for mixture assessment could be generally proposed. This should be considered if these substances frequently co-occur in technical mixtures or in the environment. Under these conditions it can be foreseen that combined exposures by these substances take place.

A registrant could perform a mixture risk assessment, if his environmental substance specific hazard assessment (derivation of PNECs) was based on “read across” quantifications, and if

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<sup>45</sup> The result of an assessment of uses and compositions could be a set of use descriptors (mainly PC, if helpful, specified by PROCs and ERCs).

<sup>46</sup> One way to go forward would be to define “typical mixtures”. These are combinations of substances which frequently occur together. Note, that “typical mixtures” are not necessarily “priority mixture” because the frequent co-occurrence of certain substances *per se* would not necessarily mean that the respective “typical mixture” is a “priority mixture” or a “mixture of concern”. In order for a typical mixture to become a priority mixture, there have to be additional indications on one or more of the priority criteria mentioned above. Technical mixtures are placed on the market with a specific composition. In this case, a typical mixture could be technically defined. Substances occur in combination, because they are used together due to physicochemical or technical reasons. A pigment, a solvent and a filler may constitute such a typical mixture used as a paint. A major difficulty is that at present there is only limited knowledge about “typical” compositions of technical mixtures and the frequency of their occurrence in aggregated evaluations

<sup>47</sup> The term “closely related substances” is already used in ECHA's guidance but is not operationalized. Hence, a definition of this term would be required to support its use in priority setting.

there are indications that some or all of the substances assessed by read across may occur in identical uses or technical mixtures.<sup>48</sup>

Some closely related substances typically occur together in the environment (like dioxins or polycyclic aromatic hydrocarbons), others may be characterised independently from their combined occurrence (like phthalates).

MATS and priority mixtures fulfilling the criteria described above would trigger a mixture risk assessment, usually starting with a tiered approach.<sup>49</sup> “Priority mixtures” and MATS could be documented in regulatory listings, available to all actors via internet documentation. Registrant under REACH are informed about their own “read across”- assessments from registration, they may directly perform a mixture risk assessment in these cases.

The following Table 14 gives a first indication which actor could use the criteria for priority mixtures described above.

**Table 14: Conformity of the option to require the use of MAF in the registrants’ CSRs with core REACH principles**

Criterion for priority setting	Actor	Reasoning
Relevant occurrence / MATS	Registrants + formulators	Registrants have to show for MATS RCR < 0.1 or to perform a tiered risk assessment, probably in cooperation with formulators
Specific critical properties	Formulators	Formulators can check which technical mixtures contain substances with these properties (if it has been defined what are these critical properties).
Critical uses	Formulators	Formulators know which of their technical products have critical uses (if criteria for such uses have been defined).
Critical combinations	Formulators	Formulators can check which of their technical mixtures contain critical combinations of substances (if it has been defined what are critical combinations).
Closely related substances	Registrants	Registrants know for which substances grouping and read-across have been used in the registration of these substances.

### 2.6.3.3 How to find priority mixtures?

There are a number of ways to detect priority mixtures. They are not described in this report in full detail. Additional information on this topic is given in section 2.6.6.

<sup>48</sup> It is realised that it may rarely be possible to find out about a common mode of action or “similarity” of different substances (see section 2.2.2 - 2.2.3). Moreover, even substances being “dissimilar” from first glance may in fact act via identical modes of action after a more details mixture effect analysis. However, if substances are registered by a “read across”-approach, this makes it highly probable that in fact a common mode of action is to be assumed. This common mode of action is the background of the type of registration justification (read across). Therefore, the “concentration addition” default assumption for mixtures would be supported beyond the default, if such substance with a similar mode of action, based on the “read across” information, occur in a mixture.

<sup>49</sup> The tiered approach can be combined with a whole mixture test approach or a specified MAF (to be discriminated from a generic untargeted MAF).

Existing monitoring programs are one of the most interesting approaches to find MATS and single substances for priority mixtures (see section 2.6.6.1). Moreover, the following two procedures address the problem quite differently with other strengths and weaknesses:

- a “reporting tool”, providing tier 1 RCR calculations from downstream users and end-users for further analysis by administrative bodies (see section 2.6.6.2),
- a SPIN linked approach related to product register evaluations (see section 2.6.6.3).

There are further ways to find candidates for priority mixtures. The details of discussions do not preclude that other approaches may be equally relevant.

Details on these ways to find priority mixtures are given in section 2.6.6. Before, two approaches for priority setting are briefly described which can be used by formulators (section 2.6.4) and by end-users of technical mixtures (section 2.6.5).

## 2.6.4 Tiered Approach by Formulators for technical Mixtures

Generally, formulators of mixtures are those actors under REACH which could best perform the tiered risk assessment described in section 2.5.2, due to their knowledge of substances in their technical mixtures. Under REACH they are responsible to communicate conditions of use for their mixtures which ensure safe use. However, at present in many cases the information which they receive from their suppliers may be inadequate and the necessary efforts may be too high to perform such an assessment on an adequate level. This limits the possibilities of formulator to do a mixture risk assessment using the tiered approach.

However, in case of the occurrence of MATS / priority mixtures, the respective tiered risk assessment of technical mixtures by the formulator should be considered. By this means the formulator may proof internally and externally that his uses of technical mixtures are safe to the environment. If, on the other hand, his calculation results in a Hazard Index above one, the formulator may initiate communications with the manufacturer/ importer and the downstream user on the reasons for this unfavourable result. This may lead to a better understanding on the parameters of the uses of his mixture and even to improvements in risk management measures if warranted. It has to be admitted, however, that a relevant exceedance of a Hazard Index may not always be corrected, if appropriate data are not available to the formulator.

## 2.6.5 Tiered Approach for End-users on aggregated Exposure

In principle, the end-user can perform a mixture risk assessment as described in section 2.5.2 for formulators. However, because of the usually limited resources and because of the fewer available data (e.g., no full information on the complete recipe of the technical mixture used) there will be few occasions where this assessment will be done by the end-user. It would be very helpful if the end-user starts communication with the formulator by contributing his local parameters on risk management measures, discharges, sewage treatment plant parameters and river flow characteristics to assure that his specific use of the mixture with the respective discharges is fully included in the assumptions used by the formulator.

However, the end-user of mixtures and single substance’ chemicals knows about data, which are not accessible easily by others actors in the supply chain, e.g. the actual amount of the technical mixture which is used or the parallel use of several technical mixtures which contain a specific substance. He may perform a relatively easy single substance risk assessment by calculating the RCR, after he has added up all the sources of single substances from all of his discharges.

An example for an aggregated exposure is given in the following Table 15. It refers to the situation of a downstream user in a tannery. In this case, three different technical mixtures are used. Each of these technical mixtures contains the same alkylsulfonate – in differing concentrations. In the resulting discharge mixture of the tannery, substances from the three technical mixtures occur together and hence an aggregated exposure to alkylsulfonate from the three products occurs.

**Table 15:** Simultaneous use of three products with the same substance (here: Alkylsulfonate) by DU. Source: own survey, related to TEGEWA 2011

Product	Amount of product used per day by DU	Content of alkylsulfonate (%)	Amount of alkylsulfonate used per day
	[kg]	[%]	[kg]
Degrace 14	50	5	2,5
Protube 25	40	10	4
Solomud TB	20	10	2

A concept for the assessment of aggregated exposures under REACH has been published by the Federal Environmental Agency (Gross et al. 2010).

For the usually low number of substances applied and discharged by the end-user from more than one mixture, he may easily calculate the aggregated exposure (sum of PECs from all uses as a single substance or in a mixture) and compare it to the PNEC. Again, the RCR should not exceed the value of 1, or be even lower (due to cumulative exposure with other substances). Similarly to the formulator, the end-user may use this information to provide evidence that aggregated single exposures – as a sum – does not lead to an environmental risk (this does not exclude all other mixture effects if those are not simultaneously assessed). If the aggregated exposure results in an  $RCR > 1$ , he may initiate risk management measures or contact the formulator for better data. It is directly related to discharge mixtures and, at the same time, is a minimum requirement that single discharged substances should not mount up to exceed the respective PNEC.

## 2.6.6 Additional Information: How to find Priority Mixtures?

### 2.6.6.1 Monitoring programs

Within the framework of other regulations monitoring programs are already well established. They serve to provide concentrations of chemicals in the environment which may be used as qualified PEC data, if representative and which may serve to nominate priority substances and mixtures. For example, the “water framework directive” makes use of such monitoring data. However, most existing data are not closely linked to the demands of REACH. The generated data often comprise of crude indicator chemical parameters like AOX or document the occurrence of pharmaceuticals and pesticides in water, but are not specifically designed to detect and quantify the occurrence of industrial chemicals. Moreover, they may not be sufficiently widespread to get a differentiated profile of the substance occurrence in the environmental media. However, an increasing number of projects provide additional output which could be further analysed and assessed and therefore could serve as substantial source of REACH related data. For example, for a priority setting process of substances in the context of the water framework directive, a recent research project identified a large number of substances in combination with details on concentration, tonnage and number of observations (IOW/INERIS, 2009). A large set of substances for a number of member states present in river



basins is also generated by an ongoing EU programme (<http://www.eea.europa.eu/data-and-maps/data/waterbase-emissions-2>). Those data could not only serve to detect single relevant substances to be nominated as MATS, but the data could also be analysed to show if certain substances occur in combination or even correlated in concentration to each other, which would help to nominate typical priority mixtures. Finally, the calculated PEC/PNEC ratios in a tiered approach as presented in section 2.5.2 could be mirrored to environmental monitoring PEC data to discuss the adequacy of the respective calculations with regard to the real risk to the environment.

### 2.6.6.2 Reporting tool

Above, we described a tiered approach for mixture risk assessment and we outlined the dilemma that of the key data for this assessment are only available to the manufacturer/importer on the one side (e.g., detailed hazard data), while other data are only available to the formulator (e.g., mixture composition) or the end-user (factual discharges, local STP characteristics and river flow rates) on the other side. Moreover, the end-user may have the appropriate data to perform a qualified high tier mixture risk assessment, but he usually will not have the resources to work with complex exposure assessment tools and to perform sophisticated calculations. The idea of a reporting tool considers to combine the capabilities of the actors under REACH including the administrative regulatory bodies and to split the burden of assessment tasks between them. However, the basic idea needs further discussions to find out about its feasibility.

In Annex 3 (section 9.3), we characterize such a possible reporting tool by an example in combination with an example template for reporting.

This tool is characterized as follows:

- Reporting here means documentation of a low tier- RCRs for all classified substances of a discharge to regulatory authorities by the discharging commercial or industrial unit.
- This reporting could only be obligatory, if the tonnage of discharge by the single discharger exceeds a certain cut-off (the size of which has yet to be specified), but no undue obligations should be assigned to SME with limited overall impact to the environment.
- The reporting has to be assisted by an electronically processed “fast & easy response spread sheet” which accompanies the substance life cycle flow from the manufacturer or importer all along to the formulator and to the end-user. Each actor fills in the information where he is most knowledgeable. For all data defaults are provided, forwarded and maintained, if no consecutive downstream user is able to include more appropriate data (see below for more detailed specification of this reporting cascade).
- Data for reporting and included in the spread sheet are taken from registration documents and SDS and may be transferred assisted by electronic tools. The downstream user as a formulator will combine the input information from various substances contained in the technical mixture and a) use it to estimate his own discharges and report them to the authorities and b) forward the aggregated spread sheet to the end-user after adding supplemental information, collected best at his position within a substances life cycle.
- The end-user should usually only be asked to contribute specific local data on realistic input amounts, sewage plant characteristics and identity, and on the effluent water flow of mixtures, where readily available and forward this information annually to the regulatory authorities. Most of those parameters are identical for all of the technical mixtures used and discharged by the end-user.

- The reported RCRs may be aggregated to hazard indices by simple follow up calculations, but this is not requested to be done by the discharger.
- The reported RCRs may exceed 1 or even result in much higher values. This exceedance has no direct regulatory consequences, as it is just low tier information. In addition, to ask for high tier documentation in cases of potential risks within a routine reporting procedure is beyond the capabilities of the discharger and would not be proportionate to ask for.

Regulatory authorities may use this information to aggregate the data and find out if there are repeating patterns of combined exposures / common occurrence of substances allowing for many targeted investigations. One of the applications can be the search for “typical mixtures” or further MATS after combined analysis of reporting protocols.

### 2.6.6.3 SPIN database

Another way to identify “priority mixtures” may consist of specific evaluations of the SPIN database (“Substances in preparations in Nordic countries”),<sup>50</sup> which is based on data from the Nordic product registers. The potential use of these data for REACH-related purposes was already discussed several years ago (Ahrens and Reihlen, 2007).

The toolbox provides semi-quantitative information (indices) on the potential exposure for several impact areas, e.g. surface water, workers and consumers, using two scores:

- A “use index” with four scores that describes the exposure potential for different impact areas and ranges from “-“(probably no direct exposure) to “XXX” (very probable exposure).
- A “range of use” referring to the range of different applications, again with four scores.

The type of information (together with a legend) is shown using an example in Annex 4 (section 9.4).

The developers of the exposure toolbox indicate that the tool provides rough estimates and may therefore primarily serve screening purposes. The scores for the use index are based on industrial categories and use categories manually assigned a low, medium or high potential exposure for the respective compartment.

Such data allow the screening for individual substances with a (very) wide range of applications and a (very) probable exposure of specific compartments, such as surface water or soil. While a direct assessment of mixtures as “priority mixtures” is impossible (SPIN is essentially substance-based), there are several options to carry out such assessments.

Obviously, it would be possible to screen all substances contained in SPIN by hand in order to identify all those chemicals with high scores for both indices. It would then be possible to identify all substances with identical use categories, pointing to potential mixtures. This, however, would be prohibitively time-consuming.

Another approach is to use the separate “use index table” provided on the SPIN website, which allows identifying all uses assigned a high exposure potential. The respective uses are described by the “use code nation” (UCN) and not by international categories, such as the former EU use category (UC). In order to further refine this list, information submitted to and evaluated by ECHA can be used.

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<sup>50</sup> <http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx>

In defining a “priority mixture”, the next steps could include a specific tonnage cut-off, specific uses or a combination of both. Both the total tonnage band and the descriptors assigned in the dossiers are most likely accessible to automatic data extraction procedures by ECHA (although the connection to product types may not be). In addition, cooperation with the national product registers of the Nordic countries, which provide the input into the SPIN database, could be fruitful. The product registers contain information on the products, i.e. the composition, and can e.g. be used to check the results of evaluations.

Overall, evaluations may be useful in identifying “priority mixtures” and may be enhanced by confidential data from ECHA (or others). It must be emphasised that the entire evaluation procedure is independent of any hazard information and solely uses exposure-related data.

For more details on evaluating the data from SPIN for the selection of priority mixtures see Annex 4 of this report (section 9.4).

## 2.6.7 Summary: Concepts for Priority Setting

Mixture risk assessment would not be implemented as a routine obligatory assessment under REACH, but could be requested in specific situations, where there is a higher probability of such mixture effects or where there is concern for mixture effects with serious endangering implications for the environment. Therefore such priority substances or priority mixtures have to be identified.

In this report, a “priority mixture” or “priority substance” has at least one of the following characteristics:

1. there is a higher probability that concentration additivity as a mixture effect occurs (in comparison, where concentration additivity is just a conservative default, without explicit support from the specific similarity properties of the ingredients), or
2. there is a higher probability that synergistic effects as a mixture effect occur (in comparison to the usual additivity default assumption), or
3. there is a relatively higher probability that a “hazard index” of 1 will be exceeded (assuming concentration additivity), or
4. there is a higher probability that – due to exposure to this mixture – certain adverse effects, which themselves are prioritised, may occur.

To identify a “priority substance” is a usual procedure under REACH, because REACH relates to single substances. A single substance would be a priority substance according to condition c) (above), if it is associated with a “risk characterisation” ratio close to 1 (e.g., 0.8), because the hazard index of 1 will often be exceeded, if other substances within a technical mixture contribute with their RCR to the mixture effect. Therefore, substances, which are known to occur with a high RCR in the environment (as derived from monitoring or high quality assessment data) induce a priority to perform a mixture risk assessment in a specific local situation, where this substance is part of a discharged mixture.

In this report, those single substances are called a “mixture assessment triggering substance” (MATS). MATS receive their priority, because they frequently occur in environmental mixtures in high concentrations (compared to their PNEC). The proposal foresees that they are usually nominated by authorities and have to be confirmed and listed. However, it is not ruled out that concepts can be developed in future where the registrant himself is enabled to identify MATS and no further activity (listing) by the competent authority is needed to nominate these mixture assessment triggering substances.

For MATS, the registrant (manufacturer/ importer or formulator) have to perform a very careful exposure assessment, because for the specific uses a RCR of (e.g.) less than 0.1 is demanded. If the local calculated/ modelled RCR is not below 0.1, a full mixture risk assessment has to be performed according to the tiered approach. This MATS-concept may be modified to more specifically nominate substances as MATS that cause certain adverse effects (condition d, above) or which are typical effect enhancers (condition b, above).

Similarly, priority mixtures can be detected. For example, if some substances occur in one mixture, which were assessed by a “read across” approach under REACH, we may reasonably assume that they may act with a similar mode of action. Therefore there is a higher probability that concentration additivity as a mixture effect occurs (condition a, above), leading to this priority. For more than one endocrine disruptor in a technical mixture, this also may be a reason to call the respective mixture a priority mixture (condition a, above) and request a full mixture risk assessment. Typical mixtures, found in the environment or probably occurring as supposed from their common use in technical mixtures, could be analysed more closely for relevant mixture effects and nominated as priority mixtures thereafter.

A way to find such typical mixtures with common occurrence could be to analyse data referring to mixture compositions as documented in SPIN (Nordic countries product data base, also containing information on preparations, i.e. mixtures) or to analyse discharge mixture compositions in combination with discharge amounts and PNECs on an aggregate level by authorities. This analysis can only be performed by authorities because authorities may combine and compare discharge data on a local and regional level and may merge data from different regions. They may, thus, be able to make appropriate generalisations to back the derived priorities. However, as authorities currently do not receive adequate information on local discharges, an additional *reporting tool* under REACH has to be supplemented, to realise the proposed procedure for to find priority mixtures.

The nomination of MATS has been criticised as it is a slow reactive tool to find single priority substances from monitoring. If authorities analyse discharges more extensively and systematically based on information gathered with the proposed reporting tool, this may not only lead to the nomination of additional priority mixtures but also to the proactive (instead of slow reactive) nomination of additional MATS. However, it is acknowledged that the implementation of a reporting tool is a laborious high effort approach, which has to be evaluated against the resulting benefits.

Priority setting is proposed, because a full mixture risk assessment may not be foreseen on a routine basis for all discharged technical mixtures under REACH. However, it may be performed independently from overall priorities on a voluntary basis by single formulators, who may want to “get a feeling” on their possible contribution to mixture effects from their own discharge. They would apply the tiered approach for their portfolio (or some discharged mixtures selected from own priority scales). Similarly, aggregate exposure to identical substances from several discharged technical mixtures or single substances by one industrial unit, could be performed accordingly on a voluntary basis. Chapter 2 briefly refers to these possible implementations of mixture risk assessments.

### 3 Evaluation of options to implement mixture assessment in REACH

#### Specific Abbreviations used in this Chapter

CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DNEL	Derived no Effect Level
DU	Downstream User
ES	Exposure Scenario
I	Importer of a Substance
M	Manufacturer
MA	Mixture Risk Assessment
PNEC	Predicted no Effect Concentration
SDS	Safety Data Sheet
SEA	Socio-economic Analysis
SEV	Substance Evaluation

#### 3.1 Introduction

The aim of chapter 3 of the report is to analyse and evaluate whether and how/in which extent the methods and approaches developed in chapter 2 of the report can be implemented under REACH or not. Hence, this part of the report presents a feasibility assessment of the options to prioritise cases, where mixture assessment should be performed and it describes the options to implement mixture assessment into the REACH procedures for different actors.

In chapter 3.4 the principle options to prioritise cases for mixture assessment outlined in chapter 2.6 are briefly described. The assessment of their feasibility from a scientific and regulatory point of view is briefly summarised. No detailed feasibility assessments with regard to benefits, efforts and costs etc. of the different options are carried out, because costs and benefits can only be determined in relation to concrete case, where an impact assessment is carried out and specific outcomes can be discerned.<sup>51</sup> However, a discussion of the principle regulatory options to implement the proposed prioritisation criteria is included.

In chapter 3.3 the different methods to assess risks from mixtures described in detail in chapter 2.5 are specified with regard to the actor who should perform them (registrants, formulators, end-users, authorities) and the processes in which they could be implemented (registration, communication in the supply chain, compliance checking, compliance checking, substance evaluation, authorisation and restriction). For all methods a detailed discussion of the legal situation, the accessibility of information to the different actors the conformity with the regulatory framework of REACH, expected benefits and costs as well as enforcement aspects are

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<sup>51</sup> It could be considered to develop an impact assessment for the different prioritisation criteria in relation to specific mixtures as examples and assessment options in order to derive concrete figures or descriptions of the related costs and benefits. This could be carried out in the context of a follow-up study.

presented and conclusions are drawn regarding the possibility to implement the options under REACH. This analysis presents the opinion of the authors and does not necessarily reflect the opinion of the Federal Environment Agency (UBA).

## 3.2 General aspects regarding mixture assessment under REACH

Several types of mixtures are defined in the 4M project which are differentiated according to the degree of knowledge of their composition and the location where they occur (c.f. chapter 1.2 and 2.3). In the following two sections it is discussed which type of substances and mixtures could be subject to mixture assessment by the authorities and by industry and which types of mixtures are very difficult to assess for practical reasons.

### 3.2.1 Assessment subjects of different actors

Industry actors are responsible for the safety of the substances and mixtures they place on the market. Each industry actor knows the characteristics of his substances or mixtures and the conditions how he produces them. Consequently, the options for mixture risk assessment proposed for manufacturers address substances or substance groups and those for formulators address technical mixtures. For both, the mixture assessment would cover the own production process (manufacturing or formulation) and the further lifecycle stages.

Consequently, the subjects of potential mixture risks assessments by registrants<sup>52</sup> are

- all substances / substance groups they register
- any substances prioritised for mixture assessment
- “very closely related and similar acting<sup>53</sup>” substances / substance groups (c.f. chapter 1.5 and 2.6.3).

Formulators can derive risks from the formulation and use of their technical mixtures (discharge mixtures at their own and/or the customers’ sites) because they know the mixture composition and can estimate emissions from the processes in a generic assessment. This means they could model the fate and concentrations of the substances in their technical mixture after release from the industrial processes in the local and regional environment. However, they have no information on the composition of the coincidental mixture (after the sewage treatment plant connected to their site or the customers’ site) or the environmental mixtures (appearing in the environment after discharge from sewage treatment plants). Consequently, the possible subjects of the formulators’ risk assessment are technical mixtures.

Industry actors are also responsible to ensure that there are no risks from their installations. Consequently, the option to assess effluents, which are mixtures of all substances simultaneously emitted from one site, is also considered as an option for manufacturers, formulators and end-users.

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<sup>52</sup> If manufacturers register UVCBs, these substances can be regarded as a mixture itself. This option is not further discussed in this study as it is already current practice.

<sup>53</sup> The term “very closely related and similar acting” is used in the ECHA guidance documents.

Table 16: Possible assessment focuses of the different industry actors

Industry actor	Manufacturer	Importer	Formulator	End-user
Registered substances	Yes	Yes	No	No
Similar and closely related substances	Yes	Yes	No	No
Technical mixtures	No	No	Yes	No
Effluents from the own site	Yes	No	Yes	Yes

The overall responsibility of authorities is to control and enforce the work of industry on the one hand and to identify risks, which cannot be observed by industry on the other hand, e.g. because individual companies have no knowledge of accumulated substance amounts in their overall uses and applications.

New compliance checking tasks for industry assessments, e.g. mixture assessments in CSRs in registration dossiers or mixture assessments by downstream users are not discussed as separate options to act for ECHA or the Member States, as this work “naturally” results from the respective industry options.<sup>54</sup>

The identification of risks from mixtures is the focus of the authorities’ potential mixture assessment work. This work could be started from two sides:

- from the identification of ‘critical exposures’ potentially resulting in mixture risks in coincidental and/or environmental mixtures; these could regard co-occurrence<sup>55</sup> of substance groups or high RCRs of substances in the environment (exposure to mixtures),
- from studies /knowledge of additive effects or synergisms of specific substances (mixture hazards).

Either perspective from which an environmental risk from mixtures could be identified could result in a proposal for substance evaluation, restriction proposals or a prioritisation of substances for authorisation.

Nevertheless, in the processes of substance evaluation, authorisation and restriction, the subject of authorities’ work is a substance or a group of substances, including aggregated exposure (c.f. chapter 3.2.1).

In conclusion it should be taken into account that

- the subject of industry mixture assessments are mixtures as placed on the market. The assessment aims to identify risks from the subject of the assessment in the local and regional environment.

<sup>54</sup> The evaluation of registration dossiers is an exemption because this option is discussed in detail; however, this is not a consequence of industry work but an option that could be performed on the initiative of the Member States.

<sup>55</sup> The term co-occurrence is used in the report to address any situation, where (often only qualitative) information is available that substances are present simultaneously in a technical mixture, a discharge from an installation of sewage treatment plant or in an environmental compartment. Information on exposure levels may not necessarily be available and or exist (in case of technical mixture or discharge from installations).

- the subject of authority assessments are substances and substance groups. The assessment aims to verify suspected risks in based on either indications of mixture hazards or exposure to mixtures.

### 3.2.2 Information on the composition of mixtures

An important question in particular for industry actors is which substances in a technical mixture or a discharge mixture (mixture which is discharged from a site into a sewage treatment plant) are to be considered in mixture assessments.

From a scientific point of view and based on the default assumption of additivity of effects, all substances in a mixture would have to be considered. There are no reasons from a scientific perspective, why certain types of substances could be excluded.

From a practical point of view and in a regulatory context, there are reasons to exclude substances from the assessment, however.

Firstly, each actor can only include those substances in his assessment, of which he knows that they are contained in the mixture he is to assess. Limitations to the knowledge of the composition of technical mixtures are posed by the provisions of communicating information on mixtures in the safety data sheet: only substances which are classified according to the CLP-regulation and which are contained above defined concentration limits have to be listed in section 3 of the safety data sheet. Consequently, in a mixture risk assessment only the substances listed in the safety data sheet can be considered by those parts in the supply chain that receive the SDS.<sup>56</sup> This means that to a certain extent a prioritization of substances for mixture assessment based on the hazardousness and the concentration in mixtures, as defined in the rules for identifying substances in the safety data sheets by the CLP-regulation exists due to practical reasons.

The same applies to discharge mixtures; also here the respective actors can only model the emissions of substances of which they know that they use them; i.e. they use them either as single substance or get information on their identity in the safety data sheets of the mixtures they use. Hence the same limitation exists as for technical mixtures.

Regarding the lack of communication on the composition of mixtures in the supply chain, it could be considered to change the current legislation and thereby improve the information situation. However, this requires an in-depth assessment of the current legal framework regarding supply chain communication and safety data sheets as well as the compatibility of respective changes with global trade policies, international competition law, patent law and chemicals legislation.<sup>57</sup>

As the consultants assume that respective legal changes would take a very long time, the current legal situation regarding confidentiality of information and communication of substance identities in the supply chain is used as basis for the following assessments.

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<sup>56</sup> Formulators producing a mixture do know their composition regarding substances they use as such. If they use mixtures, they can only refer to the substances indicated in the safety data sheet of the input mixture.

<sup>57</sup> This could be a topic for a further research project on the feasibility of implementation options on mixture assessment under REACH.



However, one change may be useful and could be considered in the context of introducing the MATS concept (see chapter 2.6.2): a requirement to indicate the content of MATs in mixtures if contained in concentrations above 0.1% could be introduced (analogous to SVHC) in order to ensure that prioritized substances / mixtures can be recognized. This proposal would be a logical consequence of prioritisation of substances for mixture assessment, which should be further explored in the context of respective discussions.

### 3.2.3 Hazard information on substances in mixtures

It may not be possible to derive PNECs for all substances which are known to be present in an assessed mixture, even if they are registered in tonnages exceeding 10 t/a. This is due to the fact that some substances identified in the safety data sheets (e.g. due to their human health or physical-chemical hazards) have a very low ecotoxicity. This means that no specific value is provided in the respective endpoint reports for the ecotoxicity in the registration dossiers (and hence the ECHA database) but that values are specified there as > xyz mg/l (limit tests). This is because respective testing is conducted with a specific aim, namely

- classification and labelling – substances with an acute toxicity of more than 100 mg/l do not trigger an environmental classification; hence testing with higher concentrations could be stopped
- PBT/vPvB assessment – relevant long-term toxicities are 0.01 mg/l; hence no testing at higher concentrations is necessary and
- PNEC derivation – this is oriented according to match potentially occurring exposures. Testing may not be performed, if exposures are regarded to be very low and or are regarded as “irrelevant” (waiving). Testing may be stopped in these cases, if the exposure value is reached (test result is  $LC_{xyz}/EC_{xyz} > xyz \text{ mg/l} > \text{expected exposure}$ ).

Advanced tier procedures to supplement missing information in order to derive a PNEC, using e.g. qualitative structure activity relationships (QSARs) are discussed in section 2.4.2.2 and may be thought of to solve the problem.

In general, information to derive PNECs is not sufficient for substances registered in amounts below 10 t/a (c.f. chapter 3.2.4) and probably not available for substances which are not registered under REACH.

### 3.2.4 Data availability for PNEC derivation

The derivation of PNECs requires at least three study results from three different trophic levels. This information is only available for substances registered in amounts exceeding 10 t/a.

However, also substances registered below 10 t/a could significantly contribute to environmental risks and to identify a mixture’s the risk level respective information is needed. As indicated in section 2.4.2, there are possibilities for circumventing the data gaps in the derivation of (higher tier) hazard indices. However, they require a high level of expertise and may not be practicable for all industry actors.

Apart from the proposals in the context of the method description of the tiered approach, the consultants see three other options how to tackle the issue, which would require further, scientific and political discussion to evaluate their feasibility and usefulness:

1. Change of Annex VII of the REACH regulation and introduction of an additional test requirement for the registration of substances between 1 and 10 t/a

2. Modification of the method for PNEC derivation for the purpose of mixture assessment to allow PNECs based on 2 data from two trophic levels.
3. Introduction of mixture assessment requirements only for substances for which a CSR is conducted (registered above 10 t/a and classified) and hence, PNECs are available.

The first option results in increased registration requirements, potentially resulting an additional vertebrate animal testing (fish test) with the benefit of data availability for PNEC derivation for any registered substance; hence there would be no limitations (in the first tiers) due to gaps in hazard data regarding which substances in a mixture could be included in a mixture assessment.

The benefits of the second option are as of the first one but the drawback is a higher level of uncertainty in the PNEC value which should be accounted for by an additional safety factor. This makes the entire mixture assessment less reliable and increases the possibility of indicated false positive risks due to potentially conservative safety factors.

The third option would not require any changes to the current procedures and assessment rules but would result in a limitation of substances that would be included in a mixture assessment (regardless of whether they are the trigger of the assessment or if they are just contained in a technical mixture) to those, which are registered in amounts above 10 t/a. This is another prioritisation for which it is unlikely that it corresponds with the actual risk level regarding mixtures in the environment.

The most appropriate option for implementation depends on which options to act for industry and authorities should actually be considered for implementation under REACH. Also a combination of options or a step-wise approach could be envisaged. The possibilities to close data gaps for PNEC derivation or the conduction of higher tier hazard assessments by all actors are not further discussed here.

In the report it is assumed that the mixture assessment is NOT limited to substances, for which a CSR exists.

### 3.2.5 Consequences of a mixture hazard index > 1

Most of the options to make mixture assessments obligatory to industry include the derivation of a hazard index<sup>58</sup> (HI) for the mixture see section 2.5.2. The consequences of a HI exceeding 1 are not further elaborated in this report. This is due to the fact that the level of uncertainty related to the mixture HI is much higher than the uncertainty related to the RCR for individual substances, because uncertainties of the single mixture components add up.

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<sup>58</sup> The term “hazard index” is used to describe the modelled risk from mixtures. It is derived by adding the RCRs of the substances contained in the mixture. In order to differentiate the “mixture RCR” from the RCR of substances, the term hazard index (HI) is used. In contrast to the terminology the term hazard index is also used for higher tier assessments, i.e. where not the sum of the PEC/PNEC ratios is considered but the PNEC value is modified (e.g. the hazard threshold for fish is used). The reason for using the term despite the use of different terms for these higher tier hazard assessments is to simply the understanding of this text and not to introduce too many different concepts, where this is not necessary. This is important to keep in mind, when comparing the concepts of this report with other studies.

An answer on the consequences of a hazard index above 1 may currently only be suggested, if the hazard index is derived with high tier input on exposure and on substance specific toxicity. If these data are just of low tier screening type (no qualified high tier data available), they may only be used to indicate the need for a more qualified assessment with higher tier data, but this elevated hazard index may not be sufficiently and quantitatively supported to directly prompt regulatory action.

It is therefore an issue for further discussion, also in relation to the methodology and in case of the tiered approach to the degree of certainty (tier) of deriving such HIs, which consequences should be introduced if the result of a mixture assessment is a hazard index exceeding 1.

### 3.2.6 Voluntary assessments

Any of the industry actors could already now conduct mixture risk assessments based on their knowledge and to cover their specific products they place on the market or use on a voluntary basis. This is not specifically mentioned in the following sections. The industry actors may want to have and should be provided with respective guidance. This could include indications of an adequate assessment method and information sources. Guidance needs are partly discussed under the sections discussing the different industry and authority options to act. A list of possibilities to include guidance on mixture assessment in the ECHA guidance documents is provided in chapter 3.12.

## 3.3 Assessment approach for the options to act

The different methods for risk assessment outlined in chapter 2 are further detailed with regard to the actors who could perform them and the REACH procedures into which they could be fitted. Based on the detailed description of options the feasibility is analysed.

The options are divided into two groups: possible requirements for industry actors and possible options for authorities.

Each option to act is described and characterized in separate sub-chapters. The list of headlines structuring the feasibility assessment of options to act is explained in the chapter 3.3.1.

- Brief description of the option and references to chapter 2 regarding the method proposed for implementation
- Interpretation of the current legal requirements and proposal of a possible way of implementing the requirement into the REACH text (if not yet existing), its annexes or the ECHA guidance documents,
- Scope of the requirement
- Conformity with REACH principles
- Limitations of the practical implementation due to information availability,
- Potential challenges in the implementation,
- Expected benefits
- Expected costs and efforts of the option (qualitative),
- Enforcement aspects,
- Open questions regarding methods and feasibility as well as potential unwanted (negative) consequences of implementing an option to act for the supply chains,

- Stakeholder opinions regarding the option

At the end of each section, a summary is provided and the consultant's feasibility assessment and conclusions are presented.

It should be noted that all options are analysed with regard to an implementation under REACH, also in cases where implementation under other legislation would be more appropriate. A recommendation for a more appropriate legislation to implement actions to opt for industry is provided in the overall assessment and conclusions.

Some of the opinions and discussion points of the project's expert workshop conducted 30/31 of January 2013 are highlighted for the different options (see chapter 9.7 for the main findings of the workshop).

The different assessment aspects are briefly introduced in the following sections. At the end of the section, it is explained how the results from the analysis were "weighted" in the evaluation and conclusions on the feasibility of options by the consultants.

The structure of the analysis is designed for the assessment of the options to act; for the discussion of the prioritisation options and the reporting tool, the structure is modified as some of the issues are not relevant or are summarised under one heading.

### **3.3.1 Explanation of assessment aspects**

#### **3.3.1.1 Brief description**

The aim of this section is to briefly present the outlined option.

It contains a description regarding which actor should do what in the context of which procedure, using which method and covering which life-cycle stage or substances/mixtures. These four aspects are reflected also in the name of the option.

#### **3.3.1.2 Consultant's interpretation of REACH and proposed implementation option**

The aim of this section is to make the interpretation of REACH transparent which underlies the assessment. Hence, it is discussed whether or not (parts of) the proposed option are regarded as already required under REACH or not. The consultant's interpretation of REACH is presented and justified with quotations from the REACH text, from the ECHA guidance documents and from personal communication with ECHA staff. The FAQs published by ECHA were also screened for further information on how to interpret the REACH text but no additional information could be found in either of the sections.

In some cases the interpretation of the REACH text by other stakeholders may differ from that of the consultant.

Based on the consultant's interpretation of REACH, at the end of the sections a way of implementing the option in the current REACH text, its annexes and/or the related guidance documents is outlined.

#### **3.3.1.3 Scope**

The aim of this section is to describe which substances or mixtures would be affected, if the requirement were implemented.

The coverage is only qualitatively described. This includes a discussion of which substances are not part of an assessment because information on their identity is not available to the actor who conducts an assessment (chapter 3.2.2).

### 3.3.1.4 Conformity with REACH principles

The aim of this section is to check, if the proposed approaches and options are in conformity with core principles of REACH.

It is assumed that the core REACH principles should either be followed if new requirements are implemented or good reasons should exist why they are not followed. These two principles are:

- Any REACH obligation should lead to an improved chemical risk management. This could be achieved either directly via the implementation of strict(er) operational conditions or risk management measures or indirectly via an improved knowledge base on potential risks.
- Industry is responsible to demonstrate the safe use of chemicals (standard procedure). Authorities are responsible to assess and manage risks at EU-level, which cannot be tackled or are not tackled by individual industrial actors. The responsibilities within industry are shared with the assessment tasks located at the top of the supply chain.

The REACH aim of enhancing the competitiveness of industry is considered in the discussion of efforts and costs (c.f. below). The assessment is presented in table form.

Table 17: Table presenting if the REACH principles are followed by the assessed option

Principle	Assessment	Principle	Assessment
Improvement of protection level		Improvement of information base	
Responsibilities within industry		Responsibilities between industry and authorities	

### 3.3.1.5 Limitations due to data availability

The aim of this section is to analyse which information an actor needs to carry out the assessment and which of this information is available to him.

Different actors have different access to information on substances, substance properties, PNECs and PECs as well as mixtures and their composition. The information access may restrict the possibility of some actors to conduct a mixture assessment or identify if they handle a priority substance or priority mixture. If the information access is limited because of the current legal requirements on forwarding information in the supply chain as outlined under REACH and the CLP-regulation, in this section it is described how this affects the possibilities of implementing the options.

### 3.3.1.6 Potential challenges

The aim of this section is to outline if and which challenges could arise in the implementation of an option.

It is possible that REACH actors implement the requirement in a way which is not intended leading to unwanted consequences. These may in general be intended by REACH (e.g. unsafe products are not placed on the market) but the extent to which this would happen due to the option would increase significantly and hence become more destructive than constructive. Potential challenges or implementation risks are discussed in this section.

### 3.3.1.7 Expected benefits

The aim of this section is to outline the expected benefits of the option.

The content of the section provides further detail regarding the improvement of chemicals risk management due to the implementation of the option, including links to other legislation. It corresponds to the table on the implementation of REACH principles (c.f. above).

#### **3.3.1.8 Expected costs / efforts**

The aim of this section is to reflect the REACH aim of enhancing competitiveness and innovation in European industry. In accordance with the REACH aim it is assumed that no disproportionate burdens should be imposed on industry.

At the current stage, it is not possible to quantify the costs and efforts of the different actors to identify if a mixture risk assessment is necessary and conduct a respective assessment. Therefore, only the type of tasks and their estimated resource demand is described. The assessment is also related to the assumed existing competences and capacities of the respective actors.

#### **3.3.1.9 Enforcement aspects**

The aim of the section is to reflect whether or not and how the implementation of the option could be enforced.

Aspects considered in this section are whether or not the implementation can be controlled by existing enforcement structures, if enforcement would be a large or small task and whether or not new competences and responsibilities are necessary.

#### **3.3.1.10 Open questions**

The aim of this section is to highlight unresolved questions regarding the implementation of the option, which may correspond to a further research need.

Open questions mainly relate to technical or scientific aspects of an option.

#### **3.3.1.11 Conclusions on the option by the consultant**

The aim of this section is to provide a conclusion on the feasibility of an option and a recommendation if it should be further considered for an implementation strategy of mixture assessment under REACH.

The conclusions are derived from the analysis of the former sections and present the opinion of the consultants. Reasoning on why an option is dismissed or favoured are given. If a final evaluation is not possible, it is outlined which activities are necessary to improve the information base for deciding on the feasibility of an option.

If stakeholder opinions are known supporting or opposing the consultants' views, these are described and discussed in this section too.

### **3.3.2 Explanation of how aspects are weighted in the feasibility assessment**

**The most important aspect considered in the assessment of an option's feasibility is the information access of the actor to which the requirement would apply.**

It is assumed that the requirements on supply chain communication, in particular regarding the components in a mixture, are not going to be changed significantly, because this would be seen to endanger confidential business information and put at risk the economic basis of all formulators. Even if a change was considered, this would require extensive legal research and impact assessment studies and would take a long time. It is however regarded possible that the

information requirements on the content of mixture assessment triggering substances in mixtures are made stricter, e.g. that the concentration limits for identifying these substances in mixtures are lowered, similar as for SVHC on the candidate list.

Consequently, an option is regarded as not feasible, if the responsible actor cannot obtain information on the composition of the mixture to be assessed that would be necessary to carry out the task, assuming the current legal situation is basically unchanged.

If there are no limitations for the implementation of an option due to information accessibility, other aspects are evaluated in the feasibility assessment. These are the expected benefits and costs of an option, the possibilities and needed efforts to control the implementation by enforcement authority and the potential for the REACH actors to avoid the obligation and the consequences if they do circumvent mixture risk assessments in an undesirable way.

It is not possible to present an actual weighting of these factors. However, in general the cost-benefit relation (although qualitative and involving many uncertainties) is regarded more important than the enforcement aspects. This is due to the fact that the cost-benefit relation is very important for the political acceptance and hence support for an option, whereas the enforcement aspects are usually an issue of technical implementation and availability of resources.

The considerations under “open questions” and “potential risks and challenges” are a list of issues that should be considered if a more in-depth assessment of the feasibility of the options to act should be performed. As these aspects indicate difficulties in the practical implementation of the options they also influenced the overall evaluation, however with the lowest weight: the more difficult the open questions appear to the consultant to be solved and the larger the potential negative and unwanted effects are believed the less feasible the option is regarded.

### **3.4 Prioritisation of cases for mixture assessment**

#### **3.4.1 Prioritisation as a precondition for options to act**

Prioritisation is regarded as precondition for the implementation of any option to act regarding mixture assessment under REACH. This is because the number of technical mixtures on the market is very large and resources should be focused on cases, where risks from these mixtures are likely to occur and could be detected by risk management under REACH.

The literature assessment (see chapter 2.2) and the discussions at the project meetings and expert workshop in January 2013 revealed that there is no agreement among the stakeholders on which criteria are most useful to identify priority mixtures, yet.

In chapter 2.6 two options to prioritise cases for mixture assessment are proposed:

- A list of mixture assessment triggering substances (MATS) is determined based on the RCR values of substances derived from their environmental toxicity and measured data in the environment. If these MATS are contained in a mixture, a mixture assessment is required
- A list of priority mixtures is developed. Priority mixtures are determined by different criteria, e.g.
  1. typical mixtures – substances which are known to frequently occur together
  2. mixtures which contain substances with specific properties regarded as of high concern in relation to mixture toxicity,

3. substance combinations with particular toxicological profiles and known modes of action– mixtures are known to have synergistic or additive effects
4. uses with known simultaneous exposures of the environment to the components of the mixture for a longer duration

In addition, structurally similar substances which frequently occur together, e.g. phthalates or which are registered as a group / where read across is applied and which are used in identical uses could be subject to a mixture assessment in the scope of registration. This would however not be a general criterion for determining MATS but a criterion for registrants to include mixture assessments in their CSRs. Therefore this is not regarded as a prioritisation in the above sense and is discussed as a case of ‘similar substances’ in the context of the options for registrants (c.f. chapter 3.6.3).

In chapter 2 as well as in the discussions at the expert workshop in January 2013 and at the project meetings, also further potential prioritization criteria were discussed, in particular substances properties, such as bioaccumulation, persistence and endocrine disruption. These properties could be used in addition or in combination with the main priority criteria proposed in this report, as is also elaborated in sections 2.6, 2.6.3.1 and 2.6.3.2.

### **3.4.2 Regulatory options for prioritisation**

In chapter 2 of the report, a preference for developing a MATS list or a list of priority mixtures by the authorities is expressed. In this part of the report, the question of who is responsible for establishing the MATS list and how is not further specified but left open.

An alternative option would be to define and identify the criteria for MATS and priority mixtures and include these either into the REACH text or into a separate annex.

The development of a MATS list by the authorities would be in analogy to the criteria for substances of very high concern in REACH Article 57 and the latter in analogy to the PBT criteria defined in Annex XIII. This option would pose the responsibility to check, whether or not a substance is a MATS or if a mixture fulfils the criteria as “priority mixture” on the individual actors for which an obligation is proposed.

Finally criteria for MATS and / or priority mixtures could be developed and included in the guidance documents in order to facilitate priority setting for all actors who want to assess mixture risks voluntarily (no obligation is triggered but assistance is provided). Here, either of the two options, the inclusion of substance lists / lists of priority mixtures or the inclusion of criteria to identify MATS or priority mixtures, e.g. via the content of substances with specific properties, specific use conditions etc. could be considered.

### **3.4.3 Assessment of prioritization options**

In the following, the two options for prioritization – MATS and priority mixtures – are briefly analysed with regard to their feasibility. The main discussion of concepts for priority is documented in sections 2.6.2 and 2.6.3.

#### **3.4.3.1 Brief description of options**

The options for prioritisation are described independently of any options to act for industry and authorities; i.e. they are not related to any type of actor or assessment task but discussed only in relation to the question of whether or not they are a good indicator for mixture risks.



## MATS

Criteria for MATS are defined and either included in an annex to REACH or, based on these criteria a list of MATS is developed and continuously updated. As a first step, the criteria and method for MATS identification need to be developed and agreed. Then the MATS list would have to be developed. The MATS criteria or MATS list would introduce a duty to all actors to check, whether the substances they manufacture or use fulfil the criteria / are on the list or not and if yes, a respective assessment of mixture risks for the mixtures in which they are included would be triggered, if the RCR of the MATS exceeds the value of 0.1 (c.f. explanation of MATS concept in chapter 2.6.2).

### Priority mixtures

Criteria for priority mixtures are defined and either included in an annex to REACH or, based on these criteria, a list of priority mixtures is developed and updated, if necessary. As a first step, criteria for the identification of priority mixtures need to be developed and agreed. Based on these criteria, the list of priority mixtures could be developed. For all mixtures / mixture types on the list, the obligation to assess mixture risks is triggered and the actors, to which the respective obligation applies, has to perform the mixture assessment.

#### 3.4.3.2 Scope

The number of substances covered by a MATS list and a list of priority mixtures is determined by the speed of agreeing on criteria, the availability of measured data on environmental concentrations and the speed of the process of nominating and agreeing on MATS or priority mixtures.

It is not possible to estimate, how many mixtures would be affected by a list of MATS or a list of priority mixtures, as too many details are not fixed in this generic proposal.

#### 3.4.3.3 Conformity with REACH principles

Both the development and inclusion of MATS criteria in an annex and the development of a MATS list would be conformity with the current REACH principles, as both types of mechanisms are already existing (Annex XIII and the candidate list).

The development of a list of priority mixtures is new to REACH, because also the type of use is used for prioritisation and triggers a task under REACH. The approach is not in contradiction to prioritization as such and could reflect a prioritization based on risk. The process of developing a list of priority uses is in conformity with REACH, as it is similar to that of the identification of SVHC on the candidate list.

#### 3.4.3.4 Limitations due to data availability

The option to develop MATS criteria and a list of MATS is limited by the lack of agreed criteria and scientific data to deduce them as well as a lack of monitoring data for many substances (see section 2.6.2.4). This leads to the situation that non-regulated substances can hardly be identified as MATS because measured data are not available.

The option to develop a list of priority mixtures is limited by the availability of information on the actual composition of technical mixtures. Some information, such as on similar substances / substances registered in groups could be identified from registration data. It may also be possible to extract information on whether or not substances are used in identical uses. If (the combination of) this information is sufficient to determine priority mixtures, they would have to be assessed in more detail.

#### **3.4.3.5 Expected benefits**

The benefits of the prioritisation options are only realized when they are combined with the assessment obligations of the different actors. Hence, it is not possible to estimate a benefit of a prioritisation approach as such.

#### **3.4.3.6 Expected costs / efforts**

Comparatively high efforts are expected to develop and agree on prioritization criteria underlying the lists of MATS and/or priority mixtures from all stakeholders (consultation process). As the approach “priority mixture” is less clear it is likely that the agreement process would be more complex and cumbersome.

The resource needs for proposing MATS appear lower than for proposing priority mixtures, as the criteria are clearly set and the justification is comparatively simple (RCR). However, if monitoring data are missing, conducting representative measurements may imply significant costs.

The development of proposals of priority mixtures depend on the criteria and types of mixtures that could be selected. The identification of critical uses, for example, may be fairly straight forward as only the use conditions and the general partitioning of substances in the technical mixtures would have to be assessed. The identification of mixtures containing substances with known critical modes of actions is likely to be more cumbersome due to the lack of data on combined effects of substances and the lack of information on the composition of mixtures.

Consequently, it can only be stated that the MATS list is expected to require less resources than the development of a list of priority mixtures.

#### **3.4.3.7 Known stakeholder opinions on the option**

At the expert workshop in January 2013 in the context of this project a general tendency of all stakeholders to regard the RCR of substances derived from hazard data and measured environmental concentrations as a good indicator for potential mixture risks was perceived.

There are no explicit opinions known to the consultants regarding the concept of using priority mixtures as trigger for mixture assessment.

#### **3.4.3.8 Summary of key issues and conclusions**

The scientific and practical aspects of the two prioritisation approaches (MATS substances and MATS mixtures) show, that both options could be useful, individually or in combination, to trigger obligations for mixture risk assessments. Due to the high number of variables in both concepts regarding the actual criteria to be applied, their precision in predicting the occurrence of mixture risks in the environment and the outcome of any agreement process on the criteria with the stakeholders, it is not possible yet to conclude on which option is better or if a combination of the two approaches should be implemented.

Independent of the introduction of obligations on mixture risk assessments, criteria to support all actors, in particular the formulators, in identifying mixtures that could cause risks due to their composition or their conditions of use should be provided in the ECHA guidance documents to enable respective voluntary actions once respective criteria are developed.

## 3.5 Information collection for prioritisation – reporting tool

### 3.5.1.1 Brief description of the option

In section 2.6.2.3 several approaches to find priority mixtures are described. Most of these approaches, such as evaluation of monitoring data, use of the SPIN database or concluding from the use conditions of mixtures involve the use of existing data. The reporting tool is proposed as second option.

The reporting tool involves new reporting obligations for all actors in the supply chain which would require a legal basis under REACH; i.e. a change of the legal text. Therefore, it is discussed regarding its feasibility.

The reporting tool does not generate indicators for prioritising substances or uses for mixture assessment but is proposed as an instrument to gather or exchange information to support the prioritisation of substances and mixtures, for which a mixture assessment could be performed.

The idea of the reporting tool is that all relevant information on mixtures is collected from the actors in the supply chain in a “reporting spread sheet” starting with the registrants including information on the substances they register and sending the spread-sheet to the formulator. The formulator collates information on all classified substances in his mixture which is necessary for his customers to calculate a tier 1 Hazard Index (HI) into one mixture-specific spread sheet and forwards it to the user of the mixtures. He also calculates an HI for his formulation process and submits that information to the authorities. If the next user is a formulator, he repeats the action of formulator 1. If the next user is an end-user, he calculates and forwards an HI to the authorities, only.

### 3.5.1.2 Consultant's interpretation of REACH

Article 31 of REACH requires that registrants and formulators provide information in the supply chain to their users. This information is required for classified substances as such, for SVHC on the candidate list and for classified mixtures. Information on classified mixtures is to include information on the classified mixture components and SVHC on the candidate list, if their concentration in the mixture exceeds the threshold values defined in the CLP-regulation or under REACH and, on request, for substances with community – wide workplace exposure limits if they exceed specific concentrations.

Article of REACH 10 b) and 14 (1) requires registrants to provide a chemical safety assessment to ECHA for the substances they register in amounts exceeding 10 t/a and which are classified as hazardous or have PBT / vPvB properties.

Article of REACH 31(1) requires formulators to provide safety data sheets for their mixtures to their customers. These are to include information on the safe use of substances (in mixtures) received from the suppliers. No information on the conditions of use, releases and exposures at the own site are to be reported to the authorities. However, they have to work within the boundaries of the conditions of use specified in the extended safety data sheets (SDS plus exposure scenarios) they receive from their substance suppliers.

Article 35 (7) of REACH requires end-users of substances and mixture to check compliance with the information they receive from their suppliers, either via exposure scenarios (ES) or in the form of safety data sheets. They are not obliged to calculate exposure levels or RCR (but may do so if that facilitates their alignment with the conditions of use described in the ES or the SDS) and there are no reporting obligations to the authorities.

If a downstream user's use is not covered by an exposure scenario, he may have to conduct a downstream user CSR for the substance or substances in a mixture. The fact that a DU CSR is conducted as well as basic information on the substance use has to be reported to ECHA within 6 months after the receipt of the information with which he is not in conformity according to REACH Art. 38(1).

In conclusion and according to the consultant's analysis and interpretation of the REACH text, it is required under the current legislation that information on substance identities, substance properties and the composition of mixtures (classified substances and SVHC if above the concentration thresholds) is forwarded with the safety data sheet in the supply chain. Apart from the registrant submitting a CSR to ECHA, no reporting to (local) authorities by registrants or downstream users exist.

Consequently, reporting by registrants and downstream users would be a new obligation to be introduced under REACH and would comprise:

- nature and composition of technical mixtures and discharges (as known from safety data sheets),
- use amounts of substances and mixtures,
- amounts of discharges and substance contents (as known the safety data sheets)
- local conditions at the sewage treatment plants

#### **3.5.1.3 Possible implementation option proposed by the consultant**

In the further discussion and assessment the following implementation of the reporting tool in the REACH-text is assumed:

- Manufacturers of MATS are required to report on their discharge mixtures containing the MATS to ECHA.
- Formulators are to report the composition of their mixtures, the amounts used, emissions and HIs for the discharge mixtures containing a MATS or a prioritized mixture to ECHA.
- End-users of MATS or priority mixtures are to report the composition of the priority mixture or the mixture containing a MATS (known components), their amounts used and HIs for their discharge mixture to ECHA.

The obligations are included in Title II for registrants and Title V for downstream users.

According to this proposal, the reporting details are either part of the main text of REACH or a new Annex.

As information on substances as such and in mixtures is forwarded with the safety data sheet and/or is available in ECHA's substance database, no additional information obligation along the supply chain is needed to enable the actors to report to ECHA.

REACH Annex II has to be amended to include a provision to communicate if a substance is a MATS (safety data sheet of substances) and to include a provision to identify MATS in a mixture or to qualify a mixture as priority mixture in the safety data sheets of mixtures.

Reporting is required once per year and is implemented by a respective IT-tool provided by ECHA. Enforcement of the obligation is in the responsibility of the Member States; respective communication between ECHA and the competent authorities is implemented without specific provisions in the REACH text. Specific provisions may have to be developed to ensure data protection and regulate which data may be published and or exchanged with other authorities.

### 3.5.1.4 Scope

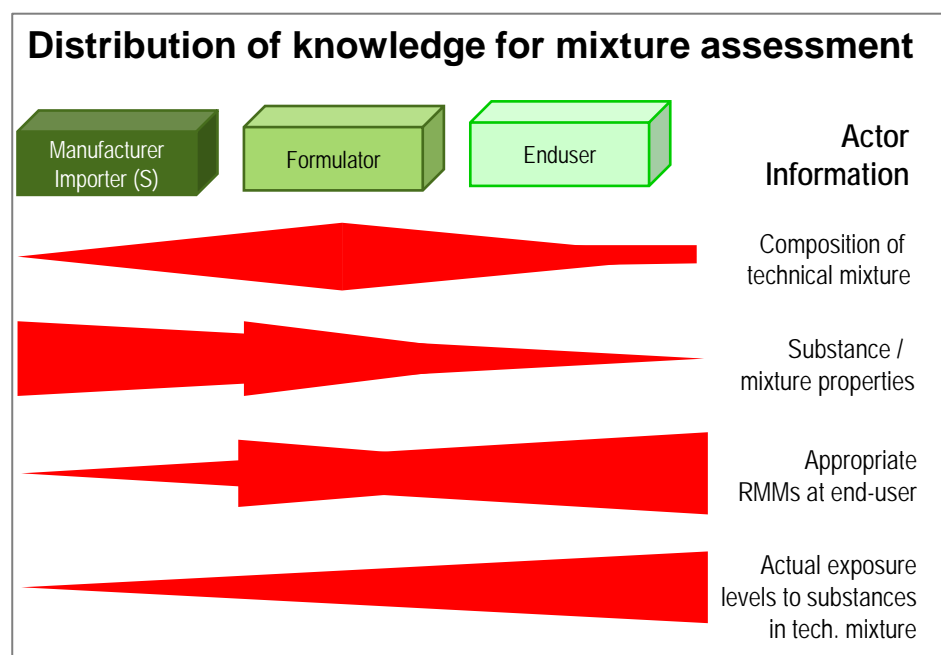
The reporting obligation is triggered, when a prioritized substance is used to produce a mixture (only formulators) or a priority mixture is used (all users of mixtures, including formulators). The reporting obligation covers any substance in the mixture of which the identity is known;

- formulators report the composition of the mixture they produce as far as known,<sup>59</sup>
- users of mixtures report the composition of the mixture in according to chapter 3 of the SDS

In conclusion, the scope of the reporting tool potentially covers any substance but is factually limited by the knowledge of the actors on the composition.

Information on mixture risks are spread along the supply chain with manufacturers knowing substance properties, formulators knowing the composition of technical mixtures<sup>60</sup> they produce and end-users knowing emissions from final use of substances and mixtures. At present, little information is available on mixtures in the environment. The spread of information in the supply chain is illustrated in Figure 20. The width of the red triangles indicate the degree of knowledge of the different actors on the mixture composition, the properties of substances and mixtures, the RMMs implemented at the end user and the actual (not modelled) exposure levels.

Figure 19: Distribution of knowledge relevant for mixture assessment along the supply chain (source: own illustration)



<sup>59</sup> If mixtures are used as input materials, only the classified substances above the identification thresholds are known

<sup>60</sup> Formulators using mixtures to produce mixtures only know the composition to the extent it has been communicated to them; i.e. hazardous substances in the used mixtures above the thresholds for identification.

Only if the information from all actors is collected and combined, a meaningful prospective mixture risk assessment can be generated. The less information is available the more generic will be the assessment and the less meaningful or realistic it will be.

#### **3.5.1.5 Conformity with REACH principles**

The reporting tool would be a new element to REACH, which implements an obligation for all actors to report information on the use of MATS as such and/or in mixtures of priority mixtures, even if the conditions in the ES are complied with.

Notification obligations currently exist for DUs if DU CSRs are prepared (or an exemption is relied on), if an authorized substance is used or if an SVHC is contained in articles. None of these notifications requires specific information on the own use. However, the type of data that would have to be reported if the reporting tool were implemented is not new.

In conclusion, the reporting tool is in conformity with REACH but would add a new reporting dimension to the current legal framework.

#### **3.5.1.6 Limitations due to information availability**

The reporting tool as proposed is limited to reporting information on all substances the identity of which is known to the respective actors. However, not for all substances PNEC data is available in the safety data sheets or ECHA's database (the tool is not limited to substances for which a CSR was prepared) and hence this information may not always be reported by the manufacturers. Furthermore, whereas information on use amounts is likely to be accessible, information on emitted amounts would have to be generated by the downstream users (either quote from ES by the registrants / suppliers, measurements, modelling e.g. using spERCs or own assumptions).

In conclusion, data access and the possibilities to generate new information limit the implementation of the requirement. This could lead to incomplete reports or reports that are generic rather than specific to a discharge mixture.

#### **3.5.1.7 Expected costs / efforts**

The efforts of implementing the reporting tool are expected to be high, because each industry actor would have to implement a new management and reporting routine for identifying the manufacture and use of MATS in their mixtures and compiling the reporting information (substance identities, use amounts and emitted amounts). The efforts of the authorities to establish requirements for the reporting tool, the efforts for the development of a data collection tool by ECHA, the processing of collected data as well as the enforcement of the obligations require resources.

Even if the reporting would be reduced to a minimum, deriving the information on the emitted amounts by downstream users would require at least modelling substance flows inside the company and/or deriving emission factors for their processes. If DUs use the respective information from their suppliers (emission factors or released amounts modelled in the chemical safety assessment, if provided in the exposure scenarios), there is no added value in the reporting. If DUs make own assessments, part of the assessment obligation for safe use of chemicals is doubled in relation to the CSR; even if more precise information could be used.

#### **3.5.1.8 Expected benefits**

There are two core benefits of the reporting tool. Firstly, information on the environmental exposures of individual substances could be improved at authority level using real data from

sewage treatment plants. Secondly, information on the co-occurrence of substances in technical/discharge mixtures and resulting combined exposures in coincidental and environmental mixtures could be structurally linked and related to each other. This would significantly increase knowledge on exposures to mixtures and could hence in particular support priority setting for mixture assessment (MATS identification).

### 3.5.1.9 Conclusions on the option by the consultant

The information that is intended to be collected by the reporting tool is very valuable and useful to identify mixture risks and action needs from technical mixtures.

It is not clear if the high efforts for reporting (industry) and processing the reported information (authorities) is justified by a respective information gain and potential risk management.

Before the idea of new reporting obligations to obtain information on technical mixtures, their uses and related discharge mixtures, is dismissed or further followed, other options to obtain the information should be assessed. Some options that could be analysed<sup>61</sup> are provided in the following. However, none of the sources would generate as specific and practical information as the reporting tool would.

Options to obtain information on technical mixtures:

- Extension of the reporting obligations on mixtures and their composition under Art. 45 CLP-Directive<sup>62</sup> to environmentally hazardous mixtures and components; it needs to be considered how information could be used without disclosing confidential business information;
- Collection and evaluation of information by the Member State authorities on the use of (prioritised) mixtures and substances from IPPC-permits and / or introduction of respective reporting obligations under the Industrial Emissions Directive (IED).

Options to obtain information on discharge mixtures:

- Collection and evaluation of information by the Member States authorities on emissions of (prioritised) substances from IPPC reporting and extension of the respective reporting obligations, if useful.

Options to obtain information on coincidental mixtures

- Municipal wastewater treatment plants could be requested to provide information on the composition and ecotoxicity of received wastewater and discharges from the treatment plant. The information could be used to identify (substances in coincidental) mixtures which may cause problems in the sewage treatment process and which mixtures are released and could hence be relevant for the environment.

Options to obtain information on environmental mixtures

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<sup>61</sup> It should be noted that a comparison of information collection options was not part of the project and hence, all respective statements are only approximations based on the consultants' expertise and qualitative considerations.

<sup>62</sup> Appointment of bodies responsible for receiving information relating to emergency health response

- Authorities from the Member States and/or ECHA could use information from monitoring under the Water Framework Directive and other environmental frameworks, as marine conventions etc.

Authorities / the EU – Commission may consider extending monitoring obligations / activities in relation to substances of which mixture risks are likely, e.g. under water and IPPC legislation but also in the context of granting authorisations under REACH or imposing restrictions.

### 3.6 Assessment of options to act for industry

This chapter contains a description of the different options to make mixture assessment obligatory for industry actors. The options are derived from the previous description of REACH tasks and responsibilities (see chapters 1.7). The scientific concepts upon which the options are based have been developed in chapters 2.2 - 2.5. The options were established by combining the different methods introduced chapter 2 with the different REACH actors and their tasks. For each possible combination an option is derived and assessed separately.

The names of the options are structured in the same way and consist of a) the type of actor to which the option would apply, b) the method connected to the implementation, c) the REACH task/obligation to which it is connected, d) the lifecycle stages the assessment would cover.

It should also be noted, as discussed in chapter 3.2.1 that potential obligations of industry actors would concern the substances or mixtures they are responsible for (produce / place on the market). This could comprise mixtures of very different substances.

The proposals for implementation of an option under REACH include suggestions for how and where in the REACH text, the REACH annexes and the ECHA guidance documents changes are necessary to make the requirement obligatory. It should be noted that the legal analysis of REACH and potential changes to the legal framework were not part of the current study and have been developed based on the consultant's understanding of the legislation. Hence, these proposals require an in-depth legal assessment regarding the question if the proposed changes

- are actually necessary or if less profound changes could be sufficient
- are sufficient to implement the option, or if additional changes are required

#### 3.6.1 Option I1: M/I use MAF in his CSR to assess mixture risks along the lifecycle

##### 3.6.1.1 Brief description

This option would require registrants to assess risks from the use of their substances in technical mixtures in the identified uses as part of the chemical safety assessment of classified<sup>63</sup> substances, if required. The assessment would be substance based and cover all discharges of the substance in mixtures along the lifecycle, including from manufacture.

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<sup>63</sup> In this context the “classified” signifies that the exposure assessment in the chemical safety assessment is triggered; however physico-chemical properties are not relevant for mixture risks and may hence be disregarded. For keeping the text simple, the term classified is used in a similar way throughout the document.



Mixture risks would be considered by the application of a mixture assessment factor (MAF). Hence, the normal CSA procedure is not changed and only an additional safety factor is to be included in the derivation of the local and regional risk characterisation ratios.

As presented in section 2.5.3, discussions related to the use of a MAF are on-going focusing on the aspect that a MAF does not consider specific information on the substances in the mixture and on an appropriate size of the value which is, assuming additivity as a default, proportional to the number of mixture components. Nevertheless, the MAF has several advantages, in particular the possibility to apply it without specific information on mixture composition and is therefore discussed as possible option (for details, see 2.5.3).

### 3.6.1.2 Consultant's interpretation of REACH and proposed implementation option

The question whether or not the assessment of risks from combined effects of substances in mixtures is covered by the current provisions of REACH is not clear from the legal text. There are different legal interpretations regarding this issue. A final and legal clarification could only be obtained, if the question would be brought to court at EU level.

Some stakeholders are of the opinion that industry is responsible to address all risks that could occur from substances as such or in mixtures – which would imply responsibility for risks that may result from mixture exposure and effects and which not yet covered by the existing safety factors and single substances assessments. This position is further supported by the recitals which assign responsibility of the assessment and management of substances as such and in mixtures and along the entire lifecycle. Furthermore, the REACH text does not explicitly exclude the assessment of mixture risks.

On the other hand, the REACH text also does not include any explicit mentioning that mixture risks should be considered in the chemical safety assessment and the entire regulation is substance based. The assessment factors defined for the derivation of PNEC values<sup>64</sup> do not include a safety assessment factor for mixtures.

In conclusion, it is not clear if the assessment of mixture risks in the CSR is currently required under REACH.

If the assessment of mixtures risks is currently not covered by the provisions of the legal text, a change would be necessary to include a respective provision or not. A respective provision could be added to Article 14(3).

If mixture risk assessment is already covered by the legal text, clarification of the issue is necessary at the level of guidance documents, as obviously this provision is not understood and hence not implemented at present. Guidance is also necessary, in case a change to the legal text is implemented.

In either case it would be useful to amend also Annex to introduce, in the case of the option described in this chapter that a mixture assessment factor should be used to implement the mixture risk assessment in practice. This could be done as follows:

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<sup>64</sup> Intra- and inter-laboratory variation of toxicity data; intra- and inter-species variations (biological variance); short-term to long-term toxicity extrapolation; laboratory data to field impact extrapolation

The RCR for mixture risks is derived by:

$PEC / PNEC * MAF$

If  $PEC < PNEC * MAF \rightarrow$  adequate control of mixture risks

Changes to the guidance documents on information requirements and chemical safety assessment (concise guidance and reference guidance) would have to include information on how to apply the MAF and what size to assume (if not fixed).

### 3.6.1.3 Scope

The option would cover all substances for which a CSR is required (i.e. registered in amounts exceeding 10 t/a and which are classified). Prioritisation of substances for mixture risk assessment (c.f. chapter 3.4) will further limit the scope.

### 3.6.1.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 18: Conformity of the option to require the use of MAF in the registrants' CSRs with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes (stricter CoUs are likely)	Improvement of information base	No
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

The use of assessment factors is common, e.g. in the derivation of DNELs and PNECs; an assessment factor for taking the joint action of substances and interaction of substances into account does not yet exist under REACH.

### 3.6.1.5 Limitations due to data availability

There are no additional information needs for the registrants or any other actor.

### 3.6.1.6 Potential challenges

It is a scientific and political challenge to derive universally applicable MAF because its justification by an additivity assumption depends on the specific mixture a substance is used in (number of components). Providing a method for deriving MAFs case-by-case by the registrants would be of limited use as its application requires information on the number of components in the mixture, which is normally not available to the registrant.

If a MAF is introduced any future discussion on the best-suited MAF value will have to balance the need for enhanced environmental protection with the additional burden for registrants and the consequences of the outcome, such as the potential need for further risk management measures. The implementation of a general MAF in all CSRs may entail a risk of an increase in supply chain communication or an increased number of DU CSRs and a factual shift of assessment responsibility to the DU, which is not intended by REACH and which may be not justified (level of conservatism of the generic risk assessment is not clear).

### 3.6.1.7 Expected benefits

More and stricter RMMs are likely to be identified and recommended by registrants in order to demonstrate safe use in the mixture assessment (refinement). If no safe use can be shown

substances with high risk potential may either be further tested (better information on PNECs / DNELs for iteration) or not recommended for unsafe uses anymore. DUs may implement emission controls, reduce the use amounts and/or make own assessments, resulting in an information gain on the use of substances from notifications.

Any actor can do the assessment without needing information on the composition of actual mixtures the substance is used in. Hence, the approach does not involve additional competences or resources for information collection.

#### **3.6.1.8 Expected costs / efforts**

Registrants are likely to need more resources for chemical safety assessment due to the need for additional refinements, communication in the supply chain or additional testing.

Downstream users may incur costs either for the implementation of (newly recommended or stricter) RMMs or for conducting DU CSRs, changing suppliers, substituting a substance or enhanced communication in the supply chain.

#### **3.6.1.9 Enforcement aspects**

No additional or new enforcement tasks are triggered by this option.

#### **3.6.1.10 Open questions**

There are some open questions which could be subject for further work to explore the option of implemented a mixture assessment using MAFS under REACH. These are among others:

Which consequences does the MAF have for PBT/vPvB substances (no PEC/PNEC ratio)?

For these substances, a quantitative assessment is not performed; hence a mixture assessment factor would not change the regulatory situation for them. In any case, for these substances no improvement in the risk management is likely to be achieved, because for PBTs/vPvBs emissions and exposures should be minimised. Nevertheless, due to their persistence and bioaccumulative properties they may be particularly relevant regarding combined exposures in environmental mixtures.

Should a general MAF be used which is applicable to any substance or should the MAF be derived individually by the registrants and only a respective method be proposed?

In both cases, it is not clear how the fact that the MAF depends on the number of components in a mixture can be taken into account and how respective knowledge could be generated.

#### **3.6.1.11 Conclusions on the option by the consultant**

There are no limitations to the implementation of the MAF approach under REACH.

Furthermore, the approach is pragmatic, conforms to the REACH principles and, once a legal clarification and a respective change to the legal text or clarification in Annex I and guidance documents will be made and a specific MAF value has been decided on is implementable with comparatively low efforts, as no new data or methods are necessary. However, the overall political justification of an increased risk reduction need based on a generic safety factor may be difficult, even considering the precautionary principle. Furthermore, the potential shift of assessment responsibility to downstream users may be an unwanted effect as well as substance withdrawal or too many limitations of the potential uses of substances, for which no alternatives exist (yet). In any case the open questions (c.f. above) need to be solved.

## Recommendations by the consultant

It is recommended to further explore the option to implement a MAF. This would comprise solving the open questions outlined above and providing more scientific evidence that the risks from chemicals regulated under REACH contribute to the mixture risks in the environment to an extent that would justify the option. The support for the option among the Member States should be checked and respective discussions be started, possibly teaming up with the Danish and other authorities having expressed support of this potential approach.

## Further opinions

The option to apply MAFs was discussed at the 4M expert workshop in Berlin in January 2013 and particularly favoured by the Member State Competent Authority of Denmark, as the only possible option to cover the structural information gap of the registrants on the composition of mixtures a substance is used in. The Danish representative specified that a MAF should be applied under all legislations in order to take account of the different uses.

Industry representatives were hesitant as they regarded the implementation of a MAF as overly strict and too conservative in the majority of cases.

It was critically addressed by all stakeholders at the workshop that the derivation of the MAF's size is challenging.

## 3.6.2 Option I2: M/I use the tiered approach to assess mixture risks along the supply chain

### 3.6.2.1 Brief description

This proposal envisages that all registrants should carry out a tiered risk assessment for the use of their substances in mixtures in the scope of the chemical safety assessment. They should derive risk characterisation ratios for the relevant technical mixtures ( $HI_{mix}$ ) below 1.

According to the tiered approach (see 2.5.2), hazard and exposure data can be iterated, whereby the nature of the RCR changes; therefore, also a different name should be used<sup>65</sup> (e.g. hazard index). The scientific evaluation provided in chapter 2 of this report shows that the method is in principle implementable.

The mixture risk assessment would cover the release of the registered substance as part of technical mixtures occurring in the registered uses<sup>66</sup>, i.e. at the manufacturer, the formulators and the end-users of the mixture.

### 3.6.2.2 Consultant's interpretation of REACH and proposed implementation option

As discussed in section 3.6.1, it is not clear from the legal text whether or not the assessment of mixture risks in the scope of the registrants' chemical safety assessment is covered by the current provisions of REACH. Consequently, it cannot be judged whether or not a change to the REACH text (and to Annex I) are necessary to make the option legally binding or if the option is

<sup>65</sup> For simplification and as the registrants may use different values, in this document the term RCR is used

<sup>66</sup> The limitations to registrants in getting access to information on mixtures are discussed in the respective section. The option is fully assessed despite this obvious restriction to the practicability of the option.

already binding and guidance is required to clarify the situation and provide support for the implementation.

In either case, the tiered risk assessment approach would have to be presented according to this option in order to ensure its implementation in CSRs; this could be either in Annex I (change of the REACH regulation) or in guidance documents (REACH already covers the option).

Respective clarification and guidance would include introducing the tiered approach for mixtures and a respective definition of a mixture risk:<sup>67</sup>

$$\sum(\text{PEC}_{\text{component}}/\text{PNEC}_{\text{component}}) = \text{HI}_{\text{mixture}}$$

$\text{HI}_{\text{mixture}} < 1$  = adequate control of mixture risks

Furthermore, guidance would have to specify how the mixture assessment can be carried out, in particular how registrants could obtain information / defaults of the “other components” in the mixture the substance is contained in.<sup>68</sup>

### 3.6.2.3 Scope

The option would cover all substances for which a CSR is required (registered in amounts exceeding 10 t/a classified as dangerous). Prioritisation of substances for mixture risk assessment (c.f. chapter 3.4) will further limit the scope.

It is not clear how the “other components” in the mixture would be addressed (c.f. chapter ‘Open questions’)

### 3.6.2.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 19: Conformity of the option to assess mixture risks in the CSR with the tiered approach with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes, stricter RMMs likely	Improvement of information base	Yes, due to detailed mixture assessment
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

The tiered approach for mixtures would follow the approach for substances in general.

<sup>67</sup> Note that the term RCR may not be appropriate for the indices derived in the mixture risk assessment, as with the change of indicators for hazard and exposure also the nature of the risk characterization ratio changes and may require a different name

<sup>68</sup> If that information were to be obtained from the supply chain, competition law would have to be checked and intellectual property rights be protected.

### 3.6.2.5 Limitations due to data availability

The core difficulty for registrants to assess risks from mixtures is to obtain information on the “other components” of the mixtures in which their substance is (assumed to be) used in and which are not necessarily manufactured by him. This is discussed in more detail in the chapter ‘open questions’.

### 3.6.2.6 Potential challenges

If registrants do obtain information on the mixture(s) the substance is used in or if default mixtures<sup>69</sup> are defined to support the mixture risk assessment, the assessment may result in the recommendation of overly strict risk conditions of use as “easiest iteration option”. There is a risk that the assessment responsibility is transferred to the DUs (as the chances registrants would refine a mixture assessment are comparably low) or additional communication may be triggered.

The consequences of a “ $HI_{mixture} > 1$ ” may be overly strict (“use advised against”). This could lead to situations, where substances cannot be used for a certain mixture (or use) anymore and no alternative exists.

### 3.6.2.7 Expected benefits

The tiered approach would lead to better information on substances and on mixtures, as during refinements new data may be generated by testing, measuring and improving predictions. Furthermore, stricter emission control is likely to be recommended and should be implemented along the supply chain, leading to an overall exposure reduction of hazardous substances in the environment and potential mixture risks.

### 3.6.2.8 Expected costs / efforts

Registrants are likely to spend more efforts on the CSR and hence incur costs due to additional refinements, communication and information collection on actual mixtures or re-assessment due to DU not meeting the conditions of the ES. Downstream users are likely to have costs for either implementation of RMMs, conducting DU CSRs, changing suppliers, substitution and / or communication efforts.

### 3.6.2.9 Enforcement aspects

If the option is implemented, ECHA will, as part of the compliance checks of registration dossiers containing a mixture assessment, check their compliance, too. This would be an additional task for ECHA but does not require any structural changes or qualitatively new resources.

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<sup>69</sup> In order to overcome the data gaps or registrants regarding the actual mixtures a substance is used in, it could be considered defining “default mixtures” or “frame formulations” with which to conduct the assessment. These generic mixtures would contain generic components and would hence simulate a group of mixtures in the identified use.

### 3.6.2.10 Open questions

The core open question for this option is which “other substances” are to be considered in the mixture risks assessment of a registered substance and how the registrant can obtain respective information.

Two options how the registrant could obtain respective information are:

- the registrant has to communicate with his customers and identify the relevant components of the mixtures which contain his substance; this would require the definition of cut-off criteria for disregarding mixture components, e.g. based on classification and/or on concentrations in the mixture
- “default mixtures” or “standard formulations” are defined with a generic composition, which can be used by any registrant having to conduct a mixture risk assessment for the respective uses. This would require that respective standard formulations are developed.<sup>70</sup>

Another option to solve the information gap would be that registrants request the formulators of using their substances to conduct a mixture risk assessment for the identified uses and ask them to confirm in writing that the assessment did not show a mixture concern. The assessment should be documented and kept for documenting compliance of both the registrant and the formulators, if authorities control the requirement.

The first option seems difficult to implement in practice due to protection of intellectual property, competition law and the amount of necessary communication. The second option appears vague and requires a lot of work to prepare the defaults. The third option entails the shift of assessment responsibility to the formulator and creates a dependency of the registrant from him. Consequently, further work would be necessary to identify, how the registrants’ information gap can be circumvented.

### 3.6.2.11 Conclusions on the option by the consultant

The option that M/I assess mixture risks in the context of their CSR using the tiered approach is largely hindered by the lack of information on the actual mixtures, the substances are used in. Even assuming an optimal information flow between registrants and formulators would not solve the question, as confidentiality would exclude the most relevant data (mixture composition) from the information exchange (c.f. chapter 3.2.2).

Consequently, the option is not regarded as feasible at the current state of knowledge.

### Consultant’s recommendation

It is recommended that the current option is not further considered as a possible option to implement mixture risk assessment under REACH.

Due to the fact that several registrants are formulators of their own substances (and hence know the composition of the mixtures they themselves produce) it could however be a subject

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<sup>70</sup> Some sectors develop so called “frame formulations” to facilitate the development of exposure scenarios for mixtures.

of further work to analyse (beyond the project 4M) to which extend registrants should perform a tiered mixture assessment in these cases.<sup>71</sup>

### Further opinions

The tiered approach was discussed at the expert workshop as potential option to achieve a targeted assessment dependent on data availability. The science of the method was generally accepted with a few issues to be clarified, e.g. the derivation of specific hazard thresholds (e.g. the CRV<sub>TL</sub>). However, all participants were critical about the required efforts to conduct such assessment and stated that the registrants' lack of data on the mixture composition would prevent the implementation of the option. Furthermore, the high assessment efforts and still remaining high level of uncertainty related to exposure levels (predicted or measured environmental concentrations) as well as to the hazard thresholds (PNECs, CRV<sub>TL</sub> etc.) were also regarded as critical. These opinions correspond to the outcome of the assessment.

### 3.6.3 Option I3: M/I use the tiered approach to assess mixture risks for 'similar substances' which occur together along the supply chain

#### 3.6.3.1 Brief description

The option would require registrants of 'similar substances' to conduct a mixture assessment using the tiered approach for the relevant lifecycle stages (manufacture, formulation, end-use of mixture).

The term 'similar substance' is not further explained in REACH or the ECHA guidance and would, according to our proposal, be pragmatically defined as substances which are either registered as / in a group (category approach) for which read across is applied. In either of the two cases the registrants assume that there is some type of similarity, which also affects the substances effects and behaviour; consequently "similarity" is implied. This definition of 'similar substance' is narrower and different from other respective definitions.

In addition to the 'similarity' of substances, a 'co-occurrence' is the second precondition for this option. Also here, a pragmatic approach is suggested where registration for the same use should be interpreted as an indication of co-occurrence (which could be disproved by the registrant in his registration dossier).

The mixture assessment should be conducted applying a tiered approach (only) for the 'similar substances' considering them as 'the' mixture to be assessed; hence, further substances which may also be present in the actual mixtures would not be taken into account.

Here, the registrant knows the components of the mixture (the similar substances) and possesses all relevant information from his registration dossier.<sup>72</sup>

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<sup>71</sup> As this would result in a discrimination of registrants who use their registered substances in mixtures they produce, it is likely that such individualized assessment obligation is not feasible from a legal point of view.

<sup>72</sup> It is possible that the manufacturer or importer needs to take account of closely related substances which he does not register. Hazard data should be available from the ECHA database.



### 3.6.3.2 Consultant's interpretation of REACH and proposed implementation option

In general, the assessment of mixture risks in the registration dossier is not required under REACH. However, the ECHA IR/CSA guidance part E states:

*"[...] where exposure occurs to a substance as well as to several very closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances), the exposure evaluation and risk characterisation should reflect this aspect. If data are available the exposure assessment should also include a scenario concerning this combined exposure. If data do not allow for a quantitative assessment, the issue can be addressed in a qualitative way."*

Hence, the intention to include respective considerations for substances where similarity is assumed and co-occurrence is evident is expressed. This is understood as a clear indication that this option is intended by the legislators.

The interpretation of "very closely related and similar acting chemical substances" proposed in this project is pragmatic rather than based on scientific considerations of mode of action. Hence, the definition of these terms should be discussed, if the option is further promoted.

In conclusion, it is regarded as possible to include the option as legal obligation into the REACH text. This would entail changing REACH Art.14 in order to include the definition of 'similar acting' substances a trigger for the mixture assessment. The limitation of the mixture assessment to cases, where the 'similar substances' occur together could be included in the Annex I as part of guidance on the mixture assessment procedure. Annex I would have to be amended by inclusion of definitions of adequate control for mixture risks:

$$HI_{\text{mix}} = \sum (PEC_{\text{component}} / PNEC_{\text{component}});$$

if  $< 1 \rightarrow$  adequate control

The IR/CSA guidance would have to be extended by an explanation of 'similar substances' and guidance on how to conduct a tiered assessment as well as on how registrants could provide arguments that similar substance registered for the same use do not co-occur.

### 3.6.3.3 Scope

The option would cover 'similar substances' which are registered for the same uses.

### 3.6.3.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

**Table 20: Conformity of the option to require mixture assessments for ‘similar substances’ in the CSR using the tiered approach with core REACH principles**

Principle	Assessment	Principle	Assessment
Improvement of protection level	Likely, due to stricter RMMs from CSAA	Improvement of information base	Yes, detailed assessment of mixture risks
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

### 3.6.3.5 Limitations due to data availability

Information is needed on the substances which are ‘similar’ to the registered ones. If hazard data is available depends on the registration status of the ‘similar substances’.

### 3.6.3.6 Potential challenges

According to the proposal, the use of the methods “grouping” and “read-across”, which are both not generally defined approaches, is the trigger for the mixture assessment. This could be a discrimination of the two methods, because other options to fulfil the data requirements would not trigger a mixture assessment, although the same substance(s) in the same uses would be concerned.

Hence, one potential and unwanted consequence of the proposal could be that registrants, in order to avoid a mixture assessment, rather carry out additional animal tests and register the substance individually than forming a group. Hence, the REACH objective of avoiding animal tests may be contradicted.

### 3.6.3.7 Expected benefits

The level of protection is likely to increase due to the consideration of mixture risks and respective identification and implementation of RMMs. Experience can be gained on a limited scale on the assessment of mixture risks (few, well known constituents). The obligation to carry out a mixture assessment may initiate more careful considerations of whether or not a read-across / category approach is actually justified.

### 3.6.3.8 Expected costs / efforts

For all uses and all (relevant) components, an additional and combined exposure and the mixture risk assessment is necessary. Efforts depend on the data availability (i.e. if the registrant registers more than one substance out of the group).

### 3.6.3.9 Enforcement aspects

ECHA would conduct compliance checks including mixture assessment. No additional tasks for MS authorities would be triggered.

### 3.6.3.10 Open questions

The core open issues of this option are the (scientifically founded) definition of ‘similar substances’ and the question of when a co-occurrence is relevant and triggers the need for a mixture risk assessment. These issues could be clarified in the ECHA guidance document. Clarification would be useful even, if no obligation is implemented in order to make the current guidance better understandable.

An additional question for this option is whether the ‘similar substances’ covered by this option are actually those causing relevant mixture risks. The obligation should only be implemented if it is demonstrated that these substances actually are likely to cause mixture risks. Respective information is not available and would need to be generated.

Finally, a solution needs to be found for cases, where only some end-points of the registration are filled using read-across and others are not. Here, the application of ‘similarity’ is not clear.

### **3.6.3.11 Conclusions on the option by the consultant**

The assessment of ‘similar substances’ is limited by the availability of hazard data on the ‘similar substances’ to consider in the registration but which are not manufactured by the registrant himself. However, this option could be a first step to further develop mixture assessment approaches for industry and to test the approaches/options in practice. Potential benefits of increasing knowledge and competence on mixture assessment may however not be fully balanced against the efforts of assessment.

### **Consultant’s recommendation**

The term “very closely related and similar acting substances” in the ECHA guidance should be defined to provide a better understanding.

In order to further assess whether the option should be implemented, projects may be started to generate further information on the potential risks caused by ‘similar substances’.

Furthermore, these projects could assess if pragmatic solutions to the open questions can be found and agreed. If so, the option may be proposed for implementation in the longer term.

### **Further opinions**

This option was not discussed in particular at the workshop but was evaluated implicitly in the context of the tiered approach. Neither industry nor the authorities commented on the degree to which the provisions of the ECHA guidance part E are already implemented. It was commented however that one common similar mode (or rather mechanisms) of action is hardly to be defined for all different organisms in the environment and a definition of ‘similar acting’ would always apply for a certain group of species. It is unclear if the option is supported or rejected by the stakeholders.

## **3.6.4 Option I4: M use the tiered approach and/or whole effluent testing to assess mixture risks from their site**

### **3.6.4.1 Brief description**

Substance manufacturers normally produce more than one substance in parallel; hence they (simultaneously) emit different substances, the identity of which they know, from their processes with their effluents. According to this option, registrants would be obliged to carry out a mixture assessment for their effluents and identify if they could cause risks in the sewage treatment plant or the environment.

Manufacturers would have two options to assess risks from their effluents. They could:

- derive a HI based on hazard and exposure data of the substances emitted during the same period of time (e.g. per day) or
- carry out whole effluent testing; in this case the sampling would depend on the (representative) production cycles and would integrate all substances emitted.

The method of whole effluent testing is discussed in section 2.5.4 and it is concluded that it provides quantitative information on mixture effects and is suitable for different types of mixtures. It is not useful for mixtures with variable composition (arising from changing discharge patterns).

### 3.6.4.2 Consultant's interpretation of REACH and proposed implementation option

REACH does not require monitoring of emissions from the own site. However, it does require registrants to assess, identify and implement the conditions of safe use as part of their chemical safety assessment (REACH Art. 14(6)). The methods how he identifies the conditions of use are not fixed and may include effluent testing.

REACH does currently not require the assessment of risks from mixtures; the entire regulation is substance based.

In conclusion, the requirement to assess mixture risks from the own effluents is currently not required under REACH and would have to be newly introduced into the REACH text.

Article 10 could be extended by including an obligation to carry out a mixture assessment at manufacturing sites as independent registration requirement. Alternatively, the obligation could be included in the provisions for the chemical safety assessment (Art. 14). If the latter option is applied, only registrants of at least one substance for which a CSR is required would have to fulfil the obligation, whereas the former covers any registration.

In addition, REACH Annex I could be amended or a new annex could be developed to specify the mixture assessment obligation for site effluents. This would include information on which substances to consider. A definition of an HI for the effluent (tiered approach) and a  $HI_{\text{effluent}}$  should be defined:

$$HI_{\text{effluent,mix}} = \sum (PEC_{\text{subst}} / PNEC_{\text{subst}});$$

adequate control if  $HI_{\text{effluent,mix}} < 1$

For whole effluent testing, the definition of adequate control of risks would be:

$$EC_{50}/IC_{50}/LC_{50} > xyz^{73} \text{ mg/l}$$

The effluent test should be correlated with the production situation, i.e. an estimate of which substances could possibly be contained in the effluent to demonstrate the representativeness of the sample (s). Whole effluent testing may have to be performed several times or for several production situations to be representative and covering different operation conditions of the installation.

Including whole effluent testing into registration requirements is not in line with the registration of single substances. It applies rather to the site than to an individual substance and the same information would be reported by a manufacture for all the substances he manufactures at one site. Consequently, it should be considered if this option would be better implanted under other legislation (namely the Industrial Emissions Directive).

### 3.6.4.3 Scope

The option principally covers all substances manufactured at one site of manufacturers. There are no limitations due to data availability.

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<sup>73</sup> The value which could be used as trigger for toxicity should be defined in accordance with existing values.

As it is assumed that some type of prioritisation is implemented (c.f. chapter 3.4.1), the assessment need would be triggered by the prioritised substances. Which additional substances to consider (“all other substance emitted”, substances with an environmental hazard etc.) is not yet defined for the option.

#### 3.6.4.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 21: Conformity of the option to require whole effluent assessment by manufacturers for their site with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Likely, undetected risks may be identified leading to stricter RMMs	Improvement of information base	Yes, more information on relation between used substances and effluent toxicity
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

The assessment of the effluent toxicity is not in conformity with the REACH procedures, however. As part of a risk assessment, it does not concern the entire lifecycle and as part of a downstream user activity to check the implementation of safe conditions of use there is a) no ES to check against and b) the result is an expression of toxicity rather than of risk.

#### 3.6.4.5 Limitations due to data availability

Registrants should have all information on their manufactured substances and emissions related to their production available. If the assessment is conducted by testing the effluent, no information is needed.

If the assessment is conducted using a tiered approach, information on the composition of used mixtures may be missing (only classified substance above the concentration thresholds are known. Sufficient data to derive a PNEC could be missing for substances, for which no CSR was conducted.

Measured data on effluent toxicity may already be available from emission monitoring and compliance actions under other legislation (e.g. Industrial Emissions Directive).

#### 3.6.4.6 Potential challenges

For the tiered approach, the core challenge appears to be the identification of PNEC values of all substances.

For whole mixture testing, approaches have to be developed to deal with changing compositions of effluents due to production campaigns, batch processes etc. Here, one or more “average” or “typical” assessments may have to be carried out, depending on the manufacturing organisation. Furthermore, it is unclear how the measured toxicity value translates to a risk characterization ratio or how it should be evaluated in the overall context.

#### 3.6.4.7 Expected benefits

Substance manufactures would have more information on potential risks from their effluents and could improve their risk management, if necessary. Information could be gathered on

mixture composition and potential effects, which could be used to develop prediction models for mixture toxicity and risk assessment (this would require linking data on the emission situation to the observed toxicity and the effluent composition).

Information on risks from the effluents would also enhance the implementation of other legislation, e.g. the Water Framework Directive and/or the Industrial Emissions Directive.

#### **3.6.4.8 Expected costs / efforts**

Substance manufacturers would have to make one or more assessments of their effluents. In the best case, information is (partly available) from other legislation. No effects are triggered for downstream users

#### **3.6.4.9 Enforcement aspects**

The existing enforcement structure and procedures are sufficient to cover this obligation, as e.g. the authorities controlling installations could be responsible to carry out the control.

#### **3.6.4.10 Open questions**

Two questions which could be solved on a methodological level are how a measured effluent toxicity should be evaluated and/or how it translates into a HI and how representative sampling can be achieved and documented.

A question of a regulatory nature is whether it is possible to include different requirements for chemicals safety assessment for different life-cycle stages, as in this option mixture risks would have to be included in the stage of manufacturing. Respective research would be necessary to develop methods and get a correlation between modelled and measured data and identify how respective measurements could be implemented.

Finally, as indicated in the earlier sections, it needs to be defined which substances should be considered. If the same conditions should apply for the two methods, all substances need to be taken into account, as the whole effluent testing integrates all emissions. This would make the assessment via a tiered approach very onerous (many components to be considered in low amounts, partly without toxicity data).

#### **3.6.4.11 Conclusions on the option by the consultant**

The obligation for substance manufacturers to assess the risks from their effluents seems to be a viable option, which is not limited by missing data or confidentiality concerns (no communication of results, no need to obtain information). Furthermore, the assessment of the effluents is regarded as rather inexpensive.

On the other hand, the assessment does relate rather to the installation than to a registered substance and it is therefore unclear how it could be fitted into a registration dossier.

#### **Recommendation by the consultant**

Due to the effluent assessment being rather installation-related than substance related, it is recommended to propose the option under other legislation, i.e. the Industrial Emissions Directive.

#### **Further opinions**

The whole effluent testing was not discussed at the expert workshop in January as a self-standing option to implement mixture risks assessment. The workshop participants did see its

value in potentially complementing a tiered approach for mixture assessment (validation of modelling results) and/or for compliance checking with the ES by the different REACH actors (not only manufacturers). Several workshop participants pointed out challenges regarding the use of testing information, in particular the difficulties in identifying which substances actually contribute to a measured toxicity.

### 3.6.5 Option 15: DU formulators use the tiered approach to assess mixture risks along the supply chain

#### 3.6.5.1 Brief description

This option would pose an obligation on formulators to make a mixture risk assessment for their technical mixture at their site (formulation) and for the uses of the technical mixture down the supply chain. A tiered approach (see section 2.5.2) should be implemented and for the assessment at their own sites, formulators may alternatively carry out a whole effluent testing (see section 2.5.4). The mixture assessment requirement would be triggered by priority criteria (c.f. chapter 2.6). The substances to be considered in the mixture assessment (other than the prioritized ones) should be limited e.g. to classified substances (c.f. chapter 3.2.2) in order to avoid data gaps.<sup>74</sup>

The formulator would be obliged to communicate upstream, if the conditions of safe use he derives for his mixture differ from those received with the safety data sheet and ES of input substances.

A control system to enforce the mixture assessment by formulators would need to be set up.

#### 3.6.5.2 Consultant's interpretation of REACH and proposed implementation option

According to REACH Art. 31.7(3),<sup>75</sup> formulators are required to consider information from exposure scenarios and safety data sheets they receive to compile their safety data sheets for the mixture. The REACH text does not explicitly mention an obligation to conduct mixture risk assessments.

The ECHA DU guidance does not specify the need for the assessment of mixture risks in the section on compiling safety datasheets, except in special situations: chapter 7.2.2.3 describes that known interaction and/or synergies of substances in a mixture should lead to further consideration of which information on safe use to communicate.

These considerations are further specified in Appendix 3. In the introduction it is stated that “The impacts on the environment of aggregated and synergistic effects are not normally taken into account by formulators” (p. 112).

Hence this is not a routine obligation. Table 17 states under number 8 and 9 that the environmental fate of components of a mixture need to be taken into account; i.e. where

<sup>74</sup> From the product safety perspective and due to the assumption of additivity, the assessment should consider any hazardous substance in the mixture. However, this would signify a much more extensive obligation for formulators than for registrants, who only make a CSA for certain registered substances. For all substance without CSR no information on PNECs could be derived.

<sup>75</sup> „Any downstream user shall include relevant exposure scenarios, and use other relevant information, from the safety data sheet supplied to him when compiling his own safety data sheet for identified uses.”

substances partition in the environment no additional considerations on the safe use need to be made. Under heading 10 it is specified that “Known interaction and combined effects between substances should be taken into account”. This supports the interpretation that default additivity is not to be considered. It is not specified throughout chapter 7 of the DU guidance what exactly the formulator is to do when considering these effects; i.e. a need for a mixture risk assessment is not mentioned.

REACH Art. 31.6 lists the headings of a safety data sheet, which do not include a section on mixture risks.

The duty or possibility of downstream users to conduct a chemical safety report for substances as such and in mixtures explicitly refers to Annex XII (General provisions for DUs to assess substances and prepare CSRs) which refers to substances rather than mixtures. The ECHA guidance on DUs also specifies that CSRs refer to the assessment of substances as such and in mixtures but not to the assessment of mixtures (chapter 5.2, p. 54; subsequent guidance only addresses substances). Art. 31.2 mentions a CSR for a mixture but this is the only place where it occurs and is a technical mistake in the regulation. It is also not mentioned in the DU guidance.

The downstream user guidance document does not contain any sections where a risk assessment of mixtures is required.

REACH Art. 34 requires actors in the supply chain to inform their suppliers of new information on hazards and the inappropriateness of RMMs available to them. Hence, the information duty stemming from differences of the mixture risk assessment to the information received is already contained in the REACH text. This provision is further explained in the ECHA DU-guidance in chapter 6. Whereas the provision of Art. 34(a) clearly relate to substances, the information calling into question the appropriateness of RMMs could be “any information” and hence may include mixture risks identified by a formulator.

In conclusion, the current REACH regulation does not require formulators to carry out a mixture risk assessment for their technical mixtures in the context of checking compliance with received information or providing information downstream. If they are aware of “interactions and combination effects”, they should (not must) consider this in their information provision downstream. If formulators, e.g. from the voluntary assessment of mixture risks, identify that the information on RMMs communicated to them is not appropriate, they are already required to communicate this to their suppliers.

Consequently, the obligation for mixture risk assessment of technical mixtures would have to be newly introduced into the REACH text, including a trigger or prioritization criteria. In addition a system of enforcement would have to be established, for which the obligations would have to be defined in the REACH text too.

Finally Annex I should be amended or a new annex be developed to define the procedure for mixture risk assessment (in analogy to the substance CSR) and define which expression should be regarded as “safe use”, e.g.

$$\sum(\text{PEC}_{\text{component}}/\text{PNEC}_{\text{component}}) = \text{HI}_{\text{mixture}}$$

If  $\text{HI}_{\text{mixture}} < 1$  = adequate control of mixture risks

### 3.6.5.3 Scope

The requirement would concern all technical mixtures, which fulfil the criteria for mixture assessment defined in the REACH text. The substances to be considered would be limited to classified substances due to pragmatic reasons.



### 3.6.5.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 22: Conformity of the option to require the use of MAF in the registrants' CSRs with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes, due conditions of safe use specifically for the mixture	Improvement of information base	Yes, from mixture risk assessment
Responsibilities within industry	New responsibility for formulators	Responsibilities between industry and authorities	Maintained

The obligation to carry out safety assessment lies primarily with the registrant; hence it could be argued that the duty to assess mixture risks should not be imposed on the downstream users. On the other hand, the assessment of mixtures is hardly possible for manufacturers and formulators should take full responsibility for their products.

### 3.6.5.5 Limitations due to data availability

Formulators have all information necessary on the composition of their technical mixtures, as only classified substances (above the concentration thresholds for identification in safety data sheets) are considered.

Sufficient information on PNECs is available only for substances for which a CSR was conducted. If Annex VI of REACH were changed (c.f. chapter 3.2.4) sufficient information for PNEC derivation would be available for all registered substances. Information for higher tier hazard assessments may not be available to the formulator (see section 2.5.2.3 and section 2.5.2.5).

### 3.6.5.6 Potential challenges

The main challenge of this option is the additional workload for the formulators which results from the needed additional expertise and information as well as the amount of formulations produced by a single company. Mixture risk assessment would be a new task requiring expertise, resources and IT-tools. Furthermore, formulators are likely to lack PNECs for their assessment and might even have to conduct tests to iterate their assessment.

Formulators may, in order to limit their workload recommend strict RMMs rather than refining an assessment (tiering exposure assessment). If these are communicated with the ES/SDS of the mixture, the responsibility for safety assessment may shift to the end-user, if the conditions are not met in practice. This becomes the more likely, the stricter the OCs and RMMs are.

### 3.6.5.7 Expected benefits

More appropriate and possibly stricter RMMs may be identified, recommended and implemented. If no safe use can be demonstrated, mixtures may be reformulated and the substances may be substituted by others resulting in an actual reduction in the use of hazardous substances.

If RMMs are too challenging for the end-users also they may opt for substitution. If DUs conduct DU CSRs if the ES does not cover their use, an information gain on the use of substances arises from notifications to ECHA.

### 3.6.5.8 Expected costs / efforts

Registrants may have to invest resources in communication with formulators on hazard information of substances in the mixture. Formulators will have to invest additional resources to mixture risk assessment, potentially including the need to conduct additional testing for tiering the hazard assessment. Downstream users (formulators and end-users) may have to spend resources for implementation of RMMs, conducting DU CSRs, changing suppliers or substitution

### 3.6.5.9 Enforcement aspects

In order to enforce the mixture assessment of formulators, responsibilities would have to be defined. ECHA could install a system to assign “registration numbers” for risk assessed technical mixtures and implement compliance checks. It is also possible that Member States would enforce the assessment obligation of formulators.

### 3.6.5.10 Open questions

Is a more extensive safety assessment of formulators compared to registrants justified?

The mixture assessment in the context of a formulator’s product safety responsibility should comprise all classified substances rather than only those, for which a CSA was made. This would extend beyond the registrants’ obligations, as these only assess substances which are registered above 10 t/a. At the first tier, formulators would derive RCRs based on a PEC/PNEC comparison and add these up for the mixture, hence they would make an assessment that would actually rather belong to the substance manufacturers / importers tasks.

What is the consequence of an inability to demonstrate safe use of a mixture?

If a mixture assessment is made, the formulator would have to demonstrate the safe use according to the relevant definition. If iterations lead to different conditions of safe use than obtained from the registrants, what does the registrant have to do? Is a refinement necessary, although the original ES was fine? Does the formulator have to stop marketing the mixture, although he may be in conformity with the conditions of use of the exposure scenarios he obtains? What is the consequence if substances for which no CSR exists are assessed as not safe (derivation of HI mixture based on RCR for the individual substances)?

### 3.6.5.11 Conclusions on the option by the consultant

Formulators should ensure the safe use of their mixtures in general and in this context could be required to assess risks from the mixture. Formulators have access to information on the composition of their mixtures,<sup>76</sup> published hazard data and are likely to have a good understanding of the exposure information at their customers or at least better access to the downstream users. Substances used in technical mixtures co-occur at the local scale (discharge mixture) and hence lead to combined short-term exposures. A respective obligation would result in a higher level of protection and lead to more information on risks from mixtures.

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<sup>76</sup> If mixtures are used as input materials to produce the mixture, only the classified components are known to the formulator; consequently the limit values for classification and / or consideration of substances are cut-off values in this approach.

However, it needs to be considered that formulators already have a high workload under REACH and their assessments may partly double the registrants' work.

### **Consultant's recommendation**

The option to require mixture risk assessment (of prioritized mixtures) from formulators is feasible and corresponds to the principle of product responsibility. However, as the REACH implementation is still on-going, the benefits of mixture risk assessment in terms of increased environmental protection from lower risk contributions of REACH-regulated substances are not fully clear. Support for this option is likely to be extremely low at present, it is recommended to postpone any related activities until 2018. Then, a discussion with the Member States should be started to further explore this option. It may also be considered to implement the requirement under separate legislation.

UBA would recommend that guidelines (as well as possibly IT tools and practical detailed guidance that lead through a mixture assessment) are developed to support formulators. This should be done – similar to the current proceedings under the water framework directive – already before this task would be legally binding. Here exchange/communication with formulators/associations is necessary and wanted. Procedures need to be tested in practice beforehand.

### **Further opinions**

At the expert workshop in January most participants regarded the formulators as the most appropriate actors to conduct a mixture assessment using the tiered approach, as they have most of the necessary information available or can derive them.

## **3.6.6 Option I6: DU formulators use the tiered approach and/or whole effluent testing to assess mixture risks from their site**

### **3.6.6.1 Brief description**

Formulators normally use several substances and mixtures simultaneously to produce mixtures and hence emit different substances from their processes with their effluents. According to this proposed option, formulators would be obliged to carry out a mixture risk assessment for their effluents.

Formulators would have two options to assess risks from their effluents. They could:

- derive a HI based on hazard and exposure data of the substances emitted during the same period of time or
- carry out whole effluent testing; in this case the sampling would depend on the (representative) production cycles and would integrate all substances emitted.

The method of whole effluent testing is discussed in section 2.5.4 and it is concluded that it provides quantitative information on mixture effects and is suitable for different types of mixtures. It is not useful for variable mixtures. The method of the tiered approach is discussed in section 2.5.2 and it is regarded as principally feasible but onerous to implement and potentially being hampered by the lack of information on hazards and exposures.

This task, if implemented under REACH could be regarded as an activity in the context of checking the implementation of the safe conditions of use.

### 3.6.6.2 Consultant's interpretation of REACH and proposed implementation option

The REACH text does not include a specific requirement to conduct effluent testing or assess risks from the substances in the effluent (mixture) with other methods, such as the tiered approach by any of the REACH actors.

REACH Art. 37.5(7) includes the provisions for DU to check compliance with the information they receive: “Any downstream user shall identify, apply and where suitable, recommend, appropriate measures to adequately control risks identified in any of the following: (a) the safety data sheet(s) supplied to him; (b) his own chemical safety assessment; (c) any information on risk management measures supplied to him in accordance with Article“.

This means that DUs are required to check information they receive and compare them with their own processing conditions. In the guidance this is further elaborated but it is not described that the DUs must conduct emission measurements (although they may use data from monitoring in checking compliance with the ES / SDS, c.f. chapter 4.2, p. 40) or need to assess if risks could occur from (different) substances in their effluents by other means.

In conclusion, there is no requirement for whole effluent testing in the REACH text or guidance documents. Consequently, a respective requirement would have to be newly introduced, most appropriately in Title V. In addition, a definition of adequate control relating to the effluent should be included in an Annex; e.g.

$\sum(\text{PEC}_{\text{component}}/\text{PNEC}_{\text{component}}) = \text{HI}_{\text{mixture}}$   
if  $\text{HI}_{\text{mixture}} < 1$  = adequate control of mixture risks

$\text{EC}_{50}/\text{LC}_{50}/\text{IC}_{50}$  of the effluent  $< \text{xyz mg/l}$  = adequate control of mixture risks

Guidance for the implementation of a tiered approach for checking risks from effluents should be included either in an Annex (analogous to Annex I for the CSR) or in a guidance document.

### 3.6.6.3 Scope

The option principally covers all substances used at the formulators' sites. There are no limitations due to data availability.

As it is assumed that some type of prioritisation is implemented (c.f. chapter 3.4.1), the assessment need would be triggered by the prioritised substances. Which additional substances to consider (“all other substance emitted”, substances with an environmental hazard etc.) is not yet defined for the option.

### 3.6.6.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 23: Conformity of the option to require risk assessment for the formulators' effluents with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Likely, stricter RMM on-site if risks are identified	Improvement of information base	Yes, more information on own effluents
Responsibilities within industry	New obligation, share of responsibilities maintained	Responsibilities between industry and authorities	New obligation, share of responsibilities maintained

The assessment of the toxicity of the whole effluent is an activity which is not in conformity with the REACH procedures and principles. If it is regarded as downstream activity to check the implementation of an ES, there is a) no ES to check against and b) the result is an expression of toxicity rather than of risk.

#### **3.6.6.5 Limitations due to data availability**

Formulators know the substances they use and can obtain information on substance hazards from their suppliers and the ECHA database of registered substances for the tiered approach. Sufficient data to derive a PNEC are missing for substances, for which no CSR was conducted.

No specific information is needed to conduct the whole effluent testing. Respective toxicity data may already be available from monitoring and documentation under other legislation (e.g. IPPC/IED).

#### **3.6.6.6 Potential challenges**

The core challenge of the option is the additional resources needed for formulators to conduct either the tiered approach or the effluent testing.

For the whole effluent testing, approaches have to be developed to deal with changing compositions of effluents due to production campaigns, batch processes etc. Here, one or more “average” or “typical” assessments may have to be carried out.

#### **3.6.6.7 Expected benefits**

Formulators would obtain information on potential risks from their effluents and could improve their risk management, if necessary. Information could be gathered on mixture composition and potential effects, which could be used to develop prediction models for mixture assessment; this requires a good documentation of the emission situation during the sampling period.

Information on risks from the effluents would also enhance the implementation of other legislation, e.g. water framework directive and/or industrial permitting.

#### **3.6.6.8 Expected costs / efforts**

Costs and efforts for tiered assessment or testing are needed. The extent to which resources are needed depends on how representative the methods are for the annual production (number of samples, number of typical effluents).

#### **3.6.6.9 Enforcement aspects**

There is no “natural addressee” of the information under REACH; the results of effluent assessment may be submitted to ECHA for evaluation and compliance checking or to the authorities of the Member States. Respective responsibilities would have to be defined.

#### **3.6.6.10 Open questions**

Two questions which could be solved on a methodological level are how a measured effluent toxicity should be evaluated and/or how it translates into a HI and how representative sampling can be achieved and documented.

A question of a regulatory nature is whether it is possible to include different requirements for chemicals safety assessment for different life-cycle stages, as in this option mixture risks would have to be included in the stage of manufacturing. Respective research would be necessary to

develop methods and get a correlation between modelled and measured data and identify how respective measurements could be implemented.

Finally, as indicated in the earlier sections, it needs to be defined which substances should be considered in the assessments. If the same conditions should apply for the two methods, all substances need to be taken into account also in the tiered approach, as the whole effluent testing integrates all emissions. This would make the assessment via a tiered approach very onerous (many components to be considered in low amounts, partly without toxicity data). If different conditions could be applied to the two methods, the WET approach would take account of all substances in the effluent whereas the tiered approach would only cover substances known to the formulator, which are classified.

### **3.6.6.11 Conclusions on the option by the consultant**

Formulators are to ensure that there are no risks from their installations. The obligation for formulators to assess the risks from their effluents seems to be appropriate regarding the required efforts and benefits and feasible with regard to information availability and existing expertise. Method development as well as generation of support tools should be considered.

#### **Consultant's recommendation**

The assessment of risks from effluents is useful and could lead to better risk management measures at site. However, the obligation relates rather to an installation than to individual substances and mixtures as placed on the market. The latter is the regulatory subject of REACH, whereas the former is regulated under the Industrial Emissions Directive. It is therefore proposed to implement the option under that legislation.

### **3.6.7 Option 17: DU end-users use the tiered approach and/or whole effluent testing to assess mixture risks at their site**

#### **3.6.7.1 Brief description**

End-users normally use several substances and mixtures simultaneously and hence emit different substances from their processes with their effluents. According to this proposed option, end-users would be obliged to carry out a mixture risk assessment for their effluents.

End-users would have two options to assess risks from their effluents. They could:

- derive a HI based on hazard and exposure data of the substances emitted during the same period of time or
- carry out whole effluent testing; in this case the sampling would depend on the (representative) production cycles and would integrate all substances emitted.

Factually, end-users are likely to lack information and expertise to conduct the tiered approach and they will hence rather conduct whole effluent testing. This task, if implemented under REACH could be regarded as an activity in the context of checking the implementation of the safe conditions of use.

#### **3.6.7.2 Consultant's interpretation of REACH and proposed implementation option**

The REACH text does not include a specific requirement to conduct effluent testing or assess risks from the effluent (mixture) with other methods, such as the tiered approach by any of the REACH actors.

REACH Art. 37.5(7) includes the provisions for DU to check compliance with the information they receive: “Any downstream user shall identify, apply and where suitable, recommend, appropriate measures to adequately control risks identified in any of the following: (a) the safety data sheet(s) supplied to him; (b) his own chemical safety assessment; (c) any information on risk management measures supplied to him in accordance with Article”.

This means that DUs are required to check information they receive and compare them with their own processing conditions. In the guidance this is further elaborated but it is not described that the DUs must conduct emission measurements (although they may use data from monitoring in compliance checking, c.f. chapter 4.2, p. 40) or need to assess if risks could occur from (different) substances in their effluents by other means.

In conclusion, there is no requirement for whole effluent testing in the REACH text or guidance documents. Consequently, a respective requirement would have to be newly introduced, most appropriately in Title V. In addition, a definition of adequate control relating to the effluent should be included in an Annex; e.g.

$$\sum(\text{PEC}_{\text{component}}/\text{PNEC}_{\text{component}}) = \text{HI}_{\text{mixture}}$$

If  $\text{HI}_{\text{mixture}} < 1$  = adequate control of mixture risks

$\text{EC}_{50}/\text{LC}_{50}/\text{IC}_{50}$  of the effluent <xyz mg/l = adequate control of mixture risks

Guidance for the implementation of a tiered approach for checking risks from effluents should be included either in an Annex (analogous to Annex I for the CSR) or in a guidance document.

The following assessments correspond to those of option I6 described in section 3.6.6, as the REACH role of a downstream user corresponds for formulators and end-users. However the information situation of formulators differs (section limitations due to data availability).

### 3.6.7.3 Scope

The option principally covers all substances used at the end-users’ sites.

As it is assumed that some type of prioritisation is implemented (c.f. chapter 3.4.1), the assessment need would be triggered by the prioritised substances or mixtures. Which additional substances to consider (“all other substance emitted”, substances with an environmental hazard etc.) is not yet defined for the option.

### 3.6.7.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 24: Conformity of the option to require risk assessment for the end-users' effluents with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Likely, stricter RMM on-site if risks are identified	Improvement of information base	Yes, more information on own effluents
Responsibilities within industry	New obligation, share of responsibilities maintained	Responsibilities between industry and authorities	New obligation, share of responsibilities maintained

The assessment of the toxicity of the whole effluent is an activity which is not in conformity with the REACH procedures and principles. If it is regarded as downstream activity to check the implementation of an ES, if there is a) no ES to check against and b) the result is an expression of toxicity rather than of risk.

#### 3.6.7.5 Limitations due to data availability

End-users only know the classified components they use in mixtures, if they are contained above the concentration thresholds. Hence, the implementation of the tiered approach would concern a much lower number of substances as if any whole mixture testing was used. Information on the hazards of the known substances may be available in the ECHA database and/or safety data sheets.

#### 3.6.7.6 Potential challenges

The core challenge of the option is the additional resources (time and competences) needed for end-users to conduct either the tiered approach or the effluent testing.

The tiered approach would in most cases be too challenging (calculation of exposure levels needed and use of hazard data on substances) that it is unlikely that the end-users would apply it.

For the whole effluent testing, approaches have to be developed to deal with changing compositions of effluents due to production campaigns, batch processes etc. Here, one or more “average” or “typical” assessments may have to be carried out.

#### 3.6.7.7 Expected benefits

End-users would obtain information on potential risks from their effluents and could improve their risk management, if necessary. Information could be gathered on mixture composition and potential effects, which could be used to develop prediction models for mixture assessment; this requires a good documentation of the emission situation during the sampling period.

Information on risks from the effluents would also enhance the implementation of other legislation, e.g. water framework directive and/or industrial permitting.

#### 3.6.7.8 Expected costs / efforts

Costs and efforts for tiered assessment or testing are needed. The extent to which resources are needed depends on how representative the methods are for the annual production (number of samples, number of typical effluents).



### **3.6.7.9 Enforcement aspects**

There is no “natural addressee” of the information under REACH; the results of effluent assessment may be submitted to ECHA for evaluation and compliance checking or to the authorities of the Member States. Respective responsibilities would have to be defined.

### **3.6.7.10 Open questions**

Two questions which could be solved on a methodological level are how a measured effluent toxicity should be evaluated and/or how it translates into a HI and how representative sampling can be achieved and documented.

A question of a regulatory nature is whether it is possible to include different requirements for chemicals safety assessment for different life-cycle stages, as in this option mixture risks would have to be included in the stage of manufacturing. Respective research would be necessary to develop methods and get a correlation between modelled and measured data and identify how respective measurements could be implemented.

Finally, as indicated in the earlier sections, it needs to be defined which substances should be considered. If the same conditions should apply for the two methods, all substances need to be taken into account, as the whole effluent testing integrates all emissions. This would make the assessment via a tiered approach very onerous (many components to be considered in low amounts, partly without toxicity data).

### **3.6.7.11 Conclusions on the option by the consultant**

End-users are to ensure that there are no risks from their installations. The obligation for end-users to assess the risks from their effluents seems to be appropriate. However, it is unclear if the required efforts and benefits are balanced. Method development as well as generation of support tools should be considered.

### **Consultant's recommendation**

The assessment of risks from effluents is useful and could lead to better risk management measures at site. However, the obligation relates rather to an installation than to individual substances and mixtures as placed on the market. The latter is the regulatory subject of REACH, whereas the former is regulated under the Industrial Emissions Directive. It is therefore proposed to implement the option under that legislation.

## **3.6.8 Option 18: DU aggregate substances amounts to check compliance with received exposure scenarios**

### **3.6.8.1 Brief description**

This option includes a requirement to DUs to add up the amounts of one substance they apply in a specific use but that they source from different suppliers or use in different mixtures in the context of compliance checking with the received information. Hence, any exposure scenario for a given substance would have to be compared with the total use and emission of that substance used in all technical mixtures (and the substance as such) products applied in that specific use.

The aggregation of amounts of the same substance is regarded as a specific case of a mixture risk assessment but not according to a strict understanding. A prioritization of substances / mixtures to which this requirement applies is not foreseen.

### 3.6.8.2 Consultant's interpretation of REACH and proposed implementation option

The REACH text, specifically Art. 37.5, does not include any provisions that the amounts of one substance from different sources needs to be summed up before compliance with one or more exposure scenarios is checked. Also the current draft of the ECHA downstream user guidance does not include respective guidance in its chapter 4. According to the current interpretation of ECHA / the EU Commission, the downstream user obligations do not include an aggregation of substance amounts used as such or in different mixtures in the checking of compliance with ES<sup>77</sup>.

In conclusion, the requirement is not currently part of the REACH text but would have to be introduced therein. This could comprise a clarification of the requirements to assess coverage of exposure scenarios in Article 37.5 - if one substance is used in one use but obtained from several sources (substances as such or in mixtures from one or from different suppliers), the amounts need to be summed up before checking if the conditions of each of the exposure scenarios are met. Alternatively it may already be sufficient to provide respective clarification only in the guidance documents. This would require more in-depth legal assessment.

The German Environment Agency is of the opinion that the aggregation of substances before compliance checking with ESs is already part of the DU obligations. In this case, it would be helpful to clarify this aspect in guidance documents and no change in the REACH text would be necessary.<sup>78</sup>

### 3.6.8.3 Scope

This provision would cover all substances as such or in mixtures for which at least one exposure scenario is received

### 3.6.8.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 25: Conformity of the option to require substance aggregation before compliance checking with ESs by DUS core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Likely, as more strict RMM may be required for higher amounts	Improvement of information base	No
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

The aggregation of use amounts at the downstream user site contradicts the principle that registrants, who forward the exposure scenarios, are responsible only for (the assessment of)

<sup>77</sup> Personal communication with ECHA staff (2013)

<sup>78</sup> For more details please refer to the study „Basic principles for the development of a concept for environmental exposure assessments of single substances released from multiple uses under REACH” by UBA under [http://www.reach-info.de/dokumente/aggregierte\\_exposition.pdf](http://www.reach-info.de/dokumente/aggregierte_exposition.pdf)

their own amounts. From the perspective of the downstream user, the principle of responsibility for “the own amount” would support the conformity of the opinion.

The fact that substance uses could occur also from other registrants could be regarded as accounted for by the use of a  $PEC_{\text{regional}}$  in the local and the  $PEC_{\text{continental}}$  in the regional assessment.

#### **3.6.8.5 Limitations due to data availability**

DUs can only aggregate the amounts of the respective substances if they are used as such or if they are contained in the mixtures they use above the concentration thresholds. Hence, substance amounts in mixtures which are not known to the end-user (due to lack of identification in the SDS) would not be considered.

#### **3.6.8.6 Potential challenges**

DU may face the situation that in the suppliers' ESs different PNECs or PECs are provided and different conditions of use are specified. If the aggregated substance amounts exceed the allowed use amounts in one or more of the ESs / SDSs received, re-calculations of the resulting PECs or scaling of the conditions of use may be necessary and complex due to differing information.

Due to the fact that only concentration ranges of substances in mixtures are provided in SDSs, DUs will have to calculate with the upper bounds (safety margin) and may hence assume much higher amounts than actually used, unless more exact information is given in the SDS.

DUs may be forced to carry out a DU CSR in the cases, where aggregated exposures indicate a risk from the use of a substance but the exposure scenarios of the individual substances are complied with. Here, the situation is different to the “normal trigger of DU CSRs” because the conditions of use and RMMs are complied with for the individual substance ES. Consequently, the likelihood that suppliers will re-assess a use with an aggregated substance amount is low (because suppliers only need to account for their own amounts).

#### **3.6.8.7 Expected benefits**

Risks from the aggregated amounts of substances applied in the same use are identified and result either in re-assessment or the implementation of RMMs. The conformity checking by DUs would be more in line with common sense regarding environmental emissions.

#### **3.6.8.8 Expected costs / efforts**

Downstream users would have to spend more time for compliance checking and the conduction of potential CSRs in case of the use is not safe or communication with suppliers is necessary. Costs would arise if new RMMs would need to be implemented and or production / use of products would have to be changed.

#### **3.6.8.9 Enforcement aspects**

There are no changes implied by the option to the enforcement of ES implementation.

#### **3.6.8.10 Open questions**

Which consequences arise from an aggregated check of coverage of the ES?

If DU adds up the use amounts of substances (including if no ES has been received from one or more of the suppliers) he may not be covered by the ES(s) received or, in case he makes an own

assessment, exceeds the HI of 1. Could all of the registrants be contacted? Does the DU have a right to request re-assessment, if only his total use amount (but not the amount supplied by the individual suppliers) is outside the ES's scope?

How can the limitation of the assessment to one use (covered by one ES) be justified assuming that there could be other uses involving the substances carried out simultaneously at the same site?<sup>79</sup> Why would there not be an overall assessment of risk from the use of the substance in all uses?

With view to the tasks of checking the implementation of exposure scenarios it makes sense to limit the aggregation of substance amounts to a specific use. In addition, if a substance is applied in one use (but from different sources), there is a high likelihood of co-occurrence, which is the pre-condition for mixture assessment. However, considering that many installations carry out several processes simultaneously and (partly) using the same substances, from the environmental point of view the overall environmental risk should be assessed and all emissions should be added up, regardless of from which use they originate.

### **3.6.8.11 Conclusions on the option by the consultant**

From the perspective of environmental risks, the assessment of the safe use of aggregated substances amounts is logical and useful. There are no limitations regarding data access to the downstream users and in most cases the implementation is expected to be possible with fairly low efforts. The obligation may result in a higher protection level. There are some practical aspects to be clarified regarding the responsibilities and duties of suppliers of substances, for which aggregated assessments show non-compliance with the received exposure scenarios.

### **Consultant's recommendation**

A clarification of the interpretation of the legal text regarding the aggregation of use amounts before compliance checking should be initiated. Based on the outcome of the legal assessment, either a change in the REACH text or, if not necessary, clarification in the guidance documents should be carried out.

## **3.6.9 Option I9: Applicants for authorization use the tiered approach to assess mixture risks and provide a SEA in their authorization application**

### **3.6.9.1 Brief description**

According to this option, an authorization for substances for which additive effects or synergistic effects have been demonstrated can only be granted via the SEA route. This would be based on the assumption that, similar to PBT/vPvB, no safe exposure levels can be determined for these substances in the environment. Consequently, these substances would be regarded as non-threshold substances. Applicants for authorization would need to identify if mixture hazards have been identified and if so, include a mixture risk assessment in their CSA and a SEA in their application.

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<sup>79</sup> This is frequently the case for e.g. solvents, which are applied in several uses / processes in a production chain and the uses are likely to be described in different ESs.

### 3.6.9.2 Consultant's interpretation of REACH and proposed implementation option

Article 60 of REACH does not mention whether or not combined exposures may be included in the decision making on risks from the use of a substance. All provisions focus on the substance itself and related information on hazards and exposures (e.g. Art. 60(2)). In the guidance document on authorisation applications only substance related aspects are discussed. Consequently, the option to consider mixture risks and/or to request consideration of mixture risks in the authorisation application is neither explicitly possible nor explicitly excluded.

The current interpretation of non-threshold substances is based on the mode of action of a substance and/or its property as PBT/vPvB which implies that concentrations add up in the environment or in organisms and eventually lead to critical exposure levels and no safe exposure level can be determined. The argumentation for PBT/vPvB substances could be extended to substances for which additive or synergistic effects have been scientifically detected, such as for endocrine disrupting chemicals.

According to the consultant's interpretation of the current provisions, it is generally possible to fit mixture concerns into the current framework of authorisation. However, this would require a respective political will and changes in the REACH text as well as guidance documents. Therefore, this option should be viewed as a possible option to be implemented in the long-term.

Necessary changes in the REACH text regard the amendment of the criteria for non-threshold substances in Art. 58(3) (inclusion of detected additive or synergistic effects) and the amendment of Article 62 regarding the content of an authorisation application (specification that a CSR for substances with detected mixture hazards needs to include an assessment of mixture risks).

The existing ECHA guidance documents would have to be revised in particular for industry actors to develop compliant authorization applications.

### 3.6.9.3 Scope

The option would cover substances included in Annex XIV, which have been prioritised for authorisation because of mixture effects. For substances where it is unclear if they have an effect threshold, such as for EDCs, the option would change or clarify its regulatory status to a non-threshold substance.

### 3.6.9.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 26: Conformity of the option to require the use of MAF in the registrants' CSRs with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes, due to stricter rules for granting authorisations and potentially stricter risk management measures	Improvement of information base	Partly, as information in the authorisation application is extended to include mixture risks; additional SEA in case of current threshold substances
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

#### **3.6.9.5 Limitations due to data availability**

Applicants for authorisation would use the available information on known additivity or synergisms. There would be no requirement to generate respective data. As cooperation of actors in the supply chain is likely in the context of authorisation, information on uses, mixtures and exposures are likely to be available.

#### **3.6.9.6 Potential challenges**

The existing challenges for industry when submitting authorisation application would be increased by the additional obligation.

#### **3.6.9.7 Expected benefits**

Detected mixture hazards (additivity/synergism) or identified mixture risks would change / clarify the regulatory status of threshold substances to non-threshold substances. This would for example concern a number of endocrine disrupting substances. As a consequence, stricter conditions in the granting of authorisations would be ensured, because a socio-economic analysis would be needed to demonstrate that benefits outweigh the risks.

Information and experience is gained on mixture assessment with a limited number of substances on the side of industry and the authorities.

The phase-out goal of the authorisation procedure and the substitution of SVHC are enhanced.

#### **3.6.9.8 Expected costs / efforts**

Resources for SEA and a mixture risks assessment in the scope of the CSR are needed by applicants. The ECHA Committees would need more time for checking the authorization applications.

#### **3.6.9.9 Enforcement aspects**

No additional enforcement tasks.

#### **3.6.9.10 Open questions**

Should there be an option for authorisation applicants to argue on safe levels?

If substances are quickly degraded or other reasons why they do not contribute to mixture effects in the environment exist, it may be necessary to allow registrants demonstrating safe use based on scientific arguments.

The consequences of mixture effects with regard to the scope of a mixture risk assessment are unclear. The consequences may directly affect the scope of mixture risk assessments to be performed (consideration of “other” substances) as well as the level of identified risk that needs to be outweighed by the benefits.

Is it actually possible to include mixture risks as criterion in the authorization process and define substances for which additivity/synergism are detected as non-threshold substances? Further (legal) assessment of the issue is necessary to answer this basic question.

#### **3.6.9.11 Conclusions on the option by the consultant**

Based on the current analysis of the REACH text it is not possible to decide if the consideration of mixture risks in the authorisation process is possible. Further legal assessment is necessary to clarify the issue.

In addition a more detailed legal assessment it is recommended to further analyse the costs and benefits of the option; e.g. in how many cases respective provisions would have changed the outcome of an authorisation decision and whether or not the respective are proportional to the gain in level of protection.

### **Consultants' recommendation**

If the legal assessment shows that the option is in principle possible and the cost/benefit analysis shows a net benefit, the implementation should still be regarded as a long term option, because it requires a change of the legal text which is likely to be very controversially discussed.

### **Further opinions**

The option was critically discussed by the participants of the workshop. On the one hand, the obligation would change the current situation only for those substances, which have a threshold and for which adequate control could be demonstrated if no account was taken of potential mixture risks. Secondly, specifically ECHA but also most national authorities regarded the authorisation as strictly limited to the risks by the individual substances. Participants expressed the expectation that the risks from aggregated exposures (from all potentially granted authorisations) would be taken into consideration in the practice of granting authorisations in the future by ECHA and the EU Commission.

### **3.6.10 Option I10: M/I and F communicate mixture hazards with (extended) safety data sheets**

In order to trigger specific requirements for communication, some type of evidence should be available on the additive / synergistic effects of substances.

Evidence of additivity may be studies / tests such effects are observed. They could concern substance(s) or groups of substances in combination with one or more other substances and should be relevant to the assessed mixture;<sup>80</sup> i.e. combined exposures of the substances or at least related substance(s) are likely. Evidence of synergism would likewise be shown in respective studies / tests. If a study result can be generalised, e.g. due to an unspecific mode of action (such as enhanced substance uptake into an organism), the synergism may be assumed to occur in relation to any other substance (general synergism). If the results cannot be generalised, the effect can only be assumed for the specific assessed substance combinations and would hence only be relevant for mixtures, where these combinations occur.

Regarding mixture risks due to combined exposures, evidence could e.g. be monitoring data or information from (precise) models indicating multiple exposures in environmental compartments.

This chapter refers to cases, where communication is triggered by some type of indication of mixture risks as described above.

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<sup>80</sup> If registrants are to communicate they don't know in which combinations the substance is used. Hence, they cannot judge on the relevance of a test result and would always have to communicate information on respective effects.

Before describing the concrete options to communicate on mixture hazards<sup>81</sup>, the types of information that could be communicated are introduced: a) generic information on mixture hazards of substances / substance groups, b) specific information on mixture hazards of a specific substance or substance group and c) observation of effects after exposure that are unexpected based on the classification of substances in the mixture / to which exposure took place.

#### a) Examples of generic information on mixture hazards

For some substances, generic information on mixture hazards is available in public literature:

- Metals have been shown to sometimes exhibit synergistic effects with other substances (e.g. iron, copper, zinc).
- Surfactants may show synergistic effects due to their function and general influence on biological systems.

For the different cases, the types of “exemplary information” shown in Table 27 could be communicated under chapter 2 of the safety data sheet (hazard information):

Table 27: Examples of standard phrases for communicating on “generic” mixture hazards<sup>82</sup>

Case Communication on...	Possible standard phrase
[Substance A] has detected general additive / synergistic effects when co-occurring with different other substances	[Substance A] may act synergistically with other substances. This should be considered during uses along the entire lifecycle and any risk assessments performed.
[Substance A] for which additive / synergistic effects with [Substance X] are detected	If [Substance A] co-occurs with [Substance X], synergistic effects may realize. This should be considered during the use of the substance along its lifecycle and any risk assessment performed.
[Substance A] for which additive / synergistic effects with (some) members of the same group [Group A] have been prove	If [Substance A] is used together with members of the [Group A], additive effects are likely. This should be considered during uses along the entire lifecycle and any risks assessments performed.”

The information basis on “general” mixture hazards is likely to improve in the future.

#### b) Examples of information on specific mixture effects

For some substances, specific information on additive or synergistic effects is available in literature:

<sup>81</sup> The term mixture hazard refers to an increased mixture toxicity due to the presence of additive or synergistic effects between the substances contained in the mixture. The term is chosen instead of mixture effects because mixture hazards, in analogy of substance hazards, refers to the potential of a substance to exhibit of the effect, regardless of the exposure concentrations. The term mixture effect implies that an exposure has taken place and the effect has realized; hence it is dependent on the exposure conditions and relates to the risk connected to a specific mixture.

<sup>82</sup> In all cases, it may be useful to add information that the actual realization of mixture effects from mixture hazards depend on the actual exposure concentration, which may be well below the exposure concentration during testing. It would also be useful to provide a reference to the source of the study, where the mixture hazard was identified.



- For some substances mixture testing may have been performed and respective information on additive / synergistic effects may be published in publicly available scientific literature.
- If scientifically valid, an extrapolation from the specific substances to substance groups could be made and “general information” be derived and communicated (c.f. above).

Table 28: Examples of standard phrases for communicating on “specific” mixture hazards

Case Communication on ...	Possible standard phrase
[Substance Z] for which significant synergism has been shown when co-occurring with [Substance X]	[Substance Z] has been shown to have synergistic effects with [Substance X]. This may lead to a higher (eco-)toxicity if these substances co-occur. This should be considered in the risk management for the substance and any risk assessments performed.
the [Group Z] to which [Substance Z] belongs to.	[Substance Z] has been demonstrated to act synergistically with [Substance X]. It is likely that other substances of [Group Z] show the same synergism. This may lead to a higher (eco-)toxicity in case of simultaneous exposures. This should be considered in the risk management during use and in risk assessments.

c) Examples of observation of unexpected effects:

It is theoretically possible that during the use of substances in a mixture, effects are observed which are not expected from the information on the ecotoxicity of the single substances and could hence be due to synergistic mixture hazards.<sup>83</sup> However, due to the fact that it is very seldom that effects in the environment are observed without explicitly looking for them, it is unlikely that this case occurs in practice. Still, unexpected effects are theoretically possible as seen for single substances (e.g. TBT, DDT). However, relating potentially observed effects to exposure to mixtures would be difficult and could only be clarified case by case with scientific studies if a concern should arise. It is therefore not further discussed.

### 3.6.10.1 Brief description

The options proposed in this section regard the communication on mixture hazards which should raise awareness and increase the availability of information on mixture hazards in the supply chain.

According to the proposal, registrants could provide information on known additive effects or synergisms to ECHA as part of the registration dossier and include it in the safety data sheet (section 2 on hazards) to their customers. Alternatively they could include respective information in the safety data sheet also without having provided it in the registration dossier.

Formulators receiving information on mixture hazards from their suppliers would be required to consider this information in the compilation of their safety data sheets; i.e. they should at least forward the information. If formulators are aware of mixture hazards of substances in their mixtures, which are not communicated by the supplier, they may include it in their information on a voluntary basis. They should also inform their suppliers of that information (upstream communication on hazards).

<sup>83</sup> The observation of unexpected effects is more likely for human health than for the environment because there is a more direct exposure response. However, effects on the effluent quality and/or on-site treatment of wastewater may be observable.

Downstream users would be required to take communicated mixture hazards into account in their handling of the mixture. If they become aware of mixture hazards not communicated to them they should inform their suppliers thereof.

### 3.6.10.2 Consultant's interpretation of REACH and proposed implementation option

There are several parts in REACH that can be interpreted with regard to the question of whether or not the provision of information on mixture toxicity is required under REACH or not.

#### Registration

Article 12 specifies that registration dossiers should include all physico-chemical, toxicological and ecotoxicological information relevant to the registrant and available to him. Whether or not information on demonstrated additivity or synergisms is “relevant” is not clear.

Annex I includes under chapter 3.0 a list of information that should be considered in the hazard assessment. The examples of information types do not include any mixture hazards; however, the list is not comprehensive. Under section 3.1 the use of “all available information” for the hazard assessment is mentioned without further specification. Annex VII on the information requirements for registration also includes a sentence specifying that if further relevant data are available, they are to be presented. Again the term “relevant” is not defined.

The concise IR/CSR guidance does not include a definition of “relevant information” in its section B.2.1 but just uses the term. Chapter B4 specifies that relevance should be understood as the extent to which data is appropriate for hazard identification or risk characterization. Hence, relevance is here directly related to endpoints of the hazard assessment. The reference guidance on the environmental hazard assessment (R.10) does only include end-point specific chapters and does not elaborate the term “relevant information”. The guidance document on registration specifies in chapter 3.1.1 “Manufacturers and importers have to collect all available existing information on the properties of the substance for registration purposes”.

Additive effects or synergisms are not part of the information requirements under REACH. Hence, the generation of respective information is not required in any case.

In conclusion, the REACH text is not fully clear on whether or not registrants are required to present and include information on mixture hazards in their registration dossiers is not clearly visible from the REACH text. The guidance documents are interpreted in a way that “relevant” concerns information either relevant to derive a classification or relevant to derive PNEC values. The use of mixture effect data for these end-points is not foreseen and hence, data on demonstrated synergism and/or additivity is understood as not required for the CSR. As no information in the CSR is required, no information needs to be included in the SDS “for reasons of consistency”.

#### Communication in (extended) safety data sheets

The provisions for safety data sheet development in Art. 31 do not specify the type of data to submit but only the headings of the SDS. Annex II includes under chapter 2.3 the statement that

*“Information shall be provided on other hazards which do not result in classification but which may contribute to the overall hazards of the substance or mixture, such as formation of air contaminants during hardening or processing, dustiness, dust explosion hazards, cross-*

*sensitisation, suffocation, freezing, high potency for odour or taste, or environmental effects like hazards to soil-dwelling organisms, or photochemical ozone creation potential.”*

The list is exemplary and not comprehensive but does not include a reference to mixture synergisms or demonstrated additivity. Under chapter 12.6 a list of other information that should be presented if available is presented, which is again exemplary and not comprehensive but does not include mixture effect data.

Article 31.6(7) states that

*“Any downstream user shall include relevant exposure scenarios, and use other relevant information, from the safety data sheet supplied to him when compiling his own safety data sheet for identified uses.”*

This provision is interpreted in a way that if a DU receives information from the supplier on mixture hazards that he then should take this into account in preparing his own safety data sheet.

In conclusion, the provisions for safety data sheets do not exclude that data on mixture hazards is provided but a requirement can only be identified from the current REACH text for downstream users which receive respective information.

### **Communication of mixture hazards upstream**

REACH Art. 34 (a) requires downstream users to inform their suppliers of “any new information on hazardous properties, regardless of the uses concerned;” This does not specify which type of hazardous properties are concerned but a definition is contained in the ECHA guidance on downstream users:

“There is no definition in REACH of what constitutes ‘new’ information, or what source and quality of data is acceptable. New information may relate either to substances or to mixtures. The main criteria for deciding whether you hold new information are that:

- the information is not communicated to you by your supplier;
- the information is not available in public data bases or literature;
- the information is relevant for the substance or mixture you receive from the supplier;
- you have good evidence to support the information;
- the information could have consequences for the management of the risks of the substance.”

According to these points, it is possible that a downstream user holds information on mixture hazards of substances for which communication is obligatory; e.g. if formulators test their mixtures for classification and identify different results than if the conventional method is applied or if effects are observed. Information that has been published, e.g. in scientific journals, but which the supplier has not included in the SDS does not fall under ‘new’ information, as indicated by the list above.

In conclusion, communication of information on mixture hazards may be required in specific cases. However, as explained above this case is not regarded as relevant.

### **Using information**

Article 31.6(7) states that downstream users shall “use other information” to compile their safety data sheets. The REACH text does not define what is meant with ‘using information’. The

ECHA guidance on downstream users specifies that formulators should collate received information, identify relevant information and communicate it downstream. The further explanation focuses on information related to exposures rather than to hazards. The ECHA guidance document on safety data sheets also does not include specific information on what the formulator should do with the information.

The consultant concludes that as information received on mixture hazards should be communicated in chapter 2 of the Safety Data Sheet under the heading “other hazards”. No further direct consequences can be deduced from available information.

### Consultant's conclusion

Consequently, according to the consultant's interpretation, registrants may (good practice), but are not required, to provide data on mixture hazards in the safety data sheets. Formulators are obliged to include information on mixture hazards if it is ‘new’ and may voluntarily include it in other cases. If formulators receive information on demonstrated mixture hazards, they are obliged to consider this information in the development of their safety data sheets or other downstream information. Information on mixture hazards should be included in chapter 2 of the safety data sheets under the heading “other hazards”. The receipt of such information does not automatically trigger a mixture risk assessment.

#### 3.6.10.3 Scope

The option would cover all substances for which additive or synergistic effects have been shown in scientific studies or testing.

#### 3.6.10.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 29: Conformity of the option to require the use of MAF in the registrants' CSRs with core REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Possible, all actors can take mixture hazards into account	Improvement of information base	Yes, information on mixture hazards is disseminated
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

#### 3.6.10.5 Limitations due to data availability

Only available information would have or could be voluntarily communicated. Hence there are no limitations due to data availability.

#### 3.6.10.6 Potential challenges

There are obvious challenges from the implementation of the option.

#### 3.6.10.7 Expected benefits

Information on mixture hazards is made known to the users of a substance. This enables them to take the information into account and decide if their current risk management and communication practices are sufficient. Producer responsibility can be better fulfilled.

#### **3.6.10.8 Expected costs / efforts**

As only available information is concerned, costs are expected to be low. The change of safety data sheets may require resources because new standard phrases would have to be developed and integrated in the communication standards / software.

#### **3.6.10.9 Enforcement aspects**

No additional enforcement tasks.

#### **3.6.10.10 Open questions**

The question how information on mixture hazards should be “used” may be further elaborated in the guidance in order to ensure communicated information is taken note of and implemented at least in further communication.

#### **3.6.10.11 Conclusions on the option by the consultant**

The option can be implemented without limitations due to data availability and with low efforts of all actors. The material benefits are likely to be limited (low number of substances for which mixture hazards have been detected, no specific consequences other than further communication) but the information gain and increase of awareness of the issue justifies the additional efforts.

#### **Consultants' recommendation**

Include information on the communication of mixture hazards in the supply chain into the ECHA guidance to make all REACH actors aware that this type of information should be communicated.

### **3.7 Summary of options to act for industry**

#### **3.7.1 Overview of options**

Table 30 gives an overview of the industry options introduced and analysed; for each option the assigned number, the section where it was analysed and its name are provided (columns 1-3). The following columns clarify the characteristics of the option: who is responsible, which substances are covered, which method should be applied for mixture assessment and which lifecycle stages would be covered by the mixture assessment.

It should be noted that it is presupposed that prioritisation for mixture assessment is implemented for most options (c.f. chapter 3.4.1); this is indicated in the column “covered substances” with the word “prioritised”. Which type of prioritisation criteria is implemented is not specified in this report but recommendations are included in chapter 2 of this report.

Table 30: Overview of options to implement mixture assessment for industry under REACH

	Section	Name	Responsible actor	Covered substances	Method	Lifecycle steps
I1	3.6.1	M/I use MAF in his CSR to assess mixture risks along the lifecycle	Registrant	Prioritised substances for which a CSR is prepared	MAF	Entire lifecycle
I2	3.6.2	M/I use the tiered approach to assess mixture risks along the supply chain	Registrant	Prioritised substances for which a CSR is prepared	Tiered approach	Entire lifecycle
I3	3.6.3	M/I use the tiered approach to assess mixture risks for 'similar substances' which occur together along the supply chain	Registrant	Substances registered in groups or for which read-across is applied	Tiered approach	Entire lifecycle
I4	3.6.4	M use the tiered approach and/or whole effluent testing to assess mixture risks from their site	Manufacturer	(All) substances emitted from manufacturing site	Tiered approach / WET	Manu- facture
I5	3.6.5	DU formulators use the tiered approach to assess mixture risks along the supply chain	Formulator	Prioritised substances (contained in mixtures) and prioritised mixtures	Tiered approach	Formul- ation, end- use of mixture
I6	3.6.6	DU formulators use the tiered approach and/or whole effluent testing to assess mixture risks from their site	Formulator	(All) substances emitted from formulators' sites	Tiered approach / WET	Formu- lation
I7	3.6.7	DU end-users use the tiered approach and/or whole effluent testing to assess mixture risks at their site	End-user	(All) substances emitted from end-users' sites	Tiered approach / WET	End-use
I8	3.6.8	DU aggregate substances amounts to check compliance with received exposure scenarios	Downstream user	All substances for which an ES is received	Aggre- gation	Down- stream use
I9	3.6.9	Applicants for authorization use the tiered approach to assess mixture risks and provide a SEA in their authorization application	Authorisation applicant	Substances subject to authorisation	Tiered approach / WET / SEA	Authorised uses
I10	3.6.10	M/I and F communicate mixture hazards with safety data sheets	Registrant and formulator	All substances for which mixture hazards have been demonstrated	Communi- cation	Not applicable

### 3.7.2 Most feasible options under REACH

In the following, the evaluation results presented in chapter 3.6 are summarized. For details of the assessment, the respective sections should be consulted.

The most feasible options to act for industry (ordered according to the degree of feasibility) under REACH according to the consultant's evaluation are the following options:

- I8: Downstream users aggregate substances amounts in ES checking (chapter 3.6.8)  
short-term option
- I10: M/I and formulators communicate information on mixture hazards in the supply chain (chapter 3.6.10)  
short-term option
- I3: M/I use the tiered approach to assess mixture risks from 'similar substances' along the supply chain (chapter 3.6.3)  
mid-term option
- I5: Formulators use the tiered approach to assess mixture risks along the supply chain (chapter 3.6.5)  
possible long-term option
- I1: M/I use a MAF in the CSR to assess mixture risks along the supply chain (chapter 3.6.1)  
possible long-term option after further assessment

#### 3.7.2.1 I8: Downstream users aggregate substance amounts in ES checking

The pros of this approach are that the aggregation of substance amounts from different mixtures used by the end-users (and also formulators) is logical as they are emitted together from the DU installation. The option can be implemented without high efforts and may result in more appropriate risk management measures on-site, in case the aggregated amounts cause a yet unidentified risk on-site.

For this option, some open questions should be resolved, e.g. whether this action is already required under REACH (legal assessment necessary) and what consequences should be triggered, if a DU complies with received ESs for individual substance amounts but not the aggregated amount.

#### 3.7.2.2 I10: M/I and formulators communicate information on mixture hazards along the supply chain

Pros of the approach include that information and awareness on mixture hazards would be raised requiring comparably low efforts because only available information would have to be included in the safety data sheets. All actors would be enabled to act more responsibly. The option is mainly voluntary, as currently no requirement to include mixture effect information in the SDSs could be identified; however, if information is included this must be used in the further communication.

The cons of the approach are that it is voluntary and may hence not have a large effect.

### **3.7.2.3 I3: Manufacturers assess risks from typical mixtures along the supply chain (tiered approach)**

The pros of this approach include that the manufacture should have the necessary information available in most cases,<sup>84</sup> the responsibility for chemical safety assessment under REACH is maintained and a high level of detail (and correspondingly lower level of uncertainty in the mixture assessment) can be achieved. Registrants are familiar with the risk assessment procedures in addition.

The main cons of this approach are that it is not clear if ‘similar substances’ actually contribute significantly to environmental risks because of their occurrence as mixture and the lack of a definition of ‘similar substances’.

### **3.7.2.4 I5: Formulators assess mixture risks along the supply chain (tiered approach) for prioritized cases**

The pros of this approach include that formulators have information on the composition of the technical mixtures subject to the assessment and can obtain at least basic hazard information on the contained substances from ECHA’s database, if the substances are registered. They are aware of the end-uses of their mixtures and they already have an expertise to assess mixtures. The formulators’ mixture assessment obligation is closely related to their producer responsibility and the obligation to develop safety data sheets.

Cons of this option are the high workload for the formulator (also if only prioritized cases would have to be assessed). Due to the higher level of uncertainty for the risk assessment of mixtures, in particular where data for the refinement of the hazard assessment are missing may lead to overly strict RMMs, which could cause problems in the availability of mixtures on the market.

### **3.7.2.5 I11: M/I use a MAF in the CSR to assess mixture risks along the supply chain**

The advantage of the MAF approach is that registrants could implement it without difficulty and that no limitations exist regarding the knowledge of actual mixtures the substance is used in. It could be assigned also under other legislation and this ensures a high level of protection.

Disadvantages of the approach are that there are no scientific<sup>85</sup> approaches to quantify the MAF other than based on the number of mixture components and that the implementation of an additional safety factor for mixtures in the chemical safety assessment may lead to overly conservative RMMs.

## **3.7.3 Options which could be considered for implementation under the Industrial Emissions Directive (IED)**

The option for substance manufacturers (chapter 3.6.4) for formulators (chapter 3.6.6) and end-users (chapter 3.6.7) to conduct a mixture assessment for their effluents, either using a tiered

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<sup>84</sup> Only if substances co-occur in technical mixtures with substances manufactured or imported by another registrant the information would have to be retrieved from ECHA’s database on registered substances and/or may not be available, if these substances are not registered, yet.

<sup>85</sup> The MAF of 10 is a politically derived factor.



approach or whole effluent testing was evaluated as possible option to act under REACH, because it could be considered as a DU obligation.

The option is implementable by all three types of actors (under the assumption that only classified substances above the concentration thresholds in mixtures are to be considered (c.f. chapter 3.2.2). However, there may be data gaps regarding substance hazards for the implementation of the tiered approach. The implementation of the WET approach requires further investigations to develop a representative sampling strategy and how the measured effluent toxicity could be translated to a risk.

Due to the fact that the option concerns installations (with all used substances and mixtures) rather than individual chemical products, the option should be considered for implementation under installation related legislation. It is not proposed for implementation under REACH

### **3.7.4 Option for further detailed assessment and, if at all to be considered for long-term implementation**

#### **3.7.4.1 I9: Authorisation applicants use the tiered approach to assess mixture risks and provide a SEA in their authorisation applications**

This option requires further assessment with regard to whether or not substances with demonstrated mixture hazards should be regarded as non-threshold substances. If so, applicants would have to consider these in their applications. This may result in stricter risk management and/or the rejection of an application resulting in a higher level of protection. However, the feasibility of the option should be further assessed before it can be decided if the implementation would be useful.

### **3.7.5 Option which is not regarded as feasible or useful for implementation under REACH**

#### **3.7.5.1 I2: M/I use the tiered approach to assess mixture risks in the CSR**

The use of the tiered approach by registrants to assess mixture risks along the entire life-cycle is hardly feasible for implementation under REACH due to a lack of (legal) possibilities to obtain information on the composition of mixtures the substance is used in. Even if data were available, e.g. by individual communication with all customers formulating mixtures with the substance, the information collection and the mixture assessment task would be very extensive and it is not clear if the benefits merit these efforts.

Further analysis beyond the project 4M is needed for a better understanding and for clarification of the following questions:

- To which extend it can be expected that registrants take into account available knowledge on mixture hazards in their registrations?<sup>86</sup> “How” and “where” – in the legal text, the annexes or the guidance – such a clarification can be made?

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<sup>86</sup> If the registrant is a formulator at the same time (role of a DU) and uses the substances he registers in formulations he does know the composition of his mixtures. However, if a requirement to make a tiered mixture assessment would be implemented for “formulating” registrants, they would be discriminated against registrants of the same substance who do not. Furthermore, a requirement would be defined for a case, where an actor has two roles, which would be against the current practice in the legal text.

- To which extend registrants should perform a tiered mixture assessment if the substance under registration is used in a mixture of known composition (e.g. in the case that the registrant by himself produces technical mixtures)? Is it possible to implement a requirement for a tiered mixture assessment including provisions how the respective registrants obtain information of the mixture composition?

### **3.7.6 Overview of evaluation results**

The assessment aspects and results are summarised in the following table.

Table 31: Overview of evaluation results of industry options to act

Option	Chapter	REACH change needed	Limited data availability	Benefits	Costs	Challenges	Enforcement	Recommendation
I1: M/I; MAF in CSR; prioritised substances	3.6.1	Text, Annex, guidance	--	No info on composition needed, more appropriate RMMs	CSR and communication; RMM implementation, DU CSR or substitution	Derivation MAF Risk of shifting assessment responsibility to DUs	No change	Explore option further
I2: M/I; tiered approach; prioritised substances	3.6.2	Text, Annex, guidance	Mixture composition	More / better information, more appropriate RMM along supply chain	CSR and communication; RMM implementation, DU CSR or substitution	Overly strict RMMs recommended leading to DU CSRs	No change	Not feasible
I3: M/I; tiered approach; 'similar' substances	3.6.3	Text, Annex, guidance	--	More / better information, more appropriate RMM along supply chain	CSR and communication; RMM implementation, DU CSR or substitution	Less use of grouping/read across to avoid mixture assessment	No change	Define similarity; explore relevance of mixture risks
I4: Registrant; tiered approach / WET; own site	3.6.4	Text, Annex, guidance	--	More appropriate RMM onsite	Measurements, assessment of effluent	Identification of PNECs, sampling strategy for WET	To be newly assigned ?	Propose for implementation under e.g. IED
I5: Formulator; tiered approach; prioritised substances / mixtures	3.6.5	Text, Annex, guidance	Substance hazards	More / better information; more appropriate RMM along the chain	Mixture assessment, communication	Identification of PNECs	To be newly assigned	Consider as long-term option
I6: Formulator; tiered approach / WET; own site	3.6.6	Text, Annex, guidance	--	More appropriate RMM onsite	Measurements, assessment of effluent	Identification of PNECs, sampling strategy for WET	To be newly assigned ?	Propose for implementation under e.g. IED
I7: End-user; tiered approach / WET; own site	3.6.7	Text, Annex, guidance	Substance hazards	More appropriate RMM onsite	Measurements, assessment of effluent			

## Mixtures under REACH – Approaches and Options to Act

Option	Chapter	REACH change needed	Limited data availability	Benefits	Costs	Challenges	Enforce-ment	Recommen-dation
I8: DU; aggregation of amounts; own site	3.6.8	(Text), guidance	--		Negligible	Total amounts unknown, up-stream communication of results, receipt of inconsistent information	No change	Clarify legal situation, initiate implement-ation
I9: Authorisation applicant; tiered approach / WET / SEA	3.6.9	Text, Annex, guidance	--	Requirement of SEA substances with mixture risks	Mixture assessment, SEA	Increase of existing challenges	No change	Explore feasibility, pursue as long-term option if at all
I10: Registrants / Formulators; communication; known effects	3.6.10	Voluntary → guidance	--	More information on mixture hazards in the supply chain	Communication, software change	No	No change	Initiate information be included in guidance

### 3.8 Conclusions on the options to act for industry

Some voluntary steps can be implemented by industry with low effort (aggregation of exposure before compliance checking with ES; communication of information on mixture hazards).

For all other options, it is recommended that further assessment of the legal situation and/or the feasibility and relevance of actions regarding risk reduction from mixtures be conducted before taking further action. This includes a methodological and political discussion on priority setting and identifying which indicators could be used to select those substances / mixtures for which an environmental risk is expected. The prioritisation of substances / mixtures where mixture risks are expected is essential to make most of the options manageable.

An assessment of mixture risks that are not already covered by the assessment of single substances, which would be the basis for determining benefits of all of the options is regarded as useful only after the REACH phase-in scheme is finished; i.e. in 2018, because only then all RMMs will have come into effect. A benefit assessment is regarded as essential part of a justification to introduce new requirements under REACH; an impact analysis must be conducted by the EU Commission prior to legal changes or new legislation.

In any case, it is recommended that UBA continues discussion with ECHA, the EU Commission and the Member States on the relevance of mixture risks in order to prepare further action.

### 3.9 Options to act for authorities

This chapter contains descriptions of different options to include elements of mixture assessment into the authorities' work under REACH.

As for the industry options, each authority option is briefly described and assessed using the same assessment questions (c.f. chapter 3.3). A more detailed description of the options is given in Annex 6 (section 9.6). Most options do not comprise the actual conduction of a full mixture risk assessment but rather an enhancement of considering related risks in the existing procedures. The results of the assessment are summarised in chapter 3.10 and recommendations are derived in chapter 3.11.

All authority options focus on groups of substances which are “similar”<sup>87</sup> and of which there is a suspicion of mixture risks. This is a significantly different approach compared to the industry options, where the mixture that should be assessed may be composed of very different substances (c.f. discussion in chapter 3.2.1). This is, among other things, due to the fact that “similarity” is the most obvious starting point for authority work under the given legal provisions.

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<sup>87</sup> Due to the lack of agreed criteria for “similar substances”, the term is not further defined or specified here. Furthermore, it is likely that the similarity will be established according to the specific option by the authorities implementing it. Similarity is not to be understood as a precondition that should be met but only as a term addressing the types of substances that are in the focus of the industry options.

### 3.9.1 Option A1: Proposals and Priority setting for the Community Rolling Action Plan

#### 3.9.1.1 Brief description

Substance groups could be included in the CoRAP and consequently be subject to substance evaluation because of concerns triggered by (suspected) risks from their use in technical mixtures or their occurrence in discharge mixtures, coincidental mixtures or environmental mixtures. The latter is the most likely, given that substances evaluation should address cumulative or aggregated exposures at EU level.

According to REACH article 45.5, a Member State can notify ECHA of substances when in possession of information that the substance is a priority for evaluation, i.e. that there is concern that risks still might be underestimated by the risk assessments of the registrants. ECHA will decide whether to add the substance to the CoRAP and nominate it for a substance evaluation based on an opinion from the Member State Committee (MSC). There may be cases where a Member State might want to use this provision to propose to include a substance or group of substances to the CoRAP based on concerns relating to their expected or known combination effects in mixtures.

For example, this could be considered for

- a set of compounds in a concrete emission scenario (technical or discharge mixture) with frequent occurrence
- a group of environmental compounds that are known to occur in the aquatic environment, leading to permanent, low-level exposure (examples could be e.g. benzotriazoles/methylbenzotriazoles; phosphor-based flame retardants such as TCEP, TPP, TCDD, TBDP)
- A group of similarly acting substances with known similar uses for them to be evaluated together, performing cumulative risk assessment where possible (examples: substances in water-borne base colours for boats and ships)
- Substances which are known to act more than additive/ synergistically.

Thus, this option could be used in cases for adding substances to the CoRAP which have not met the CoRAP criteria (see [http://echa.europa.eu/documents/10162/13628/background\\_doc\\_criteria\\_ed\\_32\\_2011\\_en.pdf](http://echa.europa.eu/documents/10162/13628/background_doc_criteria_ed_32_2011_en.pdf)) based on the concern relating to the individual substance. Depending on the results and given the invested resources, the competent authority may request further information and data from registrants and propose further risk management option, such as restriction or authorisation procedures (or regulative options apart from REACH).

Hence, mixture risks could be a main (only reason to include a substance) or an additional (additional reason to another main reason) criterion for including substances in the CoRAP. An initial concern is necessary to allow requesting respective information from registrants during substance evaluation (c.f. option requesting information during substance evaluation in chapter 3.9.3).

The option is by nature a voluntary action for ECHA or MS (proposals, prioritisation by ECHA).

#### 3.9.1.2 Consultant's interpretation of REACH and proposed implementation option

REACH Article 44(1) specifies the procedure for selecting substances for substance evaluation. It states:

*“In order to ensure a harmonised approach, the Agency shall in cooperation with the Member States develop criteria for prioritising substances with a view to further evaluation.*

*Prioritisation shall be on a risk-based approach. The criteria shall consider:*

*(a) hazard information, for instance structural similarity of the substance with known substances of concern or with substances which are persistent and liable to bio-accumulate, suggesting that the substance or one or more of its transformation products has properties of concern or is persistent and liable to bio-accumulate;*

*(b) exposure information;*

*(c) tonnage, including aggregated tonnage from the registrations submitted by several registrants.”*

The wording of Article 44 does not include mixture effects but does also not exclude that further aspects, such as suspicion of risks from mixtures, could be an additional or complementary reason for including substances in the CoRAP.

The background document on the selection criteria for substances for the CoRAP<sup>88</sup> includes some statements that also support the view that the criteria in the REACH text are neither exhaustive nor unchangeable. For example it is stated that “The criteria developed by ECHA are not an exhaustive list of all possible risks that chemicals can cause” and that “It is expected that over time on the basis of experience, the criteria will be further developed and refined, with the possibility of a shift towards a different emphasis on certain groups of substances, hazard properties or exposure patterns.”

In addition, the existing exposure related selection criteria could already support an argumentation built upon mixture risk concerns (e.g. under “wide dispersive use”) and the risk related criteria even already include a criterion “Cumulative exposure from structurally related substances with critical hazardous properties (e.g. similar endocrine disrupting property like antiandrogenic or estrogen-like effect)”.

REACH Article 45(5) specifies that “A Member State may notify the Agency at any time of a substance not on the Community rolling action plan, whenever it is in possession of information which suggests that the substance is a priority for evaluation.” The reasons for proposing a substance for inclusion in the CoRAP (notification to ECHA) are not specified here.

Based on the consultant’s interpretation of the wording of Article 44 and the related statements in the background document on the development and use of the selection criteria, the set of existing criteria and the wording of REACH Article 45(5) it is concluded that it is possible to include substances in the CoRAP if risks from mixtures are suspected and that a respective selection criterion could be added in the revision of the criteria. Both ECHA and the Member State authorities could make respective proposals for the CoRAP but ECHA takes the final decision.

It could be considered to include mixture risks as criterion for the CoRAP to increase the acceptance of related proposals by ECHA and the Member States.

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[http://echa.europa.eu/documents/10162/13628/background\\_doc\\_criteria\\_ed\\_32\\_2011\\_en.pdf](http://echa.europa.eu/documents/10162/13628/background_doc_criteria_ed_32_2011_en.pdf)

### 3.9.1.3 Scope

Substance groups for which there is at least some evidence of EU-wide risks from mixtures could be in the scope of the option. The actual number and type of substance (groups) will depend on the interests of the authorities (MS and ECHA) and be decided case-by-case.

### 3.9.1.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 32: Conformity assessment of the option to include substances in the CoRAP based on mixture concerns with REACH- principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	No direct change in risk management	Improvement of information base	Not directly, only if actual evaluation takes place and suspicion is verified.
Responsibilities within industry	No change	Responsibilities between industry and authorities	No change

### 3.9.1.5 Limitations due to data availability

Authorities may lack information on hazards and exposures such as on similar uses of the substance(s) groups or environmental monitoring data (environmental mixture). This may limit the possibility to build up an argumentation supporting that a community wide mixture risk exists that would trigger the need for substance evaluation or that would justify adding mixture risks as concern to the CoRAP proposal.

### 3.9.1.6 Potential challenges

The option is proposed as a voluntary step (as it the possibility to propose substances for evaluation as such). There is a risk that:

- Member States and ECHA do not support the criterion “mixture risks” for including substances in the CoRAP and hence respective proposals would be turned down. The chances of including substances due to mixture risks (or including a respective additional concern in the reasons for CoRAP inclusion) could be increased, if the criterion was formally added to the REACH text (with a preceding discussion and agreement on the relevance of the topic).
- Due to missing experience, it may be particularly cumbersome to provide argumentation supporting a sufficient concern to include substances in the CoRAP (which substances should get priority in evaluation; competition with other substances on resources for assessment). Here questions regarding the quality and amount of evidence necessary to prove a concern are necessary (as trigger for CoRAP inclusion or as additional concern among other concerns).

### 3.9.1.7 Expected benefits

If an additional concern could trigger a substance evaluation, (more) substances (which do not fulfil the other priority criteria) could potentially be evaluated and introduced into further risk management procedures.



Substance groups for which there is some evidence of community wide mixture risks could be evaluated together (rather than individually) during the following substance evaluation, creating a more complete picture of the actual level of risk. Existing suspicions of mixture risks could be clarified.

The option is a precondition for the possibility to address mixture risks as main or additional concern in substance evaluation (c.f. chapter 3.9.3).

#### **3.9.1.8 Expected costs / efforts**

It is not yet clear, how a notification of the Member States to ECHA should look like regarding the proposal of substances for CoRAP inclusion. Depending on the specific needs to demonstrate a concern, additional resources to demonstrate that a substance should be included into the CoRAP due to mixture-related concerns. Competences and capacities to address the issue would have to be built up in the Member States and ECHA on the long term.

If a criterion “mixture risks” would be included in the REACH text as well as the guidance document and the justification document template, resources would be needed for a respective discussion and consultation with the authority stakeholders. Resources needed are comparatively low for this step.

#### **3.9.1.9 Enforcement aspects**

Not applicable

#### **3.9.1.10 Open questions**

How much and which type of evidence (of which quality) is regarded as “sufficient” to document a concern for a potential risk caused by mixtures that needs to be addressed at Community level? Is more information necessary (or not easily available) to raise a mixture concern than for single substances? How and based on which rationale are substance groups selected that need to be evaluated together?

What should be considered as a group of substances and how can the scope of a substance evaluation be limited?

#### **3.9.1.11 Conclusions on the option by the consultant**

The inclusion of substances in the CoRAP because of mixture risks is regarded as possible without changes in the legal text and could be immediately implemented and initiated by the Member States and ECHA. Including mixture risks as “additional concern” (complementing another main concern to include a substance in the CoRAP), in the argumentation for CoRAP inclusion of single substances is also regarded as possible.

The data limitation needs to be overcome but as they concern individual cases, it is expected that respective resources for data collection (and measurements) could be provided by the authorities. The benefits and potentials of the options outweigh the necessary efforts and costs.

### Consultants' recommendation:

UBA should initiate discussions with ECHA and the Member States to identify their level of support for this option (if voluntary) and the chances of respective proposals for CoRAP being accepted. If sufficient support is available or at least a willingness to test the proposal exists, UBA and/or other interested Member States) should develop a “pilot” proposal for including a substance in CoRAP based on mixture risks. In addition, UBA could test the option to add mixture risk as an additional concern into a proposal for including a substance (group) into the CoRAP. Based on the evaluation of such pilot cases, the authorities could discuss and agree on a further process, such as the amendment of the priority criteria defined in the REACH text, an amendment of GD and template for the justification document or the background document for CoRAP inclusion.

## 3.9.2 Option A2: Evaluating mixture risks in CSRs during substance evaluation

### 3.9.2.1 Brief description

Member States could, in the scope of substances evaluations they carry out, check how combined exposures are considered in registrations dossiers of “similar substances”. The term “similar substances” is interpreted as addressing substances which are registered in groups or where read-across is applied by the registrant.

The REACH substance evaluation on the particular CoRAP substances carried out by national competent authorities will involve a close scrutiny of the registrant’s chemicals safety assessment. There is one interesting part in the risk characterisation part of the ECHA guidance addressing registrants that mentions the consideration of exposures to “several very closely related and similar acting chemical substances”:

“In special cases, where exposure occurs to a substance as well as to several very closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances), the exposure evaluation and risk characterisation should reflect this aspect. If data are available the exposure assessment should also include a scenario concerning this combined exposure. If data do not allow for a quantitative assessment, the issue can be addressed in a qualitative way.” (part E of the ECHA CSA guidance, ECHA 2008f).

It could be very interesting to pay special attention to this part during the evaluation to see if and how companies have applied the part of the ECHA guidance document. This could also give some insights as to what additional elements might be for future guidance development. This task can only be performed by national regulatory authorities or ECHA as the details of the chemical safety assessment are not open to the public via the ECHA database. The guidance refers to special cases only. However, national competent authorities could evaluate and potentially follow up on this point for substances for which very closely related and similar acting substances are known – as part of the substance evaluation process.

This option is regarded as a voluntary action which may complement the “regular and focused” SEV aiming to clarify an initial concern and which could lead to the identification of a new or additional concern, which could trigger a respective second SEV for the same substance / substance group.

The option would correspond to a scrutiny of whether or not and how the respective provision in the ECHA guidance document on chemical safety assessment and information requirements,

part E is implemented. Therefore, this option should be seen as a complement to option for registrants to assess mixture risks for “closely related substances” outlined in chapter 3.6.3.

The option does not allow an information request or any formal action as part of a draft decision on evaluation, except mixture risks are included in the initial concern for SEV.

### 3.9.2.2 Consultant’s interpretation of REACH and proposed implementation option

According to current legislation substance evaluation by the Member States may involve a close scrutiny of the registrants’ dossiers and chemical safety assessments (where available), as the work builds up on the registration information (c.f. REACH, Title VI, chapter 2 and ECHA guidance on dossier and substance evaluation, p. 59 specifying that substance evaluation starts with a full review of the existing information, including registration dossiers).

If the evaluated substances are closely related (and similar acting), registrants should, according to the current guidance on information requirements and chemicals safety assessment, part E, have included considerations on combined exposures and risks in their registration dossiers (c.f. also chapter 3.6.3).

In conclusion, the current REACH text already allows Member States to scrutinize registration dossiers. As registrants should consider combined exposures for closely related and similar acting substances (interpreted as substances registered in groups or where read across is applied), Member States should in analogy also be “allowed” to check if this has been implemented.

Consequently, according to the consultants’ interpretation it is possible to implement the option without changing the REACH text, Annexes or guidance. The implementation of the option would of course be supported, if respective guidance were developed.

### 3.9.2.3 Scope

Closely related substances understood as substances registered as group or where read-across is applied for which a substance evaluation is conducted. The number of substance(s) groups is determined by the number of substances under evaluation and the willingness and resources of the authorities to scrutinize registration dossiers in this regard.

### 3.9.2.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 33: Conformity assessment of the option if the option to scrutinize registration dossiers for “similar substances” during SEV is with REACH- principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Not directly, possible if scrutiny leads to revision of RMMs	Improvement of information base	Yes
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

### 3.9.2.5 Limitations due to data availability

Member State competent authorities have access to information in the registration dossiers. Missing information on hazards and exposure which are related to the initial concern according to the justification for the CoRAP (or further concerns that rise during evaluation) can be requested from the registrants (already during the evaluation process or via an official decision on data requests that is agreed upon in the MSC), if they are necessary for concluding on risks. This information may go beyond standard requirements of REACH.

Information relating to mixture risks in particular on the substance(s)' uses in mixtures and their occurrence in the environment can be requested from the registrants. It is unclear if it is also possible to request information on other substances, which co-occur and contribute to the potential mixture risks, as they are not responsible for them and are also not likely to have respective information, except they do register the other substances, too.

### 3.9.2.6 Potential challenges

Registrants may only register some substances in a group but quote hazard information from other group members. It is unclear which substances (in a group) should be considered regarding potential mixture risks.

It is also unclear which procedure could be found to deal with substances in a group contributing to the overall mixture risk, which are not covered by the dossiers which are scrutinized in the SEV and are submitted by other registrants.

The consequences of a scrutiny with a negative result, i.e. it is found that combined exposures of "similar substances" were not considered by the registrant, are unclear, in particular if no official information request can be made (mixture risks are not the initial or an additional concern and the scrutiny is performed only as an additional task during the SEV).

### 3.9.2.7 Expected benefits

As indirect side effect Member States will provide an additional control impulse to registrants. Member states will collect experience on mixture assessments for "similar substances". The information base for the evaluated substance is broadened. If Member States identify that combined exposures are not assessed by the registrants of "similar substances", they could inform the registrants and thereby trigger an updating of registration dossiers with potential changes in the chemical safety assessment and conditions of safe use. Furthermore, information on mixture risks would have to be communicated triggering the consideration of mixture risks downstream (c.f. chapter 3.6.10).

### 3.9.2.8 Expected costs / efforts

Efforts would arise for Member States to scrutinize registration dossiers and inform the registrants of related shortcomings in the CSR, if relevant. Also industry would have additional work in generating and/or compiling the requested information.

### 3.9.2.9 Enforcement aspects

Checking the compliance of and the testing proposals in registration dossiers is normally the task of ECHA and will usually be performed prior to a substance evaluation (for certain aspects) during a **dossier evaluation**. In the substance evaluation procedure (conducted by one assigned MS), the scrutiny of registration dossiers may be performed as "side effect" of respective data mining and potential generation of additional information for SEV. Therefore, this aspect could be regarded as an authority control of whether or not the specific

requirements regarding the consideration of combined exposures of “similar substances” are implemented. However, no classical “enforcement action” such as imposing sanctions would follow an observed incompliance but just information to the registrants.

### 3.9.2.10 Open questions

There is no clear, scientific and commonly accepted definition for “closely related” and “similar acting” substances in relation to environmental effects, exposures and risks. The pragmatic approach proposed by the consultant to use the term “similar substances” and define that this includes substances registered in groups or where read-across is used in the registration dossiers, substances may not be acceptable for all REACH actors. There is a preliminary agreement/proposal by ECHA that similar substances should be evaluated by the same member state if they are proposed for a SEV.

There is also no clear interpretation of the term “consider combined exposures”; hence it is not obvious what registrants should include in their assessment and consequently what authorities could review in their scrutiny of the available data. This could be solved e.g. by respective guidance and examples. The potential consequences following a SEV are discussed in section 3.9.3.

What type of consequence is appropriate, if registrants fail to consider combined exposures in their CSR for “similar substances”. Could Member States initiate that ECHA writes a QOBL,<sup>89</sup> which is normally only possible as a consequence of a dossier evaluation, or would formal letter from the Member State to the registrant(s) be appropriate? This issue should be discussed in relation to how other cases of incompliance are followed up, if they are not subject to an information request. As the first substance evaluations first started in 2012, there are not many experiences yet.

### 3.9.2.11 Conclusions on the option by the consultant

The option for Member States to scrutinize registration dossiers of “similar substances” during SEV regarding the consideration of combined exposures is possible under current legislation. There are no direct limitations, as work would be based on the registration dossiers and all other available data. The efforts related to the option depend on the level of ambition of the authorities and should be balanced against the indication of potential risks. However, as a small number of substances is concerned and only authorities voluntarily implementing the option would be affected, the efforts can be determined by the actors carrying out the task. There may be direct benefits triggered from this scrutiny, when the registrants update their registration dossiers. Consequently, it is suggested that the option be implemented by the evaluating Member States.

### Consultants’ recommendation

Member States should screen the CoRAP (proposals) if substances are (being) evaluated for which the criterion “similar substances” applies. The evaluating Member State(s) should be made aware of the possibility to scrutinize the implementation of the IR/CSA guidance part E.

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<sup>89</sup> QOBL = quality observation letter

If a respective scrutiny has taken place, the results should be discussed with the Member States and the registrant. Based on this discussion, further options to formalize and or motivate more respective checks and updates of registration dossiers should be explored.

Based on the “pilot cases”, guidance should be developed including a clarification of the term “closely related and similar acting substances” and how to “consider combined exposures” which would be useful for authorities and industry.

### **3.9.3 Option A3: Assessing mixture risks and requesting information during substance evaluation**

#### **3.9.3.1 Brief description**

According to this option, Member States carry out mixture assessments or make related considerations of the environmental exposures during substance evaluation and may, if relevant, request additional information from registrants during the evaluation or officially as a result of the 1 year evaluation process.

The provisions in Title VI, chapter II do not define any scope of a SEV. Hence, the evaluating Member State could perform a mixture assessment on a voluntary basis in any of their SEVs on the basis of the available data from the registration dossiers and all available further data. However, there are no procedures to implement any consequences in the evaluation process, except if mixture risks are (part of) the initial concern or additional concerns that are raised during evaluation. Therefore, voluntary mixture assessments in SEVs where mixture risks are not (part of) the initial concern are not further discussed in this section.

There may be cases where the national authority considers that more information on the mixture assessment and the potential risk is required from the registrant during substance evaluation. According to REACH article 46.1 the national authority can require further information from the registrants during substance evaluation. This provision could also be applied, if appropriate, for proposing to perform an aggregated or cumulative risk assessment in specific cases. Under this procedure, a draft decision has to be prepared, stating respective reasons, and setting a deadline for submission.

This means that theoretically, a national authority can decide to ask the registrant to perform a mixture assessment in a specific case and for a certain scenario. This could e.g. be relevant in the following two cases:

#### **The registration dossier concerns a mixture**

An example from CoRAP for 2013:

- The Netherlands will evaluate a reaction mass of mixed (3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phosphates, ammonium salts

#### **Several registration dossiers are received per registrant for substances with similar hazard and use profile.**

Example from CoRAP for 2014: Denmark will evaluate five compounds:

- 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters
- 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
- 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich
- diundecyl phthalate

- diundecyl phthalate, branched and linear

Depending on the details in the registration dossiers and the quality of the risk characterisation performed, the competent authority will have to decide if additional information is needed from the registrant. In cases where read-across approaches were used for certain endpoints for different substances/groups this may become even more relevant and justified, because it means that a sufficient similarity of the compounds was assumed. Another consequence resulting from substance evaluation will be to consider whether additional risk management measures may be required, either within REACH provisions or potentially using complementary legislation.

This type of assessment can result in a draft decision relating to a potential mixture risk. Further information needed to come to a conclusion on the concern could be requested. This may lead to a conclusion of the necessity of further risk management measures if a risk is identified when available data is sufficient.

### 3.9.3.2 Consultant’s interpretation of REACH and proposed implementation option

The option to request additional information from registrants to conclude on mixture risks in the SEV can only be performed according to Article 46.1 and the ECHA guidance on substance evaluation (chapter 3.4 page 77)<sup>90</sup> if this information is necessary to conclude on the risk related to the initial (or additional) concern (c.f. option for prioritisation of the CoRAP in chapter 3.9.1).

### 3.9.3.3 Scope

This option would cover substances which were proposed for inclusion in the CoRAP because of mixture risks ((part of) initial concern or additional concern identified during the SEV) and are being evaluated by a Member State.

### 3.9.3.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

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<sup>90</sup> “The MS-CA has to draft a request for further information where this information is essential for a conclusion on the initial concern. After the identification of missing information (see Chapter 3.3), the MS-CA shall decide whether this missing information is necessary for the MS-CA to conclude on its concern. If this information is considered essential, the MS-CA shall prepare a draft decision with a request for further information.”

**Table 34:** Conformity assessment of the option to assess mixture risks and request respective information during SEV with REACH-principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Not directly, possible if registrants need to update their CSR including RMMs to ensure safe use	Improvement of information base	Yes, new information may be generated and new conclusions on mixture risks may be possible
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

### 3.9.3.5 Limitations due to data availability

The evaluating Member States have access to the registration dossiers. Missing information to conduct a mixture assessment can be requested directly from the registrant during the evaluation process or, officially via a decision on data requirements and may concern hazard and exposure information, exceeding the data requirements of the REACH Annexes. The information shall be provided by the registrants during a set deadline, which is legally binding.

Data on the (environmental or coincidental) mixture in which the substance under evaluation occurs may be missing and hence would have to be generated by the registrants if data is requested or researched for by the evaluating Member State.

### 3.9.3.6 Potential challenges

As mixture risks are not an “acknowledged concern” under REACH, a respective justification of an information request may not be accepted by the registrants and lead to legal actions. The argumentation of a potential risk may involve information on other substances present in a (environmental or coincidental) mixture which may not be available to the evaluating Member State. Therefore, a focus on similar substances that are evaluated together seems to be appropriate.

The largest challenge of this option is the complexity of mixture assessment as such. In particular Member States will have to identify and/or establish links between the observed mixture risks in the environment and the use of substances in industry and conduct a mixture assessment based on the available data. Furthermore, if the scope of the assessment should cover an environmental mixture and is not limited to registered mixtures, issues relating to other substances in the environment (not in the scope of the assessment) which could potentially influence the overall level of risk need to be solved. A focus on the evaluation of determined “similar” or “relevant” substance group is therefore necessary. The identification of information that would enable an unambiguous risk conclusion will also be challenging.

### 3.9.3.7 Expected benefits

Member States will provide an additional enforcement impulse to registrants and collect experience on the methodology and data needs for mixture risk assessment as well as an improved understanding of indicators for mixture risks. The information base for the evaluated substance(s) is broadened, potentially providing more grounds for the proposal of subsequent risk management measures if needed.



#### **3.9.3.8 Expected costs / efforts**

The evaluation and mixture assessment conducted by authorities on the basis of registration data or other data is very complex. Experiences are needed and guidance would be needed on the long run.

The justification of information requests based on a mixture risk concern is likely to be more difficult and complex than for other information requests. Hence, the evaluating Member State is likely to need more resources to develop a draft decision.

Industry will also have to invest resources in fulfilling the information requests.

#### **3.9.3.9 Enforcement aspects**

There are no enforcement aspects involved; except if the information request is not fulfilled by the registrants / SIEFs.

#### **3.9.3.10 Open questions**

The core questions yet to be solved relate to (methods) for reducing the complexity of mixture assessment and making it manageable for Member State authorities to derive distinct risk conclusions.

#### **3.9.3.11 Conclusions on the option by the consultant**

There are no obvious limitations to the option due to data access from registrants. Additional information from other information sources, e.g. to identify environmental or coincidental mixtures posing a risk will be more difficult to obtain and may require data generation by the authorities.

The options would lead to an improved information base, method development and potentially stricter risk management of the substance as a consequence of a potential risk conclusion. Stricter or new risk management measures may be triggered from the update of registration dossiers. There are comparatively low efforts involved as only very few substances are concerned. No changes in the legal text are necessary, guidance development would be useful.

#### **Consultants' recommendation**

Member States can only start implementing the option, if substances are included in the CoRAP based on mixture risks as (one of the) initial concerns or if similar substances are evaluated together by the same MS and a mixture concern raises during evaluation. Hence, the option is dependent on the further agreements for the substance evaluation process and may first become relevant in the long or midterm.

In addition and in order to support discussions with ECHA and the Member States as well as other stakeholders, a pilot case could be established (voluntary mixture assessment without formal initial concern). The aim of the pilot case would be to find out how far an assessing Member State would get with a mixture assessment, which methods could be applied and which need to be developed, which information would actually be requested from registrants and which other information sources could be explored. The pilot case would illustrate the abstract discussion and thereby facilitate understanding the issue. Based on the experience of the pilot case, further discussions should be started to potentially formalise the inclusion of mixture risk assessment and the possibility to request respective data from the registrants and to develop respective guidance.

### 3.9.4 Option A4: Prioritisation for authorization

#### 3.9.4.1 Brief description

This option would imply that ECHA proposes substances on the candidate list for inclusion in the authorisation procedure based on concerns related to combined exposures with other substances which may be a cause of concern. This would require a respective justification in the prioritisation proposals prepared by ECHA.

While the process of nominating SVHC to the REACH candidate list should remain purely hazard based as laid out in article 57 (criteria for nominating SVHC), it could be considered to include arguments relating to the risks from combined effects in the priority setting for Annex XIV.

ECHA has already applied the group approach in the past, i.e. a group of chemicals (e.g. metal compounds) were prioritised together, mainly with the argument that one SVHC should not be replaced with another. Member States could decide to initiate a discussion in the Member State Committee as to which role the phenomenon of known co-exposures of chemicals with common adverse outcomes could play in the prioritisation for Annex XIV.

#### 3.9.4.2 Consultant's interpretation of REACH and proposed implementation option

According to the REACH, Article 58 (3) “priority shall normally be given” to substances fulfilling the listed criteria (PBT/vPvB, wide dispersive use, high volumes). This is confirmed in the “General Approach for Prioritisation of Substances of Very High Concern (SVHCs) for Inclusion in the List of Substances Subject to Authorisation”.<sup>91</sup> This means that the listed criteria are not exclusive and the other aspects may also lead to a prioritisation recommendation. Only substances already identified as SVHC may be prioritized for inclusion in the annex and an authorisation procedure.

The criterion “concern related to risks from combined exposures” could therefore either just be applied in a recommendation for inclusion in Annex XIV or could be added to the existing list (change of the REACH text) in order to provide a better legal basis for respective proposals.

The criterion “concern related to combined exposures” could enhance the practice of including substance groups in one single entry<sup>92</sup> of Annex XIV.

#### 3.9.4.3 Scope

The option covers substances on the candidate list for authorisation for which an additional mixture risk concern can be established.

#### 3.9.4.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

<sup>91</sup> [http://echa.europa.eu/documents/10162/13640/axiv\\_prioritysetting\\_general\\_approach\\_20100701\\_en.pdf](http://echa.europa.eu/documents/10162/13640/axiv_prioritysetting_general_approach_20100701_en.pdf)

<sup>92</sup> The existing group entries were justified rather by the aim of preventing substitution of candidate substances with closely related, similarly hazardous substances than due to of mixture risks.

**Table 35: Conformity assessment of the option to prioritise substances for authorisation based on concerns related to combined exposures with REACH-principles**

Principle	Assessment	Principle	Assessment
Improvement of protection level	Not directly, possible if substance(s) are included in Annex XIV	Improvement of information base	No
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

#### **3.9.4.5 Limitations due to data availability**

The recommendation for inclusion of candidate substances in Annex XIV is based on information in the registration dossiers and the Annex XV-dossiers for SVHC identification. Either information source may not contain sufficient data to identify relevant combined exposures of the SVHCs under consideration. Additional information may have to be generated based on the identified uses of the substances which are proposed for Annex XIV inclusion.

#### **3.9.4.6 Potential challenges**

As the criterion is not yet established and a respective argumentation is likely to be more complex than for the established prioritisation criteria, ECHA's recommendations may become subject to intense consultation and discussion between all stakeholders.

#### **3.9.4.7 Expected benefits**

Substitution with similar substances is excluded, if they are covered by the same (group) entry.

The authorisation of substances with known combined exposures and related risks is accelerated leading to an earlier increase of the protection level. The phase-out goal for SVHC would be enhanced.

#### **3.9.4.8 Expected costs / efforts**

The development of the recommendation justification for inclusion in Annex XIV and related discussions and consultation processes are likely to be more cumbersome than for substances prioritized according to the legally defined criteria. Even if the criterion "concern due to combined exposures" were included in the REACH text, the development of respective evidence is likely to be more resource consuming than for the other criteria.

#### **3.9.4.9 Enforcement aspects**

There is no enforcement necessary for this option.

#### **3.9.4.10 Open questions**

How should the criterion "concern related to combined exposures" be weighed against the other criteria in the legal text, in particular if the former is only applied but not legally defined?

How much and which type of evidence of concern (at which quality) are needed to justify that substance(s) (groups) are prioritised over substances fulfilling the legally defined prioritisation criteria?

Could substance related criteria, such as detected synergisms or detected additivity be an alternative criterion to address mixture risks in the inclusion of substances in Annex XIV.

Does it make sense to put effort in this option and “increase the potential risk” as it only applies for identified SVHC for which a substitution and/or phasing out is envisaged in any case.

#### **3.9.4.11 Conclusions on the option by the consultant**

The prioritisation of substances due to combined exposures seems possible under current legislation. There may be constraints due to lack of data on combined exposures necessary for the justification of a recommendation for Annex XIV-inclusion. The efforts to implement the option are comparatively low as few substances are concerned. Benefits could be reached from a (quicker) inclusion of substances in the authorisation process. Substitution with similar substances is excluded, if they are covered by the same (group) entry.

#### **Consultant's recommendation**

A discussion in the Member State Committee on the role of co-exposures in the prioritisation for Annex XIV could be initiated to develop a respective common understanding. ECHA could be requested to include mixture risk considerations in their work on recommending substances for authorisation. A pilot case could be established for one substance where mixture risks are expected in one of the next recommendations. Based on the outcome of the pilot case, next steps could be discussed regarding the formalization of the criterion in the REACH text (amendment of prioritisation criteria or respective guidance or information documents, such as that on prioritisation for Annex XIV – inclusion). It is unclear if the option would speed up substitution.

### **3.9.5 Option A5: Considering mixture risks in the granting of authorisations**

#### **3.9.5.1 Brief description**

This option concerns the procedures of ECHA and the committees (RAC and SEAC) to prepare an authorisation decision for substances, of which mixture risks exist and which are subject to authorization. While all known emissions of the same substance are taken into account, it is not mentioned that it is also possible to take into consideration potential combination effects as a result of emission of other substances.

Under authorisation, the current REACH text foresees to grant/deny authorisations for individual substances in their specific use. This can be expected to lead to many single authorisations on uses of substances based on individual assumed safe thresholds and adequate control (REACH article 60.2). However, in reality in the case of substance groups/classes with known mixture toxicity and known co-exposures it is practically impossible to determine a reliable PNEC for an individual compound which is protective of the ecosystem. In this case one could argue that the scenario becomes similar to that of the non-threshold substances where no safe levels can be determined with sufficient certainty. It will be the decision of the Risk Assessment Committee and in the end the EU Commission if in those cases authorization can only be granted based on REACH article 60.3, i.e. only when safer alternatives are not available and if the socio-economic benefits outweigh the risks.

According to this option, an authorization could only be granted via the SEA route for substances under authorization which have been prioritised, amongst others, due to mixture effects. This would be based on the assumption that, similar to PBT/vPvB, no safe exposure

levels can be determined for these substances in the environment. Consequently, these substances would be regarded as “regulatory non-threshold substances”.

Applicants for authorization would need to identify if mixture hazards have been identified and if so, include a SEA in their application. Consequently, in the process of preparing an authorization decision by the Commission, ECHA and the Committees would consider mixture risks as part of the risk assessment in the authorisation application as well as in the SEA.

This is illustrated by the case of the 4 phthalate compounds on Annex XIV. These compounds are toxic to reproduction and it is known that they are widely used in consumer articles and also frequently found in the aquatic environment. It is known that these substances have a similar mode of action and will lead to combined effects, basically replacing each other in their concentration at their respective toxic unit value. It would seem like a crucial oversight to ignore this knowledge at the authorization stage and therefore a discussion at the policy level, e.g. at meetings of the REACH competent authorities (CARACAL), may help to seek progress.

This option should be seen as complementary to the industry option to consider mixture risks in their authorisation applications outlined in chapter 3.6.9.

### **3.9.5.2 Consultant’s interpretation of REACH and proposed implementation option**

Article 60 of REACH does not mention whether or not combined exposures may be included in the decision making on risks from the use of a substance. All provisions focus on the substance itself and related information on hazards and exposures (e.g. Art. 60(2)). In the guidance document on authorisation applications only substance related aspects are discussed. Consequently, the option to consider mixture risks and/or to request consideration of mixture risks in the authorisation application is neither explicitly possible nor explicitly excluded.

The current interpretation of non-threshold substances is based on the mode of action of a substance and/or its property as PBT/vPvB which implies that concentrations add up in the environment and no safe exposure level can be determined as they eventually may lead to critical exposure levels. The argumentation for PBT/vPvB substances could be extended to substances for which additive or synergistic effects have been scientifically detected, such as for endocrine disrupting chemicals or other substance groups where mixture effects were shown.

According to the consultant’s interpretation of the current provisions, it is generally possible to fit mixture concerns into the current framework of authorisation. However, this would require a respective political will and probably also some changes in the REACH text. Therefore, this option should be viewed as a possible option to be implemented in the long-term. Some stakeholders have argued, however, that no legal changes are needed as Annex I already lays out the methodology to derive PNECs. These may not be protective in all cases due to the impossibility to derive safe PNEC values when there is evidence for known co-exposures and evidence common adverse effects.

Necessary changes in the REACH text regard the amendment of the criteria for non-threshold substances in Art. 58(3) (inclusion of detected additive or synergistic effects) and the amendment of Article 62 regarding the content of an authorisation application (specification that a CSR for substances with detected mixture hazards needs to include an assessment of mixture risks

The existing ECHA guidance documents would have to be revised in particular for industry actors to develop compliant authorization applications.

### 3.9.5.3 Scope

The option would cover substances included in Annex XIV, for which additivity and/or synergisms have been detected. For substances currently regarded as having an effect threshold, the option would change its regulatory status to a non-threshold substance.

### 3.9.5.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 36: Conformity assessment of the option to consider mixture risks in granting authorisations with REACH principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes, due to stricter rules for granting authorisations and potentially stricter risk management measures	Improvement of information base	Partly, as information in the authorisation application is extended to include mixture risks; additional SEA in case of current threshold substances
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

### 3.9.5.5 Limitations due to data availability

The Committees work on the basis of the authorisation applications. Additional information, such as evidence of additivity or synergism not presented by the authorization applicants may have to be identified from scientific literature but may in principle available, depending on the substance.

### 3.9.5.6 Potential challenges

The level of evidence necessary to “prove” additive effects would need to be defined and commonly accepted. Furthermore, criteria are needed on the consequences of detected specific additivity / synergism with specific substances and general additivity / synergism, which are based on the general mode of action of substances in the environment. The consequences may directly affect the scope of mixture risk assessments to be performed (consideration of “other” substances) as well as the level of identified risk that needs to be outweighed by the benefits.

The Committee Members and ECHA would also have to agree on how they evaluate and weight the risks from mixtures against the risks from individual substances. Criteria for the scope of a mixture risk assessment by the applicants would be needed as well as general rules on the consequences of mixture risks regarding the risk/benefit analysis in the SEA.

The authorization application is already a complex and cumbersome tasks for industry and in order to change the REACH text, the attention and importance given to the issue of mixture risks needs to increase, as a strong political will is necessary to change the REACH text.

### 3.9.5.7 Expected benefits

Detected mixture hazards or identified mixture risks would change the regulatory status of threshold substances to non-threshold substances. This would for example concern a number of endocrine disrupting substances, for which there is no scientific agreement on whether or not

an effect threshold exists. As a consequence, stricter conditions in the granting of authorisations would be ensured, because a socio-economic analysis would be needed to demonstrate that benefits outweigh the risks.

Information and experience is gained on mixture assessment with a limited number of substances on the side of industry and the authorities.

The phase-out goal of the authorisation procedure and the substitution of SVHC are enhanced.

#### **3.9.5.8 Expected costs / efforts**

The committees, ECHA and the EU – Commission have to consider mixture risks as an additional aspect of risk in the decision making process. As experience is missing, this may require method and criteria development as well as discussion and consultation processes with stakeholders.

Industry would have to invest more resources in drafting authorisation applications, even if no detected additivity/synergism exists, because at least a respective literature review is necessary.

#### **3.9.5.9 Enforcement aspects**

No enforcement aspects are involved in this option.

#### **3.9.5.10 Open questions**

Is it actually possible to include mixture risks as criterion in the authorization process and define SVHC for which additivity/synergism are detected as non-threshold substances? Further (legal) assessment of the issue is necessary to answer this basic question.

How can mixture risks be weighed against single-substance risks in granting authorisations and how these risks considered in the socio-economic analysis.

What should be the consequences for “the other substances in a potential mixture”? How could these be addressed? This would be relevant in particular if for substances under authorisation specific additivity/synergism was identified with a low number of other substances (potentially not identified as SVHC).

#### **3.9.5.11 Conclusions on the option by the consultant**

Based on the current analysis of the REACH text it is not possible to decide if the consideration of mixture risks in the authorisation process is possible. Further legal assessment is necessary to clarify the issue.

In addition a more detailed legal assessment it is recommended to further analyse the costs and benefits of the option; e.g. in how many cases respective provisions would have changed the outcome of an authorisation decision and whether or not the respective are proportional to the gain in level of protection.

#### **Consultants' recommendation**

If the legal assessment shows that the option is in principle possible and the cost/benefit analysis shows a net benefit, the implementation should still be regarded as a long term option, because it requires a change of the legal text which is likely to be very controversially discussed. The authorisation process is already a sensitive issue and the inclusion of stricter requirements will need high efforts in convincing (some of) the Member States.

### 3.9.6 Option A6: Mixture risks in restriction dossiers

#### 3.9.6.1 Brief description

This option suggests that authorities could propose restrictions for groups of substances with the justification that, due to their close relation and similar hazard profile, as well as the likelihood of combined exposures, mixture risks occur. This has been implemented for the first time in the restriction proposal for phthalates in consumer products by Denmark.

In 2011, the Danish competent authorities made a restriction proposal with the aim of limiting exposure to humans from four classified phthalates (DEHP, BBP, DBP and DIBP) in certain consumer articles. The proposed restriction aimed to cover articles intended for use indoors and articles that may come into direct contact with the skin or mucous membranes containing one or more of the four phthalates in a concentration greater than 0.1 % by weight of any plasticised material. In June 2012 the Risk Assessment Committee (RAC) decided to reject the restriction proposal and concluded that the available data does not indicate that there is currently a risk from combined exposure to the four phthalates. Even though this dossier is relating to human health while this project has a focus on the environmental risks, it is valuable to study this case more closely to draw some lessons learnt.

This was the first time since the adoption of REACH that a combined assessment approach was used. It is important to note that RAC did not question the principle of addressing risks through combined exposure if the substances act similarly (all four phthalates, they all show anti-androgenic properties).

The attempt by the Danish CA shows that it is possible in principle to use REACH for restrictions in the case of combined exposures. The disagreements for not following the restriction rather seem to be based on the respective safety factors in the risk assessments. This shows that the discussion around safety factors is always likely to lead to controversies concerning the relevance of the risk – be it for individual substances or a mixture. Another argument RAC and in particular SEAC used is the on-going trend for substitution and future declining trends due to the authorization. This is a somewhat unusual argument in particular given that authorization will not apply to imported articles. The EU Commission will decide the case in 2013. Meanwhile, in August 2012 Denmark announced to go ahead with their proposed restriction at national level and not wait for the EU.

Other groups of substances for which a joint restriction could be the relevant regulatory tool may be organotin compounds in consumer products or perfluoro compounds (PFCs) in consumer products. One of the challenges will be to select the relevant compounds to include in the grouping approach and to compile, document and assess the relevant exposures.

In addition, also for single substances, restriction dossiers could include an assessment of mixture risks and related argumentation, if combined exposures with other substances are typical or frequent. This may rather be an additional restriction argument than the core justification, as substances which are not covered by the restriction dossier would be included in the argumentation.

The proposal implies that the authorities proposing the restriction conduct a mixture assessment (tiered approach) for specific uses and or environmental compartments.

#### 3.9.6.2 Consultant's interpretation of REACH and proposed implementation option

According to REACH Art. 68, restrictions can be proposed, if an unacceptable risk for humans or the environment is identified which requires community wide measures. The nature of the



risk is not further specified in the legal text. Hence, it is not excluded that mixture risks are a reason for a restriction proposal.

This interpretation is supported by the fact that the restriction proposal by the Danish authorities based on combined consumer exposures was accepted in the committees and the principle chain of argumentation was followed (and hence implicitly accepted as valid).

In conclusion, the option can be implemented without any change in the legal text.

### 3.9.6.3 Scope

The option covers substance groups or individual substances for which (among other) mixture risks are identified and which require community wide risk management measures. The number of cases for which the option would be implemented also depends on the interests and resources of the Member States and will be case-by-case.

### 3.9.6.4 Conformity with REACH principles

The following table shows the assessment of conformity of the option with the REACH principles.

Table 37: Conformity assessment of the option to include mixture risks in restriction proposals with REACH-principles

Principle	Assessment	Principle	Assessment
Improvement of protection level	Yes, as consequence of the restriction, uses will be limited	Improvement of information base	Yes, due to detailed demonstration of risk and risk assessment in the dossier
Responsibilities within industry	Maintained	Responsibilities between industry and authorities	Maintained

### 3.9.6.5 Limitations due to data availability

Information on specific uses of substances in technical mixtures, on combined exposures as well as on the risk in the environment may not be available in detail to the authorities proposing the restriction. The Member State proposing the restriction may hence have to generate information on environmental mixtures of the substance (group). Another option could be to propose the substance for the CoRAP and conduct a substance evaluation to obtain respective data. If ECHA makes the restriction proposal, a prior dossier evaluation may also contribute additional data.

### 3.9.6.6 Potential challenges

The main challenge related to the option regards the complexity of mixture risk assessment for the environment. Authorities will have to identify the relation between the use of the substance (group) in different mixtures and their contribution to the environmental concentrations causing mixture risks. Co-occurrence in the environment has to be demonstrated and modelling data is not likely to be sufficient; hence monitoring data may have to be newly generated. Furthermore, information on the uses may be missing, hampering the identification of relationships between the use of (specific) technical mixtures and respective environmental concentrations.

The type of restriction may consequently concern the prohibition<sup>93</sup> of the use of the substance (groups) in the uses with the highest emission as these would contribute the largest share in the environmental concentrations.

#### **3.9.6.7 Expected benefits**

Mixture risks can be directly and specifically addressed, i.e. by limiting the use of the substance (group) to certain mixtures or uses.

#### **3.9.6.8 Expected costs / efforts**

The inclusion of mixture risk assessment in the restriction dossier will involve method development and more extensive data collection than for “regular” restriction dossiers. This is indicated e.g. by the comparatively extensive Danish dossier on the phthalate restriction. Consequently, also more work is triggered in the Committees to assess the proposal.

#### **3.9.6.9 Enforcement aspects**

The enforcement of a restriction based on mixture concerns is not likely to involve any additional aspects than those based on other risks.

#### **3.9.6.10 Open questions**

Open questions regarding this option concern the solutions to the named challenges (c.f. above). The phthalate restriction case showed that the principle idea of including mixture risks in the restriction proposals is accepted and that the method used by the Danish authorities could be exemplary for further dossiers.<sup>94</sup>

#### **3.9.6.11 Conclusions on the option by the consultant**

It can be concluded from the acceptance of the restriction proposal by Denmark that the Committees (and the EU-Commission) would accept the option of including mixture considerations in the restriction proposals. It is not clear how a restriction proposal concerning mixture risks for the environment would look like (Danish proposal concerned human health) and what type of evidence and data would be needed for a proposal to be accepted.

It can be assumed that there are further Member States which support the implementation of the option and would develop respective restriction dossiers on a voluntary basis.

The option can be directly implemented and is particularly useful, as mixture risks can be addressed with measures that directly relate to the (use of) technical mixtures.

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<sup>93</sup> Alternatively a concentration limit of 0.1% may be proposed, which is not based on risk considerations for the environment but has been established as politically agreed limit values for environmentally hazardous substances in mixtures in various contexts. For many substances this concentration limit would correspond to a prohibition.

<sup>94</sup> The proposal was not rejected because the methodology was questioned but because the Committees were of the opinion that the effects of the existing risk management measures are not sufficiently accounted for which would, according to the Committees, lead to an exposure level not causing a risk anymore.

### Consultants' recommendation

A pilot case should be established for a restriction proposal based on environmental mixture risks to test, if the approach is viable and accepted in the committees and by the EU – Commission. Based on this experience, further steps like e.g. preparing guidance could be discussed. This option seems to be most useful to address mixture risk specifically if data on uses/exposures is available from registration dossiers.

### 3.9.7 Summary of the assessment of authority options

Table 38 contains the main results of the evaluation of the options to integrate mixture assessment (elements) in the authorities' work.

The table lists all options introduced and refers to the respective chapters (2 left columns "name" and "chapter"). The column "REACH change needed?" specifies if a change in the legal text is a precondition to implement changes. The column "limitations due to data availability / access" specifies to which type of data is either not available at all or to which authorities have no access but which would be needed to implement the option. The column "benefits" lists the main benefits identified from the option and the column "costs/efforts" specifies the actions requiring the most resources from the authorities. In the column "Challenges", the main issues which are foreseen as difficult in the implementation are summarised. The last column lists the main open questions to be solved to implement the option. The aspect "enforcement" is not included in the table, because no specific enforcement aspects were identified for any of the options.

Table 38: Overview of evaluation results of authority options

Option	Chapter	REACH change needed?	Limited data availability	Benefits	Costs / efforts	Challenges	Open questions
A1: CoRAP priorities	3.9.1	No	Use and exposure of substance (group)	Widening of scope for substances that could be subject to evaluation	Argumentation that mixture risks justify substance evaluation process (MS)	Criterion "mixture risks" not in legislation or current background document, lack of experience, potential difficulties in acceptance	Which level of evidence sufficient to justify CoRAP inclusion?

Option	Chapter	REACH change needed?	Limited data availability	Benefits	Costs / efforts	Challenges	Open questions
A2: CSR check in SEV	3.9.2	No	Hazard, use and exposure data from other sources than registration dossiers	Control impulse for registrants, improved information base on mixture, gathering experience and improved risk management, in case mixture risks require that	Assessment of CSR (MS)	Definition of necessary scope of considering combined exposures, consequences of scrutiny	How is “closely related and similar acting substances” and “considering combined exposures” defined?
A3: MA & info request in SEV	3.9.3	No			Argumentation that information is necessary to conclude on risks from mixtures (MS)	Complexity of mixture assessment for the environment, unambiguous demonstration of risk	How to reduce complexity of the mixture assessment without missing core aspects?
A4: Priority for authorisation	3.9.4	No	Use and exposure of substance (group)	Quicker phase-out of SVHC for which mixture risks exist	Justification that mixture risks justify prioritisation for authorisation (ECHA)	Acceptance for new criterion, justification of priority over other substances	What level of evidence is necessary, how are mixture risks weighed against the other prioritisation criteria?
A5: Granting authorisation	3.9.5	Yes	Information in addition to authorization application		Scrutiny of demonstration that additive / synergistic effects exist / do not exist; assessment of CSR, evaluation of SEA and conclusion on authorisation	Defining level of needed evidence, scoping or mixture risk assessment, weighing of risks and benefits, acceptance for changes in legal text	Is it legally possible and useful (cost / benefit) to implement the option?

Option	Chapter	REACH change needed?	Limited data availability	Benefits	Costs / efforts	Challenges	Open questions
A6: Restriction dossiers	3.9.6	No	Hazard, use and exposure data from other sources than registration dossiers	Specific risk management for substance (groups) causing mixture risks	Conducting mixture assessment for the environment	Complexity of mixture assessment for the environment	What approach can be taken for the environmental mixture assessment?

### 3.10 Conclusions on options to act for authorities

According to the consultants' interpretation of the REACH text, all authority options except option A6 regarding mixture risks in granting authorisations, could be implemented without changes to the legal text and based on the Member States' or ECHA's initiative.

In the implementation of most options the availability of data on uses and combined exposures may limit the possibilities to prioritise substances, request information or make assessments of mixture risks. Authorities have limited possibilities to obtain information on technical mixtures and uses other than from the registration dossiers but could in principle initiate specific monitoring campaigns to support their argumentation.

Some options are preconditions for others (nomination of substances for the CoRAP; prioritisation of SVHC for authorization). All options would achieve benefits regarding the level of knowledge on mixture risks and some are likely to result in concrete improvements of risk management measures. Furthermore, authorities could contribute to method development and promote awareness on the issue.

Due to the voluntary nature of all options as well as the low number of substances involved, the efforts necessary to implement the options are comparatively low in absolute terms but may be rather high in relative terms, as method development and information search would be concentrated on few cases.

### 3.11 Recommendations on options to act for authorities

Regarding the implementation of the options for authorities, steps and actions are recommended in the next sections. It should be kept in mind that currently many stakeholders do not believe that mixture risks are an issue (that should be) addressed under REACH. Hence, an intense discussion with all stakeholders is necessary to create a common understanding on the relevance of the issue and how it could be addressed under REACH. This discussion should be started among the authorities but eventually has to be held with all stakeholders. Industry stakeholders should be included in discussions and experience collections very early.

In order to focus resources and ensure that learning from the implementation of options can be taken into account, it is proposed to take a step-wise approach and implement the options over a longer time period.

### 3.11.1 Actions that should be started now

1. The issue of mixture risks should be (more intensely) discussed in particular between the Member States and ECHA (but also with other stakeholders). This is useful in order to
  - a. develop a common understanding of the relevance of the issue
  - b. identify the willingness of the authorities to invest in the further exploration of the options introduced in this report and, based on this information
  - c. to develop a common strategy to efficiently and effectively integrate mixture assessment into the authorities' work under REACH.
2. Restriction proposals based on environmental mixture risks can be developed on the initiative of an interested Member State without any further condition or coordination need. Therefore, this option is recommended to start with and to develop a “pilot case” for the demonstration of an environmental mixture risk as justification of a restriction. This would provide opportunities to learn how to manage challenges in reducing complexity, evaluating mixture risks and/or data collection. The case would, if entering a public consultation, would also provide valuable feedback from the stakeholders on the overall approach.
3. The scrutiny of registration dossiers of “similar substance” in the context of on-going substance evaluations is possible and can be based on the ECHA IR/CSA-guidance part E. Before respective actions are taken, a discussion should be initiated between Member States, ECHA and the stakeholders to agree on a common understanding of the undefined terms in the guidance (with respect to the environment). If the terms “closely related and similarly acting substances” and “considering combined exposures” are defined, Member States evaluating substances to which the (new) definition applies should include a respective scrutiny into their substance evaluation process. A procedure for implementing consequences

### 3.11.2 Actions to be taken in the medium term (2-5 years)

Depending on the outcome of the overall discussion on including mixture risks in the REACH processes, further options for implementation should be discussed. These are in particular the options to include substance in the CoRAP based on mixture risks and the possibility to prioritize substances for authorization due to mixture concerns. Depending on the level of support for these options, the following steps are recommended:

1. Substances should be identified, for which mixture risks are the main or an additional concern justifying inclusion in the CoRAP. If possible, an agreement on the inclusion of the criterion “mixture risks” as reason for listing substances in the CoRAP should be found and an update of the respective background document by ECHA should be undertaken. When the SEV of these substances takes place, option A3 on the assessment of mixture risks and requesting of missing information should be implemented.
2. ECHA should be motivated to / supported in identifying SVHC on the candidate list, which should be prioritised for authorisation due to mixture risks because of combined exposures with other substances. This action could be complemented by a discussion on a potential inclusion of the criterion “mixture risks” or “combined exposures” as official prioritisation criterion for Annex XIV inclusion.

3. Methods and guidance on mixture assessment for the different options could be developed (c.f. chapter 3.12.5) as well as guidance needs mentioned in the description of the authority options).
4. A discussion should be started on whether or not detected additivity / synergism should be regarded as reason to grant authorization via the SEA route as no safe threshold for several similar acting substances in known cases of co-exposures can be determined. If an agreement can be reached, this should be communicated to all stakeholders in the context of authorization, including a guidance update.

### **3.11.3 Actions to be taken in the long term (5-10 years)**

Depending on the outcome of the discussions mentioned in the previous section and the respective substance listing in the CoRAP / Annex XIV, the options A3 on conducting mixture assessments and requesting information on mixture risks and A5 on considering mixture risks in authorisation could be implemented. The latter would require changes in the REACH text which should be coordinated with other amendments of the REACH text.

## **3.12 Proposals for changes in ECHA guidance documents**

All of the options to act for industry and authorities could be implemented on a voluntary basis. For example the communication of mixture hazards in safety data sheets as well as the aggregation of substances amounts before compliance checking could be implemented with low efforts starting from now on.

The provision of respective alerts and guidance on “when and how” to consider mixture aspects under REACH in the available guidance documents would be a first step to raise awareness and support REACH actors willing to act on a voluntary basis. This concerns industry as well as the authorities. Guidance developed now could also be used later, in case some of the proposed options are actually implemented as obligatory tasks for industry.

The following sections cover the main addressees and topics which could be included in the existing guidance documents. For each addressee and topic, the various guidance documents are listed and the sections indicated where changes / additions should be made. The nature of the change / addition is briefly described.

### **3.12.1 Information for registrants and downstream users making a risk assessment for substances or mixtures (registration CSR, DU CSR for substances, consolidation of information for mixtures, DU CSR on mixtures)**

#### **3.12.1.1 Guidance for registration**

- Chapter 3.1: Information requirements → remark to include information on mixture toxicity or risks in the registration dossier
- Chapter 5: Preparation of the registration dossier → guidance on how to integrate mixture information in the current dossier structure – information would have to be inserted in various places
- Chapter 6.1.1: Provide a safety data sheet to the customer → information to include information on mixture hazards in chapter 2 of the SDS to enable the customers to conduct mixture assessments

### 3.12.1.2 Concise IR/CSR guidance part B (hazard assessment)

- Chapter B 1.2: Steps in hazard assessment → remark that information on mixture hazards should be provided
- Chapter B 2.2: Info gathering and evaluation → information and examples on which information may be relevant regarding mixture hazards
- Chapter B.4: Evaluation of available information → guidance on how to interpret information on mixture hazards
- Chapter B 5.2: Other factors influencing further information needs → what to assess if there is a suspicion of relevance of mixture hazards
- Chapter B 7.2.1: General principles of derivation of PNEC → guidance that if mixture risks should be considered, an additional assessment factor would have to be included (MAF)
- Chapter B. 8.2: Scope of exposure assessment - general principles → inclusion of a remark that mixture risks could occur and hence combined exposures may have to be assessed
- B 8.5.2: types of exposure assessment – environment → inclusion of a section on mixture risk assessment and the possibility to derive HIs for mixtures

### 3.12.1.3 Concise IR/CSR guidance part D (exposure assessment)

- Chapter D 2.2: Overview of core information to be taken into account in ES development → general information that ES could be used in tiered mixture assessment for all substances in technical mixtures
- Chapter D 4.2: Activities and processes within the lifecycle of a substance → indication that the lifecycle thinking is also relevant for substances in a technical mixture, if a mixture assessment is performed
- Chapter D 4.5: Conditions of use for controlling risks → remark that the CoU may have different impacts on different substance in mixtures regarding release and exposure from processes; this influences the co-occurrence of substances after release of technical mixtures
- Chapter D 5.5: Exposure estimation – environment → description that the PEC of a mixture is derived from the sum or PECs of all relevant mixture components
- Chapter D 7: Risk characterization → description of the method of the tiered approach to derive an HI for a mixture including an equation and how to derive it
- Chapter D 8.1: Derivation of final ES → general alert that this should ensure safe use for all substances in a mixture
- Chapter D 9: Use of the final ES in the supply chain → alert that DUs should be informed of potential mixture hazards; however possible rather in the SDS than in the ES.

### 3.12.1.4 Concise IR/CSR guidance part E (risk characterization)

- Chapter E 4.1: General aspects → information that the assessment of risks could also be relevant and may be implemented at a voluntary basis, in particular where additive or synergistic effects are known



- Chapter E 4.3: Calculation of RCR → Explanation of how HIs for mixtures (or hazard index) are calculated
- Chapter E 4.5: Combined exposures → definition of the terms “very closely related and similar acting substances”, potentially using the pragmatic approach proposed in this report (group registrations and/or read-across applied)
- Chapter E 4.7: Finalisation of CSA → guidance on how to describe mixture risks in the CSA

#### **3.12.1.5 Concise IR/CSR guidance part F (chemical safety report)**

- Chapter F 2.1: General requirements → hint that a mixture CSA could also be presented in a CSR on a voluntary basis
- Chapter F 2.2: Making use of the template → guidance on how/where to document mixture CSA in the template for CSR

#### **3.12.1.6 Reference IR/CSR guidance part R 2 (Framework for generation of information on intrinsic properties)**

- Chapter R.2.1: REACH Information requirements - Annexes VI – X → indication that information on mixture hazards should be regarded as “other relevant information” and included in the registration dossier
- Chapter R.2.2.13: Step 1: Gather and share existing information - Information on use and exposure → guidance on where to find information on combined exposures, alert for common uses

#### **3.12.1.7 Reference IR/CSR guidance part R 4 (Evaluation of available information)**

- Chapter R.4.1: Relevance of information → indication that information on mixture hazards should be regarded as relevant, although not contributing to classification or the derivation of PNECs
- Chapter R.4.4 Evaluation and Integration of all available Information including Weight of Evidence → remark that mixture hazards and combined exposures should be considered in the evaluation of available information

#### **3.12.1.8 Reference IR/CSR guidance part R 6 (QSARs and grouping of chemicals)**

- Chapter R 6.2: Guidance on grouping → general alert that substances registered as groups or where data gaps are closed by read-across (‘similar substances’) should be considered for mixture risk assessment if co-occurrence is likely; definition of the term ‘very closely related and similar acting substances’
- Chapter R 6.2.7: Example → possibility to include an example of mixture risk assessment

#### **3.12.1.9 Reference IR/CSR guidance part R 10 (Characterisation of dose (concentration) response for environment)**

- Chapter R 10.2: Derivation of PNECs – introduction → remark that if mixture hazards (additive/synergy) have been demonstrated it may be considered to include an additional safety factor in the PNEC derivation
- Chapter R 10.8: Assessment of secondary poisoning → indication that due to simultaneous internal exposures there could be mixture effects

### **3.12.1.10 Reference IR/CSR guidance part R 13 (risk management measures and operational conditions)**

- Chapter R 13.2.4: Operational conditions and risk management measures related to the environment → general alert that OC and RMM can have different impacts on substances in mixtures

### **3.12.1.11 Reference IR/CSR guidance part R 16 (Exposure assessment for the environment)**

- Chapter R 16.2: Exposure assessment principles → indication that if combined exposures are known, this could be considered in exposure assessments for mixtures
- Chapter R 16.4: Measured data – introduction and general principles → indication that measured data on co-occurrence with other substances in the environment may be considered
- Chapter R 16.6.3 Exposure intake estimation – general principles → alert regarding combined exposures and internal simultaneous exposures for persistent and bioaccumulative substances

## **3.12.2 Guidance of actors preparing safety data sheets**

### **3.12.2.1 Concise IR/CSR guidance part G (Extending the safety data sheet)**

- Chapter G 2.2: Extended safety data sheet to the immediate downstream users → indication that information on combined exposures and potentially conducted mixture risk assessments should be included into the extended safety data sheet
- Chapter G 2.3: Inclusion of the ES into the safety data sheet for subsequent downstream users → guidance on which information on mixture hazards and potentially conducted mixture risk assessments to include in the SDS
- Chapter G 4.1: Guidance on how to use Chapters 7 and 8 of the safety data sheet → guidance on which information to include to enable mixture assessment by DUs, including information on PNECs and primary data from testing
- New chapter: Chapter 2 of the SDS (hazard information) → alert that information on mixture hazards should be included.

### **3.12.2.2 Guidance on compiling safety data sheets**

- Chapter 3.7: Necessary degree of completeness → alert that information on mixture hazards and risks should be included, if available and
- Chapter 3.8: Need to update SDS → alert that new information on mixture hazards and risks could be a reason to update the SDS
- Chapter 3.22: When attachment of ES to SDS is required → highlighting that following a DU CSR for a mixture it is required to attach an ES
- Chapter 3.23 Alternative ways to incorporate ES information into the SDS for mixtures → listing information need for mixture assessment by downstream users
- Chapter 3.27: Testing for the purpose of generating information on SDS for mixtures → general alert on mixture toxicity
- Chapter 4.2: Chapter 2 → alert that information on mixture hazards, combined exposures and mixture risks should be included.

### 3.12.3 Alerts for downstream users

#### 3.12.3.1 Downstream user guidance

- Chapter 4.1: Requirements related to compliance with exposure scenarios → information that substance amounts should be aggregated before compliance checking. Discussion of consequences of outcome of compliance checking with aggregated exposures.
- Chapter 4.2.3: Checking the conditions of use (OC and RMM) → information and guidance on how to aggregate substances amounts before compliance checking with the ES. Discussion of consequences of outcome of compliance checking with aggregated exposures.
- Chapter 5: Use not covered: preparing a downstream user chemical safety report (DU CSR) → information to consider available information on mixture risks and guidance on how mixture risk assessment could be carried out (annex)
- Chapter 6: Communicating new information on hazards and risk management measures upstream → guidance that information on the existence of mixture hazards should be communicated as well as when mixture risks cause adaptation of risk management measures
- Chapter 7: Communication in the supply chain related to mixtures → information to include data on mixture toxicity and results of potentially conducted mixture risk assessments in the SDS / attached ES and to include further (hazard) information to enable downstream users to make a mixture assessment
- New Annex: method for assessment of mixture risks using the tiered approach

#### 3.12.4 Alerts in the context of authorisation

Respective changes to the guidance document should only be implemented, when an implementation of mixture aspects in the authorisation process (identification of SVHC and prioritisation for authorisation as well as respective authorisation applications) are implemented.

#### 3.12.5 Alerts for authorities

##### 3.12.5.1 Guidance for priority setting in evaluation

- Chapter 2.1: Parameterisation & utilisation of information on use and exposure from registration dossiers → general alert that co-occurrence and combined exposures should be considered in priority setting for the CoRAP
- Chapter 2.1.1: Generation of exposure information on the basis of the use descriptor system → general alert that significant occurrence of a substance could be an indication for risks from mixtures
- Chapter 4. Priority setting for compliance checking → remark that group registrations / closely related substances could be prioritized because of potential mixture risks

### 3.12.5.2 Guidance on dossier and substance evaluation

- Chapter 1.3: Evaluation processes under REACH → indication that mixture risks should be a prioritisation criterion for evaluation processes in general.

#### Chapter on dossier evaluation

- Chapter 2.2.2.2: Selection of dossiers – non random → information that registration dossiers containing group registrations or where read-across was used should be prioritised for compliance checking in order to assess, if the provisions of the IR/CSA guidance part E (consideration of combined exposures for ‘similar substances’) is implemented.
- Chapter 2.2.3: Targeting of a compliance check → alert that for substances registered in groups or where read across is applied checking the CSR for consideration of combined exposures should be a target

#### Part on substance evaluation

- Chapter 3.1.2.1: Inclusion of substances in the CoRAP → indication that demonstrated additive or synergistic effects can be a reason to propose a substance for inclusion in the CoRAP.
- Chapter 3.2.1: Targeting – principles → remark that if substance evaluations should (among others) target possible risks from mixtures, this should pertain to the initial concerns for CoRAP inclusion.
- Chapter 3.2.2.1: Grounds for concern relating to human health and the environment → alert that risks from mixtures indicated by known additive and/or synergistic effects as well as co-occurrence in the environment should be a relevant ground for concern
- Chapter 3.3.: Methods for substance evaluation → indication that a tiered approach for assessing mixture risks should be applied
- Chapter 3.3.1.2: Exposure related → remark that combined exposures should be considered for substance groups / similar substances
- Chapter 3.3.1.3: Risk related → remark that mixture risks should be included in the substance evaluation
- Chapter 3.4: Requests for further information → alert that information could be requested to support mixture assessment in the substance evaluation if mixture risks were (among others) the initial concern for CoRAP inclusion

### 3.12.5.3 Guidance on Restrictions

- Chapter 4.1: Information sources → alert that information sources on combined exposures should be searched and included for substance groups proposed for restriction
- Chapter 4.2.3: Grouping → alert to consider mixture assessment for substance groups proposed for restriction
- Chapter 5.1.2: Workflow → alert where to include mixture assessment, if relevant
- Chapter 5.1.3: Key terms → include terms relevant for mixture risk assessment, e.g. mixture toxicity, combined exposure etc.
- Chapter 5.2: Information on risk: → general alert to include mixture risk assessment

- Chapter 5.2.3: Exposure assessment → guidance (how) to include information on combined exposures of substance groups in the exposure assessment
- Chapter 5.2.3.2: Environmental exposure → information sources on measured data and combined exposure in general
- Chapter 5.2.3.4: Measured concentrations → information on available monitoring data
- Chapter 5.2.4 Risk characterization → guidance on how HIs (hazard indices) for mixtures are derived, if substance groups are proposed for restrictions.
- Chapter 5.4.2: Risk to be addressed → inclusion of risks from combined exposures of substances in a group proposed for restriction as risk to be addressed in the restriction proposal

#### **3.12.5.4 Guidance on socio economic assessment - restrictions**

- Chapter 1.4.2: Setting the aims of the SEA → general alert to include mixture risks in the scope of a SEA of substance groups, if regarded relevant

Further information to consider risks from potential co-occurrence of substances in a group that is proposed for restriction, could be included in various sections of the guidance. The introductory sections where this is relevant are listed in the following but no sub-sections are specified:

- Chapter 1.4.3: scoping phase → alert that mixture hazards need to be explicitly included or excluded (based on justification)
- Chapter 1.4.4: Identification and assessment of impacts → alert that impacts through mixture risks are to be described
- Chapter 1.4.5: Interpretation and conclusion drawing → alert to include considerations regarding mixture risks

#### **3.12.5.5 References for section 3.12**

ECHA: Guidance on registration; Version 2, May 2012

ECHA: Guidance on information requirements and chemical safety assessment, Part B: Hazard assessment; Version 2.1; December 2011

ECHA: Guidance on information requirements and chemical safety assessment, Part D: Exposure Scenario Building; Version 1.1, May 2008

ECHA: Guidance on information requirements and chemical safety assessment, Part E: Risk Characterisation; May 2008

ECHA: Guidance on information requirements and chemical safety assessment, Part G: Extending the SDS; Version 1.1, May 2008

ECHA: Guidance on information requirements and chemical safety assessment, Chapter R.2: Framework for generation of information on intrinsic properties; Version 2.1, December 2011

ECHA: Guidance on information requirements and chemical safety assessment; Chapter R.4: Evaluation of available information; Version 1.1, May 2010

ECHA: Guidance on information requirements and chemical safety assessment; Chapter R.6: QSARs and grouping of chemicals; May 2008

ECHA: Guidance on information requirements and chemical safety assessment, Chapter R.10: Characterisation of dose [concentration]-response for environment; May 2008

ECHA: Guidance on information requirements and chemical safety assessment; Chapter R.13: Risk management measures and operational conditions; Version 1.1, May 2008

ECHA: Guidance on information requirements and chemical safety assessment, Chapter R.16: Environmental Exposure Estimation; Version 2, May 2010

ECHA: Guidance on the compilation of safety data sheets; Draft Version 2.0, July 2013

ECHA: Guidance for downstream users; Draft Version 2.0, July 2013

ECHA: Guidance on the preparation of an application for authorization; Version 1, January 2011

ECHA: Guidance on priority setting for evaluation; August 2008

ECHA: Guidance on Dossier and Substance Evaluation; June 2007

ECHA: Guidance for the preparation of an Annex XV dossier for restrictions; June 2007

ECHA: Printer friendly version of the REACH FAQ as published on the ECHA website on 13 February 2012; Version 4.2 - 13/02/2012

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

ECHA: General Approach for Prioritisation of Substances of Very High Concern (SVHCs) for Inclusion in the List of Substances Subject to Authorisation; 28 May 2010

## 4 Next Steps

### 4.1 Introduction

At the beginning of the project 4M, it was intended to develop decision matrices for different actors under REACH – to define and to prioritise situations which require a risk assessment of technical mixtures. As a starting point for this, an intense analysis of the state of the art of mixture assessment was performed. Possibilities to define and identify priority technical mixtures were described. In a following step, the feasibility of the different options to prioritise mixtures has been evaluated. In addition, possibilities to prioritise mixtures have been discussed on the project workshop.

From these steps and discussions in the project it can be concluded that prioritisation of mixtures for further assessment is a key requirement.

- to focus activities of risk assessment of technical mixtures under REACH and
- to support actors under REACH to identify the next steps to perform or to support a risk assessment of technical mixtures under REACH.

During the 4M project, a first discussion started on proposed criteria and approaches how to define and how to find priority technical mixtures (see section 2.5.5 (“Mixture Assessment Triggering Substances”) and chapter 2.5.6 (“Priority mixtures”), and work package 4.3, chapter 2 (“Overview on potential prioritisation criteria indicating the need for mixture assessment”).

It has been a consensus in the discussions of the 4M workshop in Berlin in January 2013, that criteria for prioritisation of mixtures have not been developed yet. In addition, there is

- lack of experience with the concepts for priority setting as described in section 1.4 and section 2.6
- lack of experience with the application of approaches for the assessment of technical mixtures, as described in section 2.5

The approaches developed and discussed in chapter 2 have to be tested to gain more experiences and to clarify the open questions on the assessment of technical mixtures under REACH.

Therefore in the following section it is described how different actors under REACH can try out the proposed approaches. This leads to a better understanding in which situations risk assessment of technical mixtures can be an important issue. It is a first necessary step before appropriate and realistic criteria for priority setting can be defined. In addition, it will lead to an experience-based improvement of the proposed approaches for the environmental risk assessment of technical mixtures.

### 4.2 Assessment of technical mixtures: next steps for different actors

The following sections refer to registrants, formulators, end-users and authorities. The sections describe how these actors could use the proposed criteria and approaches– to set priorities and to gain first experience with the environmental risk assessment of technical mixtures. We refer to the approaches for risk assessment of mixtures, described in chapter 2.5, the different concepts for priority setting, described in chapter 2.6, and the options to act described in chapter 3.

We start with the actors which we identified as the one who has the best conditions to do a tiered mixture risk assessment: the formulator. The second section refers to the registrant; the third to the end-user of technical mixtures. Finally, possibilities of authorities to set priorities are briefly addressed.

#### 4.2.1 Formulators, mixture risk assessment and priority setting

From all actors in the supply chain, formulators have the best knowledge of the composition of the technical mixtures which they produce. (There is only one limitation: in many cases they use by themselves mixtures as “raw materials” for their mixtures. In general, they do not know the composition of these mixtures which they buy from their suppliers. If they receive a safety data sheet for such a mixture, it contains only information about substances in the mixture which are classified as dangerous or assessed as PBT/vPvB substances and which are above the concentration limits set in REACH Art. 14).

In many cases formulators produce several hundreds or several thousands of technical mixtures. As first step for prioritisation we recommend for each formulator to identify the ten or twenty technical mixtures which may have the highest potential for mixture effects in their portfolio. For this identification the following criteria can be applied:

- **1a. Substances with a risk characterisation ratio close to 1.** At present, formulators receive for a limited amount of their substances extended safety data sheets with risk characterisation ratios for the substances. They can use them to calculate the risk characterisation ratios for the substances in the technical mixture. They can identify substances which have a risk characterisation ratio close to 1. Note: As discussed in chapter 2.4.4.8, in most cases RCRs from registration dossiers do not reflect the real exposure situation. Therefore they can only be used as a first screening tool to find substances which might have a significant occurrence in reality too. Consideration of risk characterisation ratios in assessment of technical mixtures could lead to more realistic exposure estimations for single substances within registrations.
- **1b. Substances with relevant occurrence.** At a later point in time authorities may have proposed substances as MATS – based on data on real exposure (for criteria and how to find MATS, see section 2.6.2). Formulators can control whether they use MATS (if a list exists) or whether they use substances which fulfil the criteria defining a MATS (proposals for criteria (such as relevance occurrence) are described in chapter 2.6.2 and have to be further elaborated). At present no MATS have been identified. However, formulators can check whether they use priority substances of the Water Framework Directive – for these substances a relevant occurrence has been shown already.
- **1c. Substances with critical intrinsic properties:** Certain intrinsic properties increase the likelihood that substances contribute to environmental effects more than others. In a first step, substances are prioritised which have the following properties: persistence, bioaccumulation, reproductive toxicity, endocrine disruption. Formulators can check which substances of their portfolio are classified as dangerous for the environment with the potential of longlasting effects, or which are assessed as PBT or vPvB substances or as endocrine disrupting substances. In addition, it should be checked for which of these substances a risk characterisation ratio close to 1 is communicated (see point 1a above).

After the identification of these substances, an analysis of the technical mixtures which contain these substances can follow. It consists of a sequence of steps addressing the following questions:



- 2. In which technical mixtures these substances are used and in which fractions/concentrations?
- 3. Which of these technical mixtures contain more than one of these substances?
- 4. Which of these technical mixtures have the highest Hazard Index = Sum of the Risk Characterisation Ratios of the substances?
- 5. Which of these mixtures have wide dispersive uses leading to diffuse emissions into the environment or have local applications with a high release potential?
- 6. Which of these mixtures are produced in highest amounts?

These steps should allow to identify and weight technical mixtures which have the highest potential for mixture effects not covered by the assessment of the single substances of the mixture. They can be assessed more in detail using the tiered approach described in section 2.5.2

In addition, formulators can evaluate whether their mixtures contain a critical substance or a critical combination of substances that are suspected to enhance mixture effects. This means: mixture effects which go beyond effects due to concentration addition. Examples are surface active substances used which enhance the mobility of substances, or complexing agents, which reduce the bioavailability of other substances in the mixture (see section 2.5.2.3, subsection “Module: typical enhancers in CA Assessments”). For such mixtures an individual mixture risk assessment can be performed. Practical experience with such individual assessments would be helpful to develop guidance how such effects can be taken into account in the risk assessment of technical mixtures.

At present, available knowledge about the composition of technical mixtures and the relevance of mixture effects in technical mixtures is very limited. The approach described above could give valuable information for a better understanding of the complexity, the structure and the characteristics of technical mixtures in different sectors.

#### **4.2.2 Registrants, mixture risk assessment and priority setting**

In general, registrants do not always know in which technical mixtures their substances are used. Therefore registrants have limited knowledge about composition of technical mixtures. Exemptions are cases in which the registrant himself acts as a formulator. Theoretically formulators can inform their suppliers about some properties of their mixtures – in order to ensure that the exposure scenarios for the substances cover the use of the substances in mixtures. At present it is unknown whether this kind of information is given and no examples have been discussed yet. Therefore we assume that this is a rare situation. However, according to REACH the registrant has the obligation, to evaluate the safe use of his substance during the full life cycle.

The feasibility evaluation in chapter 3 shows that registrants could make a mixture assessment for similar substances which occur together along the supply chain (see section 3.6.3). At present, this is linked to closely related substances which are used as a group or for which read-across has been applied and for which co-occurrence exists or which have been registered for the same use.

1. In a first step, registrants can analyse which of their substances
  - are closely related;
  - are registered as a group;

- are known to be used together in technical mixtures. Note: In general, registrants have no or only very limited knowledge on the composition of a mixture.
2. In a second step, the substances identified in step 1 can be evaluated whether
- they have a risk characterisation ratio close to 1 (see above, section 4.2.1, point 1a. Note: It has to be considered that in most cases the RCR does not reflect the real exposure situation, see section 2.4.4.8);
  - they show a relevant exposure (see above, section 4.2.1, point 1b). At present, registrants can check whether they use priority substances of the Water Framework Directive – for these substances a relevant occurrence has been shown already. Later, registrants could check whether they use MATS (see chapter 2.6.2). At present, no MATS have been identified.
  - they have critical intrinsic properties; this is indicated by an assessment as PBT or vPvB substances, as endocrine disrupting substances or by a classification as dangerous for the environment with the potential of longlasting effects (see section 2.6.3.2).

At present it is not known, whether a registrant should consider mixture effects for a majority of his substances or only for a small fraction. The two steps described above would help to clarify this point.

A further prioritisation can be made using the criteria

- Total amount of the substance produced
- Substances in wide disperse uses or with high emission rates

For the substances

- which have the highest priority according to these criteria
- and for which it is known that they are used together

an assessment of mixtures risks should be made using the proposed tiered approach. As a precondition for this, registrants need to have at least generic formulations for important uses of their substances.

Independent from this prioritisation, registrant could collect cases in which they know for their substances that mixture effects beyond concentration addition can be relevant (e.g. synergistic effects). These cases are expected to be use-specific and sector-specific. It is likely that they require a case-specific consideration within the risk assessment of the substances – and the knowledge which substances are involved in these effects. Collection of such cases is a first important step to find out how to include knowledge on mixture effects in the risk assessment of substances.

### 4.2.3 End-users and priority setting for aggregated exposures

Assessment of aggregated exposures to the same substance appears to be a feasible option to act for end-users (see section 3.7.2.1, in addition: see Groß et al. 2010). Experience with exposure scenario development in the leather sector indicated that mixtures with the same substances are used at the same time and are emitted together from the downstream user installation. Therefore aggregated exposures take place in real life and have to be taken into account.

At present no examples have been reported on assessment of aggregated exposures by downstream users. The first steps should set the focus on situations which are likely to have the highest impact on the environment. In order to identify these situations, we propose the following steps:

- Step 1: Identify substances classified as hazardous for the environment or as PBT/vPvB substances which are present in more than one of the mixtures used in the company. This information should be available in the registry of hazardous substances of the company.

It would already be interesting to know for how many substances this is the case in different sectors of industry. This could be clarified in a pilot project with interested sectors.

- Step 2: Identify for which of these substances extended safety data sheets are available with PNEC values and exposure scenarios.
- Step 3: For the substances identified in step 2, add up the total amount of the substances used in the company.
- Step 4: Check compliance with the received exposure scenarios for the total amount of the substance used.

At present only for a limited number of mixtures extended safety data sheets are available. Therefore it is expected that aggregated exposures can be assessed only in a limited number of cases. If the number of cases of aggregated exposures appears to be high, first assessments should be made

- for cases in which the risk characterisation ratio for a single mixture is closed to one or
- for cases in which the amount of a single mixture which can be used daily is relatively low.

Such priority setting and the related assessment of aggregated exposures in different branches by downstream users will help to clarify in which situations meaningful aggregated exposures occur and how to deal with them.

#### 4.2.4 Authorities and priority setting for cumulative and aggregated exposures

Authorities have different possibilities to support the European discussions and decisions on mixture assessment – under REACH and for risk management of mixtures beyond REACH.

- **Identification of MATS:** As described in section 2.6.2, “Mixture assessment triggering substances” (MATS) can be used to identify mixtures which require further assessment. The process is slow and reactive, nevertheless it could be an important starting point to implement mixture assessments. In order to test this approach, authorities could use comprehensive data from monitoring to identify a first set of MATS.
- **Use of MATS for the chemical safety assessment:** For a limited set of potential MATS, their use as triggers for a mixture risk assessment could be tested (as described in chapter 2.6.2)
- **Identification of environmental mixtures of concern:** Technical mixtures of industrial chemicals are only one source which leads to complex environmental mixtures. Authorities could use data from effect monitoring to document environmental mixtures of concern and to demonstrate which technical mixtures give a relevant contribution to environmental mixtures (compared to pharmaceuticals, biocides,

pesticides and other groups of chemicals). Establishing of credible links is essential to allocate responsibilities for mixture risk assessment and/or respective risk management measures.

- **Substance evaluation:** From the different options to act proposed, substance evaluation seems to be the most relevant starting point for authorities to take into account mixture risks in their assessments. For this task the legal situation and the responsibilities are clear.
- **Authorisation:** Besides substance evaluation, authorization should consider combined exposure. During the workshop 4M it has been clarified that authorities take care of aggregated amounts from different applicants and uses. In addition, they can perform an assessment of combined exposures (beyond substances which are structurally closely related). However, actions which could result from the knowledge that aggregated or combined exposure could lead to a risk for the environment are unclear at the moment.
- **Restrictions** are a suitable risk management tool that could address mixture risks at EU level. Also in this case exposure data of high quality are needed.

Substances on the Community Rolling Action Plan, identified for substance evaluation, offer a set of possibilities to support the mixture risk assessment. In more details these options are described in sections 3.9, 3.9.1 and in Annex 6, chapter 9.6.

## 5 Conclusions

Results of the analysis done in the project 4 M start out with the finding that there is evidence for environmental effects caused by mixtures. The arguments to include risk assessment of technical mixtures under REACH could be supported if more examples were described for the causal link between the use of a technical mixture and adverse effects in the related coincidental mixture or in a complex environmental mixture.

REACH requires that manufacturers and importers of substances show the safe use of their substances along their entire life cycle. This includes use in mixtures. Formulators have to identify and communicate conditions of safe use for substances and mixtures which they place on the market. A risk characterisation ratio below 1 is agreed to under REACH as an indication for the safe use of a substance. However, REACH does not define an indication for the safe use of a mixture as a whole.

The analysis of the state of the art in mixture risk assessment methodology shows that concentration addition is a conservative default to consider mixture effects. Several tiered approaches have already been proposed for the assessment of mixtures, which, so far, are not linked to technical mixtures of substances registered under REACH.

The proposed tiered approach developed in the project 4M allows the environmental assessment of technical mixtures in the aquatic compartment with increasing degrees of precision. It uses different variations of hazard indexes as indicators for safe use. In its simplest form (tier 1), the proposed approach requires to sum up the risk characterisation ratios using PEC-values and PNEC-values as used for single substances under REACH.

Taking examples of real mixtures, it has been shown that the tiered approach can be used for the assessment of technical mixtures under REACH. However, it became evident that assessment of technical mixtures requires more precise exposure data on exposure than the assessment of single substances.

In many cases, risk characterisation ratios for substances developed within the chemical safety assessment are only indications that no further refinement of the assessment is required for the registration. They are based on generic exposure scenarios. These risk characterisation ratios do not reflect the real exposure situation. They aim to show a safe use, indicated by a risk characterisation ratio  $< 1$ . It can be assumed that in many cases a more profound assessment would show that the real exposure is lower than the modelled exposure using generic data (and has a risk characterisation ratio much lower than 1).

For the assessment of a technical mixture, in the first step of the tiered approach, risk characterisation ratios for the components are added up to calculate the hazard index for a technical mixture. If these risk characterisations are already close to 1, the hazard index for the whole mixture will be above one. Even if the real exposure to the components is lower than assumed.

This means: a generic exposure assessment of the components often leads to figures which are too conservative to allow a realistic calculation of the hazard index of the technical mixture.

Regarding hazard assessment within the tiered approach, publicly available PNEC values can be used only for calculation at the first tier. For more precise calculation, ecotoxicity data for specific trophic levels (e.g. for algae, daphnids and fish, separately) are required. Obviously, expert knowledge is necessary to carry out assessments on hazards tiers of 2 and higher. More testing of the proposed tiered approach is needed to gain experience with its application on

real technical mixtures. Based on this, recommendations can be given how to proceed for hazard indices above 1.

Current limitations for risk assessment of technical mixtures under REACH are identified and acknowledged. Those are, inter alia, the generic and very crude substance exposure levels (PECs) generated by REACH risk assessment tools, the disparity in the availability of suitable data across the supply chain limiting the possibilities of different actors to assess mixture risks and the missing link between the responsibilities of the single REACH actor (producing or using technical and discharge mixtures and the components (quantitatively and qualitatively) of the actual local coincidental mixture in the receiving water volume which, however, determine the real environmental risk.

Due to the large number of technical mixtures, setting of priorities is a key requirement. Two approaches have been proposed which should be tested in parallel: MATS and priority mixtures.

REACH offers several options for the risk assessment of technical mixtures. In the short term, the obligation to assess aggregated exposures during compliance checking of the ES by downstream users and the obligatory communication on known mixture hazards of substances could be implemented. These options require fairly low efforts and have benefits regarding an improved risk management (aggregated exposures) and knowledge dissemination and awareness raising. All other industry options identified as possibly feasible should not be discussed for short term implementation but be subject to further assessment, testing and discussion with all stakeholders.

Authorities should use the possibilities to assess mixture risks in the different tasks they perform under REACH. More coordination with other legislations is required to develop a common strategy not only on REACH, but including also other regulations.

For more detailed conclusions regarding specific items see the following chapters:

- Availability of exposure data under REACH (see section 2.4.4.8 )
- Availability of exposure and toxicity data (see section 2.4.7 )
- Options to act for industry (see section 3.8)
- Options to act for authorities (see section 3.10 and section 3.11).

## 6 Recommendations for further activities (case studies and research)

The analysis of possible starting points, existing requirements and options to act under REACH as well as the discussions at the expert workshop clearly show that there are a number of items to clarify in order to integrate (elements of) mixture assessment into REACH. For clarification the following five activities are recommended – based on the findings and conclusions described before:

- Assessment of aggregated exposures by end-users
- Communication and use of existing knowledge on mixture effects in the supply chains
- Development of prioritisation criteria for mixtures
- Application and further development of the tiered approach by formulators
- Mixture assessment as an element of the tasks of authorities

### ad 1: Assessment of aggregated exposures by end-users

Simultaneous use of the same substance in different technical mixtures by end-users is common practice. Guidance for the assessment of these aggregated exposures is already available. However, practical experience is missing. In order to support the implementation of this important task, we recommend case studies on aggregated exposure assessments. They can be performed together with end-users of technical mixtures in different sectors (see Groß et al. 2010, study on aggregated exposures). These case studies demonstrate the occurrence of aggregated exposures due to the parallel use of several technical mixtures. They show what the end-user should do in these situations.

### ad 2: Communication and use of existing knowledge on mixture effects in supply chains

For an increasing number of substance combinations mixture effects are documented in mixture toxicology. At present it is not clear how this knowledge could be used in supply chains – to support the safe use of substances in technical mixtures. Together with formulators and registrants case studies could be elaborated, which address technical mixtures for which mixture effects are expected. They should aim to clarify

- how knowledge from mixture science can become more easily accessible for companies (may be presented in a specific portal);
- how this knowledge is communicated by the registrants (e.g. in extended safety data sheets or in another form) and
- how it could be used by the formulators in the assessment of their technical mixtures.

The starting point should be well -documented cases of additive or synergistic effects of industrial chemicals and related technical mixtures which are on the market. In addition it can be analysed whether and how first indications for mixture could be communicated.

### ad 3: Development of prioritisation criteria for mixtures

Which are the technical mixtures of a formulator which should be assessed first? The setting of priorities has been found to be a key condition for the assessment of technical mixtures. Proposals for the setting of priorities have been made. However, experience in this field is missing.

Progress can be expected if examples for technical mixtures of real concern are collected in different sectors. Concern (adverse effects) can relate to coincidental mixtures from specific end-users or from environmental mixtures. These examples can be analysed to develop prioritization criteria for mixtures. The criteria should be discussed with external experts.

#### **ad 4: Application and further development of the tiered approach by formulators**

The proposed tiered approach for the risk assessment of technical mixtures can be subject to several options described in the project. However, it has not been tested in detail yet. Practical experience with the approach would help to develop it further to a ready-to-use assessment tool. Therefore we recommend using this approach in case studies related to typical technical mixtures placed on the market.

The selection of the technical mixtures, the assessment and the evaluation could be done in cooperation with formulators (and their associations) and with the end-users of the technical products. This would address the following questions:

- How to perform the different tiers in practice?
- How to get the required information from the registrants?
- What consequences result from Hazard Indices > 1?
- How to communicate the results into the supply chains?

In this approach, modelled exposure data for the technical mixture could be validated by concentration measurements and effect monitoring in the related coincidental mixtures of specific end-users. This would help to verify and demonstrate the link between the use of a REACH-registered substance in a technical mixture, combined exposures and mixture effects in the receiving water bodies.

The proposals 3 and 4, described above, lead to case studies of tiered risk assessment of technical mixtures. These case studies can be used to assess the added values of these mixture assessments. The proposed risk management measures for a technical mixture can be compared to the measures proposed for the substances of the mixture without considering mixture effects.

#### **ad 5: Mixture assessment as element of the tasks of authorities**

In chapter 3.11, we proposed several actions for authorities to integrate mixture assessment in their contributions to EU risk management work. They range from short term actions (such as scrutiny of registration dossiers of “similar substance” in the context of on-going substance evaluations) to long term actions such as considering mixture risks in authorisation (for details, see 3.11).

Restriction proposals based on environmental mixture risks can be developed on the initiative of an interested Member State without any further condition or coordination need. Therefore, this option is recommended to start with and to develop a “pilot case” for the demonstration of an environmental mixture risk as justification of a restriction. This would provide opportunities to learn how to manage challenges in reducing complexity, evaluating mixture risks and/or data collection. The case would, if entering a public consultation, would also provide valuable feedback from the stakeholders on the overall approach. Based on the experience from such first pilot cases, a strategy for information collection from industry can be developed.

In addition, the proposal of MATS can be tested by authorities. As long as no official MATS are nominated, priority substances from the Water Framework Directive can be used. In



cooperation with formulators the risk characterisation ratio can be assessed. If it exceeds 0.1 the consequences of this finding can be determined.

Regarding the assessment of aggregated exposures by downstream users, it would be helpful to clarify the legal requirement within REACH at European level. In addition, it should be clarified that the requirement to consider all available knowledge within a registration includes scientific evidence for mixture effects.

These activities would

- help in gaining a better understanding of what can be done under REACH to address mixture effects;
- help to support the required horizontal approach on mixture effects in the EU;
- start to reduce the impact of technical mixtures on the environment.
- raise awareness that mixture risk assessment is part of the general producer responsibility.

They give valuable input for

- the development of accepted concepts for the environmental risk assessment of technical mixtures under REACH and
- further development of the related guidance, supported by practical experience.

The proposed activities refer to REACH and technical mixtures.<sup>95</sup> At the same time clarification of what can be done under REACH supports the horizontal discussions on mixtures. It helps to identify interfaces to other regulations such as the WFD and the Industrial Emissions Directive. The proposed activities are necessary to identify and to agree on areas where technical mixtures of industrial chemicals regulated under REACH lead to relevant risks which go beyond the impact of single substances and which require additional action.

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<sup>95</sup> An important element in each of these activities should be workshops with external experts. They allow an in-depth discussion with all stakeholders on which actors should make the mixture risk assessment (registrant / formulator / end-user) and at which local dimension (discharge mixture, coincidental mixture, environmental mixture – local or regional assessment).

## 7 Glossary

**Aggregated exposures:** Exposures to one substance from different sources, pathways and/or routes.

**Coincidental mixture:** A mixture in the environmental compartments which receive the emissions from the sewage treatment plant, e.g. the receiving water volume after the STP. This coincidental mixture can result from one or more discharge mixtures after treatment in the sewage treatment plant and after dilution in the receiving water volumes.

**Combined exposures:** Exposure to two or more different substances, or to one substance from different sources, pathways and routes. This term is used if no differentiation between aggregated and cumulative exposure is made.

**Cumulative exposures:** Exposures to two or more different substances. Exposure can result from different emission sources, emission pathways and exposure routes.

**Discharge mixtures:** Substance combinations which are present directly at the “end of the pipe” of a single discharging production unit of different actors (substance manufacturers, formulators of mixtures, end-user of substances and/or mixtures). For the aquatic compartment, the discharge mixture is the influent to the sewage treatment plant.

**Environmental mixture:** A substance combination in an environmental compartment (this definition includes biota). It results from substances accumulating according to their environmental fate properties and degradation after emissions from different sources and uses to different pathways. In many cases, environmental mixtures show a large complexity.

**Mixture:**<sup>96</sup> Generic term for all different types of combinations of two or more substances. Mixtures can be produced on purpose or can be the unintended result of a magnitude of different processes. (We distinguish between four types of mixtures – see the next section for more details on this.)

**Mixture assessment:** Risk assessment of mixtures. It consists of hazard assessment, exposure assessment and risk characterisation. “Mixture toxicity” refers to the hazard assessment of mixtures only. It is a synonym to “mixture effects”.

**Mixture toxicity:** Hazard assessment of mixtures (a synonym to “mixture effects” and “hazard assessment of mixtures”).

**Mixture effects:** Hazard assessment of mixtures (a synonym to “mixture toxicity” and “hazard assessment of mixtures”).

**Substance:** a single pure element or a single pure chemical compound without impurities and without additives. Substances which are part of a mixture are simply called “substances”. In most cases, it is specified in which type of mixtures they occur, e.g. “substance in a technical mixture”. We do not use terms such as “components” or “raw materials” for substances in a mixture, because these terms have different meanings for different actors.

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<sup>96</sup> The Competent Authorities in Germany proposes the term „substance combination“ as a generic term for all different types of combinations of two or more substances.

**Technical mixture:** A mixture which consist of at least two substances. They are produced on purpose by formulators (under REACH, such technical mixtures are called “mixtures”). They are used by downstream users.

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## 9 Annexes

### 9.1 Annex 1: Classification of Substances into Exposure Categories (from Götz et al. 2010)

The authors propose to group potential micropollutants in seven exposure categories with decreasing priority for water pollution control. Exposure Category (EC) I substances are highly persistent chemicals that are continuously released into surface waters; EC II substances are highly persistent chemicals with a complex input dynamic. Rapidly degradable substances (EC VI) and unclassifiable substances (EC VII) have the lowest priority.

Table 39: Candidate substances, main use / compound classes, subclasses, and assigned exposure categories (source: Götz et al., 2010)

Compound	Main use / compound class	Compound subclass	Exposure category
pentachlorophenol	biocide	micobicide	I
perfluorooctane acid (PFOA)	biocide	surfactant	I
perfluorooctansulfonat (PFOS)	biocide	surfactant	I
azithromycin	pharmaceutical	antibiotic	I
ofloxacin	pharmaceutical	antibiotic	I
clarithromycin	pharmaceutical	antibiotic	I
erythromycin + Erythromycin-H2O	pharmaceutical	antibiotic	I
roxithromycin	pharmaceutical	antibiotic	I
fluconazole	pharmaceutical	Antifungal	I
diatrizoat (=amidotrizoeic acid)	pharmaceutical	contrast media	I
pentachlorobenzene	industrial chemical	flame retardant	I
epoxyconazol	pesticide	fungicide	II
flusilazole	pesticide	fungicide	II
prochloraz	pesticide	fungicide	II
diflufenican	pesticide	herbicide	II
trifluralin	pesticide	herbicide	II
dieldrin	pesticide	insecticide	II
endosulfan	pesticide	insecticide	II
endrine	pesticide	insecticide	II
hexachlorcyclohexan (isomeric mixture)	pesticide	insecticide	II
hexachlorcyclohexan (lindane)	pesticide	insecticide	II
chlorpyrifos	biocide	insecticide	II
enrofloxacin	veterinary pharmaceutical	antibiotic	II
tylosin	veterinary pharmaceutical	antibiotic	II
pentachlorobiphenyl (PCB 101)	industrial chemical	cooling and insulating liquid	II
carbendazim	biocide	fungicide	III
diazinon	biocide	insecticide	III

Compound	Main use / compound class	Compound subclass	Exposure category
octylisothiazolinone (OIT)	biocide	fungicide	III
benzisothiazolin (BIT)	biocide	fungicide / micobicide	III
dichlorooctylisothiazolinone (DCOIT)	biocide	fungicide / micobicide	III
IPBC (=iodocarb)	biocide	herbicide	III
chlormethylisothiazolinone (CMIT)	biocide	micobicide	III
methylisothiazolinone (MIT)	biocide	micobicide	III
triclosan	biocide	micobicide	III
benzyltrimethylammonium-chloride (BAC-C12)	biocide	surfactant	III
benzyltrimethylstearyl ammonium-chloride (BAC-C18)	biocide	surfactant	III
cetalkoniumchloride (BAC-C16)	biocide	surfactant	III
miristalkoniumchloride (BAC-C14)	biocide	surfactant	III
irgarol-descyclopropyl	biocide (dp)		III
diclofenac	pharmaceutical	analgetic	III
ibuprofen	pharmaceutical	analgetic	III
ketoprofen	pharmaceutical	analgetic	III
mefenamic acid	pharmaceutical	analgetic	III
naproxen	pharmaceutical	analgetic	III
paracetamol	pharmaceutical	analgetic	III
phenazone	pharmaceutical	analgetic	III
tramadol	pharmaceutical	analgetic	III
ciprofloxacin	pharmaceutical	antibiotic	III
norfloxacin	pharmaceutical	antibiotic	III
clindamycin	pharmaceutical	antibiotic	III
amoxicilline	pharmaceutical	antibiotic	III
sulfadiazine	pharmaceutical	antibiotic	III
sulfamethoxazole	pharmaceutical	antibiotic	III
sulfapyridin	pharmaceutical	antibiotic	III
trimethoprim	pharmaceutical	antibiotic	III
fluoxetine HCl (= Prozac)	pharmaceutical	antidepressant	III
venlafaxine	pharmaceutical	antidepressant	III
carbamazepine	pharmaceutical	anticonvulsant	III
primidone	pharmaceutical	anticonvulsant	III
atenolol	pharmaceutical	beta blocker	III
metoprolol	pharmaceutical	beta blocker	III
propanolol (=propranolol)	pharmaceutical	beta blocker	III
sotalol	pharmaceutical	beta blocker	III
iohexol	pharmaceutical	contrast media	III
iomeprol	pharmaceutical	contrast media	III
iopamidol	pharmaceutical	contrast media	III

Compound	Main use / compound class	Compound subclass	Exposure category
iopromid	pharmaceutical	contrast media	III
ioxitalaminic acid	pharmaceutical	contrast media	III
bezafibrat	pharmaceutical	lipid lowering agent	III
fenofibrate	pharmaceutical	lipid lowering agent	III
lidocaine	pharmaceutical	local anaesthetic	III
furosemide	pharmaceutical	loop diuretic	III
pantoprazole	pharmaceutical	proton pump inhibitor	III
4-acetamidoantipyrin	pharmaceutical (dp)		III
fenofibric acid	pharmaceutical (dp)	lipid lowering agent	III
clofibric acid	pharmaceutical (dp)	lipid lowering agent	III
N4-acetyl-sulfadiazine	pharmaceutical (dp)	antibiotic	III
N4-acetyl-sulfamethazine	pharmaceutical (dp)	antibiotic	III
N4-acetyl-sulfamethoxazole	pharmaceutical (dp)	antibiotic	III
N4-acetyl-sulfathiazole	pharmaceutical (dp)	antibiotic	III
caffeine	tracer		III
2-hydroxy-4-methoxybenzophenon	consumer product	UV-filter	III
AHMI (phantolide)	consumer product	fragrance	III
estradiol	Estrogen	natural estrogen	III
estrone	Estrogen	natural estrogen	III
ethinylestradiol	Estrogen	synthetic estrogen	III
5-methylbenzotriazol (=tolytriazol)	industrial chemical	anticorrosive agent	III
benzotriazole	industrial chemical	anticorrosive agent	III
azoxystrobin	pesticide	fungicide	IV
cymoxanil	pesticide	fungicide	IV
cyproconazol	pesticide	fungicide	IV
cyprodinil	pesticide	fungicide	IV
fludioxonil	pesticide	fungicide	IV
hexazinone	pesticide	fungicide	IV
ioxynil	pesticide	fungicide	IV
kresoxim-methyl	pesticide	fungicide	IV
metalaxyl	pesticide	fungicide	IV
oxadixyl	pesticide	fungicide	IV
penconazol	pesticide	fungicide	IV
tebuconazole	pesticide	fungicide	IV
2,4,5-T	pesticide	herbicide	IV

Compound	Main use / compound class	Compound subclass	Exposure category
2,4-D	pesticide	herbicide	IV
acetochlor	pesticide	herbicide	IV
alachlor	pesticide	herbicide	IV
atrazine	pesticide	herbicide	IV
bentazone	pesticide	herbicide	IV
bromazil	pesticide	herbicide	IV
bromoxynil	pesticide	herbicide	IV
carbetamide	pesticide	herbicide	IV
chloridazone	pesticide	herbicide	IV
clomazone	pesticide	herbicide	IV
cicamba	pesticide	herbicide	IV
cichlorprop	pesticide	herbicide	IV
cimethenamide	pesticide	herbicide	IV
dinoseb	pesticide	herbicide	IV
ethofumesate	pesticide	herbicide	IV
fluazifop (free acid)	pesticide	herbicide	IV
fluroxypyr (free acid)	pesticide	herbicide	IV
linuron	pesticide	herbicide	IV
mecoprop	pesticide	herbicide	IV
mesotrione	pesticide	herbicide	IV
metamitrone	pesticide	herbicide	IV
metazachlor	pesticide	herbicide	IV
metobromurone	pesticide	herbicide	IV
metolachlor	pesticide	herbicide	IV
metribuzin	pesticide	herbicide	IV
metsulfuron-methyl	pesticide	herbicide	IV
monurone	pesticide	herbicide	IV
napropamide	pesticide	herbicide	IV
nicosulfuron	pesticide	herbicide	IV
orbencarb	pesticide	herbicide	IV
prometon	pesticide	herbicide	IV
propachlor	pesticide	herbicide	IV
propaquizafop	pesticide	herbicide	IV
prosulfocarb	pesticide	herbicide	IV
rimsulfurone	pesticide	herbicide	IV
simazine	pesticide	herbicide	IV
sulcotrione	pesticide	herbicide	IV
tebutam	pesticide	herbicide	IV
terbumeton	pesticide	herbicide	IV
thifensulfuron-methyl	pesticide	herbicide	IV
aldicarb	pesticide	insecticide	IV

Compound	Main use / compound class	Compound subclass	Exposure category
carbofuran	pesticide	insecticide	IV
chlorfenvinphos	pesticide	insecticide	IV
3,5-dibromo-4-hydroxybenzoic acid	pesticide		IV
fenpropimorph	biocide	fungicide	IV
primicarb	biocide	insecticide	IV
irgarol	biocide	herbicide	IV
isoproturon	biocide	herbicide	IV
propiconazol	biocide	fungicide	IV
diuron	biocide	herbicide	IV
chlortoluron	biocide	herbicide	IV
terbutylazine	biocide	herbicide	IV
terbutryn (+ prometryn)	biocide	herbicide	IV
diethyltoluamide (DEET)	biocide	insecticide	IV
dimethoat	biocide	insecticide	IV
2,4-dimethylphenylformamide	pesticide (dp)		IV
2,6-dichlorbenzamide	pesticide (dp)		IV
2-Amino-4-methoxy-6-methyl-1,3,5-triazine	pesticide (dp)		IV
2-aminobenzimidazole	pesticide (dp)		IV
2-aminosulfonyl-benzoicacid-methylester	pesticide (dp)		IV
3-(2,2-dichlorvinyl)-2,2-imethylcyclopropanecarboxylic acid	pesticide (dp)		IV
3-phenoxybenzyl alcohol	pesticide (dp)		IV
4-chlor-2-methylphenol	pesticide (dp)		IV
4-isopropylanilin	pesticide (dp)		IV
alachlor-ESA	pesticide (dp)		IV
acetochlor-OXA	pesticide (dp)		IV
alachlor-OXA	pesticide (dp)		IV
atrazine-desethyl-2-hydroxy (=prometon-hydroxy-desisopropyl)	pesticide (dp)		IV
atrazine-2-hydroxy	pesticide (dp)		IV
bifenox acid	pesticide (dp)		IV
chlorothalonil-4-hydroxy	pesticide (dp)		IV
desethylatrazine	pesticide (dp)		IV
desisopropylatrazine	pesticide (dp)		IV
dimethenamide-ESA	pesticide (dp)		IV
dimethenamide-OXA	pesticide (dp)		IV
diuron-desdimethyl (=1-(3,4-dichlorophenyl)urea)	pesticide (dp)		IV
diuron-desmonomethyl (DCPMU)	pesticide (dp)		IV
DMSA (=N,N-dimethylaminosulfanilid)	pesticide (dp)		IV
ethofumesate-2-keto	pesticide (dp)		IV

Compound	Main use / compound class	Compound subclass	Exposure category
isoproturon-didemethyl	pesticide (dp)		IV
isoproturon-monodemethyl	pesticide (dp)		IV
metamitrone-desamino	pesticide (dp)		IV
metolachlor-ESA	pesticide (dp)		IV
metolachlor-OXA	pesticide (dp)		IV
metribuzin-Desamino (DA)	pesticide (dp)		IV
metribuzin-Diketo (DK)	pesticide (dp)		IV
N-(2,4-dimethylphenyl)-N-methylformamidine	pesticide (dp)		IV
N,N-dimethyl-N'-(4-methylphenyl)-sulfamide	pesticide (dp)		IV
Propazine-2-hydroxy + Terbutylazin-2-hydroxy	pesticide (dp)		IV
sulcotrione-CMBA	pesticide (dp)		IV
sulfadimethoxine	veterinary pharmaceutical	antibiotic	IV
sulfamethazine (=sulfadimidin)	veterinary pharmaceutical	antibiotic	IV
sulfathiazole	veterinary pharmaceutical	antibiotic	IV
morantel	veterinary pharmaceutical	anthelmintic	IV
pyrantel	veterinary pharmaceutical	anthelmintic	IV
deoxynivalenol (DON)	mycotoxine		IV
zearalenon (ZON)	mycotoxine		IV
benzo(b)fluoranthene	industrial chemical	combustion product	IV
fluoranthene	industrial chemical	combustion product	IV
naphthalene	industrial chemical	combustion product	IV
bisphenol A (BPA)	industrial chemical	formulation additive	IV
anthracene	industrial chemical	formulation additive	IV
benzothiazole	industrial chemical	formulation additive	IV
nonylphenol	industrial chemical	formulation additive (manufacturing NPEO)	IV
octylphenol	industrial chemical	formulation additive (manufacturing OPEO)	IV
biphenyl	industrial chemical	cooling and insulating liquid	IV
monochlorbiphenyl	industrial chemical	cooling and insulating liquid	IV
dichlorbiphenyl	industrial chemical	cooling and insulating liquid	IV
trichlorbiphenyl (PCB 28)	industrial chemical	cooling and insulating liquid	IV
hexachlorbenzene (HCB)	pesticide	fungicide	V
hexachlorobutadien	pesticide	fungicide	V
aldrine	pesticide	insecticide	V
dichlordiphenyltrichlorethan (DDT)	pesticide	insecticide	V

Compound	Main use / compound class	Compound subclass	Exposure category
isodrin	pesticide	insecticide	V
permethrin	biocide	insecticide	V
clotrimazole	pharmaceutical	Antifungal	V
octocrylene	consumer product	UV-filter	V
AHTN (tonalide)	consumer product	fragrance	V
ADBI (celestolide)	consumer product	fragrance	V
ATII (traseolide)	consumer product	fragrance	V
HHCB (galaxolide)	consumer product	fragrance	V
benzo(a)pyrene	industrial chemical	combustion product	V
benzo(k)fluoranthene	industrial chemical	combustion product	V
benzo(g,h,i)perylene	industrial chemical	combustion product	V
pentabromodiphenylether (pentaBDE)	industrial chemical	flame retardant	V
diethylhexylphthalate (DEHP)	industrial chemical	plasticizer	V
diisodecylphthalate (DiDP)	industrial chemical	plasticizer	V
diisononylphthalate (DINP)	industrial chemical	plasticizer	V
benzene	industrial chemical	formulation additive	V
carbontetrachloride	industrial chemical	formulation additive	V
1,2-Dichlorethan	industrial chemical	formulation additive	V
tributyltin	industrial chemical	formulation additive	V
dichlormethane (methylenchloride)	industrial chemical	formulation additive, solvent	V
tetrachloroethylene	industrial chemical	formulation additive, solvent	V
trichloroethylene	industrial chemical	formulation additive, solvent	V
1,2,4-trichlorbenzene	industrial chemical	formulation additive, solvent	V
trichloromethane (chloroform)	industrial chemical	formulation additive, solvent	V
tetrachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
hexachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
heptachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
octachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
nonachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
decachlorobiphenyl	industrial chemical	cooling and insulating liquid	V
indeno(1,2,3-cd)pyrene	industrial chemical	combustion product	V
asulam	pesticide	herbicide	VI
desmedipham + phenmedipham	pesticide	herbicide	VI
trinexapac-ethyl	pesticide	growth regulator	VI
malathione	biocide	insecticide	VI
3-phenoxybenzoic acid	pesticide (dp)		VI
dibutylphthalate (DBP)	industrial chemical	plasticizer	VI
glyphosate	pesticide	herbicide	VI
MCPA	pesticide	herbicide	VI
didecyldimethylammoniumchloride (DDAC-C10)	biocide	surfactant	VI



Table 40: General rules for input dynamics according to chemical classes (source: Götz et al., 2010)

General rules for input dynamics according to chemical classes			
Point sources (municipal waste water, industrial inputs)			
Substance class	Subclass		Input dynamic
biocides	fungicides herbicides insecticides micobicides	(in material protection)	complex complex complex complex
biocides	fungicides herbicides insecticides micobicides	(in consumer products)	continuous continuous continuous continuous
Biocide - metabolites			complex
pharmaceuticals	analgetics antibiotics antidepressants anticonvulsants beta blockers contrast agents lipid lowering agents		continuous continuous continuous continuous continuous continuous continuous
Pharmaceutical - metabolites			continuous
estrogens			continuous
personal care products	UV-filters musk fragrances		continuous continuous
Industrial - chemicals	Additives flame retardants solvents surfactants anticorrosive/complexing agents cooling and insulating liquids plasticizers		no general rule can be given
Diffuse sources (agriculture, atmospheric transport, waste deposits und contaminated sites)			
Substance class	Subclass		Input dynamic
pesticides	Fungicides herbicides insecticides growth regulators		complex complex complex complex
pesticide- metabolites			complex
veterinary- pharmaceuticals	anthelmintics antibiotics		complex complex
veterinary- pharmaceutical- metabolites			complex
mycotoxines phytoestrogens			complex complex

General rules for input dynamics according to chemical classes		
Industrial - chemicals	combustion products formulation additives	complex complex

## 9.2 Annex 2: REACH registrations - Availability of Data for environmental Assessment of Substances according to Annexes VII – X

According to REACH Art. 10, registration of substances requires a technical dossier with substance-specific physico-chemical, toxicological and ecotoxicological data.

The type and amount of data to be submitted for a given substance depend on the tonnage manufactured or imported per year by the registrant (REACH Art.12). REACH Annexes VII–X define the standard information requirements for substances for the different tonnage bands. They describe information which has to be given in addition to the general information defined in REACH Annex VI.

Annex VII: standard data requirements for substances produced/ imported in quantities of **1 tonne/year** or more;

Annex VIII: standard data requirements for substances produced/ imported in quantities of **10 tonnes/year** or more;

Annex IX: standard data requirements for substances produced/ imported in quantities of **100 tonnes/year** or more;

Annex X: standard data requirements for substances produced/ imported in quantities of **1000 tonnes/year** or more;

The higher the tonnage produced or imported, the more data are required for registration. This refers also for data which are relevant for the environmental assessment of substances. For substances, which are manufactured or imported in high volumes, more detailed information is available than for low tonnage substances.

The following tables show which kind of data can be expected in REACH registration dossiers according to the requirements of REACH Annex VI–X. They refer to data relevant for the environmental assessment of substances. They have been prepared by Antonia Reihlen, Ökopol, within a research and development project on consolidation of information for mixtures under REACH. This project was conducted on behalf of the German Federal Environmental Agency.<sup>97</sup>

The information requirements for registration of substances and chemical safety assessment (CSA) were compiled and analysed using the REACH text including its annexes and related ECHA guidance documents. Information for the environmental risk assessment is listed in table form, specifying from which tonnage the information is required and for what it can be used.

### 9.2.1 Information on physico-chemical (PC) Properties

Table 41 lists the most relevant types of physico-chemical properties (PC properties) for environmental safety assessment and specifies from which registration tonnage it is required. Waiving options are not considered. The last column indicates the use of information in environmental risk assessment.

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<sup>97</sup> Research project FKZ 3710 63 403, „Consolidation of information for mixtures under REACH“, Antonia Reihlen, Dirk Jepsen, Olaf Wirth, Ökopol, Hamburg, January 2012, on behalve of the German Federal Environmental Agency, Dessau.

Table 41: PC-information for environmental risk assessment

PC info / mobility	Tonnage	Use of information / comments
Molecular weight	any	Indicator for permeation of biological membranes
Boiling point	> 1 t/a	Indicator for physical state, state in the environment and volatility, input value to calculate vapour pressure
Relative density	> 1 t/a	Indicator for distribution within compartments, gases: indicator behaviour in air, insoluble liquids and solids, determining factor for settling.
Vapour pressure	> 1 t/a	Indicator for partitioning, atmospheric concentrations, potential for airborne transport, relevance of photo degradation. Input value to derive partitioning coefficients and select emission factors. Information for test designs.
Surface tension <sup>98</sup>	> 1 t/a	Influence of solubility and availability of hydrophobic materials to organisms, potentially increased penetration of membranes → relevance for mixture toxicity
Water solubility	> 1 t/a	Indicator for bioavailability, partitioning and mobility in soil. Information for test design.
Log K <sub>ow</sub>	> 1 t/a	Indicator for partitioning, sorption, bioavailability, bioaccumulation and ecotoxicity and PBT assessment.
Adsorption / desorption	> 10 t/a > 100 t/a	Indicator for binding capacity to solid surfaces; elimination with sludge, mobility and accumulation in soil and sediments. Calculation of partitioning coefficients and PNECs from PNEC <sub>water</sub> .
Dissociation constant	> 100 t/a	Relevant to determine accumulation in soil, may determine fate in the environment and bioavailability

The PC properties are important indicators for identifying the emission pathways of substances from processes. As the emission pathways are the actual point of exposure control under REACH, the PC properties are important for the assessment and information generation for mixtures.

### 9.2.2 Information on Degradation and Bioaccumulation

In Table 42, types of tests on substance properties determining persistence and bioaccumulation are listed and it is specified for which tonnage ranges they are required. The last column exemplifies how information may be used in environmental risk assessment.

<sup>98</sup> Surfactant molecules typically contain both polar (hydrophilic) and non-polar (lipophilic) moieties. Such a chemical structure is used as an initial indicator (alert) of surface-active properties as well as foaming of aqueous solutions.

Table 42: Compilation of relevant information on fate and behaviour in the environment

Type of information	Tonnage	Use of information
Biodegradation (ready)	> 1 t/	Screening value for P-criterion, indicator for long-term risks incl. secondary poisoning, classification, waiving criterion
Abiotic degradation (e.g. oxidation, hydrolysis)	> 10 t/a	Half-lives in compartments, indicator for long-term risks incl. secondary poisoning
Simulation testing: surface water, soil, sediment	> 100 t/a	Values to check P-criterion, half-lives in compartments, indicator for long-term risks
Identification of degradation products	> 100 t/a	Indicator for long-term effects, relevant for soil toxicity
Aquatic bioaccumulation potential (Log K <sub>ow</sub> )	> 1 t/a	Screening value for B-criterion (not applicable if accumulation not driven by lipid partitioning), indicator for long-term risks including secondary poisoning, indicator for fate in the environment
Aquatic bioaccumulation potential (BCF fish)	> 100 t/a	Value to check B-criterion, long-term effects, accumulation in food chain
Terrestrial bioaccumulation potential (BSAF)	> 1000 t/a	Indicator for accumulation in terrestrial food chain and secondary poisoning, values on plants used for estimating concentrations in food crops
Results of a PBT/vPvB assessment	> 10 t/a	If PBT/vPvB, further requirements are triggered under REACH, such as identification in SDSs or specific rules for CSA

For substances registered between 10 and 100 t/a only a screening of PBT properties is possible: both biodegradation and accumulation testing do not allow to compare results with the PBT/vPvB criteria of Annex XIII.

### 9.2.3 Information on Ecotoxicity

Table 43 lists the information requirements on ecotoxicological substance properties and specifies for which registration tonnage it is required. End-point specific waiving options mentioned in the REACH Annexes are not discussed. The last column gives examples for the use of information in environmental risk assessment.

Table 43: Compilation of relevant information on environmental toxicity

Hazard information	Tonnage	Use of information / comments
Acute toxicity to fish	> 10 t/a	PNEC <sub>water</sub> ; PNEC <sub>water,marine</sub> ; PNEC <sub>sediment</sub> and PNEC <sub>soil</sub> if no suitable other data available For PBT-assessment: chronic test if LC50 < 0,1 mg/l Algae: NOEC derived from the same test as LC50
Acute toxicity to crustaceans	> 1 t/a	
Acute & chronic toxicity to algae & other aquatic plants	> 1 t/a	
Inhibition of activity in sewage treatment plants	> 10 t/a	PNEC <sub>STP</sub>

Hazard information	Tonnage	Use of information / comments
Chronic toxicity to fish	> 100 t/a	PNEC <sub>water</sub> PNEC <sub>water,marine</sub> ; PNEC <sub>sediment</sub> and PNEC <sub>soil</sub> if no suitable other data available Not for PBT/vPvB, if data on algae and crustaceans available
Chronic toxicity to fish: a) early life stage b) embryo and sac fry c) juvenile growth	> 100 t/a	PNEC <sub>water</sub> In-depth assessment of potential adverse effects
Chronic toxicity crustaceans	> 100 t/a	PNEC <sub>water</sub> , PBT/vPvB assessment
Chronic toxicity sediment organisms	> 1000 t/a	PNEC <sub>sediment</sub>
Toxicity on soil micro- and macro-organisms	> 100 t/a	PNEC <sub>soil</sub>
Toxicity on invertebrates	> 100 t/a > 1000 t/a	PNEC <sub>soil</sub>
Toxicity on plants	> 100 t/a > 1000 t/a	PNEC <sub>soil</sub>
Long-term or reproductive toxicity to birds	> 1000 t/a	Secondary poisoning from aquatic and terrestrial food chain
Toxicity on bees	--	--
Other known effects (Ozone depletion and formation, endocrine disruption etc.)		Classification, assessment of non – toxic risks, assessment of “equivalent concern”

In the context of safety assessment under REACH, the PNECs for most compartments are derived from the PNEC<sub>water</sub>. Hence, in the lower tonnage bands, where specific test results on other organisms are missing, the toxicity for different protection targets is proportional to the aquatic toxicity.

For the following effects, no PNECs are available and no “traditional” risk assessment is performed.

Table 44: List of “other” environmental effects, explanation and information needed to derive them

Type of endpoint	Protection target	Exposure compartment	Minimum data for direct derivation	Comments
Global warming	Atmosphere	“Earth”	Gases contributing to GW known	Amounts from industrial chemicals may be relevant for a few gases, such as SF <sub>6</sub>
Ozone depletion	Atmosphere, all organisms	Atmosphere	Halogenated organic compounds, Montreal list	Covered by classification and RMMs as part of normal SDS development
Ozone formation	All organisms	Air	Vapour pressure	VOC definition sufficient
Long range transport	All organisms	Air to water and soil	Persistence, half-life in air, vapour pressure	Half-life in air frequently not available

Type of endpoint	Protection target	Exposure compartment	Minimum data for direct derivation	Comments
Acidification	Water, soil	Air, water, soil	PH-values; behaviour in the environment	Amounts from industrial chemicals mostly not relevant.

Information on the ecotoxicity of substances to organisms is essential for deriving PNEC values for the risk assessment. As a minimum acute tests from aquatic species from three different trophic levels are required to derive an aquatic PNEC.

PNECs for marine waters, sediments and soils can be derived from the aquatic PNEC if no testing information is available by using an assessment factor method. For the latter method, information is likely to be available only for substances registered above 100 t/a (testing proposals), if at all.

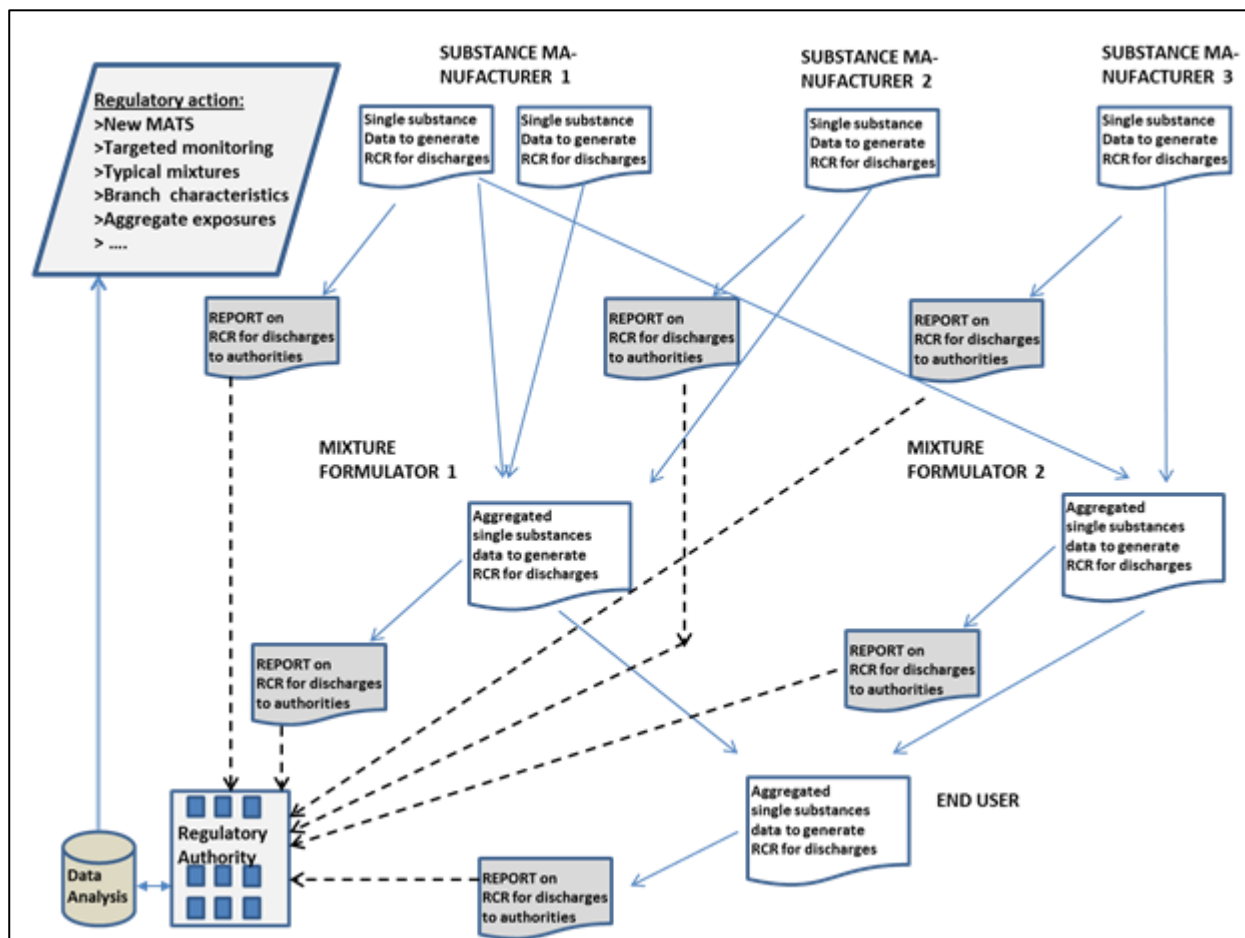
### 9.3 Annex 3: Elements of a reporting Tool

In section 2.5.2, a tiered approach for mixture risk assessment has been described. The problem has been shown that of the key data for this assessment are only available to the manufacturer/importer on the one side (e.g., detailed hazard data), while other data are only available to the formulator (e.g., mixture composition) or the end-user (factual discharges, local STP characteristics and river flow rates) on the other side. Moreover, the end-user may have the appropriate data to perform a qualified high tier mixture risk assessment, but he usually will not have the resources to work with complex exposure assessment tools and to perform sophisticated calculations. The idea of a reporting tool considers to combine the capabilities of the actors under REACH including the administrative regulatory bodies and to split the burden of assessment tasks between them. However, the basic idea needs further discussions to find out about its feasibility.

This tool is characterized as follows:

- Reporting here means documentation of “tier 1” - RCRs for all classified substances of a discharge to regulatory authorities by the discharging commercial or industrial unit.
- This reporting could only be obligatory, if the tonnage of discharge by the single discharger exceeds a certain cut-off (the size of which has yet to be specified), but no undue obligations should be assigned to SME with limited overall impact to the environment.
- The reporting has to be assisted by an electronically processed “fast & easy response spread sheet” which accompanies the substance life cycle flow from the manufacturer or importer all along to the formulator and to the end-user. Each actor fills in the information where he is most knowledgeable. For all data defaults are provided, forwarded and maintained, if no consecutive downstream user is able to include more appropriate data (see below for more detailed specification of this reporting cascade).
- Data for reporting and included in the spread sheet are taken from registration documents and SDS and may be transferred assisted by electronic tools. The downstream user as a formulator will combine the input information from various substances contained in the technical mixture and a) use it to estimate his own discharges and report them to the authorities and b) forward the aggregated spread sheet to the end-user after adding supplemental information, collected best at his position within a substances life cycle.

Figure 20: Schematic presentation of reporting for mixture effect assessment during substances life cycle with resulting regulatory action (source: own illustration)



- The end-user should usually only be asked to contribute specific local data on realistic input amounts, sewage plant characteristics and identity, and on the effluent water flow of mixtures, where readily available and forward this information annually to the regulatory authorities. Most of those parameters are identical for all of the technical mixtures used and discharged by the end-user.
- The reported RCRs may be aggregated to hazard indices by simple follow up calculations, but this is not requested to be done by the discharger.
- The reported RCRs may exceed 1 or even result in much higher values. This exceedance has no direct regulatory consequences, as it is just low tier information. In addition, to ask for high tier documentation in cases of potential risks within a routine reporting procedure is beyond the capabilities of the discharger and would not be proportionate to ask for.

Regulatory authorities may use this information to aggregate the data and find out if there are repeating patterns of combined exposures / common occurrence of substances allowing for many targeted investigations.

Below, we characterize such a possible reporting tool by an example in combination with an example template for reporting. One has to acknowledge that this reporting tool could be elaborated in much more detail if regarded as a useful instrument to collect data close to reality on a local level for single substances, technical mixtures and discharge mixtures.



Such a reporting tool may be based on a simple Microsoft Excel® spread sheet, since many manufacturers, formulators and end-users will have access to this software. In addition, this software allows import from and export to many different formats, making integration with other software potentially easy. The reporting tool described here uses a single file, which can be passed down the reporting cascade. It contains different worksheets for the manufacturer, the formulator and the end-user, which are shown in the following example of two substances being used in the formulation of an industrial coating. Only one manufacturer is shown in this example, but the formulator will in fact receive two files for the two different substances.

The manufacturer ABC starts by filling in the data shown in the following printscreen for substance “1,2-dichlorotest”. In this example, two different exposure scenarios (assumed to correspond to the identified uses) are shown: the industrial formulation of coatings and the industrial use in coatings, both assessed by the manufacturer with ESVOC/ESIG spERCs. The manufacturer also provides the underlying assumptions, which most often will be the defaults used in environmental exposure estimation. Besides the amount assumed to be used locally in the assessment, only STP characteristics and the receiving surface water flow rate are included, since these measures are the ones that are most accessible to adaptations by the downstream user. Note that no physico-chemical data are handed down the reporting cascade, since these are intrinsic properties not amenable to adaptations by downstream user. In addition, this example of the reporting cascade does not include any information on risk management measures and operational conditions (apart from the amount used locally; see discussion below).

**Table 45:** Example of a reporting template with data as part of a possible improved reporting tool under REACH; PART 1 (manufacturer)

Manufacturer name	Company ABC	
<b>Basics</b>		
Substance name	1, 2- dichlorotest	
EC no.	222-333-4	
CAS no.	1234-56-7	
PNEC freshwater [µg/L]	1,000	
<b>Exposure scenario</b>		
ES no.	2	3
ES short title	Industrial formulation of coatings	Industrial use in coatings
<b>Underlying assumption</b>		
Amount used locally [kg/d]	100,000	50,000
Basis (e.g. ERC, m-spERC, estimate)	ESVOC 4 (ESVOC SpERC 2.2.v1)	ESVOC 5 (ESVOC SpERC 4.3a.v1)
STP discharge rate [m3/d]	2,000	2,000
Receiving surface water flow rate [m3/d]	18,000	18,000
Resulting dilution factor	10	10
Basis (e.g. default, site-specific)	default	default
<b>Exposure estimation and Risk characterisation results</b>		
PEC freshwater [µg/L]	34.9	61.0
RCR	0.035	0.061

Formulator 123 receives this file and accesses the second worksheet in the file. The product “paint 456” is formulated of two different substances, with exposure scenario 2 being the relevant one for the formulator. The formulator receives data for the second substance (“nitrosurrogate”) in a different file from the manufacturer of this substance (not shown here) and integrates the data into the same worksheet. Note in the following printscreen that the title for the relevant ES is “industrial formulation”, chosen here to illustrate that different manufacturers will use different ES titles. Both manufacturers assessed environmental exposure with the same spERC, using the default values in the assessment tool.

**Table 46:** Example of a reporting template with data as part of a possible improved reporting tool under REACH; PART 2 (formulator)

Formulator name	Formulator 123	
Formulated product	Paint 456	
<b>Basics</b>		
Substance name	1,2-dichlorotest	nitrosurrogate
EC no.	222-333-4	333-444-5
CAS no.	1234-56-7	56-78-9
PNEC freshwater [µg/L]	1,000	3,000
Received from manufacturer	Company ABC	Company DEF
<b>Exposure scenario</b>		
ES no.	2	2
ES short title	Industrial formulation of coatings	Industrial formulation
<b>Underlying assumption</b>		
Amount used locally [kg/d]	100,000	100,000
Basis (e.g. ERC, spERC, site-specifics)	ESVOC 4 (ESVOC SpERC 2.2.v1)	ESVOC 4 (ESVOC SpERC 2.2.v1)
STP discharge rate [m3/d]	2,000	2,000
Receiving surface water flow rate [m3/d]	18,000	18,000
Resulting dilution factor	10	10
Basis (e.g. default, site-specific)	default	default
<b>Exposure estimation and Risk characterisation results</b>		
PEC freshwater [µg/L]	34.9	5.52
RCR	0.035	0.0018
<b>Adaptations formulation</b>		
Specific amount used locally [kg/d]	100,000	100,000
Site-specific STP discharge rate [m3/d]	2,000	2,000
Site-specific receiving surface water flow rate [m3/d]	18,000	18,000
Site-specific resulting dilution factor	10	10
<b>Refined exposure estimation and risk characterisation</b>		
PEC freshwater [µg/L]	34.900	5.520
RCR	0.03490	0.00184

The formulator – as the first downstream user with site-specific information – will be able to adapt the exposure estimation and risk characterisation by a) changing the amounts used locally, b) changing the STP discharge rate and c) changing the receiving surface water flow rate. The following printscreen shows the results by adaptations entered by the formulator using site-specific data for the STP discharge rate and the surface water flow rate. Note that the respective fields have a different format when site-specific data are entered.

**Table 47:** Example of a reporting template with data as part of a possible improved reporting tool under REACH; PART 3 (end-user)

Formulator name	Formulator 123	
Formulated product	Paint 456	
<b>Basics</b>		
Substance name	1,2-dichlorotest	nitrosurrogate
EC no.	222-333-4	333-444-5
CAS no.	1234-56-7	56-78-9
PNEC freshwater [µg/L]	1,000	3,000
Received from manufacturer	Company ABC	Company DEF
<b>Exposure scenario</b>		
ES no.	2	2
ES short title	Industrial formulation of coatings	Industrial formulation
<b>Underlying assumption</b>		
Amount used locally [kg/d]	100,000	100,000
Basis (e.g. ERC, spERC, site-specifics)	ESVOC 4 (ESVOC SpERC 2.2.v1)	ESVOC 4 (ESVOC SpERC 2.2.v1)
STP discharge rate [m3/d]	2,000	2,000
Receiving surface water flow rate [m3/d]	18,000	18,000
Resulting dilution factor	10	10
Basis (e.g. default, site-specific)	default	default
<b>Exposure estimation and Risk characterisation results</b>		
PEC freshwater [µg/L]	34.9	5.52
RCR	0.035	0.0018
<b>Adaptations formulation</b>		
Specific amount used locally [kg/d]	100,000	100,000
Site-specific STP discharge rate [m3/d]	3,000	3,000
Site-specific receiving surface water flow rate [m3/d]	64,000	64,000
Site-specific resulting dilution factor	22	22
<b>Refined exposure estimation and risk characterisation</b>		
PEC freshwater [µg/L]	15.6	2.47
RCR	0.016	0.00082

Besides the calculation for formulation itself, the formulator will also need to integrate the information from the manufacturer for the end use (here: industrial use in coatings) in one file, since the manufacturer cannot provide these directly to the end-user. In this sense, the formulator is certainly the position in the supply chain with the most reporting duties under this scheme.

For the end-user, the procedure for filling in the file is basically the same as for the formulator. The respective end-user table thus looks the same.

The reporting tool presented above may be seen as a first proposal, which could be modified in several ways. For example, it only contains relatively simple adaptations of parameters considered easily accessible for the formulator and end-user. Other potential adaptations could e.g. include risk management measures with refined (site-specific) efficiencies. However, it will be quite difficult for formulators/end-user to “disassociate” their RMMs from the ones already contained in the release fractions in spERCs. If a spERC was already used by the manufacturer, the release fraction included in the spERC may already include some common RMMs, which, however, are currently not documented in a transparent manner. It will therefore be difficult for the formulator/end-user to decide whether RMMs in place are already considered in the spERC-associated release fraction or not. One possible option, of course, would be to assume complete release (no ERC/spERC release fraction) and then apply the site-specific RMMs with their efficiency. But this is certainly a more advanced step.

The simplified calculations in the reporting tool are also liable to some error, since it disregards the regional (“background”) exposure. If high tonnage are used in manufacture or other uses

than the one considered and if these are associated with comparatively high release rates, a reduction in the amount used locally by a formulator/end-user may underestimate PEC<sub>local</sub>.

## 9.4 Annex 4: Finding of Priority Mixtures with SPIN Database

One way to identify “priority mixtures” may consist of specific evaluations of the SPIN database (“Substances in preparations in Nordic countries”),<sup>99</sup> which is based on data from the Nordic product registers (see section 2.6.6.3 of this report). The potential use of these data for REACH-related purposes was already discussed several years ago (Ahrens and Reihlen, 2007).

The SPIN database was recently extended by an “exposure toolbox”, which generates information on the exposure potential from the information contained in SPIN. This development was explicitly initiated by the increasing demand for exposure information due to REACH.<sup>100</sup>

The toolbox provides semi-quantitative information (indices) on the potential exposure for several impact areas, e.g. surface water, workers and consumers, using two scores:

- A “use index” with four scores that describes the exposure potential for different impact areas and ranges from “-“(probably no direct exposure) to “XXX” (very probable exposure).
- A “range of use” referring to the range of different applications, again with four scores.


The type of information (together with a legend) is shown in the following SPIN screenshot using the example of glutaraldehyde (Figure 22).

---

<sup>99</sup> <http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx>

<sup>100</sup> For more information, see <http://188.183.47.5/fmi/xsl/spin/SPIN/guide/menuguide.xml?-db=spinguide&-lay=overview&-view>

Figure 21: Screenshot for data presentation in SPIN<sup>101</sup>; example of glutaraldehyde



SPIN

SUBSTANCES IN PREPARATIONS

IN NORDIC COUNTRIES

Help

Search mode

List

Guide

Reports

Exit

Cas no: 111-30-8

Name: Pentanedial

EC no: 203-856-5

Nr. 1 of 1

Names/Exposure

Total use

Industr. NACE

Industr. Nation

Use Cat. UC62

Use Cat. Nation

References

Technical

Names/Exposure

Namecode

Name

CAS

Pentanedial

FIN

Glutaraldehydi

PRD

PENTANDIAL

PRN

GLUTARALDEHYD

SPIN Exposure Toolbox

Exposure information based on data from the Nordic product registers

Help

Country	Latest year	Use Index						Range of Use
		Surface water	Air	Soil	Waste water	Consumer	Occupational	
DK	2010	xxx	xx	xxx	xxx	xxx	xxx	*****
NO	2010	xx	xxx	xx	xxx	xxx	xxx	*****
SE	2010	xx	xx	xx	xxx	xxx	xxx	*****

Parameter	Symbol	Value	Explanation
	Blank		The substance is not registered in the country, or no data calculated
Use Index	X	3	One or several uses indicate a potential exposure
	XX	4	One or several uses indicate a probable exposure
	XXX	5	One or several uses indicate a very probable exposure
	-	0-2	The registered use do not indicate direct exposure*
Range of Use	*	1-3	Very narrow range of applications
	**	4-10	Narrow range of applications
	***	11-32	Intermediate range of applications
	****	33-100	Wide range of applications
	*****	>100	Very wide range of applications

The data indicate a wide to very wide range of applications and a (very) probable exposure of all compartments. The figure also shows that some differences between the Nordic countries may exist.

The developers of the exposure toolbox indicate that the tool provides rough estimates and may therefore primarily serve screening purposes. The scores for the use index are based on industrial categories and use categories manually assigned a low, medium or high potential exposure for the respective compartment. The industrial category “water transport”, for example, is assigned a high exposure potential for surface water. The respective data are made available in a separate Microsoft Excel® file (the so-called “use index table”).<sup>102</sup>

Such data allow the screening for individual substances with a (very) wide range of applications and a (very) probable exposure of specific compartments, such as surface water or soil. While a direct assessment of mixtures as “priority mixtures” is impossible (SPIN is essentially substance-based), there are several options to carry out such assessments.

Obviously, it would be possible to screen all substances contained in SPIN by hand in order to identify all those chemicals with high scores for both indices. It would then be possible to identify all substances with identical use categories, pointing to potential mixtures. This, however, would be prohibitively time-consuming.

Another approach is to use the separate “use index table” provided on the SPIN website, which allows identifying all uses assigned a high exposure potential. The respective uses are described

<sup>101</sup> Online and offline version available at <http://195.215.202.233/DotNetNuke/>

<sup>102</sup> [http://188.183.47.5/fmi/xsl/spin//SPIN/guide/webgeneral%20info/UI\\_ExpTal.xls](http://188.183.47.5/fmi/xsl/spin//SPIN/guide/webgeneral%20info/UI_ExpTal.xls)

by the “use code nation” (UCN) and not by international categories, such as the former EU use category (UC). The following printscreen shows an extract of the “use index table” (Figure 23). The highlighted use with the UCN M05144 is an example for an exposure potential score of 2 for both surface water and soil (note that the highest score for these compartments is only assigned very rarely, mostly for biocides and pesticides).

Figure 22: Screenshot from “use index table” in SPIN<sup>101</sup>

1 = Low exposure potential ; 2 = Medium exposure potential ; 3 = High exposure potential																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
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The stand-alone version of the SPIN database offers the possibility to extract detailed data for the entire dataset. With the function “export use by category detailed”, more than 320000 datasets are extracted and can be processed further. The following printscreen shows the datasets filtered for the UCN M05144 for the year 2009 (Figure 24).

Figure 23: Screenshot for specific use category information in SPIN<sup>101</sup>

cas	count	ye	code	codesour	numb	amount
7732185	SE	2009	M05144	ucn	6	7
64175	NO	2009	M05144	ucn	5	0
77996	NO	2009	M05144	ucn	5	0
108010	NO	2009	M05144	ucn	5	0
111762	NO	2009	M05144	ucn	5	1
121915	NO	2009	M05144	ucn	5	0
126307	NO	2009	M05144	ucn	5	0
126863	NO	2009	M05144	ucn	5	0
147148	NO	2009	M05144	ucn	4	0
1330207	NO	2009	M05144	ucn	4	0
1333864	NO	2009	M05144	ucn	4	0
2778429	NO	2009	M05144	ucn	4	0
4767037	NO	2009	M05144	ucn	5	0
61788894	NO	2009	M05144	ucn	5	0
64742898	NO	2009	M05144	ucn	4	0

This exercise thus results in a preliminary list of substances used in water-borne base colours for boats and ships with a potentially high exposure in surface waters and soils. It may well be assumed that some of these substances can be found in one and the same preparation.

In order to further refine this list, information submitted to and evaluated by ECHA can be used. For illustration purposes, we checked the total tonnage band on the ECHA website. In addition, we evaluated whether wide-dispersive outdoor uses in coatings or similar products were among the identified uses in the dossier of each substance (where available). This step focussed on professional and consumer uses and analysed the respective identified uses for ERC 8d (Wide dispersive outdoor use of processing aids in open systems) or ERC 8f (Wide dispersive



outdoor use resulting in inclusion into or onto a matrix), suggesting indeed a high exposure potential for surface waters. The results presented for this step are not exhaustive, but may only serve as an illustration. The results of this evaluation are shown in the following Table 48.

Table 48: Results of total tonnage band and identified use information\*

CAS number	Name	Total tonnage band [tpa]	Identified uses in dossier
<i>7732-18-5</i>	<i>Water</i>	-	<i>Not relevant</i>
64-17-5	Ethanol	10,000,000–100,000,000	PROF & CONS: ERC 8d, 8f (coatings)
77-99-6	Propylidynetrimethanol	100,000–1,000,000	PROF & CONS: ERC 8d, 8f (coatings)
<i>108-01-0</i>	<i>2-dimethylaminoethanol</i>	<i>10,000+</i>	<i>PROF: 8f (additive in concrete/cement)</i>
111-76-2	2-butoxyethanol	100,000–1,000,000	PROF & CONS: ERC 8d (coatings)
121-91-5	Isophthalic acid	100,000–1,000,000	PROF & CONS: ERC 8d (coatings)
126-30-7	2,2-dimethylpropane-1,3-diol	100,000–1,000,000	PROF & CONS: ERC 8d, 8f (construction chemicals/coatings)
126-86-3	2,4,7,9-tetramethyldec-5-yne-4,7-diol	not yet registered	No dossier
147-14-8	29H,31H-phthalocyaninato(2-)-N29,N30,N31,N32 copper	10,000–100,000	PROF & CONS: ERC 8d, 8f (coatings)
1330-20-7	Xylene	1,000,000–10,000,000	PROF & CONS: ERC 8d (coatings)
1333-86-4	Carbon black	1,000,000–10,000,000	PROF: ERC 8d, 8f (coatings); CONS: ERC 8f (coatings)
<i>2778-42-9</i>	<i>1,3-bis(1-isocyanato-1-methylethyl)benzene</i>	<i>100–1,000</i>	<i>Only one industrial use identified (not relevant here)</i>
4767-03-7	2,2-bis(hydroxylmethyl)propionic acid	1,000–10,000	Uses described as oligomer (polymer uses), but product category descriptors point to coatings; CONS: ERC 10a
61788-89-4	Fatty acids, C18-unsatd., dimers distillation product	10,000–100,000	PROF & CONS: ERC 8d, 8f (coatings; no ERCs assigned for the many prof. uses, but implicit in descriptions)
64742-89-8	Solvent naphtha (petroleum), light aliph.	1,000,000–10,000,000	PROF: ERC 8d; CONS: ERC 8d (cleaning agents, coatings implicit from product category descriptors)

\* Substances considered not being relevant in italics

The additional data extracted from the ECHA website clearly suggest that the use of these substances in water-borne base colours for boats and ships is indeed relevant for most of these chemicals, with only few exceptions (shown in italics). With the substances retrieved, this simple exercise in fact appears to be so sensitive that one can almost envisage the formulations, e.g. with ethanol, 2-butoxyethanol and xylene as solvents, carbon black and 29H,31H-phthalocyaninato(2-)-N29,N30,N31,N32 copper (Pigment Blue 15) as pigments for either black or blue colours etc.

In defining a “priority mixture”, the next steps could include a specific tonnage cut-off, specific uses (e.g. with ERC 8d and 8f) or a combination of both. Obviously, such manual data

extraction exercises can only serve as an indication, what type of evaluations would be possible. Both the total tonnage band and the descriptors assigned in the dossiers are most likely accessible to automatic data extraction procedures by ECHA (although the connection to product types may not be). Also, while the evaluation presented above is not able to relate tonnages to specific uses, ECHA or CAs, will be able to perform such analysis – at least if a CSR is available. Substances from the table above may then be more specifically assigned to a “priority mixture”, e.g. if the tonnage for the specific use (wide-dispersive outdoor use in coatings) is above a certain threshold.

In addition, cooperation with the national product registers of the Nordic countries, which provide the input into the SPIN database, could be fruitful. The product registers contain information on the products, i.e. the composition, and can e.g. be used to check the results of evaluations of the type presented above.

Overall, evaluations as shown above may be useful in identifying “priority mixtures” and may be enhanced by confidential data from ECHA (or others). It must be emphasised that the entire evaluation procedure described above is independent of any hazard information and solely uses exposure-related data.

## 9.5 Annex 5: Background Data on Case Study (Leather Industry)

### Description

The producer of leather goods has to perform several activities to achieve the required durability, flexibility, and other quality characteristics of his products. He is a downstream user (end-user) of tannery chemicals and other technical mixtures containing substances for leather conditioning. Those substances and mixtures are provided by substance manufacturers/importers, formulators and trade companies. In an earlier project in cooperation with the Öko-Institut e.V, exposure scenarios for tannery chemicals have been developed. This includes some realistic parameters on exposure characteristics, risk management measures and products characteristics. Exposure scenarios had been developed in cooperation with formulators and tanneries. They are used as starting point in order to illustrate a tiered approach calculation for some technical mixtures and for a discharge mixture for a virtual tannery.<sup>103</sup> Safety data sheets were received directly from formulators. Those data should enable us to perform the respective calculations. However, the associated companies take no responsibility for correctness and currentness of the data, which are just illustrative examples.

Five products are included in our assessment:

- PROD\_1\_TAN, a glutaraldehyde-containing mixture for the tanning process;
- PROD\_2\_COLOUR, a colouring/ pigment preparation for leather goods
- PROD\_3\_GREASE, a greasing agent for leather goods.
- Prod\_4\_Sodium sulphide 60/62% flakes, auxiliary product (dehairing agent)
- PROD\_5\_ Luster, a tannery auxiliary product, finishing effects

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<sup>103</sup> [http://www.tegewa.de/uploads/media/2011\\_06\\_Lederhersteller\\_Leitfaden\\_final\\_Vers.1.1\\_02.pdf](http://www.tegewa.de/uploads/media/2011_06_Lederhersteller_Leitfaden_final_Vers.1.1_02.pdf)



These products have already been described in TEGEWA (2011). However, some updated SDS were used in our case study. The composition of these products according to the SDS is given in Table 49.

Table 49: Composition of 5 tannery products used in this case study

Product	Composition	Amounts according to SDS	SDS edition from
Prod_1_TAN	Glutaraldehyde (CAS: 111-30-8) Methanol (67-56-1) Sodium hydrogen glutarate (3343-88-2) Sodium succinate (14047-56-4) Sodium hydrogen adipate (18996-34-4)	±15- (<) 25% ±0.1- (<) 0.5% ±2 - 10 % ±2 - 10 % ±2 - 10 %	April, 25, 2012
PROD_2_COLOUR	Chrome (III), organic metal complex (72403-66-8)	>60%	August, 24, 2010
PROD_3_GREASE	Hexylene glycol (107-41-5) Tetradecanesulfonic acid, sodium salt (6994-45-2) Lard, oil, sulfated, sodium salts (68153-10-6)	1-5 % <5% 20-30 %	April, 8, 2009
Prod_4_Sodium sulphide 60/62% flakes	Sodium sulphide (1313-82-2)	50-75%	April, 16, 2012
PROD_5_luster	1-Methoxy-2-propanol (107-98-2) 4-Hydroxy-4-methyl-pentan-2-on (123-42-2) Aromatic naphtha, type I (64742-95-6)	41-45% 33-37% 13-17%	January, 27, 2011

Note that two of these products consist of only one single declared classified substance. Percentages do not add up to 100% and are given as ranges. There was no declared substance occurring in more than a single product.

SDS reported the CLP - or DSD - classification of all of the substances listed in Table 49. In the example below, we start with the assumption that the assessor has no access to extended SDS providing additional data like M (safe), RCR, or PEC-data. However, for some, of the substances in those products, EC<sub>50</sub> effect concentrations (IC<sub>50</sub>; EC<sub>50</sub>, LC<sub>50</sub>) were provided.

PEC data on most substances were provided by an Öko-Institut EUSES calculation at a low tier level as a starting point. The case study consists of 5 parts:

- Derivation of PNEC for all substances in the five products (hazard tier 1) and derivation of CRV<sub>TL</sub> for the dominating substances (hazard tier 2), including a discussion on the problems arising for the assessor to obtain suitable data from the information provided under REACH or easily available elsewhere.
- Derivation of PEC at various exposure tiers for an example substance, including a discussion on the problems arising for the assessor to obtain suitable data from the information provided under REACH or easily available elsewhere.

- Performing a mixture risk assessment for the single technical mixtures at tier 1 level, including a discussion of the basic results.
- Performing a mixture risk assessment for the complete discharge mixture at tier 2 level, including a discussion of the basic results and a comparison to a similar proposal by Backhaus et al. (2012)
- Overall conclusions from the case study.

The main findings of the case study are described in the following subsections.

### Ecotoxicological Information

For a first tier hazard assessment, PNECs have to be collected. There were only few PNECs available from the SDS. Most PNECs could be found in the REACH dissemination data base. However, as not all substances were registered yet, we also had to look for further sources to assign a PNEC, or we had to derive the respective values directly from experimental or modelled test data. Table 50 presents the PNECs for all declared substances in the five products.

In the scope of this project, no in-depth-analysis of single study-records was possible. For some compounds it was a considerable challenge to derive PNECs due to insufficiencies/inconsistencies in reporting, studies relating to different molecular entities of the test item formed in water, studies with analytical verification for some endpoints / trophic levels to be compared with studies giving only nominal results for other endpoints / trophic levels.

Table 50: PNECs and chronic reference values (CRVTL) for substances in five products of this case study

Product	Substance	CAS-Nr.	PNEC (ug/L)	CRV Algae	CRV daph.	CRV fish
Prod_1_TAN	Glutaraldehyde	111-30-8	2.5	25	500	160
	Methanol	67-56-1	154000	nc		
	Sodium hydrogen glutarate	3343-88-2	Non-toxic	nc		
	Sodium succinate	14047-56-4	Non-toxic	nc		
	Sodium hydrogen adipate	18996-34-4	Non-toxic	nc		
SELLA FAST OLIVE C-SG	Chrome (III), organic metal complex	72403-66-8	2	2	2	2
PROD_3_GREASE	Hexylene glycol	107-41-5	429	nc		
	Tetradecanesulfonic acid, sodium salt	6994-45-2	76	nc		
	Lard, oil, sulfated, sodium salts	68153-10-6	0.1	0.1	0.18	0.18
Prod_4_Sodium sulphide 60/62% flakes	Sodium sulphide	1313-82-2	0.27	0.78	0.44	3.5
PROD_5_luster	1-Methoxy-2-propanol	107-98-2	10000	nc		
	4-Hydroxy-4-methyl-pentan-2-on	123-42-2	2000	nc		
	Aromatic naphtha, type I	64742-95-6	10	50	260	5.2

Some examples on the uncertainties and discrepancies in reported data are presented

- PROD\_1\_UP; Glutaraldehyde: This substance is registered under REACH. The PNEC apparently is derived from a NOEC, which is lower by a factor of 10 compared to the EC10. Therefore, the PNEC is quite conservative compared to earlier published hazard assessments.
- SELLA FAST Olive C-SG, Chrome (III)-organic metal complex: The substance is not registered under REACH. The only data reported are those provided in the SDS with a LC<sub>0</sub> and an LC<sub>50</sub> in fish. The derived PNEC therefore is highly uncertain.
- PROD\_3\_GREASE; tetradecanesulfonic acid, sodium salt: we derived a PNEC by ECOSAR modelling, because this substance is not yet registered under REACH. However, the new SDS, which was not available for our assessment, reports elevated toxicity for fish and also provides additional data for algae. Therefore, the provided PNEC is highly uncertain.
- PROD\_3\_GREASE; lard oil, sulphated, sodium salts: we derived a PNEC with a TTC approach, because modelling resulted in implausible low values. This substance is not yet registered under REACH. However, the new SDS, which was not available for our assessment, reports a low toxicity (> 100 mg/L) for daphnids. This makes it highly uncertain to maintain the much lower extrapolated values for fish (and, possibly, of algae). There are no experimental data available for these trophic levels.
- Prod\_4\_Sodium sulphide flakes: in an earlier safety data sheet from 2002, there also was a classification as environmental toxicant. However, no respective Risk phrases were provided. For this registered substance now a very low PNEC is documented in the REACH dissemination database. But this PNEC is not reported in the SDS. The substance is classified as H400 (“very toxic to organism in water”).
- die tiefgestellten PROD\_5\_ Luster; 1-Methoxy-2-propanol: in an earlier safety data sheet, the PNEC<sub>(water)</sub> was given with 208 mg/l. In the REACH registration document we found a PNEC<sub>(freshwater)</sub> of 10 mg/l; no PNEC is reported in the SDS any more
- PROD\_5\_ Effect luster; Aromatic naphtha: in an earlier safety data sheet, the PNEC<sub>(water)</sub> was given with 1µg/l. In the REACH registration document we found no PNEC<sub>(freshwater)</sub>, even though the substance is registered. In the new SDS no environmental toxicity data are reported anymore and the substance is not mentioned in section 12.1.

When moving to tier 2 similarly uncertain values for CRV<sub>TL</sub> are calculated. If there were reported data in REACH registration documents, we had to select the most suitable experimental information, which was not easy without original study reports. Moreover, some of the published results apparently contained errors or implausible transformations due to the negligence of water solubility, and/or pH-values. It has to be acknowledged that any CRV<sub>TL</sub> – calculation needs extended experience in ecotoxicological hazard assessment, which may not be readily available for the downstream user or the end-user. Apparently, also for registrants this step will not be accomplished without mistakes. The results of our assessment are summarised in Table 50. Details are provided in Annex III.

For all of the five products a “lead substance” was determined in TEGEWA (2011). Based on the hazard characteristics, these lead substances may not always be identical to the most critical substances in this project. However, the selection of lead substances, if considered at all, should not only be decided based on a PNEC, but also based on exposure and the resulting RCR and is, therefore, discussed later.

## Exposure Assessment

Predicted exposure concentrations (PEC) for the substances applied and discharged by tanneries in leather goods production may be calculated with suitable software ECETOC TRA or EUSES. In Annex III the parameters for the various tiers are provided for all substances except for sodium sulphide, where measured data were used for exposure calculation. The lowest tier included a dilution factor of 10, no specific “operating conditions” (OC) and no risk management measures (RMM). Amounts used, percentages in the product, fixation to the material, process dependent emission reduction, resulting emission fractions, dilution factors, and number of emission days were applied as calculated within another project (Bunke et al., 2011; CEFIC, 2010; TEGEWA e.V., 2011).<sup>104</sup> However, those factors were only included in the appropriate tier, in order to illustrate the consequences of less qualified information. The very specific data may not always be available for other industrial sectors and uses. Table 51 presents tier 0 information for all substances within the five products and a high tier assessment as detailed in Annex III.

Table 51: PEC data for 5 products in case study (for details see Annex III)

Product	Substance	CAS-Nr.	PEC [ug/L]	
			Tier 0 <sup>1</sup>	Tier (high) <sup>2</sup>
Prod_1_TAN	Glutaraldehyde	111-30-8	934	0.467
	Methanol	67-56-1	918	1.91
	Sodium hydrogen glutarate	3343-88-2	nc	nc
	Sodium succinate	14047-56-4	949	39.6
	Sodium hydrogen adipate	18996-34-4	949	39.5
PROD_2_COLOUR	Chrome (III), organic metal complex	72403-66-8	7500	0.75
PROD_3_GREASE	Hexylene glycol	107-41-5	949	94.9
	Tetradecanesulfonic acid, sodium salt	6994-45-2	942	28.3
	Lard, oil, sulfated, sodium salts	68153-10-6	91.4	54.8
Prod_4_Sodium sulphide 60/62% flakes	Sodium sulphide	1313-82-2	0.214	nc
PROD_5_luster	1-Methoxy-2-propanol	107-98-2	4390	176
	4-Hydroxy-4-methyl-pentan-2-on	123-42-2	948	77.8
	Aromatic naphtha, type I	64742-95-6	6730	256

By most registrants PEC are currently interpreted as upper bound exposure levels to ensure safe usage of a single substance for all stages of the life cycle and for all respective uses. For one of the substance, glutaraldehyde, a more detailed analysis was performed, with specified tiers using ECETOC TRA and not only EUSES, as for the other substances. We found that differences in the calculated PEC may vary over three orders of magnitude from a tier 0 (worst case) to a higher tier scenario, where operational conditions, more realistic assumptions on the water

<sup>104</sup> See scaling tool available from <http://www.tegewa.de/de/reach/arbeitshilfen-leitfaden-und-scaling-tool-fuer-gerber.html>

flow and “state of the art” risk management measures were included. The following Table 52 demonstrates the range of PECs derived for glutaraldehyde.

**Table 52:** Example (glutaraldehyde, use in leather tanneries): Range of possible exposure estimates (PEC) based on different levels of information

Tier	PEC	Parameters/ assumptions (calculated with ECETOC TRA)
Tier 0	934 ↔g/l	100% discharge, usage 150 kg/d; no OCs, no RMMs; default STP discharge and river flow rates (dilution factor 10)
Tier 1	467 ↔g/l	ERC-based; ERC 5; 50% release fraction, no further OCs, or RMMs; default STP discharge and river flow rates
Tier 2a	280 ↔g/l	spERC-based; high release; release fraction 30% instead of 50% (ERC); no further OCs, or RMMs; default STP discharge and river flow rates
Tier 2b	46.7 ↔g/l	spERC-based; low release; release fraction 5% instead of 50% (ERC); no further OCs, or RMMs; default STP discharge and river flow rates
Tier 3	93.4 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90% no further RMMs; default STP discharge and river flow rates
Tier 4	9,34 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90% no further RMMs; river flow rate increased, resulting in a 10-times higher dilution
Tier 5	0,467 ↔g/l	Calculated with specific information by the formulator : OC: fixation 90%; removal/ reaction in wastewater streams 95%; river flow rate increased (identical to tier 4)
Tier 6	?	Measured data if qualified and if they may be attributed to a single technical mixture or to a discharge mixture (not available for this example)

Additional knowledge contributed by the tannery (end-user) is used to further reduce the PEC in a tier 5 assessment, where specific (“real”) parameters on the STP and river flow are added. Finally, a refinement of the PEC estimate with reliable measured data is possible. In some cases, only limited measured data are available, which are not reliable as such, but can be used to support modelling approaches.

Note, that registrants could usually only proceed until tier 2 (a or b). Information contributed in tier 3 to 5 may only be contributed by the formulator or the end-user. Access for the formulator may also be restricted. For example, the 95% reduction of the substance in tier 5 assumes that there always is a mix with a simultaneous alkaline stream from the water workshop which contains relevant amounts of proteins to remove glutaraldehyde quantitatively. For tanneries, this is common practice and described in the BAT document. Therefore, the formulator can assume this procedure for his customers. This kind of sector-specific end-user information is necessary for the tier 5 (and 6) calculations. Otherwise the estimated PEC (at tier 4 level) deviates by a factor of up to 20 from an exposure concentration, which resembles more closely the “real” contribution of this substance to freshwater concentrations.

In the case study, elaborated exposure scenarios based on a detailed exchange between end-users and formulators have been the starting point. Therefore the higher tier estimations have been possible. We question that such specific information is available for many sectors.

### Risk Assessment for the Technical Mixtures

The toxicity of all of the five products is determined by one single substance, which is trivial for the two single substance products, but is also true for the three mixtures. Table 53 gives an overview on the resulting RCRs. The critical single substance is highlighted by a shaded cell in the table.

**Table 53:** RCR for five products of this case study, mixture risk assessment tier 1 (Hazard Index dominated by 1 single substance each for all the technical mixtures) with hazard tier 1 and two alternative exposure tiers

Product	Substance	CAS-Nr.	RCR	
			Exposure Tier 01	Exposure Tier (high)2
Prod_1_TAN	Glutaraldehyde	111-30-8	373.6	0.19
	Methanol	67-56-1	0.006	low
	Sodium hydrogen glutarate	3343-88-2	low	low
	Sodium succinate	14047-56-4	low	low
	Sodium hydrogen adipate	18996-34-4	low	low
PROD_2_COLOUR	Chrome (III), organic metal complex	72403-66-8	3750	0.38
PROD_3_GREASE	Hexylene glycol	107-41-5	2.2	0.22
	Tetradecanesulfonic acid, sodium salt	6994-45-2	12.4	0.37
	Lard, oil, sulfated, sodium salts	68153-10-6	914	548.00
Prod_4_Sodium sulphide 60/62% flakes	Sodium sulphide	1313-82-2	0.79	0.41
PROD_5_luster	1-Methoxy-2-propanol	107-98-2	0.44	0.02
	4-Hydroxy-4-methyl-pentan-2-on	123-42-2	0.47	0.04
	Aromatic naphtha, type I	64742-95-6	673	25.60

Note that the resulting RCRs (which are nearly equivalent to the HI for this example) are highly uncertain because of the reasons discussed in sections 2.4.7 and 2.5.2.5. If some of them were confirmed (aromatic naphtha, lard oil, sulfated, sodium salts) this would evoke additional extensive RMM already according to the single substance risk assessment as regularly demanded currently under REACH. If the marked substances are confirmed with their contribution to the mixture effect, they should be selected as lead a substance, which means some change compared to the approach in TEGEWA (2011). It is important to note that the RCR apparently may be a better indicator of the critical toxicity compared with the isolated classification of an ingredient substance of a mixture, an isolated PNEC or a PNEC just weighted with the content of the substances in the preparation.

### Assessment for the Discharge Mixture (Receiving Waters)

As pointed out above, the assessment is restricted to the 5 compounds vastly dominating risk in the respective technical mixtures with high individual RCR. These are azo-dye complexing Cr(III), sodium sulfide, aromatic naphtha type I, glutaral and Lard, oil, sulfated, sodium salts. For these, tier 1 and tier 2 hazard assessments with  $CRV_{TL}$  as outlined in Table 50 is performed in this section. As exposure tiers only the high tier data (see Table 13 and – for an example – Table 52) were used. Table 54 summarizes the results.

**Table 54:** Compounds assessed for the  $RQ_{STU}$  discharge mixture, their PNECs, chronic reference values for the trophic levels ( $CRV_{TL}$ ) and predicted environmental concentrations (PEC, high tier level, see Table 51). From the PNEC and the  $CRV_{TL}$  the risk characterization ratio (RCR) and the  $RCR_{TL}$ , respectively, are calculated.

Name, CAS	PNEC ↔g/L	$CRV_{Algae}$ ↔g/L	$CRV_{inv.}$ ↔g/L	$CRV_{Fish}$ ↔g/L	Comment	PEC ↔g/L	RCR	$RCR_{Algae}$	$RCR_{inv.}$	$RCR_{Fish}$
Azo-Dye-Cr(III)-complex, 72403-66-8	2	2	2	2	All values based on acute fish toxicity reported in SDS – no QSAR possible	0.75	0.38	0.38	0.38	0.38
Sodium sulfide, Na <sub>2</sub> S, 1313-82-2	0.27	0.78	0.44	3.5	Acute studies: Fish most sensitive; chronic study for fish only	0.21	0.78	0.27	0.48	0.06
Aromatic naphtha, type I, 64742-95-6	10	50	260	5.2	Chronic studies for inv. and algae only	256	25.6	5.12	0.98	49.23
Glutaral, 111-30-8	2.5	25	500	160	Chronic studies for all three trophic levels	0.47	0.19	0.02	0.00	0.00
Lard, oil, sulfated, sodium salts, 68153-10-6	0.1	0.1	0.18	0.18	All values based on QSAR estimations (ECOSAR class "Surfactants") and the ETNC-approach (TTC)	54.8	548	548	304	304

The HI of 575 is highly dominated by the RCR of Lard, oil, sulphated, sodium salts in this example. Moving to a higher tier will only marginally influence the result to THI of 554, because of the high influence of the toxicity assumptions on algae, although the mixture effects to fish and invertebrates would be clearly lower.

This means that THI is indeed lower than HI, however by a small factor of only. This is far from the theoretically determined maximally possible difference of 3 (Backhaus and Faust, 2012).

The concept of THI as described was developed to enable the exhaustive use of a very diverse data set including acute and chronic data, data gaps or data where due to poor solubility no toxicity could be observed. The basic concept is largely identical to the one proposed by Backhaus and Faust (2012). Following this concept however, toxic units of the individual compounds  $i$  (e.g.  $PEC_i/EC_{50}(TL)_i$ ) are summed up for each trophic level yielding the  $RQ_{STU}(TL)$  - the risk quotient based on the sum of toxic units for a trophic level – and the highest  $RQ_{STU}(TL)$  of three trophic levels, the  $RQ_{STU}$  is multiplied by an appropriate assessment factor. This however implicates that the assessment factor must be appropriate for all data included, i.e. if AF 1000 is used, only uniform usage of acute data is possible, while in principle also uniform use of chronic data would enable to use an AF of 10 (the use of chronic data is however not outlined in the publication of Backhaus and Faust).

Thus, with the current data base including acute, chronic, and QSAR-data, only the lowest common denominator, i.e. acute and QSAR-data (regarded as acute) can be used.

The resulting  $RQ_{STU}$  differs relevantly from our result (data not shown). The main reason for this difference in result is due to two factors: 1) the use of the algal  $EC_{50}$  and the final application of an assessment factor of 1000 in the Backhaus et al.-concept leads to a, probably, overestimated toxicity of the discharge mixture to algae because of the very low acute  $EC_{50}$  for lard oil, sulphated sodium salts; 2) the use of acute data multiplied by the assessment factor sometimes leads to much lower calculated chronic data compared to our formula, where available chronic data are integrated directly. Therefore, while both calculations should principally provide similar results, the outcomes may differ fundamentally, as demonstrated with this realistic data example. We conclude that

- tier 2 calculations may not be performed without a highly qualified analysis of the toxicological input data,
- the THI – approach as developed in this project (and outlined in Annex II) is more flexible to handle heterogeneous input data and therefore may be better adapted to data availability under REACH compared to trophic concentration addition models, which are directly linked to “toxic units” and an overall assessment factor.

In conclusion, both concepts, THI and  $RQ_{STU}$  are expected to lead to the same results given a homogenous data set of acute or chronic data only. The advantage of THI-concept is that a highly heterogeneous data set may be used. Meaningful results e.g. in regard to the trophic level mostly at risk can only be expected with a sound ecotoxicological data base. Considering long term exposure, the more acute or even QSAR-data present involving high assessment factors the more artificial becomes the result.

Compared to the established HI-approach THI as second tier assessment results in slightly lower and more realistic values for the risk from mixture toxicity. However to be able to take advantage of the full potential of the method, reliable and mostly chronic data would be needed. As from theoretical considerations the risk estimated by  $RQ_{STU}$  and THI can maximally be lower by a factor of 3 by these refined approaches (Backhaus and Faust, 2012), the work load and expert knowledge which is currently necessary for the in-depth analysis of data provided by the REACH dissemination DB and required by these concepts is not proportionate and most probably cannot be handled in the framework of routine assessment.

### Conclusions from the case study: leather industry

In this case study we examined the feasibility to assess mixture effects with the information available under REACH. Firstly, we analysed whether the information on all the single substances within the mixture is sufficient to perform a mixture hazard assessment. It had to be acknowledged that

- not all substances in mixtures are classified. Therefore there may be a relevant reporting lack on substances that contribute to mixture effects but are not disclosed;
- those substances classified may not all have PNECs assigned and reported, even if they are already registered under REACH. In this case, highly qualified assessment of original data or modelling is necessary in order to generate substitute information and to introduce a PNEC analogue reference value;
- further selection problems will occur, if a tier 2 mixture hazard assessment is attempted. There may be more than one suitable study and the assessor may have difficulties to decide on the choice of the appropriate experimental data and the corresponding assessment factors, when deriving CRVTL;



- using the modeling tools like ECOSAR, which is often necessary, this increases the uncertainties of the hazard assessment. As long as not all classified substances in a mixture are registered, this accumulates to an overall high degree of uncertainty, which is carried forward from the single substances to the mixture assessment.

Secondly, we analysed the “predicted exposure information” (PEC) provided under REACH. This information is significantly improved if specific information for a producing sector (like the leather industry in this case study) is added to the basic ERC data available to the registrant. There are, however, uncertainties whether operation conditions and risk management measures are uniform and guaranteed for all leather goods producing industries all over Europe. Moreover, REACH provides *generic* exposure scenarios that may significantly deviate from *locally* relevant parameters, which are necessary to provide meaningful PEC data for mixture risk assessments. It was demonstrated with the example of glutaraldehyde that the range of PEC may be considerably influenced by the tier of the assessment.

Thirdly, the mixture risk assessment combines hazard and exposure assessment and therefore combines the uncertainties. Therefore a “hazard index” HI above 1 is not easily to be interpreted as a beginning mixture effect but may also be understood as a mere calculation result of some upper bound estimates for single substances in combination, which is far from a realistic exposure estimate. Only high tier mixture risk assessments may be meaningful with respect to regulatory consequences like imposing obligatory risk management measures. On the other hand, a low tier HI below 1 would provide an ample margin of safety if this may be demonstrated. (Remark: In the case study, only three of the five technical mixtures contain more than one substance. From these three mixtures, one has a low HI below 1. Two technical mixtures show a high HI. The reasons for these high values will be checked in a second step.).

The case study demonstrates that one has to be careful to select lead substances characterizing and representing a technical mixture. Without adequate data on the RCR, the selection of a lead substance will not be an obvious choice.

We compared two approaches for a second tier mixture risk assessment using the “trophic level” reference values (CRV<sub>TL</sub>). We conclude that the CR<sub>TL</sub> calculation with individual assessment factors based on the heterogeneous acute or chronic input data, is a more flexible and appropriate procedure under REACH compared to the “trophic toxic unit” approach with an overall assessment factor proposed in prior discussions.

This case study is limited if examination concentrates on actual concentration addition effects: because in all products a single substance was greatly dominating the overall effect of a mixture, the contributions of the other substances was insignificant. This is consistent to an analysis by Price and Han (2012), who claim, that usually one or two substances statistically are determining the hazard index for a mixture for environmental mixtures. However, for technical mixtures with only few ingredient substances this phenomenon is regarded more a matter of chance than a systematic finding.

The case study is not appropriate to be used for discussions of aggregated exposure to single substances as there were not a number of mixtures containing identical substances. This precludes the possibility to calculate meaningful figures an aggregated exposure to single substances from multiple sources within a discharge mixture.

The case study was not designed to answer the question, who should perform a mixture risk assessment. However, it became evident, that the generation of data, which are not documented directly in a published REACH dossier or in a SDS may need considerable efforts, where the respective actors under REACH are faced with relevant deficits. These deficits may be lacking data or lacking skills to generate appropriate data, if those are missing. The key

problem is, that the progress to a higher tier mixture risk assessment needs knowledge from both ends of the supply chain. Only if we succeed to combine competence available at the different ends of the chain an overall high quality mixture risk assessment will be feasible. Below that level, we will probably only be able

- a) to detect and confirm really safe uses of mixtures, or to
- b) uncover the most urgent cases of intolerable mixture effects.

## 9.6 Annex 6: Options to act on Mixture Assessment for Authorities

This chapter explores several options for national authorities to address the issue of mixture toxicity in the context of their on-going REACH implementation tasks and activities. As already mentioned in the introduction, we expect that the discussions at EU level will be a long- term process. It is therefore unlikely that the REACH review (now postponed to 2013) will address specific points concerning any legal changes to REACH to address combination effects from chemical substances. Therefore, also the following chapter aims to describe possibilities for regulatory authorities to use current REACH provisions and lay a greater emphasis on the existence of mixture effects. The motivation for the activities at Member State level would be to improve the risk management by taking into account the more realistic exposure situation due to the fact that in reality an exposure to multiple chemicals takes place. The proposed options below are partly new initiatives that a respective Competent Authority can decide to launch, or they can be combined with on-going activities during the REACH implementation process.

### 9.6.1 Nomination for the Community Rolling Action Plan for Substance Evaluations

According to REACH article 45.5, a Member State can notify ECHA of substances when in possession of information that the substance is a priority for evaluation, i.e. that there is concern that risks still might be underestimated by the risk assessments of the registrants. ECHA will decide whether to add the substance to the CoRAP and nominate it for a substance evaluation based on an opinion from the Member State Committee (MSC). There may be cases where a Member State might want to use this provision to propose to include a substance or group of substances to the CoRAP based on concerns relating to their expected or known combination effects in mixtures.

For example, this could be considered for

- a set of compounds in a concrete emission scenario (technical or discharge mixture) with frequent occurrence
- a group of environmental compounds that are known to occur in the aquatic environment, leading to permanent, low-level exposure (examples could be e.g. benzotriazoles/methylbenzotriazoles; phosphor-based flame retardants such as TCEP, TPP, TCDD, TDBP)
- A group of similarly acting substances with known similar uses for them to be evaluated together, performing cumulative risk assessment where possible (examples: substances in water-borne base colours for boats and ships)
- Substances which are known to act more than additive/ synergistically.

Thus, this option could be used in cases for adding substances to the CoRAP which have not met the CoRAP criteria (see

[http://echa.europa.eu/documents/10162/13628/background\\_doc\\_criteria\\_ed\\_32\\_2011\\_en.pdf](http://echa.europa.eu/documents/10162/13628/background_doc_criteria_ed_32_2011_en.pdf))

based on the concern relating to the individual substance. Depending on the results and given the invested resources, the competent authority may request further information and data from

registrants and propose further risk management option, such as restriction or authorisation procedures (or regulative options apart from REACH).

### 9.6.2 Check Risk Characterization in Chemical Safety Assessment (according to ECHA Guidance on Information Requirements and the Chemical Safety Assessment, Part E)

The REACH substance evaluation on the particular CoRAP substances carried out by national competent authorities will involve a close scrutiny of the registrant’s chemicals safety assessment. There is one interesting part in the risk characterisation part of the ECHA guidance addressing registrants that mentions the consideration of exposures to “several very closely related and similar acting chemical substances”:

“In special cases, where exposure occurs to a substance as well as to several very closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances), the exposure evaluation and risk characterisation should reflect this aspect. If data are available the exposure assessment should also include a scenario concerning this combined exposure. If data do not allow for a quantitative assessment, the issue can be addressed in a qualitative way.” (part E of the ECHA CSA guidance, ECHA 2008d)

It could be very interesting to pay special attention to this part during the evaluation to see if and how companies have applied the part of the ECHA guidance document. This could also give some insights as to what additional elements might be for future guidance development. This task can only be performed by national regulatory authorities or ECHA as the details of the chemical safety assessment are not open to the public via the ECHA database. The guidance refers to special cases only. However, national competent authorities could evaluate and potentially follow up on this point for substances for which very closely related and similar acting substances are known – as part of the substance evaluation process.

### 9.6.3 Request further Information from Registrant as a Result of a Substance Evaluation

There may be cases where the national authority considers that more information on the mixture assessment and the potential risk is required from the registrant during substance evaluation. According to REACH article 46.1 the national authority can require further information from the registrants during substance evaluation. This provision could also be applied, if appropriate, for proposing to perform a aggregated or cumulative risk assessment in specific cases. Under this procedure, a draft decision has to be prepared, stating respective reasons, and setting a deadline for submission. This means that theoretically, a national authority can decide to ask the registrant to perform a mixture assessment in a specific case and for a certain scenario. This could e.g. be relevant in the following two cases:

The registration dossier concerns a mixture. An example from CoRAP for 2013:

- The Netherlands will evaluate a reaction mass of mixed (3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phosphates, ammonium salts

Several registration dossiers are received per registrant for substances with similar hazard and use profile. Example from CoRAP for 2014: Denmark will evaluate three compounds:

- 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters
- 1,2-benzenedicarboxylicacid, di-C9-11-branched and linear alkyl esters
- 1,2-benzenedicarboxylicacid, di-C11-14-branched alkyl esters, C13-rich

Depending on the details in the registration dossiers and the quality of the risk characterisation performed, the competent authority will have to decide if additional information is needed by

the registrant. In cases where read-across approaches were used for certain endpoints for different substances/groups this may become even more relevant and justified, because it means that a sufficient similarity of the compounds was assumed. Another consequence resulting from substance evaluation will be to consider whether additional risk management measures may be required, either within REACH provisions or potentially using complementary legislation.

#### **9.6.4 Prioritisation for REACH Authorization (Annex XIV)**

While the process of nominating SVHC to the REACH candidate list should remain purely hazard based as laid out in article 57 (criteria for nominating SVHC), it could be considered to include arguments relating to the risks from combined effects in the priority setting for Annex XIV. REACH article 58.3 stipulates that priority for Annex XIV shall normally be given to substances with a) PBT/vPvB properties, b) wide dispersive use, or c) high volumes. This means that it is possible to consider additional aspects. ECHA has already applied the group approach in the past, i.e. a group of chemicals (e.g. metal compounds) were prioritised together, mainly with the argument that one SVHC should not be replaced with another. Member States could decide to initiate a discussion in the Member State Committee as to which role the phenomenon of known co-exposures of chemicals with common adverse outcomes could play in the prioritisation for Annex XIV.

#### **9.6.5 PNEC based on individual Substance not reliable for “adequate Control”**

Under authorisation, the current REACH text foresees to grant/deny authorisations for individual substances in their specific use. While all known emissions of the same substance are taken into account, it is not mentioned that it is also possible to take into consideration potential combination effects as a result of emission of other substances. This can be expected to lead to many single authorisations on uses of substances based on individual assumed safe thresholds and adequate control (REACH article 60.2). However, in reality in the case of substance groups/classes with known mixture toxicity and known co-exposures it is practically impossible to determine a reliable PNEC for an individual compounds which is protective of the ecosystem. In this case one could argue that the scenario becomes similar to that of the non-threshold substances where no safe levels can be determined with sufficient certainty. It will be the decision of the Risk Assessment Committee and in the end the EU Commission if in those cases authorization can only be granted based on REACH article 60.3, i.e. only when safer alternatives are not available and if the socio-economic benefits outweigh the risks.

This example can be illustrated by the case of the 4 phthalate compounds on Annex XIV. These compounds are toxic to reproduction and it is known that they are widely used in consumer articles and also frequently found in the aquatic environment. It is known that these substances have a similar mode of action and will lead to combined effects, basically replacing each other in their concentration at their respective toxic unit value. It would seem like a crucial oversight to ignore this knowledge at the authorization stage and therefore a discussion at the policy level, e.g. at meetings of the REACH competent authorities (CARACAL), may help to seek progress.

#### **9.6.6 Prepare a Restriction for a group of Substances for certain Uses – the Phthalate Case**

In 2011, the Danish competent authorities made a restriction proposal with the aim of limiting exposure to humans from four classified phthalates (DEHP, BBP, DBP and DIBP) in certain consumer articles. The proposed restriction aimed to cover articles intended for use indoors

and articles that may come into direct contact with the skin or mucous membranes containing one or more of the four phthalates in a concentration greater than 0.1 % by weight of any plasticised material. In June 2012 the Risk Assessment Committee (RAC) decided to reject the restriction proposal and concluded that the available data does not indicate that there is currently a risk from combined exposure to the four phthalates. Even though this dossier is relating to human health while this project has a focus on the environmental risks, it is valuable to study this case more closely to draw some lessons learnt.

This was the first time since the adoption of REACH that a combined assessment approach was used. It is important to note that RAC did not question the principle of addressing risks through combined exposure if the substances act similarly (all four phthalates, they all show anti-androgenic properties).

The attempt by the Danish CA shows that it is possible in principle to use REACH for restrictions in the case of combined exposures. The disagreements for not following the restriction rather seem to be based on the respective safety factors in the risk assessments. This shows that the discussion around safety factors is always likely to lead to controversies concerning the relevance of the risk – be it for individual substances or a mixture. Another argument RAC and in particular SEAC used is the on-going trend for substitution and future declining trends due to the authorization. This is a somewhat unusual argument in particular given that authorization will not apply to imported articles. The EU Commission will decide the case in 2013. Meanwhile, in August 2012 Denmark announced to go ahead with their proposed restriction at national level and not wait for the EU.

Other groups of substances for which a joint restriction could be the relevant regulatory tool may be organotin compounds in consumer products or perfluoro compounds (PFCs) in consumer products. One of the challenges will be to select the relevant compounds to include in the grouping approach and to compile, document and assess the relevant exposures.

## 9.7 Annex 7: Main findings from the Workshop “4M\_ Mixtures under REACH”.

At the end of January 2013, the German Federal Environment Agency invited experts from authorities, industries, NGOs and academia to discuss and clarify options for an assessment of chemical mixtures under REACH. The workshop addressed potential upcoming tasks of manufacturers, formulators, downstream users and authorities. During the workshop, main findings of the project “4M: Mixtures under REACH” were presented.<sup>105</sup> The proposed methodology for the assessment of mixtures, the options to act, as well as decision criteria for mixture assessment were discussed with 48 participants.

In the following sections, the main findings from the workshop are documented.

### Part I: Introduction: European activities on mixtures – and REACH

The welcome address from Adolf Eisenträger (German Federal Environment Agency) and an introduction to the workshop by the 4M project team was followed by brief presentations of 5 invited speakers. They highlighted different perspectives on mixtures under REACH, including from authorities, NGOs, academia and industry.

<sup>105</sup> The project of the German Federal Environmental Agency has the title: „Mixtures under REACH. Approaches and options to act“. In the following, as a short form of the title, the abbreviation „4M“ is used.

In the subsequent discussion the point was made that it would be problematic to base a regulatory strategy for mixtures assessment on the knowledge of the “Mode of action” (MoA), which are not known in many cases (or only known for individual species). This was supported by another speaker who advocated for the use of concentration addition as a default rather than using species specific mode of action data. MoA can be used to refine the assessment, whenever available. Chrystele Tissier from ECHA was asked why the given examples had mainly referred to human health. She clarified that their starting point for looking at combination effects for now had been classified CMRs, also taking similar structures into account, and that they also intend to look into the topic from the environmental side. One participant made the general point that many more long term data were needed on the effects of environmental contaminants, but that the narcotic effects could be used for a start (reflecting minimum toxicity). As several speakers had referred to the use of existing monitoring data someone cautioned that monitoring data are only available for a very limited number of substances. Still, for those substances where data are available they should be taken into account for prioritization for the Community Rolling Action Plan (CoRAP) and substance evaluation.

It was pointed out that the use of monitoring data as the only starting point would allow only retrospective mixture risk assessments, whereas the REACH safety assessment is intended to precede the marketing. The real question therefore should be how a prospective mixture assessment can be done under REACH. Others felt however, that a real problem needs to be demonstrated first. This controversy was discussed further, and while some participants felt the evidence of the concerns for mixture effects are clear and well-established, others felt that current single substance risk assessment already leads to “overprotection”.

## Part II – V: The discussion of the interim results of the project 4 M

The following points summarize the main impressions and findings from the discussion of the interim results of the project 4M. Detailed discussions of specific items took place in working groups on four topics (Tiered approach for mixture risk assessment / Mixture assessment triggering substances (MATS) / Priority setting for mixture risk assessment / Options to act for authorities).

### Clarification of terms and relevance of mixture risk assessment

- The differentiation between four types of mixtures as proposed in the project 4M is very helpful for a structured discussion on “mixtures” and options to act. (It has been proposed to differentiate between technical mixtures, discharge mixtures, coincidental mixtures and environmental mixtures, see section 1.1 of the background document).<sup>106</sup>
- Technical mixtures of industrial chemicals are only one of the sources that lead to complex environmental mixtures. It is important to show which technical mixtures give a relevant contribution to environmental mixtures (compared to pharmaceuticals, biocides, pesticides and other groups of chemicals). Establishing of credible links is

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In brief, the four types of mixtures are defined as follows: technical mixtures are produced on purpose by formulators / discharge mixtures effluents from a single discharging production unit / coincidental mixtures are mixtures in the environmental compartment which receives the emissions from a sewage treatment plant / environmental mixtures are substance combinations in environmental compartments including biota - from different sources.

essential to allocate responsibilities for mixture risk assessment and/or respective risk management.

- It is important to clarify the mixture related obligations under REACH and to show the differences between a consolidation of information (e.g. DPD+) and a mixture risk assessment;
- Acceptance for the need to assess mixture risks must be increased. This requires examples for the added value of a mixture assessment. In order to stimulate actions under REACH, these examples should come from well characterised technical mixtures or uses of obvious concern. For the same reason case studies are needed to conclude on priorities, to clarify relevance and to indicate exposures and risks by mixtures.
- If REACH is fully in force and the risk management for single substances is improved, also the risks from mixtures is likely to be partly addressed, as exposures to the environment are expected to be reduced by increased risk management measures.
- Data from environmental monitoring can be used to identify areas of concern for mixture assessment. However, this should be supplemented by a prospective, modeling-based assessment of specific cases – to avoid unacceptable impacts on the environment.

#### **Tiered approach for mixture risk assessment and quality of exposure estimates**

- In the project, a tiered approach for mixture risk assessment has been proposed. Case studies with technical mixtures are needed to identify pitfalls and data gaps related to this proposal. In order to implement such an approach, more realistic exposure assessment tools as available yet might be necessary.
- Some representatives from industry argued that refinement of the risk characterization ratio could be easier done on the hazard side than on the exposure side. This way might lead to additional testing requirements (to get more data on chronic toxicity which are not available in many cases at the moment). The examples in the project interim reports show more possibilities for refinement from the exposure side.
- It has been acknowledged that data in registration dossiers have primarily a generic character (see point 2 of the next section to the same topic). Therefore RCR values as currently provided should not be interpreted to reflect the real exposure situation. It is a crucial problem that currently in most cases PECs generated under REACH cannot be used directly for a mixture risk assessment. This requires higher tiers in exposure assessment. The current generic character (of a modeled) PEC does not permit an adequate (technical) mixture risk assessment. Hazard indices, generated from generic assessment, do not provide adequate information. A generic assessment of environmental mixtures by the authorities, which have better data available, may be possible; however also this possibility needs to be checked. A hazard index > 1 of a technical mixture could trigger consequences such as additional risk management measures. In such a case, the hazard index should be based on a robust exposure prediction. It should not be based only on generic data on predicted environmental concentrations. Due to the current generic exposure estimations, registration dossiers might not provide adequate data to address mixture risk assessment. In addition, in general registrants do not know the other substances in the mixtures produced by formulators.

- For petroleum substances, which are complex mixtures, CONCAWE<sup>107</sup> developed a specific methodology to calculate risk characterization ratio. The so-called “Overall substance risk” is assessed by summing PEC/PNEC ratios across constituents. The Hydrocarbon Block Methodology (HBM) is implemented in the tool “PetroRisk” –for the risk assessment of petroleum substances.
- An analysis would be helpful whether it is possible to integrate existing whole mixture tests in mixture assessment or priority setting procedures under REACH. The scope of these tests has to be clarified in order to decide how they can be used for the assessment of technical or coincidental mixtures.
- It may be useful to distinguish between mixture assessment tasks with a local and with a regional relevance. Local tasks are related to the assessment of technical mixtures and their impacts on a local scale. Regional tasks are related to complex environmental mixtures due to multiple sources. Mixture risk assessments of technical mixtures and coincidental mixtures could be assigned to industry, mixture risk assessments of complex environmental mixtures to authorities.

#### **Mixture assessment triggering substances (MATs), priority setting and related issues**

- In the project, a proposal has been made to use “mixture assessment triggering substances” (MATs) to identify mixtures which require further assessment. The process is slow and reactive, nevertheless it could be an important starting point to implement mixture assessments. It requires qualified exposure data. Priorities can only be set, when hazard indices are available.
- The identification of indicators for the need of an additional mixture risk assessment should mainly be “risk based”. However, analysis of registration dossiers showed that the risk characterization ratios (RCR) in most cases are “1”; they do not reflect the real exposure situation (see also point 3 in the previous section). Within REACH, RCR is provided as a “process figure” in a decision process. It indicates in the process of exposure assessment and risk characterization that the conditions of use describe a “safe use”. Because RCRs in most cases do not describe real exposure situations, it is difficult for authorities to use the RCRs for additional purposes, e.g. prioritization of substances or mixtures for further assessments.
- Generic exposure data, which are generated with the current methodology for deriving PECs under REACH, were by many participants not seen as useful to prioritise mixtures or single substances for further assessments. They refer to a low tier assessment. Requirements for further mixture assessments should be based on exposure data of high quality, which reflect real exposure situations. The question is how to get them and who should generate them.
- Environmental mixtures of concern may reflect some (eco)toxicological properties of technical mixtures. The presence of specific substance(s) in a technical mixture could indicate such a property. A mixture with such a substance would be of concern because of potential mixture effects which lead to a risk. This property could be used as a priority criterion to identify priority technical mixtures. Beside this, concerns identified

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<sup>107</sup> CONCAWE is the abbreviation for The European Oil Companies' Association for Environment, Health and Safety in Refining and Distribution.



from environmental mixtures may be the legitimate cause to perform a mixture risk assessment on a technical mixture (if there is a causal link between the concern, found in the environment, and the technical mixture).

- Besides a prioritization based on risks, it should be checked whether technical mixtures containing “Close – to – PBT – substances” (which do not fulfill all three REACH Annex XIII PBT criteria) should belong to priority mixtures for an additional assessment.
- Category building might help to identify priorities; for each category registration a mixture risk assessment could be performed for similar uses.
- There is some doubt about the function of monitoring to identify priority mixtures. Currently for many substances no data are available, as the data are restricted to a limited number of substances included in the programs. On-going activities to use monitoring for mixture assessment in the United States have been mentioned in the workshop.

### **Mixture risk assessment by industry**

- Possibilities for industry to perform a mixture risk assessment are limited due to the inhomogeneous distribution of knowledge in the supply chains. For a specific actor (e.g. a registrant or a formulator) not all required parameters on a technical mixture are known. Mixture assessment would require an intense exchange of information between different actors.
- The project team assumes that the most appropriate industry actor for mixture risk assessment of technical mixtures could be the formulator, if he is supplied with additional information from upstream (registrant) and downstream (final user of the mixtures).
- The combined assessment of closely related substances within the chemical safety assessment has been considered as self-evident from some participants. They argue that they use “read across”. However, this is not the same as mixture assessment.

### **Mixture risk assessment by authorities and related tasks**

- Authorities can have a special function: they may look beyond the fences of a factory and integrate data in order to provide indications of the existence of combined exposures and of mixture risks. In this way they can come up with crucial additional information (leading to MATS or priority mixtures). Such information could link emissions of technical mixtures to environmental mixtures and vice versa.
- From the different options to act proposed, substance evaluation seems to be the most relevant starting point for authorities to take into account mixture risks in their assessments. For this task the legal situation and the responsibilities are clear. Besides substance evaluation, authorization should consider combined exposure. Consequences for “adequate control” remained unclear. Authorities should clarify whether they look at aggregated amounts from different applicants and uses and/or include assessment of combined exposures (beyond substances which are structurally closely related).
- Restrictions are a suitable risk management tool that could address mixture risks at EU level. Also in this case, exposure data of high quality are needed.
- Consideration of aggregated exposures by downstream users seems useful. It would be helpful if the German Federal Environment Agency clarifies the position on aggregated

exposure and on current understanding of mixture risk assessment under REACH in relation to single substances.

- At present, focus of priorities from authorities often refers to human health aspects. Environmental aspects are lagging behind. Priorities of member states and competent authorities, which refer to human health, should be extended / should include environmental effects.

#### **Further discussion points**

- The assumption/finding that a few substances drive the risk in many mixtures and the consequences for the assessment of mixtures should be discussed more in detail.
- It has been proposed from some participants to limit the accepted risk characterisation ratio for a specific regulation to a value below 1. It reflects the position of the Nordic Council to consider different legislations in a holistic approach. This could become a trigger to improve the quality of the exposure estimations. A similar approach has been used in the project with the MATS cut off of 0.1.
- Some participants had the impression that methods for mixture risk assessment of technical mixtures are already available and should be implemented (e.g. under biocidal products legislation and the pesticides legislation). These approaches use a tiered structure – as usual for the assessment of single substances. However, even if tiered methods for mixture assessments of technical mixtures are available – in most cases no adequate data are available to perform such a tiered approach with sufficient quality to get meaningful results (see point 3 in section 2.2.2 and point 2 in section 2.2.3 ).

#### **Part VI: Final discussion**

All presenters from the first day were asked to give some feedback on the discussions during the workshop.

Enken Hassold from the German Federal Environmental Agency concluded that there are already lots of ideas for starting points and that this complex issue has to be taken step by step; it will be a long term process. Crucial point is that data are missing on exposure and it is necessary to plan measures to address this. Substance evaluation is a good step to start and gain experiences. All stakeholders need to be involved and contribute their part (research, industry, authorities).

Chrystele Tissier from ECHA sees the main relevance in the task to find a good way for priority setting. However, in some of presented 4M concepts it was sometimes too unclear if the technical mixture is meant (job for industry) or the environmental mixture (job for authority). In principle, MATS may be a good idea, but maybe not quite worked out, yet. Indeed, RCR should not be used as a stand-alone prioritization tool, as it needs to be seen in combination with the RMMs and OCs. The issues of potential mixture toxicity should be more addressed during their substance evaluation activities (finding the right substances for the CoRAP!) On the exposure data: the starting point should be the registration dossiers, but in many cases the data situation does not allow a detailed assessment of mixture risks.

Lone Mikkelsen from the Danish EcoCouncil took the view that the scientific concepts are all available and the question is rather how determined the policymakers are to put them into regulatory practice. Real life exposure means being exposed to many substances at the same time, so that the general exposure to harmful substances should be reduced and safer alternatives should be used. The Danish EcoCouncil is in general very concerned about the

quality of registration dossiers and REACH compliance seems to be very low already for the single substances.

Kristian Syberg from Roskilde University made the strong request to use concentration addition as the default method (and not demand the knowledge of mode of action which does not make sense for the environment, see day 1). Grouping chemicals should be based rather on relevance (e.g. co-occurrence in environmental media), but not on similarity of action. He encouraged also to focus on the “almost SVHC” chemicals, i.e. those that may be nearly PBT but don’t quite qualify for the REACH candidate list. Here the mixture assessment could lead to a real different outcome and better protection of the environment.

Mercedes Vinas from CEFIC requested to clarify the relevance of the project. Moreover, it should always be specified which mixtures are meant in a specific context. The RCR should not be overestimated because the value itself is a process figure in a decision finding context. Therefore, she did not consider it useful for further triggering of action. The main aim should be to use existing REACH elements better (e.g. substance evaluation) and use other existing laws to address the missing links. Industry has proven safe uses of their chemicals and lots of data were submitted and this should be given credit.

In the discussion it was raised that whatever can be done within REACH, it will always be limited to industrial chemicals, but what is needed in the future is a more horizontal, crosscutting approach which considers the cumulative exposure from pesticides, biocides, pharmaceuticals, cosmetics etc. Within REACH, only small steps can be gained, but obviously it’s good to take these. Industry reiterated the fact that they are already taking the mixtures in consideration and they are removing chemical risks of the individual substances and thereby reducing risks. Another participant saw an urgent need to improve the communication between local authorities (problem at local/regional level) and national authorities so that this can lead to tackling the problem more at a generic level.

It was critically questioned whether industry and authorities are ready to go as there is little knowledge on priority mixtures and even if the issue is relevant at all. One should wait for full implementation of REACH and then see if something is missing. One reply to this was that quite a lot of useful activities in this area were already started and we know that mixture assessment can be done in relevant cases – of course it is always important to consider the added value. Regarding the different options to act, it was recommended to set priorities and to differentiate between short, middle and long term actions.