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Basic principles for the development of a concept for environmental exposure assessments of single substances released from multiple uses under REACH

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Basic principles for the development of a concept for environmental exposure assessments of single substances released from multiple uses under REACH

by

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Annotation

The terms and definitions used in the ECHA guidance documents are not clearly defined and an overall harmonised definition on European and international level is not yet agreed. Due to this fact the present study uses the following wording as working definition:

“Cumulative exposure” to a chemical substance is the overall exposure to one substance resulting from releases through different uses, different sources or different products.

However, the German authorities agreed to use the term "aggregated" for the assessment of one substance from several sources or routes in the future under the REACH regulation.

Abstract

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 a cumulative 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 objective of the present study is a further specification of the guidelines on cumulative risk assessment according to the REACH Regulation.

Besides the definition of the key terminology, guidelines on cumulative 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 a cumulative exposure assessment might be relevant have been worked out. A distinction was made between cases where the responsibility for cumulative exposure assessment falls into the hands of the registrant as part of the Chemical Safety Report and other cases, where the responsibility lies with the downstream users (DU) or the Member State Competent Authorities (MS-CA).

Initial proposals have been elaborated for a technical implementation of the cumulative 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.

Kurzbeschreibung

Die ECHA Leitfäden R.12 bis R.18 enthalten detaillierte Vorgaben zur Durchführung der Expositionsbeurteilung im Rahmen des Stoffsicherheitsberichts. Die Leitfäden gehen allerdings nur eingeschränkt auf die Berücksichtigung von Einträgen eines Stoffes in die Umwelt ein, falls die lokalen Einträge aus verschiedenen Verwendungen des gleichen Stoffes stammen und in einer kumulativen Exposition resultieren. Bei einer Chemikalie mit mehreren Verwendungen an einem Standort kann es jedoch dazu kommen, dass sich die Einträge von verschiedenen und für sich betrachtet risikoarmen Verwendungen addieren und die resultierende Konzentration ein unannehmbares Risiko für die Umwelt darstellt.

Vor diesem Hintergrund zielt die vorliegende Studie auf die weitere Ausgestaltung der Leitlinien zur kumulativen Risikobewertung gemäß REACH-Verordnung.

Neben der Definition wichtiger Fachbegriffe werden bereits vorhandene Vorgaben zur kumulativen Expositionsabschätzung aus anderen rechtlichen Regelungsbereichen ausgewertet und deren Übertragbarkeit auf die Umweltexpositionsbeurteilung gemäß REACH geprüft. Des Weiteren werden Anwendungsbereiche herausgearbeitet, für die eine kumulative Expositionsabschätzung als relevant betrachtet wird.

Dabei wird unterschieden zwischen Fällen, in denen die Verantwortung für kumulative Umweltexpositionschätzungen beim Registranten im Rahmen des Stoffsicherheitsberichts liegt und anderen Fällen, in denen diese Aufgabe den nachgeschalteten Anwendern (DU) oder bewertenden Behörden der Mitgliedsstaaten (MS-CA) zufällt.

Es werden erste Vorschläge für eine technische Umsetzung der kumulativen Expositionsschätzung von Chemikalien im Rahmen der Erstellung und Evaluierung von Stoffdossiers durch den Registranten bzw. MS-CA gegeben sowie Vorschläge für die Berücksichtigung kumulativer Exposition durch den DU.

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List of Abbreviations

BPD	Biocidal Products Directive
CA	Competent Authority
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DMEL	Derived Minimum Effect Level
DNEL	Derived No Effect Level
DU	Downstream User
ECHA	European Chemicals Agency
ERC	Environmental Release Category
ES	Exposure Scenario
MS-CA	Member State Competent Authorities
NOEC	No Observed Effect Concentration
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentrations
PT	Product Type
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SDS	Safety Data Sheet
STP	Sewage Treatment Plant
TNsG	Technical Notes of Guidance on Annex I Inclusion[1]
vPvB	Very Persistent and very Bioaccumulative

[1] Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market

1 Background

In the framework of registrations for all substances which are manufactured or imported in quantities of >10 t/a, REACH requires the manufacturers/importers of these substances to carry out a Chemical Safety Assessment and to provide a Chemical Safety Report. If a substance is classified as "dangerous"[2] or if it is a PBT or vPvB substance, the Chemical Safety Report must contain an exposure assessment and a risk characterization for manufacture and all identified uses of the substance (REACH Art. 14.4).

According to the REACH concept, the objective of the exposure assessment shall be to make a quantitative or qualitative estimate of the dose/concentration to which the population and the environment is or may be exposed (for the environment: predicted environmental concentration, PEC). The exposure assessments have to consider all stages of a substance's life cycle arising out of the production, the identified uses and the waste stage. In order to obtain a risk assessment, the predicted environmental concentration is compared to the substance concentration at which no harmful effect on the environment will be provoked any more. In this respect, it is decisive not to underestimate the environmental exposure and to take care that emissions from different sources into the same compartment are not incorporated separately into the risk assessment but that the cumulative exposure is considered.

The ECHA Guidance Documents R.12 to R.18 include detailed provisions on how to conduct an exposure assessment. The guidance documents, however, do not specifically address emissions to the environment from various uses of the same substance i.e. cumulative 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 if they are released to the surface water via a point source, for example, and thus may adversely affect other environmental compartments.

Against this background, a concept taking into account the cumulative exposure in the environment is to be developed. The objective of the project is a further specification of the guidelines on cumulative risk assessment according to the REACH Regulation.

The project considers itself as a feasibility study for precise realization of the cumulative environmental exposure assessment in the framework of the Chemical Safety Assessment. Besides the definition of the key terminology, guidelines on cumulative exposure assessment already laid down in other legal regulations have been evaluated. Furthermore, their transferability to the environmental exposure assessment according to REACH has been investigated. Moreover, the ranges of application for which a cumulative exposure assessment might be relevant have been worked out. Initial proposals have been elaborated for a technical implementation of the cumulative exposure assessment of chemicals as part of the preparation and evaluation of chemical dossiers. These proposals are intended to be tabled to the EU with view to an implementation in the medium-term, thus enabling a harmonised approach throughout the EU.

[2] Classification in accordance with the criteria of "Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and preparations" (CLPVO)

2 Terms und Definitions

2.1 Terms and definitions in other regulatory areas

In the context of cumulative exposure and risk assessments a large variety of different terms and definitions is used. A detailed compilation of these terms and definitions is given in Groß et al. (2010).[3] Table 1 summarises the most often used terms and definitions applied in the context of cumulative risk assessment in the different regulatory areas.

Frequently used are for example the terms “additive”, “aggregate(d)”, “cumulative”, “combined”, in terms of both exposure and risk. However, the terms and definitions may have different meanings depending on the regulatory area (e.g. chemicals, pesticides and/or medicinal products) or the scientific context (e.g. toxicology, ecotoxicology, environmental fate) where they are applied (see Table 1). For example, in many regulatory areas dealing mainly with human health aspects the risk associated with multiple pathways/routes of exposure to a single chemical is often defined as “aggregate(d)” exposure or risk whereas “cumulative” risk/exposure applies to the impact of multiple chemicals with the same mode of action (e.g. US EPA 2002; EFSA 2008; WHO/IPCS 2009; BfR 2009). In contrast, Article 10(1) of the EU Biocide Directive 98/8/EC mentions “cumulation effects” in connection with the use of biocidal products containing the same active substance. Groß et al. (2010) proposed the following definition in the context of “cumulative” environmental exposure assessments of biocides:

“Cumulative exposure” to biocides is the overall exposure to the same biocidal active substance by emissions during the use, service life or waste phase of different biocidal products belonging to the same product type (PT) or different PTs. This definition takes the provisions of the BPD into account which only addresses cumulative exposure of one active substance within the boundary of this legislation.

[3] Definitions from the International Society of Exposure Science (ISEA glossary 2005), IUPAC Recommendations (IUPAC 2006) as well as documents from the regulatory authorities US EPA, from the European Food Safety Authority and documents from European (Kortenkamp & Hass 2009) and international panels (WHO/IPCS 2009) have been evaluated.

Table 1 Terms and definitions in the context of cumulative exposure assessment respectively cumulative risk assessment

Term	Definition (reference)	Comment
Additive Effect	Consequence that follows exposure to two or more physicochemical agents which act jointly but do not interact. The total effect is the simple sum of the effects of separate exposure to the agents under the same conditions (IUPAC 2006; cited from BfR 2009)	EFSA 2008 refers to the IUPAC definition
Aggregated consumer exposure	Exposure to a substance from multiple sources, because products contain many substances and a substance may be present in multiple products in many different forms (EU TGD 2003, Part I)	The term aggregated exposure is used in the EU TGD solely within the scope of consumer exposure assessment.
Aggregate Exposure	Sum total of all exposure to pesticides through inhalation, dermal, oral, or optic contact (IUPAC 2006; cited in BfR 2009)	
	Exposure to one chemical from all sources, for example; total exposure for someone living near to an industrial site from food, air, water and soil (UK Food Standards Agency 2002)	
	The demographic, spatial and temporal characteristics of exposure to a single chemical through all relevant pathways (e.g. food, water, residential uses, occupational) and routes (e.g. oral, dermal, inhalation) (WHO/IPCS 2009)	
	"[…] "aggregate" and "cumulative" are used as adjectives to modify "exposure" or "dose" without further elaboration. Often, "aggregate" and "cumulative" seem to be used interchangeably, suggesting (1) exposures that are from multiple sources, received via multiple exposure pathways, or doses received through multiple routes; (2) exposures or doses that accumulate over time, often over a lifetime; or (3) exposures or doses from more than one chemical or stressor simultaneously or sequentially" (IPCS 2004)	The Exposure Assessment Terminology Working Group [of the IPCS] identified four terms that were particularly difficult to define due to their relatively recent emergence as exposure terms. These are aggregate exposure, aggregate dose, cumulative exposure, and cumulative dose. In studying the literature, the Exposure Assessment Terminology Working Group found very few formal definitions of these terms (IPCS 2004)
Aggregate Exposure Assessment	Aggregate exposure assessment combines exposure from different pathways such as food, air and water and is important in considering the total personal exposure to a given chemical (UK Food Standards Agency 2002)	Focus on human health risk assessment; definition in connection with pesticides
Aggregate Risk	The risk associated with all pathways and routes of exposure to a single chemical (EFSA 2008 according to definition by US EPA 2002; cited from BfR 2009)	
	Aggregate risk is the risk associated with multiple pathways / routes of exposure to a single chemical (WHO/IPCS 2009)	
Aggregate Risk	Different routes of exposure to the same active substance, which considers:	Focus on human health risk assessment

Term	Definition (reference)	Comment
Assessment	the use of the same active substance in different biocidal PTs (e.g. wood preservative and insecticide) the use of the same active substance under different regulations (e.g. biocides, pesticides, veterinary drugs) the exposures from food, drinking water, and residential / nonoccupational uses (US EPA 2002; cited from BfR 2009)	
	Risk assessment taking all sources of intake of a given pesticide into account (UK Food Standards Agency 2002; cited from BfR 2009)	UK Food Standards Agency restricts the definition to a given pesticide that might contain several active compounds.
Combined exposure	Combined exposure of humans via two or more routes (EU TGD 2003, Part I); Exposure to a substance under different circumstances (e.g. exposure at the workplace and exposure from consumer products / indirect exposure via the environment) (EU TGD 2003, Part III)	The term "combined exposure" is used in the EU TGD solely within the scope of consumer exposure assessment.
Combination effect, mixture effect, joint effect	The response of a biological system to several chemicals, either after simultaneous or sequential exposure. The terms are used synonymously (Kortenkamp & Hass 2009)	
Concomitant exposure	Situations where the same person is potentially exposed to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance (REACH guidance Part E).	
Concurrent exposure	Interpreted as potential human exposure by all relevant pathways, durations, and routes that allow one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures as well as any sequential exposures that could contribute to the same joint risk, either by overlapping internal doses or by overlapping toxic effects (US EPA 2002, EFSA 2008; cited from BfR 2009)	
Cumulative Assessment Group (CAG)	A group of chemicals that could plausibly act by a common mode of action, not all of which will necessarily do so. Membership of a CAG can usually be refined (reduced) by application of successively higher tiers of the approach described in this Opinion (EFSA 2008; cited from BfR 2009)	
Cumulative ecological risk assessment	A process that involves consideration of the aggregate ecological risk to the target entity caused by the accumulation of risk from multiple stressors (EPA/630/R-95/002F April 1998 Guidelines for Ecological Risk Assessment)	

Term	Definition (reference)	Comment
Cumulative effect	Overall change which occurs after repeated doses of a substance or radiation (IUPAC 2006)	
	Effect resulting from repeated releases of a chemical that gives rise to a "background concentration" in the environment (EU TGD 2003, Part II)	The EU TGD, Part II Environmental Risk Assessment does not mention the term "aggregate" and does not define the terms "combined" and "cumulative". However, unlike the term "cumulative", "combined" rather refers to "multiple chemicals".
Cumulative Exposure	Exposure to multiple chemicals on the basis of whether they have a common mechanism of action (UK Food Standards 2002)	
	Cumulative exposure defines the aggregate exposure to multiple chemicals (WHO/IPCS 2009)	
Cumulative Exposure Assessment	Cumulative [exposure] assessment estimates exposure to multiple chemicals on the basis of whether they have a common mechanism of action (WHO/IPCS 2009)	
	An assessment that describes concurrent spatial and temporal characteristics of exposure performed for a set of chemicals (ILSI 1999; cited from BfR 2009)	
Cumulative Risk	Probability of any defined harmful effect occurring through a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity (IUPAC 2006; cited from BfR 2009)	EFSA 2008 also refers to the IUPAC definition, with an additional note: "in the context of this opinion, it is intended more specifically to be the risk deriving from the exposure to compounds that share the same mode of action (dose addition) or that have similar effects but do not act at the same molecular target (response addition) and is contrasted to synergistic risk. Although the term "cumulative risk" has sometimes been used when referring generally to the risk from exposure to more than one pesticide (see EFSA colloquium), in the context of this opinion, it refers more specifically to the risk deriving from combined exposure to compounds that share the same mode of action or that have similar effects but by different modes of action (EFSA 2008; cited from BfR 2009)
	The risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity (US EPA 2002; cited from BfR 2009)	
	Cumulative risk is the combined risk from aggregate exposure to multiple	

Term	Definition (reference)	Comment
	chemicals (and may be restricted to chemicals that have a common mechanism of toxicity) (WHO/IPCS 2009)	
Cumulative Risk Assessment	Taking intake of more than one pesticide into account (UK Food Standards Agency 2002; cited from BfR 2009)	
	Risk assessment approaches that consider the impact of multiple chemical exposures, from multiple sources, routes and pathways, over multiple time frames (Kortenkamp & Hass 2009)	Cumulative risk assessment (CRA), mixtures risk assessment: The terms are used synonymously by Kortenkamp & Hass (2009) "It is worth noting that the European use of the term "cumulative risk assessment" encompasses multiple sources, routes and pathways, but restricts considerations to one chemical, not multiple chemicals. For the purposes of this report, the European use of the term is ignored." (Kortenkamp & Hass 2009)
	Exposure to multiple substances by multiple pathways (including food, drinking water, and residential / non-occupational exposure to air, soil, grass, and indoor surfaces) (US EPA 2002; cited from BfR 2009)	
Effect assessment	Combination of analysis and inference of possible consequences of the exposure to a particular agent (e.g., pesticide) based on knowledge of the dose-effect relationship associated with that agent in a specific target organism, system, or (sub-) population (IUPAC 2006)	
	The effects assessment comprises the following steps of the risk assessment procedure: 1) hazard identification: The aim of the hazard identification is to identify the effects of concern; 2) dose (concentration) – response (effect) assessment: At this step the predicted no effect concentration (PNEC), shall, where possible, be determined. (EU TGD 2003).	
Exposure	Contact between an agent and a target. Contact takes place at an exposure surface over an exposure period (ISEA glossary 2005; cited from BfR 2009)	
	Concentration or amount of a pesticide (or agent) that reaches a target organism, system, or (sub-) population in a specific frequency for a defined duration (IUPAC 2006; cited from BfR 2009)	EFSA 2008 refers to IUPAC 2006
	Relates to the following options: simultaneous and/or sequential exposure, nature of exposure: duration, frequency, timing, magnitude of exposure: exposure concentration and dose (US EPA 2002; cited from BfR 2009)	

Term	Definition (reference)	Comment
	Exposure to the same substance by multiple pathways and routes is likely best described as "Single Chemical, All Routes" (referenced in some jurisdictions as "Aggregate Exposure"). Similarly, it is recommended that exposure to "Multiple Chemicals by a Single Route" be distinguished from "Multiple Chemicals by Multiple Routes". To this end, the framework being developed addresses "Combined Exposures to Multiple Chemicals" (WHO/IPCS 2009)	
	Exposure (of the environment) results from discharges and/or releases of chemicals. (EU TGD 2003)	
Exposure Assessment	The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment (ISEA glossary 2005; cited from BfR 2009)	EFSA 2008 refers to ISEA glossary 2005
	Evaluation of the exposure of an organism, system, or (sub-) population to a pesticide or agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment (IUPAC 2006; cited from BfR 2009)	
	The environment may be exposed to chemical substances during all stages of their life-cycle from production to disposal or recovery. For each environmental compartment (air, soil, water, sediment) potentially exposed, the exposure concentrations should be derived. (EU TGD 2003)	
Exposure Pathway	The course an agent takes from the source to the target (ISEA glossary 2005; cited from BfR 2009)	EFSA 2008 refers to ISEA glossary 2005
	The physical course a substance takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential substance / biocidal uses). (US EPA 2002; cited from BfR 2009)	
Exposure Route	The way an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption) (ISEA glossary 2005; cited from BfR 2009)	EFSA 2008 refers to ISEA glossary 2005; US EPA very similar definition
Exposure Scenario	A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, micro-environment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure. (ISEA glossary 2005; cited from BfR 2009)	EFSA 2008 refers to ISEA glossary 2005; US EPA very similar definition
	Generic exposure scenarios assume that substances are emitted into a non-	

Term	Definition (reference)	Comment
	existing model environment with predefined agreed environmental characteristics. These environmental characteristics can be average values or reasonable worst-case values depending on the parameter in question. Generic exposure scenarios have been defined for local emissions from a point source and for emissions into a larger region. When more specific information on the emission of a substance is available, it may well be possible to refine the generic or site-specific assessment. (EU TGD 2003)	
Mixture risk assessment	Risk assessments for substances that are mixtures themselves, products that contain more than one chemical, chemicals jointly emitted during production, transport, use and disposal and chemicals that might occur together e.g. in environmental compartments or food items. (Kortenkamp et al. 2009)	
Mixture toxicity	Unwanted adverse effects of mixtures of chemicals. (Kortenkamp et al. 2009)	Synonym for combined effect
Overall environmental risk	Caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments (REACH Annex 1)	
Overall exposure	Overall exposure (combined for all relevant emission/release sources) Human health (combined for all exposure routes) Environment (combined for all emission sources) (REACH Annex 1)	

2.2 REACH Guidance Documents

Taking into account the different and not harmonised meanings of the terms and definitions used in the context of exposure assessments (see Table 1), it is important to define their exact meaning in the context of REACH.

Therefore, the respective guidance documents under REACH[4] have been screened and evaluated for terms, definitions and principles used in the context of "cumulative"[5] exposure and risk assessments (both for human health and environment).

Guidance on Information Requirements and Chemical Safety Assessment under REACH consists of Concise guidance (Part A to G) and supporting reference guidance (Chapters R.2 to R.20). The structure of the Guidance under REACH is illustrated in Figure 1.

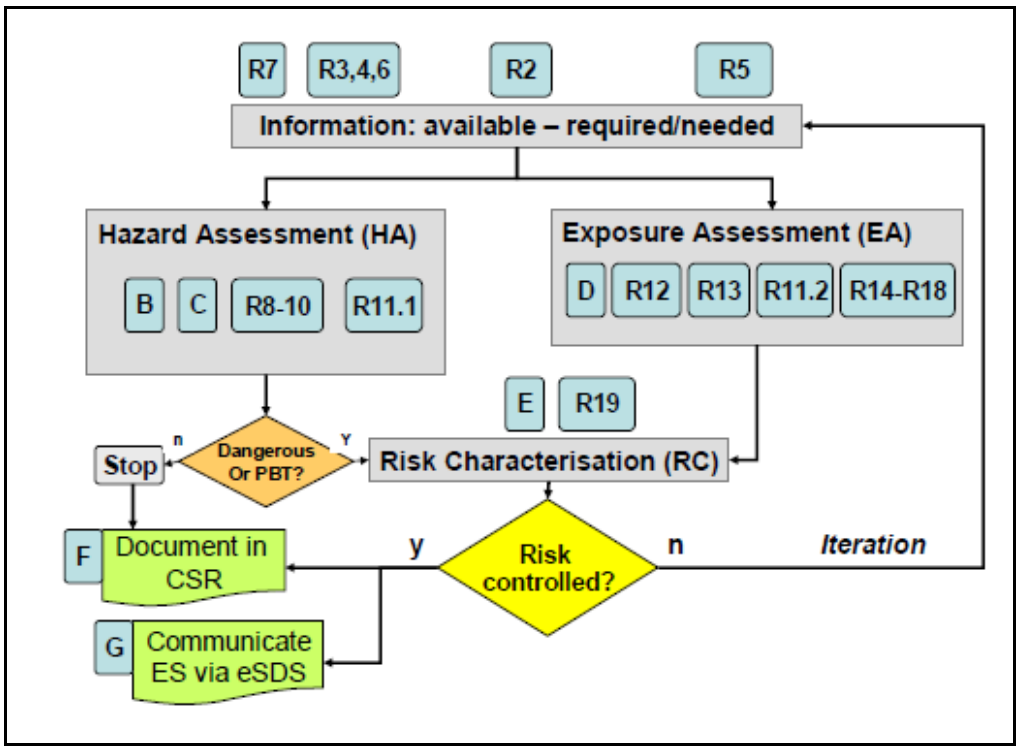

Figure 1 Structure of Guidance Documents under REACH (© ECHA)

The following guidance documents and chapters were identified as relevant for this project:

- Part B (Hazard Assessment),
- Part C (PBT Assessment),
- Part D (Exposure Scenario Building),
- Part E (Risk Characterisation),

[4] ECHA Guidance on information requirements and chemical safety assessment: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm? time=1258970710#E

[5] The documents were screened for the terms „cumulative", „combined", „aggregate", „concomitant" and „additive".

- Part F (Chemical Safety Report),
- Chapters R.12 to R.18 ; with special focus on Chapter R.16 : Guidance on environmental exposure estimation.

2.2.1 Part B: Hazard Assessment

In Part B, one reference is made to "combined" exposure assessments. Section B.7.1.3 gives an overview of aspects to be considered in derivation of DNEL(s) / DMEL(s) (page 36):

> *"DNELs may have to be derived for workers (dermal and inhalation exposure) and the general population (consumers and humans via the environment; dermal, inhalation, and/or oral exposure). If relevant, also* ***combined exposures*** *via different routes may need to be assessed."*

2.2.2 Part C: PBT Assessment

In Part C, no reference is made to terms used in the context of "cumulative" exposure assessments.

2.2.3 Part D: Exposure Scenario Building

In Part D, no reference is made to terms used in the context of "cumulative" exposure assessments.

2.2.4 Part E: Risk Characterisation

Starting with the risk characterisation for human health (E.3.), the following guiding principle can be found in Part E:

> *"In situations where the same person is potentially exposed to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance, exposure scenarios reflecting these* ***concomitant exposures*** *should be assessed in the exposure estimation. These scenarios – typically related to workplaces and* ***aggregated exposure*** *for consumers – need specific attention in the risk characterisation step." (page 27)*
>
> *"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****. One way to conduct risk characterisation for* ***combined exposure*** *to closely related analogues could be to add exposures and to use a toxicological descriptor from a representative substance among the analogues. If data do not allow for a quantitative assessment, an attempt should be made to address the issue in a qualitative way. (page 27)*

> *"Additionally, in each case the applicant has to assess the need for an assessment of* ***combined exposure****, i.e., exposure from different uses of a substance. Normally, occupational exposure will greatly exceed all other exposure, and the contribution from consumer use or from exposure via the environment may not need to be added. However, for substances with consumer use, and which may be present in potential food items (as indicated by the EUSES-modelling), the combined exposure may need to be assessed for the general public exposed both via the food and via consumer products." (page 29)*

For the risk characterisation relating to the environment the same principle applies:

> *"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." (page 36, step 5 on combined exposures)*

2.2.5 Part F: Chemicals Safety Report

In the Appendix to Part F (CSR template with explanation) the following terms and definitions with regard to "cumulative" exposure assessment can be found:

Section F.10.1.1 on Risk characterisation of human health (page 87):

> *"Systematically go through the risk characterization ratios (Exposure / DNEL) for each population and exposure pathways relevant to the ES, and report the risk characterization ratios for these pathways or the relevant* ***combined pathways****."*
>
> *"Document the outcome of the* ***combined risk*** *via all pathways for the different populations separately, and* ***combined*** *(i.e.,* ***cumulative*** *for workplace, exposure from consumer products and via the environment). If such* ***combinations*** *are considered unrealistic, justify the relevant combinations of exposure."*
>
> *"Guidance on* ***combined exposure*** *via different routes (dermal & inhalation) is provided in Part E.3.5.1."*

Section F.10.1.2 on Risk characterisation of the environment (page 91):

> *"Systematically go through the risk characterization ratios (PEC / PNEC) for each population and exposure pathways relevant to the ES, and report the risk characterization ratios for these pathways or the* ***relevant combined pathways****."*

Section F.10.3 explicitly refers to the "Overall exposure (**combined** for all relevant emission/release sources)":

> "This section should present an evaluation of the risks due to combined exposure from the uses covered by different exposure scenarios. It is possible that uses of the same substance described in different ESs can lead to **combined exposure**, e.g. different consumer uses combined with exposure via the environment. In such cases the overall risk needs to be evaluated and presented here."

Here, for the risk characterisation relating to human health (**combined** for all exposure routes), the following guidance is given in chapter F.10.3.1 on page 92:

> *"When relevant select the **combinations of exposure scenarios** which could result in **concomitant exposure of humans**. Guidance on combined exposure is provided in Part E.3.5."*

For the risk characterisation relating to the environment (combined for all emission sources) the same principle applies (chapter F.10.3.2 on page 93):

> *"Identify whether local exposure could occur through different exposure scenario and estimate the risk for such a situation when relevant.*
>
> *In addition, if exposure occurs to a substance as well as to several very closely related and similar acting chemical substances the exposure evaluation and risk characterisation should reflect this aspect."*

2.2.6 Chapter R.14: Occupational exposure estimation

The following references are given in R.14 with regard to "cumulative" assessments:

> *"In scenarios where a person is potentially exposed to the same substance from different products – typically related to **combined exposure** at a workplace and as a consumer, e.g. in hobbies – exposure scenarios reflecting these **concomitant exposures** should be assessed in the exposure estimation in the risk characterisation step (see further Guidance Part E)." (page 13)*

2.2.7 Chapter R.15: Consumer exposure estimation

Section R.15.2.1. defines the scope of the consumer exposure estimation and specifies that:

> *"The registrant should consider addressing **combined risks** from different uses of his substance in chapter 10 of the chemical safety report (CSR). He is, however, not obliged to carry out a risk characterisation related to uses of the substance not covered in his own registration." (page 3)*

R.15.2.2. Reasonable worst-case situations

> *"Exposure due to the use of a consumer product or article can occur via different pathways, e.g. both via inhalation and dermal contact. In such cases, **combined exposure** is calculated to estimate the total exposure." (page 4)*

R.15.2.6. Combined uptake

> *"If the same substance (for a single registration) occurs in different consumer products or articles that could reasonably be expected to be used jointly and frequently by an average consumer, it is advised to also calculate the* ***combined risk****, in order to prevent underestimation of risk" (page 4)*

R.15.7. Risk Characterisation

> *„If a consumer is exposed to a substance via several consumer products or articles that are likely to be used in combination, the contribution of each product and the corresponding routes to the total risk should be summed. .... The* ***combined risk characterisation ratios*** *for different products can be documented and evaluated under chapter 10 of the CSR." (page 37)*

2.2.8 Chapter R.16: Environmental exposure estimation

The following references are given in R.16 with regard to "cumulative" assessments:

> *"The 'Wide dispersive use' scenario (R.16.2.2) describes releases derived from consumers, professional and service life uses. ... Since all releases to water from each identified wide disperse use will by default enter into the same sewage system,* ***combined risk*** *should be considered. For assessing the* ***combined risk****, the local releases to water of all wide dispersive uses should be summed up." (Document History and Guidance for implementing the updates)*

> *"Releases from uses in industrial settings are assessed as independent point source releases; it means that each identified use of the substance is assumed to occur at a different site. However, in some cases, it is needed to combine those assessments in the "****combined risk****" section of the CSR, e.g. when manufacture and formulation take place at the same site." (page 5)*

In this context a combined exposure assessment is also deemed necessary by Competent Authorities in such situations where several indirect dischargers are located in close vicinity to each other releasing the substance into the same surface water.

> *"A wide disperse use of a substance is characterised by the assumption that the substance is used by consumers or by many users in the public domain, including small, non industrial companies. ... The local tonnage used by consumers or by many users in the public domain (including small companies) is calculated from the manufactured tonnage. This calculation is carried out for each wide disperse use of the substance. Since all these releases will by default enter into the same sewage system,* ***combined risk*** *should be considered in section 10 of the CSR (see part F)." (page 6)*

> *"In a situation where a substance is released through several point sources into the same river, the resulting* ***cumulative concentration*** *may in a first approach be estimated by assuming it to be released from one point source." (page 62)*

This paragraph implies also that in a situation where a substance is released both from industrial settings and from wide dispersive uses into the same river, the local releases to water of all these uses should be summed up.

2.2.9 Chapter R.17: Estimation of exposure from articles

R.17.4: Release and exposure estimation for the environment

> *"For environmental exposure to substances in articles, the **aggregate emissions** from the total weight or area of the articles in which the substance is contained should be taken into account instead of the weight or shape of a single object handled, chewed on or ingested as when human exposure is assessed."*

2.2.10 Guidance on Dossier and Substance Evaluation

The above mentioned Guidance on Information Requirements and Chemical Safety is part of a series of guidance documents which aim to help **registrants** with their preparation for fulfilling their obligations under the REACH Regulation. Thus, the focus lays on the registration dossiers of single registrants. However, the requirement of "cumulative" exposure assessments is also expressed in guidance documents that are intended mainly for the use by authorities who need to keep in mind all registration dossiers submitted by various registrants for the same substance.

The Guidance on Dossier and Substance Evaluation specifies grounds for considering that a substance constitutes a risk to human health or the environment (section 3.2.2.1).

These grounds of concern include the following aspects related to exposure data:

- Aggregated tonnage from all registrants is significantly higher than the tonnage per registrant and raises concern with respect to high exposure on a local and/or regional scale (in case of long-range-transport-pollutants, even global exposure may be of importance).
- Aggregated exposure from similar acting substances.
- Dossiers from several registrants of the same substance indicate exposure concentrations (PECs) close to the PNEC values.

2.2.11 Guidance for the preparation of an Annex XV dossier for restrictions

The Guidance for the preparation of an Annex XV dossier for restrictions emphasises that

> *"For the purposes of a restriction proposal, exposure assessment may need to take into account other sources of the exposure than those resulting from (a single) registration."*
>
> *Consideration of the **aggregated** emissions to the environment will lead to changes in the regional emissions to the environment and hence to the regional concentrations (and in the local PECs too) (section 5.2.3).*

The following references are given in section 5.2.3.2 (Environmental exposure) with regard to "cumulative" assessments:

> ***Aggregated or total exposures***
>
> *A common reason for preparing an Annex XV restriction dossier is likely to be that there are a number of registration dossiers for a substance and the Authority has concerns that the **overall exposure** is not addressed in the individual registrations.*

*In such cases an estimate of **total exposure** is required, using estimates of **total emissions**.*

2.2.12 Overview on terms and definitions used in ECHA Guidance Documents

Table 2 gives an overview on the terms and definitions used in ECHA Guidance Documents in the context of "cumulative" exposure assessments. The compilation illustrates that the terms are not clearly defined and have different meaning. The term most often used in this context is "combined". It is used to express

- exposure to closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances
- exposure to the same substance from different uses or from different products
- exposure to the same substance via different routes (e.g. dermal & inhalation)

The terms "combined", "concomitant" and "aggregated" are often used synonymously.

Table 2 Overview on terms and definitions used in ECHA Guidance Documents

Term	Context in which the term is used in ECHA Guidance Documents	Reference (ECHA Guidance Documents)
Aggregate emissions	Emissions from the total weight or area of the articles in which the substance is contained (in contrast to the weight or shape of a single object)	Chapter R.17
Aggregated exposure	Exposure to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance	Part E
	Exposure from similar acting substances	Guidance Document on Dossier and Substance Evaluation
Aggregated tonnage	Total tonnage produced/imported from all registrants	
Concomitant exposure	Exposure to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance	Part E; Appendix to Part F; Chapter R.14
	Combination of all exposure routes	Appendix to Part F
Combined exposure	Exposure to closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances	Part E
	Exposure to the same substance from different uses or from different products	Part E; Appendix to Part F; Chapter R.14
	Exposure to the same substance via different routes (e.g. dermal & inhalation)	Appendix to Part F; Chapter R.15
Combined risk	Risk via all pathways (i.e. cumulative for workplace, from consumer products and via the environment)	Appendix to Part F
	Risks from different uses of a substance	Chapter R.15
	Risk resulting from all (local) releases from each identified (wide dispersive) use	Chapter R.16
Overall exposure	Exposure combined for all relevant emission/release sources	Appendix to Part F; Guidance for the preparation of an Annex XV dossier for restrictions
Cumulative concentration	Substance concentration resulting from releases through several sources	Chapter R.16

Due to the fact that the terms and definitions used in the ECHA guidance documents are not clearly defined and have quite different meanings (see Table 2), the present study uses the term **"cumulative exposure"** in order to express the environmental exposure to a single substance resulting from its multiple use.

In this regard, the following wording is proposed as working definition in the present study: **"Cumulative exposure"** to a chemical substance is the overall exposure to the same substance resulting from releases through different uses, different sources or different products.

For further discussion it needs however to be kept in mind that this definition is not necessarily in agreement with other regulatory areas, especially those ones dealing with human health aspects.

Here, an agreement with other regulatory areas and an overall harmonised definition on European and international level is necessary and reasonable.

3 Compilation of existing approaches other than REACH

The following subchapters summarise approaches of cumulative risk assessments discussed or already applied in other regulatory areas outside the scope of REACH. Further approaches have already been summarised by Groß et al. 2010.

Up to now, each regulatory area follows its own legislation with regard to human and environmental risk assessments without any integrated approach. These lacking interlinkages between the regulations are discussed in chapter 7.1.

3.1 Biocidal Product Directive 98/8/EC

Article 10(1) of the EU Biocidal Products Directive 98/8/EC (BPD) states that for the inclusion of an active substance in Annex I, Annex IA or IB cumulation effects from the use of different biocidal products containing the same active substance shall be taken into account, where relevant. It has to be noted that this refers to both environmental and human health risk assessment and refers to one active substance contained in different products of the same Product Type (PT) or of different PTs[6]. These provisions have also been considered in Article 8 (3) of the draft Regulation for biocidal products. [7]

Additionally, in the TNsG on Annex I inclusion it is stated that

> *"For the first evaluation of the active substance the applicant (in the dossier) and the Competent Authority (in the report) should consider what combination of exposures to the active substance from all the representative uses is realistically possible. This should be based on the combined exposures for each use. A relevant time period for the pattern of use of the products and the nature of the active substance should*

[6] Annex V to Directive 98/8/EC provides a detailed description of the different biocidal product types (PTs).

[7] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2009:0267:FIN:EN:PDF

> *be decided and explained in each case. The assessment should reflect normal lifestyles and emission patterns. Realistic worst case possible combinations of exposures should also be considered." (ECB 2008a).*

According to the provisions given in the BPD cumulative risk assessments shall not be carried out routinely in the Review Programme but only where relevant. Such relevance arises if sufficient scientific support is available indicating that cumulative exposure could lead to additional adverse effects beyond those that have already been estimated in the risk assessment of the single uses (European Commission 2007).

A view on the number of biocidal active substance to be assessed in the Review programme reveals that from about 270 different active substances about 716 "active substance – product type" – combinations are currently under evaluation. The actualised data basis was provided by the European Commission in May 2010. This means that one active substance on average is included in three PTs. Some substances, such as glutaraldehyde, 2-biphenylol or didecyldimethylammonium chloride (DDAC) are included in up to 9 PTs, silver chloride even in 11 PTs. In principle, the different PTs are considered as different application areas and therefore different exposure routes of the same chemical to the environment. Exposure of the same active substance from other uses such as plant protection products, medicinal products, general chemicals etc. are outside of the scope of the BPD and therefore not considered. According to the TNsG on product evaluation, the BPD requires that the risks from products are assessed (ECB 2008b). For the life cycle stages "production of the active substance" and "formulation of the biocidal product" the BPD refers to REACH. REACH does not exclude biocidal active substances from its scope. Active substances used in biocidal products are considered substances for the purposes of REACH. However, the quantities of active substances intended for biocidal uses only are subject to specific provisions of the REACH Regulation in relation to the obligation to register. Additionally, uses of all substances (active or non-active) in biocidal products only are exempted from the authorisation requirements under REACH.[8]

At the Arona Workshop for PTs 1 to 6 (European Commission 2008), the question was raised whether PECregional should be used for the cumulative exposure assessment (at least for wide dispersive uses).[9] According to the Technical Guidance Document on Risk Assessment for chemical substances the regional concentration for each environmental compartment is calculated from the sum of releases from all uses in all life cycle stages of the substance in a particular region (EU TGD, 2003). The regional system is an area of 200 by 200 km with 20 million inhabitants. Unless specific information on use or emission per capita is available, it is assumed that 10% of the European production and use of a chemical takes place within this area, i.e. 10% of the estimated emission is used as input for the region. Although according to Annex II A, point 5.8 of the BPD industry should provide data on the likely tonnage to be placed on the market, these data are considered confidential and are often not available for the

[8] CA-Sept08-Doc.12.1. Inter-linkages between the REACH Regulation and the Biocides Directive (98/8/EC)

[9] PTs 1-6 include: PT 1: Human hygiene biocidal products; PT 2: Private area and public health area disinfectants and other biocidal products; PT 3: Veterinary hygiene biocidal products; PT 4: Food and feed area disinfectants; PT 5: Drinking water disinfectants and PT 6: In-can preservatives.

exposure assessment. Also, Regulation (EC) No 1185/2009 concerning statistics on pesticides does not consider biocides so far but indicates that the scope may be expanded at a later stage so as to include biocides. Any data that improve knowledge about production, use pattern, typical applications and consumption data would be very useful for the risk assessment of biocides. Thus, cumulative exposure and the contribution of the PECregional are difficult to assess. Summarising, the BPD only considers cumulative exposure of the same active substance from uses of different product types where relevant.

In the Umweltbundesamt research project FKZ 360 04 030 a concept on how to assess cumulative environmental exposure of biocides has been elaborated (Groß et al. 2010). Different parameters were identified which might serve as indicators for the relevance of cumulative exposure assessments for biocidal active substances:

1. One indicator is whether the active substance is covered by other regulatory areas such as plant protection products, human or veterinary medicinal products, preservatives for cosmetics, food or feed additives etc. If the overall biocides use is lower than a trigger value of e.g. 10%, it can be assumed that emissions to the environment from non-biocidal uses predominate and that therefore a cumulative exposure assessment only for biocides does not seem reasonable.
2. The strongest indicator of possible cumulative exposure to the environment is the overlap of different biocidal uses in space and time.
3. The number of PTs for which an active substance is defended was identified as another indicator for possible cumulative exposure. This trigger was set to a value of 4 different PTs meaning that if an active substance is defended for 4 or more different PTs, cumulative exposure is very likely to occur. For those active substances included in 2–4 PTs it is suggested that a rough estimate of the risk quotient (PECsingle uses/PNEC) is carried out. If the risk quotient for one single use exceeds 0.1, for example, a cumulative exposure assessment should be carried out.

It was concluded that each cumulative exposure assessment must consider the possibility that there might be an overlap in time and space. A level of concern is reached where the risk quotient (∑PECsingle uses /PNEC) exceeds 1.

Example calculations which were performed to illustrate the relation between PEClocal and PECregional revealed that cumulative PEC calculated on basis of the PECregional are significantly lower than the sum of the Clocal of all single uses. The higher the number of single uses, the higher is the discrepancy between the two approaches. Consequently, the "PECregional approach" might underestimate the environmental concentrations resulting from simultaneous and/or spatial overlapping uses of the same active substance. The summation of local concentrations of all single uses (∑Clocal) approach is more conservative and for some cases even more realistic. However, no final conclusion was possible to decide upon which approach describes better a specific emission situation. Also for the ∑Clocal approach the precision is highly depending on the availability of data. A huge disadvantage of the ∑Clocal approach is for sure the summing up of several realistic worst case scenarios. It is questionable if this approach is really satisfactory to derive conclusions of risks and with that on legal consequences for active substances.

3.2 Medicinal products

The assessment of environmental safety for **veterinary medicinal products** according to Directive 2001/82/EC is carried out in two phases. In the first phase the extent of environmental exposure is estimated and in the second phase the fate and effects of the active residue are assessed. The environmental risk assessment considers only the use phase of a veterinary medicinal product, but not the production or the waste phase. The revised guidelines on environmental impact assessment for veterinary medicinal products consider cumulative exposure from different pathways but do not account for cumulative exposure from different sources of different regulatory areas. In Phase I, a 100% release to the environment will normally be assumed (total residue approach). If there is no direct route to the manure (spilling, shedding from skin), there may be adsorption through the skin and subsequent excretion. In that case the pathways for internal administration should be considered. The fractions of externally applied products, which enter the environment via different routes should sum to 100% to provide a total residue approach (EMEA 2008).

Considering aquatic exposure scenarios in Phase II, it is recognised that there are different ways that contamination of the aquatic environment may occur and more than one of the described scenarios (e.g. excretion from animals, contamination of hard-standing areas, entry of animals treated with ectoparasiticides into surface waters, use and disposal of sheep dip, sheep wool processing effluent) may be relevant to an individual product. Therefore, it may be necessary to add the PEC values from the different routes of exposure to arrive at a PECtotal. On the other hand, by different routes of exposure the contamination of surface water may occur over a longer period of time. These factors should be considered when estimating the initial PECsurfacewater (EMEA 2004). However, in the supporting document no guidance is given on how to calculate PECtotal from different routes (EMEA 2008). Instead, only the most relevant routes are considered in practice and no examples are known where PECtotal has been calculated (Koch 2011).

In general, the data generated in Phase II will be on the parent compound following the total residue approach. But it is stated that the risk assessment should also consider relevant metabolites, especially from pro-drugs (drugs that are administrated in an inactive form) that are efficiently metabolized into a single metabolite for which testing may be more appropriate.

Where excretion data are available the active substance and relevant metabolites (defined as representing 10% or more of the administered dose and which do not form part of biochemical pathways) should be added to the PEC when it is recalculated (EMEA 2004).

The environmental risk assessment of **medicinal products for human use** according to Directive 2001/83/EC is routinely applied to all new marketing authorization for a medicinal product for human use. Phase I consists in a pre-screening of the exposure based on consumption data and the log Kow. As action limit value a PECsurfacewater value of 0.01 μg/L has been defined, which is calculated according to the following formula:

$$PEC_{Surfacewater} = \frac{\text{Dose}_{\text{Ai}} * F_{Pen}}{\text{Wastewater}_{\text{Inhabitant}} * \text{Dilution}}$$

where:

Dose_{Ai}	is the maximum daily dose consumed per inhabitant [mg *inh^{-1} d^{-1}]
F_{Pen}	is the fraction of market penetration [default = 0.01 or 1%]
$\text{Wastewater}_{\text{Inhabitant}}$	is the amount of wastewater per inhabitant per day [default = 200 L * inh^{1} d^{1}]
Dilution	is the dilution factor of wastewater in surface water [default = 10]

Phase II consists in an initial prediction of risk by a base set of aquatic toxicology and fate data (Tier A) and a compartment-specific refinement by an extended data set on emission, fate and effects (Tier B). Cumulative exposure of the active substance might be considered during the refinement of the PEC estimation as is described in the following.

In Phase II the market penetration factor F_{pen}, which represents the proportion of the population being treated daily with a specific drug substance, might be refined by consumption data as follows:

$$F_{Pen}\ [\%] = \frac{consumption\ [mg * a^{-1}] * 100}{DDD\,[mg * d^{-1}\ inhab^{-1}] * inhab * 365d\ a^{-1}}$$

where:

Consumption	is the overall consumed amount of the drug substance [mg*year^{-1}]
DDD	is the defined daily dose [mg * d^{-1} * inhabitant^{-1}]
Inhabitants	corresponds e.g. to the German population of 82,012,000 inhabitants

The consumption corresponds to the overall consumed amount of the drug substance from all suppliers (tonnage approach). Here, a market share of 100% of the drug substance is assumed for each applicant. The market share of 100% corresponds to one drug substances from all suppliers for the same medicinal indication including all generic drugs. However, the market share of chemically different drug substances used for the same indication of a disease is not considered.

In Phase I the action limit value of PECSurface water ≥ 0.01 µg L^{-1} is obtained by applying the default values and its exceeding always triggers a Phase II assessment. If an Fpen refinement is performed in Phase I and the resulting value is higher than the default value (0.01), the higher value is to be used in the ERA (EMEA 2010).

It should be noted, that the concept of the market penetration factor refers to the average amount released to the area of the country considered without taking into account urban centres. Therefore the PECSurface water rather corresponds to a PECregional than to a PEClocal.

The exposure assessment might be carried out by the applicant or by authorities. For (human) medicinal products consumption data are available e.g. from the Institut für Medizinische Statistik, Frankfurt (IMS Health) which maintains a data bank “Chemical Country Profile” containing statistics for annual German consumption of about 2700 drug substances. Thus, the data basis on total consumption is better than that for REACH where the aggregate volumes of substances produced / imported from different registrants is only voluntarily exchanged.

However, the exposure assessment of human medicinal products reflects the average load and therefore corresponds to a regional PEC while under REACH also local releases are being assessed.

3.3 Plant protection products

The evaluation, marketing and use of plant protection products (PPP) are regulated under Council Directive 91/414/EEC which will be replaced by Regulation (EC) No 1107/2009 from 14th June 2011 on. Neither the old Directive nor the new Regulation concerning the placing of plant protection products on the market explicitly state that cumulative exposure assessments have to be taken into account for the approval of an active substance in accordance with Annex II to the Regulation.

However, with regard to effects on human health, Article 4(2) of the Regulation states that:

> *"The residues of the plant protection products, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements:*

they shall not have any harmful effects on human health, including that of vulnerable groups, or animal health, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available, or on groundwater; (...)

> *(a) they shall not have any unacceptable effect on the environment."*

Similarly, Article 4(3) of the Regulation mentions that:

> *"A plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements:(...)*
>
> *(b) it shall have no immediate or delayed harmful effect on human health, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect effects, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available; or on groundwater; (...)"*

The focus of cumulative exposure considered in the Regulation is on human health aspects while it is not explicitly referred to environmental exposure.

The estimation of exposure concentrations of plant protection products in water usually follows the FOCUS Surface water model which considers three different exposure routes (drift, runoff and drainage).[10] Indirect exposure scenarios through discharge via sewage treatment plants (STP) and through application on hard surfaces (pavements) have not been elaborated in the EU which is considered as a shortcoming (van Griethuysen et al. 2010). The FOCUS Surface water

[10] http://focus.jrc.ec.europa.eu/sw/index.html

model considers the cumulative 90th percentile value for all applications during the season as in-put to the water bodies from spray drift in order to describe 'realistic worst-case' scenarios (Linders et al. 2003). Thus, cumulative exposure from repeated applications on the same field is considered although this could be regarded as one representative use.

Indirectly, cumulative exposure to the environment is considered in the uniform principles for decision making (Annex VI to 91/414/EEC). Here it is stated that no authorization shall be granted if the concentration of the active substance or of relevant metabolites, breakdown or reaction products is expected to exceed the limit values for surface water intended for the abstraction of drinking water (Annex VI 2.5.1.3). Directive 91/414/EEC also refers to acceptable concentrations of "active substances or of relevant metabolites" in groundwater for drinking water purposes. The Drinking Water Directive 98/83/EC requires that concentrations of pesticides and their relevant metabolites in drinking water must not exceed 0.1 µg/L. The occurrence of residues of plant protection products in plants or plant products, drinking water or elsewhere in the environment indirectly implies that cumulative exposure from all sources should be considered. In particular the Drinking Water Directive as well as the Groundwater Directive 2006/118/EC do not distinguish between plant protection products and biocides but consider both (and their relevant metabolites and degradation products) under the umbrella term "pesticides". This is not accounted for in dossier preparation by applicants but appeals to authorities to carry out this kind of cumulative exposure assessments beyond legislative boundaries.

The German Federal Environment Agency (Umweltbundesamt) investigated the combination effects of plant protection products with regard to the ecotoxicological risk assessment in different research projects (Coors et al. 2008, 2009, 2010). The focus of these investigations laid on the ecotoxicological effects of combination products (i.e. products containing two or more different active substances) and of tank mixtures (i.e. mixture of two or more products with different active substances in the application tank). This simultaneous exposition of the environment to more than one active substance (i.e. to pesticide mixtures) is up to date not regulated by the Plant Protection Products Regulation/Directive and thus, is not routinely carried out in the Pesticide Review Programme. The same applies to the cumulative or combined exposure of the environment to different products containing the same active substance: up to now this type of cumulative environmental risk assessment is not considered within the Pesticide Review Programme.

3.4 Mixture toxicity

In common chemical risk assessments the effects of individual chemicals are compared with their exposure covering all uses and preferably all life cycle stages within the respective legislation. Risks are often expressed as risk quotients (PEC/PNEC) for the different environmental compartments. The PNEC is derived from the No Observed Effect Concentration (NOEC) of the most sensible species while applying safety factors depending on the tests performed and the data available. Recently, this approach has been questioned because low concentrations of individual substances (e.g. tested at their NOEC level) have been shown to cause toxicity if exposed in mixtures. For example, the mixture toxicity of 11 priority pollutants from different chemical classes has been analysed in an algae growth inhibition test. When each individual compound was present at its individual NOEC, a far higher mixture toxicity of 64% was observed (Walter et al. 2002). Similarly, mixture toxicity of different brominated flame-

retardants (BFR) has been tested applying the copepod *Nitocra spinipes* partial life cycle test. For this purpose, six different brominated flame-retardants were mixed in a series of NOEC proportions. The test concentrations (termed NOEC proportions) were set to 0.008, 0.04, 0.2, 1, and 5 times the NOEC concentration determined in the partial life cycle test on the larval development for each of the six BFRs. Significantly increased mortality was observed after six and 26 days exposure at a NOEC proportion that equals the NOEC for each BFR in the mixture. At the concentration which corresponded 5 times the NOECs all animals were killed. This highlights the need to consider mixture toxicity to a greater extent in regulatory work (Breitholtz et al. 2008).

It is recognised that the effect of chemicals on ecosystems and human health is mainly due to exposures to mixtures rather than to individual chemicals. However, most regulatory areas for chemical risk assessment (e.g. REACH, BPD, PPP) and for emission control (e.g. Water Framework Directive) primarily use approaches that assess the toxicity of single chemicals (see section 7.1). Only specific types of mixtures, such as oil compounds, are covered by REACH. Currently there are two main models to address mixture toxicity:

1. “Concentration addition”: estimating mixture effects of chemicals that act in a similar way, and
2. “Independent action”: estimating mixture effects of chemicals that act differently to each other.

Within a study commissioned by the Danish EPA the practicality of the models was evaluated by investigating their use in existing legislation. The authors concluded that since grouping of environmental chemical mixtures on the basis of mode of action is unfeasible, and because the scientific findings over the last decades indicate that concentration addition can be applied regardless of mode of action, it is recommended that the concentration addition model should be used as a general mixture prediction model. The authors also refer to the US Agency for Toxic Substances and Disease Registry, which suggests reducing the number of mixtures to be assessed by means of hazard quotients. In principle these are similar to PEC/PNEC ratios used in EU legislation. Therefore the authors suggested that assessment could be limited to mixtures containing chemicals with individual ratios of PEC/PNEC > 0.1 (Syberg et al. 1999).

The need of assessing complex risks for human health and the environment has also been challenged by the European Commission who dedicated a thematic issue on the combination effects of chemicals. It is stated that even if Maximum Permissible Concentrations for individual contaminants are not exceeded in water, in combination they can still be potentially hazardous to wildlife (European Commission 2010). The European Commission provides an own web-site concerning the “Combination effects of chemicals” where the discussions among the Council of Environment Ministers is documented.[11]

In 2007 the Commission (DG Environment) contracted a study to review the current scientific knowledge and regulatory approaches regarding combination effects of chemicals. The "State of the Art Report on Mixture Toxicity" describes several examples of synergistic effects of different biocidal active substances which resulted in the conclusion that for biocidal products

[11] http://ec.europa.eu/environment/chemicals/effects.htm

containing more than one active substance the combined effects should be tested for the biocidal product itself. The European Council adopted conclusions on combination effects of chemicals where the European Commission is asked *"to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways"* (Council of European Union 2009).

The EU's NoMiracle project has adopted a biology-based approach to assess combination effects, which considers the interaction of mixtures with biological processes.[12]

In the UK the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was commissioned to assess the risks associated with mixtures of pesticides and veterinary medicines from a human health point of view. The report made a number of recommendations on how to address toxic effects of different substances in combination within regulatory systems. The impact of combined exposure to multiple pesticides is only rarely addressed by European regulatory authorities. Moreover, the impact of multiple sources of exposure is not often considered. Because many of the procedures for the regulation of pesticides and veterinary medicines are harmonised at the EU and international level, many of the conclusions of the Committee would have to be acted upon at EU level to be effective (Hughes 2002). A UK action plan on the risk assessment of mixtures of pesticides and similar substances has been developed which addresses the recommendation of COT (Food Standards Agency 2009).

It remains the question for which chemicals/chemical groups mixture toxicity should be envisaged. In scientific literature cumulative exposure is mainly discussed in the context of exposure to different chemicals with the same mode of action (such anticoagulants interfering with the vitamin K cycle or organophosphates inhibiting acetylcholinesterase) and/or mixture toxicity of complex mixtures such as wastewater samples in the context of "Whole Effluent Assessment" (WEA) of OSPAR (2007). Mixture toxicity is eventually assessed for authorisation of biocidal products or plant production products (as an example) containing different active substances. The OECD (2007) developed guidance for considering closely related chemicals as a group, or chemical category, rather than as individual chemicals. The objective of this guidance is on providing scientifically justifiable approaches for read across and to limit the number of tests to be conducted. The use of toxicity equivalency factors and the estimation of toxic units for mixtures of chemicals which contribute to a biological effect through a common toxicity pathway is a useful approach for filling data gaps in the assessment of chemical mixtures. In the Toxic Equivalents approach, the most toxic compound is used as the reference compound. Examples are dioxin and furan mixtures, Polychlorinated biphenyls (PCBs) or metals. Because mixture toxicity concerns the effect part of the risk assessment it is out of the scope of this project.

REACH and Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) distinguish two types of mixtures: individual substances that are in fact mixtures from a chemical perspective (type I mixtures) and manufactured mixtures of different

[12] Novel methods for integrated risk assessment of cumulative stressors in Europe, project duration 11/2004-10/2009 http://nomiracle.jrc.ec.europa.eu

substances, formerly called “preparations” (type II mixtures). Additionally, mixtures resulting from joint emission of substances from a common source (e.g. wastewater) and mixtures from different origins that coincidentally co-occur in environmental media should be considered in a wider context of chemical risk assessment and management. REACH does not provide specific guidance on the hazard, exposure and risk assessment of mixtures. However, the ECHA guidance document on the application of the CLP criteria in Chapter I.4 provides guidance on substances which are difficult to test for their aquatic toxicity and on type I mixtures which are termed “complex substances”. All guidelines on addressing mixture toxicity from regulatory authorities so far focus on human health. No comprehensive guideline for the ecotoxicological assessment of chemical mixtures has been developed yet, although approaches have been developed and discussed in the scientific literature (Backhaus et al. 2010).

3.5 Transferability of existing approaches to the requirements under REACH

Environmental risk assessments for biocidal active substances and for industrial chemicals base on quite similar principles, namely the Technical Guidance Document on Risk Assessments (TGD 2003) and the ECHA Chapter R.16 which builds on the TGD 2003, respectively.

The approach proposed for a cumulative environmental exposure assessment of biocidal active substances (see chapter 3.1) includes either

- the addition of the regional background concentration to the local worst case concentration (Clocal (worst case) + PECregional) or
- the summation of local concentrations of all single uses (∑Clocal).

This approach may also be a good starting point for the development of a concept for cumulative environmental exposure assessments under REACH.

In Council Directive 91/414/EEC and its replacement Regulation (EC) No 1107/2009 on the evaluation, marketing and use of plant protection products (PPP) the focus of cumulative exposure is on human health aspects while it is not explicitly referred to environmental exposure. Thus, it is not possible to transfer any elements of this Directive/Regulation to the requirements relating to environmental exposure assessment under REACH.

The environmental risk assessment of medicinal products for human use optionally considers a refinement of the market penetration factor, which represents the proportion of the population being treated daily with a specific drug substance, based on the consumption of the overall amount of the drug substance from all suppliers. Here, a market share of 100% of the drug substance for each applicant is assumed. This approach could also be used for assessing cumulative exposure of an individual substance from multiple registrants. Also the provision of the guideline on environmental impact assessment for veterinary medicinal products to consider cumulative exposure of the active substance and relevant metabolites (>10% of the administered dose) by adding the respective PECs could be transferred to individual chemicals and their metabolites. No practical experience with this concept has been obtained so far with medicinal products (Koch 2011).

Most of the other existing approaches summarised in Groß et al. 2010 focus on cumulative exposure to multiple chemicals from multiple sources on living organisms. The starting point of these approaches is clearly effect-based. All these data and information from other regulatory areas might be used for refinements of environmental exposure estimates but do

not give guidance on how to perform cumulative environmental exposure assessments for individual substances.

4 Requirements related to environmental exposure assessments under REACH

4.1 Substance-oriented regulation

REACH is primarily a single-substance oriented regulation focusing on "individual substances".[13] Thus, despite its professed aim to "ensure a high level of protection of human health and the environment" (Article 1), REACH does not provide a mandate for considering the toxicity of so-called "coincidental" mixtures of industrial chemicals – multicomponent cocktails that are found in the environment or the human body as a result from the concurrent use of different chemicals in a given area (Backhaus et al. 2010). Consequently, exposure and risk assessments under REACH deal primarily with the release, exposure and effects of individual substances.

However, one exception to this rule is mentioned in Part E of the REACH guidance on Information Requirements and Chemical Safety Assessment (Risk characterisation):

> *"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."*

4.2 Life cycle stages

The exposure assessment needs to cover manufacture and all identified uses of the substance and to consider all life-cycle stages (including corresponding waste stages) resulting from the manufacture and identified uses (ECHA Part A.1.2.4.). To each identified use the tonnage needs to be assigned. [14]

In principle, each identified use of the substance is assumed to occur at a different site under REACH. Consequently, releases from uses in industrial settings are assessed as *independent point source* releases. However, if different uses (e.g. different stages of the life cycle of a substance such as manufacture and formulation) take place at the same site, it is needed to combine the releases from the single uses in a combined assessment (ECHA Chapter R.16.2.1.1.).

[13] According to Article 1 of REACH, the Regulation concerns the manufacture, import, placing on the market and use of substances on their own and in preparations and articles. This also includes the corresponding waste stage for each life cycle step.

[14] Under REACH the "use" of a substance means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation (REACH article 3(24)). "Identified use" means a use of a substance that is intended by an actor in the supply chain (REACH article 3(26)).

4.3 PEClocal and PECregional

Under REACH the exposure to the environment is assessed on two spatial scales: locally in the vicinity of (single) point sources and regionally for a larger area which includes all point sources and emission from wide dispersive uses in that area.[15] For both the PEClocal and the PECregional default parameter values are chosen which reflect typical or reasonable worst-case settings.

4.3.1 PEClocal

The local concentration (PEClocal) close to a point source emission is calculated as the sum of the concentration from the point source and the background concentration:

PEClocal = Clocal + PECregional

where:

Clocal: local concentration (e.g. in surface water) during the release episode

PECregional: background concentration (see section 4.3.2)

At the local scale, two scenarios are distinguished to assess the release to the environment:

1. Release from industrial settings
2. Release from wide dispersive uses

(1) Release from industrial settings are assessed as independent point source releases meaning that each identified use of the substance is assumed to occur at a different site. If, however, different uses (e.g. different stages of the life cycle of a substance) take place at the same site, it is needed to combine the releases from the single uses in a combined assessment (see section 4.2).

(2) Wide dispersive uses refer to applications of a substance by consumers or by many users in the public domain (including small, non-industrial companies). In the sense of REACH, all releases from an identified wide dispersive use enter the same sewage treatment plant (STP) which then acts as point source for releases into surface water.

Local release assessments are carried out for each wide dispersive use of the substance separately. The respective PEClocal are calculated on the basis of a daily release rate.

Since all the releases from each identified wide dispersive use will by default enter into the same sewage system, a combined risk of all uses should be considered by summing up the local releases of all wide dispersive uses (in section 10 of the CSR) (ECHA Chapter R.16.2.1.1).

[15] In addition, releases to the continental scale are considered to provide inflow concentrations for the regional environment, however, PECcontinental are not used as endpoints for exposure and are therefore not explicitly presented in the CSR.

4.3.2 PECregional

The regional concentration (PECregional) is calculated by accounting for all releases over a wider, regional area and by accounting for the distribution and fate of the chemical after the release to the environment. The assessment is done for a generic regional environment which is represented by a typical densely populated EU-area of 200 x 200km² located in Western Europe with approximately 20 million inhabitants. All releases to each environmental compartment for each use are summed and averaged over the year. Thus, PECregional represents steady-state concentrations (i.e. background concentrations) in the environmental compartments.

In obtaining the regional concentration, the registrant has to account for all releases into the environment for his supply chain. However, it can be useful on a voluntary basis to consider exposure resulting from emissions of the same substance manufactured or imported by other registrants (e.g. the overall estimated market volume) (ECHA Part D 5.5).

The regional concentrations are used as background concentrations in the calculation of the local concentrations (see section 4.3.1).

4.4 Risk characterisation ratios (RCRs)

The risk characterisation procedure is generally described in ECHA Part E:

> *In risk characterisation, exposure levels - caused by each use - are compared to quantitative or qualitative hazard information. When suitable predicted no-effect concentrations or derived no-effect levels are available, risk characterisation ratios (RCRs) can be derived in order to decide if risks are adequately controlled for each environmental sphere and for each human population known to be or likely to be exposed. For the environmental end-points, this is the ratio of predicted environmental concentration (PEC) to predicted no-effect concentrations (PNEC):*
>
> $$RCR = \frac{PEC}{PNEC}.$$

If the PEC/PNEC ratio (the risk quotient) is < 1, the risk of environmental effects is considered to be at an acceptable low level.

5 Relevance of cumulative exposure assessments

Cumulative exposure assessments are no standard requirements within the Chemical Safety Assessment (CSA) under REACH. There may be many application situations where concomitant exposure of a substance resulting from different uses can be excluded or where it is very unlikely to occur. Therefore, the present chapter aims at identifying fields of application where cumulative environmental exposure is considered relevant and consequently, cumulative assessments should be carried out.

A distinction has to be made between cases where the responsibility for cumulative exposure assessment falls into the hands of the registrant within the registration dossier and other cases,

where the responsibility lies with the downstream users (DU)[16] or the Member State Competent Authorities (MS-CA).

5.1 Registrant with more than one (industrial) use or life cycle stage of a substance at the same site

ECHA Chapter R.16.2.1.1 provides first indications for the need of "combined risk" assessments: If more than one identified *(industrial) use* of a substance occurs at the same site (e.g. when manufacture and formulation take place at the same site), it is needed to combine the single assessments meaning that cumulative exposure assessments are required (see section 4.2). This case may generally be characterised as:

Case 1) Registrant with more than one (industrial) use or life cycle stage of a substance at the same site

In principle, each identified use of the substance is assumed to occur at a different site under REACH.

However, in practice, different life cycle steps of a substance often take place in the same legal entity. Many companies manufacture and/or import substances and then use these substances in their own company, or they formulate mixtures of these substances (the latter are so-called formulators) [17]. In this case, emissions during manufacturing and during formulation occur at the same location.

In an early survey made by the Ministry of Environment, Baden-Württemberg (Germany), 18 companies and their tasks under REACH have been examined (LfU 2004). More than 75% of the companies (i.e. 14 companies out of 18 examined in the survey) have been identified to be manufacturers and formulators of a substance at the same time.

This case can be illustrated in more detail by an example described within the European SPORT project (Ahrens et al. 2005): A medium-sized company produces a large variety of mixtures e.g. for the construction sector and for textile finishing. However, this company does not only produce the mixtures, it is also a manufacturer of some of the raw materials which are processed. For example, the company produces silicones in large amount. These silicones are then used as raw materials for the formulation of silicon-based softeners for the textile industry.

Here, emissions of the silicones may take place both during manufacturing and formulation at the site of this company. Consequently, releases of the silicones from manufacture and from the formulation of silicon-based softeners need to be combined in a cumulative environmental exposure assessment.

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[16] A downstream user is someone who uses a substance, either on its own or in a preparation, in the course of his industrial or professional activities. Many different types of companies can be downstream users, including formulators of preparations, producers of articles, craftsmen, workshops and service providers or re-fillers. (ECHA Guidance for Downstream Users)

[17] According to the definitions given in REACH, the companies described here are not downstream users. However, they are manufacturers and/or importers of the respective substances. Only formulators who do not manufacture and/or import the substances are considered as downstream users under REACH.

5.2 Registrant with more than one wide dispersive use of the same substance

With regard to releases from *wide dispersive uses* it is assumed by default that all releases enter the same sewage systems. In this case, too, a cumulative exposure assessment is considered necessary according to ECHA Chapter R.16.2.1.2 (see section. 4.3.1).

This case may generally be characterised as:

Case 2) Registrant with more than one wide dispersive use of the same substance

The term "wide dispersive use" characterises application situations where a substance is used by consumers or by many users in the public domain (including small, non-industrial companies), or that is to say a large number of small point sources like households, public buildings or small companies emit into the same sewage system. Emission reduction measures are usually not common practice for wide dispersive uses.

If a substance is used in different consumer products which are concomitantly applied in households and public buildings, like for example ingredients of laundry detergents, dishwashing detergents, lavatory and all purpose cleaners (ERC 8A)[18], then it is very likely that the substance will be released from all these uses into the same sewage treatment system.

One example is the anionic surfactant linear alkylbenzene sulphonate (LAS) which is used in many different household detergents. Important application products are laundry powders, laundry liquids, dishwashing products and all purpose cleaners. Fragrances are another prominent example of substances that are used in a large variety of consumer products starting from detergents, personal care products and air fresheners. Despite of the large number of different fragrances on the market, it is very likely that different consumer products contain the same fragrances.

Generally speaking, if a substance is used in applications falling under the environmental release categories (ERC) 8 (namely 8A and 8D; wide dispersive indoor/outdoor use of processing aids in open systems), ERC 10 (namely 10B; wide dispersive outdoor use of long-life articles with high or intended release) and ERC 11 (namely 11B; wide dispersive indoor use of long-life articles with high or intended release) it is very likely that the substance is released from more than one use into the same sewage treatment system. [19]

The resulting exposure concentrations of the substance in the different environmental compartments will be underestimated if each wide dispersive use is considered separately. Consequently, the local releases to water of all these wide dispersive uses of a substance should be summed up by the registrant to assess the cumulative environmental exposure.

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[18] ERC: Environmental Release Category

[19] In relation to releases to water, the scenario for both indoor and outdoor wide dispersive uses is based on the assumption that they occur in the urban infrastructure, are collected in a central public sewage system and are then treated by an STP. For outdoor uses, this scenario can be considered as a reasonable worst case. Assuming that all releases occur on a paved surface of an urban infrastructure and are collected in a sewage system may be conservative, but this is balanced by the assumption that all releases to water are treated in an STP (ECHA Chapter R.16.3.2.2).

5.3 DU purchasing a substance from different suppliers

Even if the registrant considers a possible cumulative environmental exposure caused by his own identified uses within his chemical safety assessment (CSA), it is nevertheless possible that cumulative exposure of a substance occurs at the level of the DU without being covered in the CSR of the registrant. This may be the case if the DU purchases the same substance or products containing this substance from different suppliers (registrants). Exposure scenarios provided to the DU by a supplier refer only to one single use of the substance. However, the registrant does not need to consider the other possible uses of "his" substance in products which are supported by other registrants within their CSA. Within this case, two different scenarios are possible: The DU purchases the same substance or products containing this substance from different suppliers and then applies the substance/product 1) in one single use or 2) in different uses (Figure 2).

Thus, the total consumption of a substance by the DU also may not be covered in the CSA of a registrant in those cases where the DU has more than one supplier for the same substance or products containing the same substance. The total release of the substance to the environment by the DU may result in cumulative concentrations not covered in any CSR.

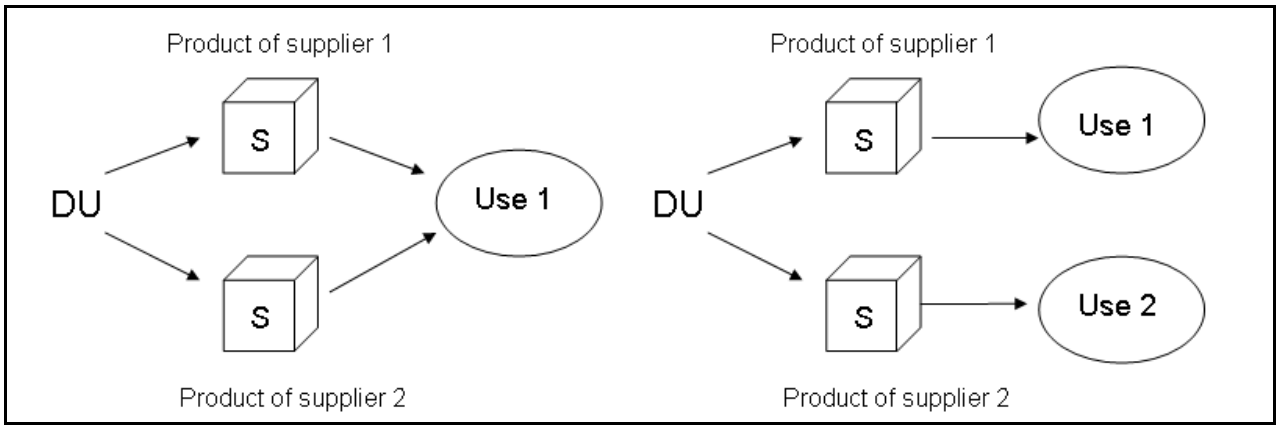

Figure 2 DU purchasing a substance from different suppliers to be applied (1) in one single use (left side) or (2) in different uses (right side)

This case may generally be characterised as:

Case 3) DU purchasing a substance (as such or as a part of formulations) from different suppliers

In many cases DU apply a range of products with a similar composition in a specific process. If these products contain the same substance as active ingredient, the total emission load results from the amount used of each of these products.

This case can be illustrated by two examples of substances used in tanneries.

1. In tanneries, glutaraldehyde is used as active substance for the tanning of skins. A recent survey has shown that in practice often two different products with glutaraldehyde are used at the same place for the tanning process. The total amount per year can be 200.000 kg/tannery.

2. Sodium sulphide is used in tanneries to remove hair from the skins. Up to four products are used in the same tannery for this process. Main compound in all of these products is sodium sulphide. The total amount per year can be 2 million kg/tannery.

The following table illustrates the variety of process chemicals typically used in tanneries. In each case more than one product is used for a specific process step.

Table 3 Product types and number of similar products (containing the same or similar process chemical) used in tanneries

#	Product type	Number of similar products used by one company	Range of amount used per year for individual products [kg/a]	Total amount of process chemical used per year [kg/a]
1	Metal complex dyes	50	10 – 2.000	10.000
2	Finishing materials	120	25 – 30.000	220.000
3	Fat liquors	25	100 – 60.000	150.000
4	Tanning agents	2	5.000 – 150.000	200.000
5	Dehairing agents	4	5.000 – 1.500.000	2.000.000

(Source: own compilation based on information from European tanneries)

Similar to the example described above for tanneries, in textile industry cumulative exposures may occur by the use of different products with the same active ingredient. Optical brighteners are an important group of products used in the textile industry. Many of them contain identical or structural related active substances. A survey from 2004 has shown that German textile finishers in general use 3 to 6 optical brighteners in parallel, in some cases up to 13 – 15 products, with a total amount ranging from some kilograms/year up to more than 12 tons/year (Bunke et al. 2004).

5.4 Substance evaluation by CA considering cumulative exposure from all registrants

Within his CSA, the registrant has to account for releases into the environment from his own identified uses, only. The registrant is not obliged to consider exposure resulting from emissions of the same substance manufactured or imported by other registrants. It is therefore the task of the MS-CA to consider all releases of a substance into the environment from all identified uses by all registrant.

This case may generally be characterised as:

Case 4) Substance evaluation by CA considering cumulative exposure from all registrants

For the performance of a substance evaluation all registration dossiers submitted for the same substance are as far as relevant examined together and any other relevant information available is taken into account.

The Guidance on Dossier and Substance Evaluation specifies in its section 3.2.2.1 grounds for considering that a substance constitutes a risk to human health or the environment.

These grounds of concern include the following aspects related to exposure data:

- Aggregated tonnage from all registrants is significantly higher than the tonnage per registrant and raises concern with respect to high exposure on a local and/or regional scale (in case of long-range-transport-pollutants, even global exposure may be of importance).

- Aggregated exposure from similar acting substances.
- Dossiers from several registrants of the same substance indicate exposure concentrations (PECs) close to the PNEC values.

Thus, the ECHA guidance includes cumulative exposure assessments considering combinations of emissions from multiple registrants within the substance evaluation process.

5.5 Overview

To sum up, the following different cases have been identified where cumulative environmental exposure is considered relevant and consequently, cumulative assessments should be carried out (see Figure 3):

1. Registrant with more than one (industrial) use or life cycle stage of a substance at the same site
2. Registrant with more than one wide dispersive use of the same substance
3. DU purchasing a substance (as such or as a part of formulations) from different suppliers for a single use or for different uses
4. Substance evaluation by CA considering cumulative exposure from all registrants

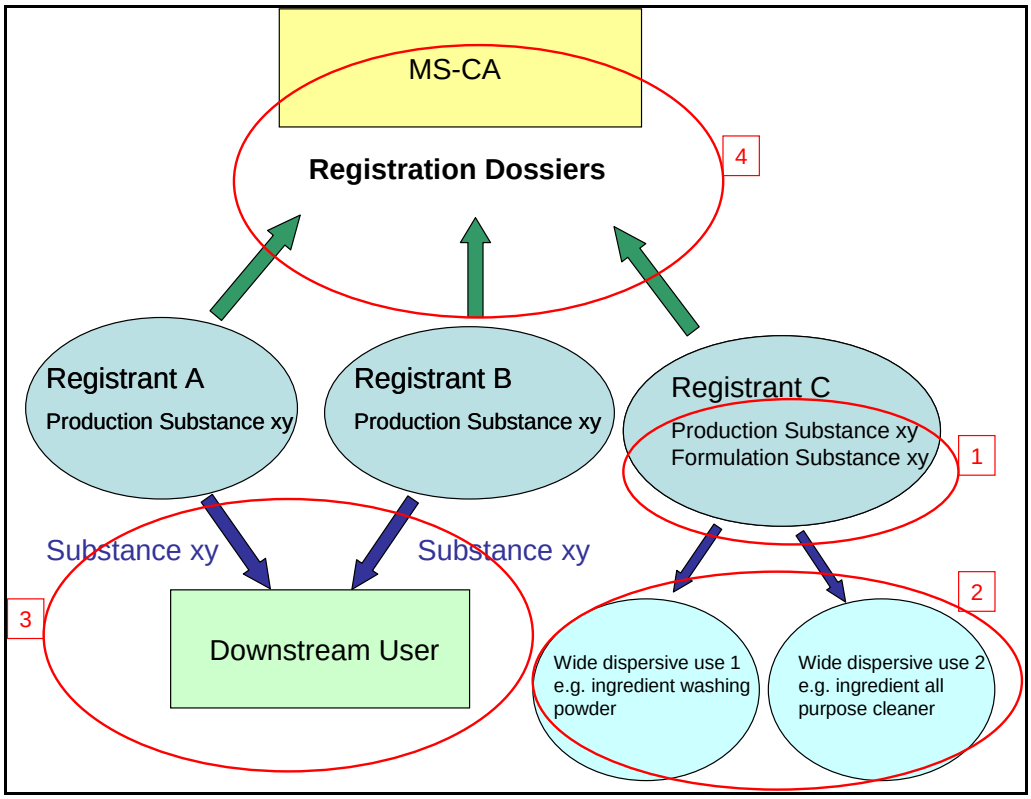

Figure 3 Relevance of cumulative exposure assessments

The examples illustrate that cumulative environmental exposure assessments may be relevant on all levels of the REACH process, starting with the CSA of single registrants, the purchase pattern of downstream users and substance evaluation by the CA.

However, the existing legal provisions under REACH do not (yet) cover all situations where cumulative exposure of a substance may be relevant. For example, DU who purchases a

substance from different suppliers do not (yet) have to consider the cumulative or total release of this substance to the environment.

6 Basic principles for a technical guidance on cumulative exposure assessments under REACH

Although the ECHA guidance documents mention the need for cumulative exposure assessments in different chapters (see section 2.2), only limited technical guidance is given on how to realise it.

In the following chapter basic principles for cumulative environmental exposure assessments under REACH are formulated considering the different levels of the REACH process where cumulative exposure assessments may be relevant (see section 5).

6.1 Registrant with more than one (industrial or wide dispersive) use of a substance

If the registrant identifies more than one use of a substance or a mixture containing the substance, he should check whether a spatial and temporal overlap of releases from the different uses is realistically possible which may result in a cumulative exposure of any environmental compartment. In case concomitant releases are possible, the registrant is obliged to combine those assessments in the "combined risk section" of the CSR (ECHA Chapter R.16.2.1).

6.1.1 Existing ECHA guidance

The respective ECHA guidance (ECHA Appendix to Part F – CSR Template with Explanation) gives the following instruction with regard to cumulative exposure assessments:

> *"10.3 Overall exposure (combined for all relevant emission/release sources)*
>
> *This section should present an evaluation of the risks due to combined exposure from the uses covered by different exposure scenarios. It is possible that uses of the same substance described in different ES can lead to combined exposure..."*

With regard to the human health risk assessment the ECHA guidance requires that *"for each combination the total risk has to be calculated, summing the risk characterisation ratio for combined routes."*

With regard to the risk assessment for the environment, the respective ECHA guidance in the Appendix to Part F (10.3) only states:

> *"Identify whether local exposure could occur through different exposure scenario and estimate the risk for such a situation when relevant.*
>
> *In addition, if exposure occurs to a substance as well as to several very closely related and similar acting chemical substances, the exposure evaluation and risk characterisation should reflect this aspect."*

6.1.2 Proposal for technical realisation

Concerning the combined risk assessment for human health the ECHA guidance requests to sum up the RCRs of the single uses (see chapter 6.1.1 above).

A similar approach can be followed in the cumulative environmental exposure and risk assessment:

Cumulative Clocal = Clocal (use 1) + Clocal (use 2) + Clocal (use x)

Cumulative PEClocal = Cumulative Clocal + PECregional (see chapter 4.3.1)

For the cumulative risk assessment the ratio of the cumulative PEClocal to predicted no-effect concentrations (PNEC) is derived:

$$\text{Cumulative RCR} = \frac{\textit{Cumulative PEClocal}}{\textit{PNEC}}$$

Alternatively, it is possible to sum up the RCRs of the single uses:

Cumulative RCR = RCR (use 1) + RCR (use 2) + RCR (use x)

The proposed approach can be illustrated using the example mentioned in section 5.1: A medium-sized company is both manufacturer of silicones/siloxanes and formulator of silicon-based softeners for the textile industry. PEClocal values resulting from the single uses (here: manufacture of siloxane derivates and formulation of silicon-based softeners) are added to a cumulative PEC value (Table 4).

Table 4 Proposed approach for a cumulative exposure assessment of a manufacturer / formulator of siloxane derivates and silicon-based softeners, respectively, for the textile industry

Life cycle step	$PEClocal_{surface\ water}$ [µg/L]	$PNEC_{surface\ water}$ [µg/L]	RCR	Cumulative RCR
Manufacture of siloxane derivate	38	55	0,69	1,3
Formulation of silicon-based softeners	32	55	0,58	
Cumulative Exposure (i.e. Cumulative PEClocal)	70	55	1,3	

PEClocal and PNEC values are only exemplary and do not base on real model calculation. PECregional is neglected in the above given calculation assuming that Clocal = PEClocal.

6.1.3 Suitability of PECregional versus Cumulative PEClocal

According to ECHA Chapter R.16.2.2, the concentrations of a substance released from all identified uses (including all point sources and all wide dispersive sources of a substance in larger area) are to be assessed in the regional exposure assessment, i.e. in the calculation of PECregional. In obtaining the regional concentration, the registrant has to account all releases into the environment for his supply chain (see Chapter 4.3.2). The regional concentrations are then used as background concentrations in the calculation of the local concentrations.

PECregional is normally significantly lower than PEClocal. This is, among other things, due to the fact that PECregional is yearly average concentration calculated for a large standard region whereas PEClocal is calculated based on daily release rates locally in the vicinity of point sources. For this reason the calculation of PECregional cannot substitute a cumulative local exposure assessment for multiple uses of a substance.

Groß et al. 2010 performed example calculations to illustrate the relation between PEClocal and PECregional. These calculations confirmed that cumulative PEC calculated on basis of the

"PECregional approach" (i.e. sum of the local worst case concentration and the regional background concentration (Clocal (worst case) + PECregional)) are significantly lower than the sum of the Clocal of all single uses. The higher the number of single uses, the higher is the discrepancy between the two approaches. Consequently, the "PECregional approach" might underestimate the environmental concentrations resulting from simultaneous and/or spatial overlapping uses of the same active substance.

The cumulative Clocal approach (∑Clocal approach) is more conservative. A huge disadvantage of the ∑Clocal approach is, however, the summing up of several realistic worst case scenarios. It is questionable if this approach is really satisfactory to derive conclusions of risks and with that on legal consequences for active substances. According to Groß et al. 2010 no final conclusion was possible to decide upon which approach describes better a specific emission situation.

There is still a need for further research regarding this technical detail.

6.2 DU purchasing a substance from different suppliers

If a DU receives an extended safety data sheet with an exposure scenario, he is obliged to assess whether his use is covered by the exposure scenario. (If this is not the case, he has to perform his own CSA to demonstrate safe use of the product (REACH Art. 37.4)[20].

This legal requirement is restricted to the single product and the related exposure scenario. The possibility that the substance is used in the same company simultaneously in other products (either for the same use or for different uses, see Chapter 5.3) does not need to be considered by the DU according to the current legal requirements.

In order to avoid critical exposures by the simultaneous use of products containing the same substance, it should therefore be recommended to DU to assess possible cumulative exposures.

A simple assessment tool as illustrated in the following Table 5 could support DU in this task.

Table 5 Assessment of simultaneous use of three products with the same substance (here: Alkylsulfonate) by DU

	Maximum acceptable amount per day according to ES [a)]	Amount used per day by DU	Percentage of max. acceptable amount used per day by DU	Sum of percentages[b)]
Product	[kg]	[kg]	[%]	[%]
Degrace 12	200	50	25	25
Protube 15	120	40	33	58
Solomud RZ	100	20	20	78

a) Maximum amount of the product which can be used without reaching or exceeding a PEC/PNEC ratio of 1

b) The sum of the percentages should not exceed 100%

Key parameter for the assessment is the maximum amount of the products which can be used without reaching or exceeding a PEC/PNEC ratio of 1. This information should be given in the exposure scenarios of the products.

[20] REACH Art. 37.4 specifies several exemptions when a DU does not need to prepare a CSR.

If for one of the products used by the DU no ES is available, the maximum acceptable amount of this product used per day can be estimated on basis of the concentration of the active substance together with information on the maximum acceptable amount taken from the ES of a similar product. It is assumed that the maximum acceptable amount used per day is proportional to the concentration of the substance in the product.

The following equation can be used to determine the maximum acceptable amount used per day for a product without ES (product B):

$M(B) = M_{ES}(A) \times C_a(A) / C_a(B)$

where:

A = Product A
B = Product B
M = Max. amount
M_{ES} = Max. amount taken from ES
C_a = Concentration of active substance

The estimation is based on the assumption of similar conditions of use for all products under consideration.

This extrapolation is illustrated in Table 6 using the example product from Table 5.

Table 6 Estimation of the maximum acceptable amount per day on basis of the concentration of the substance in the product

Product	Concentration of active substance in product [%]	Maximum acceptable amount used per day [kg/d]	Comment
Degrace 12	20	200	Information taken from ES (see example product from Table 5)
Protube 15 ZV	3	1333	Maximum acceptable amount calculated on basis of Product Degrace 12
Solomud RZ	4	1000	Maximum acceptable amount calculated on basis of Product Degrace 12

6.3 Substance evaluation by CA considering cumulative exposure from all registrants

For the substance evaluation, the respective MS-CA should examine all registration dossiers submitted for the same substance together, as far as relevant. Substance evaluation does not focus only on substances but also on break-down products and takes into account suspicion from structural alerts/similarities to other substances of concern (ECHA Guidance on Dossier and Substance Evaluation, section 1.3.2).

Guidance on estimating emissions and exposure in the context of substance evaluation is included in the Guidance on the Chemical Safety Report for individual registrants where the basic approaches are described.[21]

The guidance for Annex XV dossiers[22] takes into account additionally the combination of emissions from multiple registrants and the inclusion of emissions from other sources (ECHA Guidance on Dossier and Substance Evaluation, section 3.3.1.2).

7 Future challenges and recommendations for further research

7.1 Challenges beyond single regulations

The Scientific Steering Committee's Working Group on Harmonisation of Risk Assessment Procedures advising the European Commission criticises that exposure assessments usually follow the respective legislation, but do not follow an integrated approach. Thus, only certain uses of chemicals, e.g. in plant protection are considered regardless whether the same chemicals are used for other purposes or whether exposure takes place by other media than those in the focus of legislation. A realistic description of the exposures of consumers and environment requires a stratification of input-data in relation to ways and means of primary production and primary products and the full life-cycle of the product. When different pathways can be envisioned, there is a need to take all of these into consideration. Interaction between the different scientific committees and regulatory agencies in this regard is an important issue (European Commission 2000).

Kortenkamp et al. (2009) argue along these lines in their “State of the Art Report on Mixture Toxicity”. They criticise that there is presently no vehicle to deal with exposure to substances that come from areas that are covered by separate EU regulations, for example, cumulative exposure to plant protection products, biocidal products, pharmaceuticals, household chemicals, food additives etc. Each sector performs its own risk assessment almost all fully neglecting that there may be contributions from the other sectors. Even in REACH feed additives, veterinary medicines, plant protection products, biocides, and human medicine are not considered.

In a report for the Swedish Chemicals Agency about the state of the art, gaps and options for improvement with regard to the hazard and risk assessment of chemical mixtures under REACH, it is challenged that there is the need to cut across the existing pieces of chemicals legislation, and not to limit the assessment by substance- and product-oriented regulations such as REACH and PPP. Process- and media-oriented forms of legislation, such as for instance the Integrated Pollution and Prevention Control Directive (IPPC) and the Water Framework Directive (WFD) need to be included. Approaches that directly address cumulative exposure scenarios, as put forward for example in the WFD, might provide particularly valuable options for improved protection of humans and the environment against risks from mixtures of

[21] ECHA Part F: Chemical Safety Report and Appendix to Part F CSR Template with explanation

[22] ECHA Guidance for the preparation of an Annex XV dossier for restrictions, section 5.2.3.2

chemicals. In contrast to media-oriented regulations such as the WFD, REACH is primarily a single-substance oriented regulation at the moment. With respect to chemical mixtures, it might therefore be of main interest to characterize the background exposure to which the particular chemical of interest is added. For this purpose a scenario-specific joint exposure modelling needs to be performed (Backhaus et al. 2010).

Therefore, cumulative exposure and risk assessments within one regulatory area like the REACH regulation can only be a starting point. Future work is required to develop a concept considering all releases into the environment from all uses of a substance.

7.2 Guidance for downstream users

If a DU receives an extended safety data sheet with an exposure scenario, he is obliged to assess whether his use is covered by the exposure scenario (see chapter 6.2). This legal requirement is, however, restricted to the single product and the related exposure scenario. Thus, if the DU purchases the same substance or products containing this substance from different suppliers (registrants), he does not need to consider his total consumption of the substance. The total release of the substance to the environment by the DU may result in cumulative concentrations not covered in any CSR.

In order to avoid critical exposures by the simultaneous use of products containing the same substance, it should therefore be requested by the DU to assess their possible cumulative exposures.

Here, harmonised guidance for the DU is requested.

7.3 Assessment of very closely related chemical substances

Part E of the REACH guidance requires that 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.

Metabolites and breakdown products of active substances might be considered as closely related substances per se. Metabolites and breakdown products of active substances may occur in many environmental compartments such as soil, surface waters, groundwater and air as well as in animal feed or in food for human consumer. The Drinking Water Directive requires that concentrations of pesticides and their relevant metabolites in drinking water must not exceed 0.1 µg/L. With reference to the Water Framework Directive 2000/60/EC the same value has also been established as “groundwater quality standard” for pesticides, including their relevant metabolites, degradation and reaction products according to the Groundwater Directive 2006/118/EC. (The term “pesticides” refers to both plant protection products and biocides). Because neither of the two Directives defines the term “relevant metabolite” and because this has led to uncertainty for regulators and notifiers, the European Commission (2003) elaborated a guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Directive 91/414/EC. The document describes a scheme to determine whether a metabolite is relevant (and thus subject to the 0.1 µg/L limit) or not relevant using criteria of biological activity, genotoxicity and toxicological hazards. All metabolites

found in lysimeter studies at annual average concentrations exceeding a concentration of 0.1 µg/L in the leachate should be identified and subject to further assessment. For practical reasons it has been suggested that the relevance of all metabolites, which account for more than 10 % of the amount of active substance added in soil at any time during the studies should be assessed (or those accounting for 5 % of the amount in at least two sequential measurements). Non-relevant metabolites which passed the criteria respective biological activity, genotoxicity and toxicological hazards, but for which levels of estimated concentrations in groundwater lie between 0.75 µg/L and 10 µg/L shall be subjected to a refined assessment of their potential toxicological significance for consumers (European Commission 2003).

One example where cumulative exposure from very closely related substances has been assessed are phthalate esters mainly used as plasticizers, which might be degraded to the same or structural similar derivates of phthalic acid (Treye 2010). Here, the main focus is on cumulative exposure of humans from consumer and occupational as well as from environmental sources. Also the family of alkylphenols might be considered as closely related. The most commonly detected environmental metabolites of nonylphenol ethoxylates are nonylphenol monoethoxylate, nonylphenol diethoxylate, nonylphenol ether carboxylates, and nonylphenol. The toxic equivalency approach was used to assess the aggregate hazard of these nonylphenol ethoxylates. Assuming an additive based interaction of toxicities the data suggest a low likelihood that aggregate concentrations of nonylphenol ethoxylates and their metabolites will exceed the US national chronic water quality criteria for nonylphenol (Coady et al. 2010).

Blaser et al. (2008) assessed cumulative exposure of silver nanoparticles. In 2010 up to 15% of the total silver released into water in the EU is from biocidal use in plastics and textiles. Modelled PECs in the Rhine River were in satisfactory agreement with monitoring data from other river systems. The authors concluded that no PEC/PNEC ratios above 1 are expected for freshwater ecosystems, sediments, and for microbial communities in sewage treatment plants.

The US EPA conducted several case studies on cumulative risk assessments for “very closely related substances” that have a common mechanism of toxicity, such as organophosphate pesticides or triazine pesticides with main emphasis on risks to human health (US EPA 2002).

In Germany the Federal Environment Agency published a recommendation for the evaluation of substances (including metabolites) in drinking water that are not (yet) possible to evaluate. Here different “health based guide values” are defined for non-genotoxic and genotoxic substances. Genotoxic substances in drinking water are only acceptable in concentrations below 0.1 µg/L while for non-genotoxic substances up to 3 µg/L might be allowed (German Environment Agency 2003). In a concept paper of the German Association for Water, Wastewater and Waste a health based guide value of 0.01 µg/L has been proposed for strong genotoxic compounds (DWA 2008).

Future work is required to develop a concept considering the assessment of very closely related chemical substances.

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