Case Studies Putting the ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers) into Practice

Technical Report No. 133-3

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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Version 1

DISCLAIMER: This Technical Report reflects current experience and knowledge and shall be adapted, amended and refined as new evidence on polymer risk assessment becomes available.

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SUMMARY

Polymers are currently being reconsidered in the context of regulatory programmes, and this raises a number of technical and scientific challenges as polymers represent a diverse chemical space and are quite different from discrete mono-constituent substances. Against this background, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) decided that a review of relevant scientific methods and knowledge applicable to the risk assessment of polymers would be helpful to provide a scientific perspective for the safety assessment of polymers. Therefore, in April 2018, ECETOC launched the 'Polymers Task Force' (TF) that brought together specialists of polymer chemistry, toxicologists, ecotoxicologists and environmental fate modellers.

As an outcome of its work, the ECETOC Polymers TF has been preparing the ECETOC Technical Report (TR) No. 133 series, of which this report is the third and final part. The first part, ECETOC (2019) TR No. 133-1, presented the ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers). The second part, ECETOC (2020) TR No. 133-2 reviewed the applicability of tools, test methods and models for polymer risk assessment. In completing the trilogy, this ECETOC TR No. 133-3 presents *Case Studies Putting the ECETOC CF4Polymers into practice*. Seven case studies were selected from the diverse universe of polymers to further evaluate (1) the usefulness of the CF4Polymers (ECETOC TR No. 133-1) for the safety assessment of different types of polymers and (2) the information on the applicability of tools, methods and models for the hazard and risk assessment of polymers presented ECETOC TR No. 133-2.

It is important to make clear that the case studies were not intended to document a comprehensive risk assessment for any specific polymer. Rather, publicly available data and unpublished TF company data were collated and assigned to the eight steps of the CF4Polymers presented in ECETOC TR No. 133-1 to evaluate the scientific usefulness and comprehensiveness of the process through use of examples. The examples covered different types of polymers and/or different types of intended uses. Thereby, the case studies have also served to illustrate how the CF4Polymers *can be used* for polymer hazard and risk assessment. Further, the collated data were used to assess the applicability of tools, methods and models for polymer risk assessment presented in ECETOC TR No. 133-2.

The seven case studies have revealed issues to consider when running the selected types of polymers through the eight steps of the CF4Polymers:

Case Study 1 – polycarboxylates, polyacrylates and polymethacrylates: This case study focussed on water soluble poly(acrylic/maleic acid) copolymers (P-AA/MA) and linear poly(acrylic acid) homopolymers (P-AA) as used in laundry detergents and additionally, for P-AA, as used in personal care products. Further, this case study referred to insoluble poly(methyl methacrylate) (PMMA) and moderately soluble ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA). P-AA/MA and P-AA are relatively data rich since they have wide dispersive consumer uses. The available database covers all relevant ecological and toxicological endpoints, and it confirms that P-AA and P-AA/MA can be submitted to the battery of test methods that is relevant for hazard and risk assessment. Since P-AA and P-AA/MA are water soluble, poor solubility does not pose any problems when submitting them to ecological and/or toxicological test methods. Nonetheless, as complex polymer products, that may include polymeric substances of different molecular weights, solubilities, etc., they do pose the 'usual' challenges during analytical assessment. For example, the molecular weight of polycarboxylates is best expressed as mean value (together with the minimum and maximum values). As regards environmental fate, there is a fairly good correlation between dissolved organic carbon removal and molecular weight of the different P-AA / P-AA/MA. Additionally, most P-AA and P-AA/MA

generally possess low ecological hazard and, if they meet respective molecular weight requirements, that they also fulfil the criteria for polymers of low concern.

Case Study 2 – cationic polymers: This case study considered polyquaternium-6 (PQ-6) and polyquaternium-10 (PQ-10) as used in conditioning shampoo, and PQ-6 additionally as used in flocculant for wastewater treatment. Due to their wide dispersive consumer use, PQ-6 and PQ-10 are also fairly data rich. They are further water soluble or otherwise dispersible in water, and they sorb strongly to any negatively charged surfaces present in the aquatic compartments including respiratory surfaces (e.g. gills). Thereby, PQ-6 and PQ-10 depending on the cationic charge may pose a hazard concern towards aquatic species in standardised aquatic toxicity tests. However, cationic polymers have a propensity to sorb to organic matter. Such behaviours likely mitigate the aquatic toxicity potential in the natural aquatic environment. Similarly, sorptive processes to sludge solids in wastewater treatment or dissolved organic matter in the water column are considered the dominant removal process. As regards human health toxicity endpoints, the data available for a broad spectrum of chemically diverse polyquaterniums consistently indicate that their systemic bioavailability is likely low and that they thus do not exhibit systemic toxicity potential. Some polyquaterniums do exhibit potential for mild local irritation, however, mostly at concentrations exceeding realistic human exposures. Case Study 2 showed that, even though high charge density is commonly considered a parameter indicating potential hazard concerns, the ecotoxicological and toxicological profile of the given cationic polymer will need to be established on a case-by-case basis.

Case Study 3 – polyolefins: This case study focussed on polypropylene while also considering low-density polyethylene, linear low-density polyethylene and high-density polyethylene. Use as food contact material for fatty food (olive oil bottle) was selected as intended use for this case study, further referring to use in medical devices. This case study was different from the other case studies in that it did not only refer to scientific evidence of relevance to fill in the eight steps of the CF4Polymers for polyolefins, but also considered the specific and highly demanding end-use legislation that applies to plastic food contact materials and medical devices, respectively. The case study showed that the polymeric substance (polypropylene) itself fulfils the criteria to identify 'polymers of low concern'. Further, all intentionally added substances (IAS) that may be present in the polymer product will have been approved for use and/or are expected to fulfil the safety requirements set out in the food contact material legislation. Therefore, the further exposure and hazard assessment of the polypropylene focussed on the oligomers that might migrate from the polymer matrix. Taken together, the level of oligomers (or other non-intentionally added substances (NIAS), or IAS) that can migrate from the polypropylene matrix is very low, and that the degree of migration is also very low. Such evidence provides the scientific rationale for exposure-based waiving of hazard assessment needs. Further, a number of technical challenges that are specifically related to the hazard assessment of NIAS were highlighted, including difficulties in isolating different NIAS and in synthesising sufficient test material to develop and validate analytical or testing methods for the evaluation of NIAS.

Case Study 4 – solid bisphenol-A diglycidylether (BADGE) polymers (solid BADGE epoxy resins): This case study considered solid BADGE epoxy resins, BADGE oligomers and as well as the underlying BADGE monomer. Solid BADGE epoxy resins are used exclusively in closed industrial settings, i.e. for the preparation of solvent-based and powder coatings. Focus of Case Study 4 was the application of CF4Polymers (Step 4) grouping approach evaluation. It was hypothesised that the BADGE monomer, as common key constituent, drives the hazard and risk assessment of all members of the group of solid BADGE epoxy resins. The solid BADGE epoxy resins included in this case study contain 0-16% BADGE monomer. Thus, it was further hypothesised that all these BADGE epoxy resins have at most the same, but rather less hazard potential than the BADGE monomer itself. The BADGE monomer has been assigned the Classification, Labelling and Packaging (CLP) hazard classes

of skin and eye irritation 2 (at concentrations ≥ 5%), skin sensitisation 1, and aquatic chronic toxicity 2. To address these endpoints, Case Study 4 considered lower-tier toxicity and ecotoxicity data that have been gathered for two types of BADGE epoxy resins. While the findings were inconsistent with respect to the classification for skin irritation and skin sensitisation, they did point to an overall low local toxicity potential of the solid BADGE epoxy resins. Performance of the aquatic toxicity screening studies using daphnids was impaired by the very poor water solubility of the materials. The only suitable vehicle for acute aquatic toxicity testing was Tween 80. Taken together, it was not yet possible to determine if any skin sensitisation that may be elicited by solid BADGE polymers was rather caused by the BADGE monomer or by the free epoxide groups of the BADGE polymer itself. The grouping approach described in Case Study 4, which fits in the first instance for reactive polymers, might also be adapted for various types of polymers. Thereby, the monomers would be grouped according to their use in respective polymerisation chemistries prior to the grouping of the polymers.

Case Study 5 - polyetherols (PEOLs; or polyether polyols): This case study addressed PEOLs and the corresponding oligomeric polyols. PEOLs are used exclusively in closed industrial settings where they usually undergo further reactions with methylene diphenyl diisocyanate and toluene diisocyanate to form foams that are used in e.g. mattresses and insulation boards. Focus of Case Study 5 was to apply CF4Polymer (Step 4) grouping approach evaluation to PEOLs. It was hypothesised that data gaps for the group of PEOLs can be filled by read-across from the corresponding oligomeric polyols. The underlying assumption was that the chemistry of the initiator molecule and of the repeating units provide an indication for the physico-chemical and/or ecological / toxicological properties of the polyols. If the initiator molecule exhibits ecotoxicological and/or toxicological properties, these properties will likely diminish with increasing numbers of repeating units. Generally, the oligomeric polyols are devoid of aquatic toxicity potential. This is regarded an intrinsic property since these oligomers do have the potential to reach aquatic species on account of their high water solubility. Further, the oligomeric polyols have the potential to become systemically bioavailable on account of their low molecular weight. The current database indicates that the human health hazard potential of the PEOLs group is low to absent as regards both acute systemic toxicity and local toxicity. None of the PEOLs included in Case Study 5 show acute dermal toxicity, skin irritation, eye irritation, or skin sensitisation. Preliminary data do indicate that glycerol- and propane-1,2-diol-started PEOLs of a certain molecular weight range (> 500 Da and < 2,000 Da) might elicit slightly more pronounced acute oral and inhalation toxicity. However, these preliminary data deserve further elaboration before reliable conclusions on their hazard properties and consequentially their consideration in the grouping approach can be drawn. Taken together, Case Study 5 provided evidence to support the hypothesis that data gaps for the group of PEOLs can be filled by read-across from the corresponding oligomeric polyols.

Case Study 6 – surfactant polymers: This case study focussed on linear alcohol ethoxylates (AEs) that have (1) medium C-chain length and medium degree of ethoxylation (C12-15EO7), or (2) high degree of ethoxylation (C16-18EO≥20). (In AEs, whose alcohols were produced via the synthetic ‘oxo-process’, a small percentage of the alkyl chains may have an internal methyl branching (so-called ‘essentially linear’ AEs); nonetheless, for improved readability these polymer products are also referred to as linear AEs in this report.) C12-15EO7 has wide dispersive consumer uses in household and personal care products, including those with down-the-drain release; therefore, the intended use considered here was in household laundry detergents. C16-18EO≥20 is used exclusively in industrial settings, and the selected intended use was for the manufacturing of water-based dispersions and textile, leather, and paper. Both AEs are data rich, and they were taken through all steps of the CF4Polymers. The comprehensive dataset did not indicate any specific difficulties in evaluating the physico-chemical, ecological or toxicological properties of C12-15EO7 or C16-18EO≥20 beyond the specific considerations that are relevant for complex polymer products or for poorly water-soluble test materials (for

the hydrophobic AEs). Case Study 6 applied the details of the CF4Polymers (Step 4) grouping approach evaluation to AEs. To facilitate the grouping, this part of the case study considered all biodegradable linear AEs that are based on primary alcohols and have C = 8-18 and EO = 3-50. For some human health endpoints, branched and unsaturated AEs were also considered. Case Study 6 showed that differences in chain lengths between AEs may affect the extent of systemic bioavailability and hence the hazard potential and potency for specific toxicological endpoints (that are common between all group members), but not in inherent differences in the (spectrum of) potentially relevant toxicological endpoints. Trends in acute aquatic toxicity and in eye irritation, likely due to membrane interaction of the AEs, could be established and were considered in defining subgroups for the different hazard classifications for these endpoints. By contrast, the toxicological database did not indicate relevant differences in skin sensitisation, genotoxicity, repeated-dose toxicity or reproductive and developmental toxicity over the entire group of AEs.

Case Study 7 – selected professional and consumer uses of polyurethane and polyurea: Whereas the other case studies started out from a specific (chemical) type of polymer, Case Study 7 showed how different intended uses of the same types of polymers, i.e. polyureas and polyurethanes, should be considered for exposure assessment. Intended uses included in Case Study 7 were (1) the use of polyureas / polyurethanes as shell materials for the microencapsulation of fertilisers and crop protection products in professionally used horticultural / agricultural products, respectively; (2) the use of polyureas for the microencapsulation of fragrance oils used in laundry detergents and fabric softeners for consumer use; and (3) the use of polyurethane / polyurea in professional paint / coating applications. All polyureas and polyurethanes considered in Case Study 7 were assessed as inert, and they fulfilled the criteria to identify 'polymers of low concern'. The exposure, hazard and risk assessment of the polymers used for horticultural / agricultural and fragrance microencapsulations are at the intersection to the hazard and risk assessment of the core material, i.e. the fertiliser, active substance, and fragrance oil. Similarly, the example of professional paint applications, where the polymers themselves are only produced in the final article, has shown how the hazard and risk assessment will generally focus on the monomers and/or other starting substances that are regulated as non-polymeric substances e.g. under the respective applicable chemical legislation.

As expected, the seven case studies have confirmed that polymers represent a large and broad aspect of the chemical space. This necessitates a careful characterisation of the materials under investigation as well as their complex uses while considering that some polymer products can change their form during different life cycle stages. Polymers are usually present in their applications as complex polymer products, and some even have properties resembling those of substances of unknown or variable composition, complex reaction products or biological material (UVCBs). The seven case studies clearly only cover a small fraction of the seemingly infinite world of polymers. Nonetheless, they cover different polymer chemistries, including polymers that are considered to have some hazardous properties, and others that are not.

Generally, the case studies have confirmed the value of the eight steps of the CF4Polymers for the hazard and risk assessment as applied to a diverse spectrum of polymers. All case study substances were readily processed through the steps of the CF4Polymers. The case studies did not reveal evidence that would suggest that the approach described in the CF4Polymers would be inappropriate, incomplete or misleading.

The case studies have demonstrated that there is no 'one size fits all' polymer hazard and risk assessment process of polymers. This confirms the relevance of having designed the CF4Polymers to be both flexible and non-prescriptive. The order of the eight steps can be changed as required depending on the risk assessment needs and/or on data availability.

In the same way, the case studies have demonstrated that there is no 'one-size-fits-all' approach to determine if any given tool, test method or model is, nor is not, applicable for the assessment of all polymers. Conclusions that have been derived for the specific polymers considered in this report are not necessarily transferable to all other types of polymers (and possibly not even to other variants of the same types of polymers). However, the findings of this report do highlight the need for critical, case-by-case, assessment of the suitability and relevance of models, methods and concepts by suitably qualified and experienced professionals involved in the assessment of products containing polymers.

The further elaboration of CF4Polymers (Step 4) grouping approach evaluation is a major topic addressed in the present report. Details to the grouping approach are described that go beyond the generic outline provided in the ECETOC TR No. 133-1 CF4Polymers. Just as fit-for-purpose polymer identification needs to be more targeted than substance identification for simpler chemicals, the information to be considered when judging if multiple polymers can be regarded 'the same', or not, needs to go beyond that which is commonly applied to establish 'similarity' for mono-constituent substances. The polymer grouping approach outlined in this report includes three Criteria to describe similarity:

- Criterion 1: Initial grouping according to the chemical nature of the polymers (e.g. PEOLs, AEs) and their common key feature(s). Groups are further subdivided in subsequent iteration steps until a final group is reached.
- Criterion 2: The iteration groups share similar key physico-chemical properties (e.g. molecular weight and polydispersity, fraction of low molecular weight components, degree of cross linking, water solubility, charge density) and associated functionality.
- Criterion 3: The final groups share a similar hazard profile for ecologically and toxicologically relevant hazard properties of the group.

Hence, polymer grouping requires consideration of what can be regarded as sufficiently similar for the purpose of hazard assessment, and/or of which grouping criteria are fit-for-purpose from a safety perspective. Such criteria may vary between different types of polymers.

Finally, the five recommendations spelled out in ECETOC TR (2019) No. 133-1 and ECETOC TR (2020) No. 133-2 were revisited to discuss how the seven case studies provided further insight to address and/or refine these.

Recommendation 1: *Identify sets of structural and/or morphological descriptors as well as physico-chemical and fate properties that are key parameters for different types of polymer products*.

In further evaluating the evidence collated for the seven case studies, sets of structural and/or morphological descriptors as well as physico-chemical and fate properties have been identified that appear as key parameters for the respective types of polymers. Such key parameters are summarised in Table Disc-2 in Section 9.3 (page 202), and this overview confirms the view expressed in ECETOC TR No. 133-1 and 133-2 that polymer identification should be fit-for-purpose and that those properties that are key for the given type of polymer under investigation need to be established on a case-by-case basis. The CF4Polymers allows for the necessary flexibility to determine those key parameters that are relevant for the given type of polymers.

Recommendation 2: *Consider prevailing technical limitations of available tools, test methods and models for polymer risk assessment*.

The seven case studies have served to advance the information presented in ECETOC TR No. 133-2 while at the same time highlighting knowledge gaps that should be addressed to ensure that tools, test methods and

models are applied for the assessment of the given polymer in a meaningful manner (Table Disc-1 in Section 9.3; pages 193-200).

In this regard, work on the case studies has revealed opportunities to revise Section 3.6 (Surface tension) in ECETOC TR No. 133-2 and specifically, to update Table 3 therein (*Analytical methods potentially suitable to determine the surface tension-lowering properties of polymers*) to reflect the state-of-the-art in science and industrial practice as well as commercially available equipment. While an update of ECETOC TR No. 133-2 is being planned, Appendix CS6-A.1 of the present report proactively summarises the new insight.

Recommendation 3: *Maintain the CF4Polymers as a 'living', flexible framework, and review and update it in line with emerging knowledge on how it can efficiently and effectively support polymer risk assessment.*

ECETOC TR No. 133-3 complements the two previous reports, ECETOC TR No. 133-1 and 133-2, by providing further evidence to support the general outline of the CF4Polymers and more detailed guidance on how to pass through its eight steps. Importantly, the information evaluated for the seven case studies did not indicate any need to fundamentally change the CF4Polymers. Indeed, it was not necessary to deviate substantially from the eight-step structure for any of the case study polymers considered. This is not necessarily surprising since the CF4Polymers was designed to follow the general outline for hazard and risk assessment implemented e.g. by the WHO IPCS (2004, 2010). The most important addition to this internationally agreed paradigm is (Step 3) Polymer component strategy, an organisational step to ensure transparency on the components of the polymer product considered.

Nonetheless, due to the broad chemical space covered by polymers, the CF4Polymers has been designed to be both flexible and non-prescriptive. The order of the eight steps can be changed as required depending on the risk assessment needs and/or on data availability.

In the present report, further details have been provided for how to conduct CF4Polymers (Step 4) grouping approach evaluation (Section 1.3). These further details complement the outline for this step presented in ECETOC TR No. 133-1.

Recommendation 4: *Expand the knowledge base to (1) substantiate the polymers of low concern concept and (2) to identify under which conditions the presence of specific structural alerts or physico-chemical properties could be an indicator of environmental or human health hazard concerns*.

The polyolefins (Case Study 3) and polyurethane / polyurea (Case Study 7) typically fulfil the criteria for polymers of low concern. These case studies have shown how specific parameters related to the polymer of low concern concept can be measured. While this concept has been implemented in different non-EU jurisdictions for many years, or even decades, without indications to disprove its validity, the recommended research work shall serve to eventually extend the criteria, if sufficient experimental justification becomes available. Table Disc-2 in Section 9.3 (page 202) demonstrates that the key properties identified by the case studies (e.g. molecular weight and relative content of functional groups) often reflect properties that are also used in the polymers of low concern criteria. All seven case studies, also those that did not consider polymers that typically fulfil the criteria for polymers of low concern, have served to advance the evidence collated in ECETOC TR No. 133-1 and 133-2 that is relevant for the advancement of Recommendation 4. Also, they have served to enhance an understanding on the opportunities to group polymers by common physical, chemical and/or biological properties.

Recommendation 5: *Develop environmentally relevant models, methods and/or criteria to assess (bio)degradation to improve the reliability of exposure and fate assessments important to the risk assessment of polymers*.

The seven case studies have provided further details on the applicability of specific types of models and/or criteria to assess (bio)degradation (up to mineralisation) or other key parameters for polymer risk assessment taking into account the type of (bio)degradation, its duration (i.e. half-lives), and whether it is intended during the given life cycle stage of the polymer, or not. Also, they have highlighted limitations of the currently available exposure models and have confirmed the need to develop models that are applicable to different types of polymers (or to expand existing models to enable such assessments).

It is recognised, however, that the state-of-knowledge is continually evolving and that further investigations, building on this trilogy of reports, may be necessary in the future.

In summary, the seven case studies presented in this ECETOC TR No. 133-3 complement the ECETOC TR No. 133-1 presenting the CF4Polymers and the ECETOC TR No. 133-2 reviewing the applicability of tools, test methods and models for polymer risk assessment. Clearly, the seven case studies only cover a small fraction of the seemingly infinite world of polymers. Nonetheless, they cover a broad spectrum of polymer chemistries, including polymers that are considered to have some hazardous properties, and those that do not. In the case studies, publicly available data and unpublished TF company data were collated and assigned to the eight steps of the CF4Polymers presented in ECETOC TR No. 133-1 to evaluate the scientific usefulness and comprehensiveness of the process through use of examples. The case studies were not intended to document a comprehensive risk assessment for any specific polymer, and they also did not describe how any specific legal requirements should be met. Instead, the seven case studies, just as the entire ECETOC TR No. 133 series, have described how polymer risk assessment can be undertaken, regardless of the underlying motivation and/or legal requirements. Further, the case studies have enhanced the understanding on the applicability and/or technical limitations of the corresponding tools, test methods, and models. Overall, the case studies have demonstrated that there is no 'one size fits all' polymer hazard and risk assessment process of polymers. In the same way, the case studies have demonstrated that there is no 'one-size-fits-all' approach to determine if any given tool, test method or model is, nor is not, applicable for the assessment of all polymers**.** It is recognised that the state-of-knowledge is continually evolving and that further investigations, building on this trilogy of reports, may be necessary in the future. ECETOC has mandated an *ad-hoc* committee to follow up such new insight and proactively update the TR No. 133 series to keep abreast of the state-of-the-art within this domain.

1. INTRODUCTION

1.1 The ECETOC TR No. 133 series on polymer risk assessment

Polymers represent a large and broad aspect of the chemical space. They are currently being reconsidered in the context of regulatory programmes, and this raises a number of technical and scientific challenges as polymers represent a diverse chemical space and are quite different from discrete mono-constituent substances. Against this background, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) decided that a review of relevant scientific methods and knowledge applicable to the risk assessment of polymers would be helpful to provide a scientific perspective for the safety assessment of polymers. In April 2018, ECETOC launched the 'ECETOC Polymers Task Force' (TF) that brought together specialists of polymer chemistry, toxicologists, ecotoxicologists and environmental fate modellers (see list of TF members at the end of this Technical Report). The terms of reference of the ECETOC Polymers TF included the development of (1) a conceptual framework for the hazard and risk assessment of polymers, mapping polymer types and their life cycles and associated environmental and human health protection goals; and (2) an approach for the grouping of polymers during risk assessment.

In fulfilling these terms of reference, the ECETOC Polymers TF is preparing the ECETOC Technical Reports (TR), No. 133 series, of which the present one is the third and final part. The first part, ECETOC TR No. 133-1 (ECETOC, 2019), presented the ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers). The second part, ECETOC TR No. 133-2 (ECETOC, 2020) reviewed the applicability of tools, test methods and models for polymer risk assessment. Finally, the present ECETOC TR No. 133-3 describes seven *Case Studies Putting the ECETOC CF4Polymers into practice*. It is recognised, however, that the state-of-knowledge is continually evolving and that further investigations, building on this trilogy of reports may be necessary in the future.

The CF4Polymers, as described in ECETOC TR No. 133-1, provides basic guiding principles to be considered in assessing potential ecological and human health hazards and risks posed by polymer products. The CF4Polymers generally follows the internationally agreed paradigm for chemical risk assessment as published by the World Health Organisation – International Programme for Chemical Safety (WHO IPCS, 2004, 2010), but includes some deviations therefrom. These are necessitated by the chemical and physical attributes of polymeric substances and polymer products and their complex markets and uses. Polymers are usually not present as mono-constituent substances, but as complex polymer products consisting of the polymeric substance (polymeric macromolecules), intentionally added substances (IAS; e.g. additives, stabilisers) and non-intentionally added substances (NIAS; e.g. impurities) (Box 1; see Glossary for definitions of all key terms). Further, polymer products can change their form during different life cycle stages.

The CF4Polymers consists of eight steps, i.e.

1. Problem formulation - risk assessment scope and protection goal definition
2. Polymer identification
3. Polymer component strategy
4. Grouping approach evaluation

5. Determination of exposure scenarios – the first part of exposure assessment
6. Exposure characterisation – the second part of exposure assessment
7. Hazard assessment – hazard identification and characterisation
8. Risk characterisation

Box 1: Polymer product and its components - definitions

Polymer product: A chemical product with a polymeric substance as main component, and NIAS and sometimes IAS as other components (ECETOC Polymers TF working definition*). Polymer products are only in some cases finished articles.

Polymeric substance (polymeric macromolecules): The chemical (co)polymer and possibly present oligomers (both are composed of the same monomeric units) (ECETOC Polymers TF working definition*).

Intentionally added substance (IAS): *"A substance added to something in small quantities to improve or preserve it."* (https://en.oxforddictionaries.com/definition/additive); *"A substance which is intentionally added to plastics to achieve a physical or chemical effect during processing of the plastic or in the final material or article; it is intended to be present in the final material or article"* (European Commission, 2011).

Non-intentionally added substance (NIAS): *"An impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product"* (European Commission, 2011).

Low molecular weight (LMW) compounds: Small oligomers, IAS, and NIAS, including unreacted monomers.

Monomer, unreacted: Depending on the manufacturing process and intended use of the polymer product, unreacted monomers can either be IAS or NIAS.

Oligomer: Part of the polymeric substance (at the low end of its molecular weight range). In some contexts, also referred to as NIAS; see also Box 3 for distinction between oligomer and polymer.

Constituent: *"Any single species present in a substance that can be characterised by its unique chemical identity"* (ECHA, 2017a).

Component: *"Substance intentionally added to form a mixture"* (ECHA, 2017a).

Homologue: For example, for alcohol ethoxylates (AEs): different AEs with different C-chain length and different ethylene oxide (EO)-chain length that are included in the same polymer product (that hence has a certain molecular weight distribution as determined by the different polymeric substances). (ECETOC Polymers TF working definition; see also http://www.chem.ucla.edu/~harding/IGOC/H/homolog.html

Variant: For example, for AEs: Different AE polymer products that are composed of the same starting materials but that have e.g. different mean molecular weight and different molecular weight distributions. (ECETOC Polymers TF working definition)

* See Section 2 in ECETOC TR No. 133-1 (CF4Polymers; ECETOC, 2019) for further discussion, e.g., on how the ECETOC Polymers TF working definitions were selected to comply with current chemical and products legislation.

The CF4Polymers has been designed to be flexible and it is not prescriptive. The order of the eight steps can be adapted as necessary depending on the risk assessment needs and/or on data availability. For each step of the CF4Polymers, the ECETOC TR No. 133-1 provides a detailed outline for how it can be completed, accompanied by explanatory notes and illustrative examples. Appendix 1 of the present report presents the details of the eight steps of the CF4Polymers (adapted from ECETOC, 2019).

Further, knowledge gaps that currently restrict the polymer hazard and risk assessment process are identified in the ECETOC TR No. 133-1. Many of the identified knowledge gaps relate to the applicability of tools, methods and models for polymer hazard and risk assessment. Therefore, the second report, ECETOC TR No. 133-2 (ECETOC, 2020), further advances the topic of polymer hazard and risk assessment by providing a detailed review of the applicability of standard analytical tools, *in vitro* and *in vivo* test methods and *in silico*

models to assess the physical, chemical, fate, exposure-related, ecotoxicological, and toxicological properties of polymers.

In this regard, the ECETOC TR No. 133-2 refers to formally agreed test guidelines (TGs), such as the ones adopted by the Organisation for Economic Co-operation and Development (OECD) and the United States (US) Environmental Protection Agency (EPA) Office for Chemical Safety and Pollution Prevention (OSCPP). Since these TGs were mostly developed for mono-constituent, water-soluble substances, they may have technical limitations when assessing e.g. poorly soluble or solid polymers. Therefore, the ECETOC TR No. 133-2 also considers standards and technical specifications published by the International Standardisation Organisation (ISO) or national / regional standardisation bodies that were developed for the testing of plastics and as such are generally also applicable to solid, particulate polymers.

For each physical, chemical, fate, exposure-related, ecotoxicological, and toxicological parameter, the ECETOC TR No. 133-2 presents and discusses scientific evidence on the applicability of the corresponding tools, methods and/or models, while highlighting their technical limitations for the assessment of specific types of polymers. Such technical limitations may depend e.g. on polymer size, molecular weight / molecular weight distribution, solubility, or charge density, and they may also relate to the complexity of the polymer products. Also, the different components of the polymer product may exhibit different properties, so that it may be more appropriate to express measurements as ranges instead of individual values. Suggestions are made in ECETOC TR No. 133-2 as to how some specific TGs might be adapted to facilitate the testing of polymers. The examples cited are not exclusive, and it is likely that further adaptations may be identified with experience of applying these methods for specific polymer types.

As an outcome of ECETOC TR No. 133-1 and 133-2, a total of five recommendations were identified to promote the conceptual approach developed for the hazard and risk assessment of polymers (Box 2).

Box 2: ECETOC TR No. 133 series recommendations (ECETOC, 2019, 2020)

Recommendation 1: *Identify sets of structural and/or morphological descriptors as well as physico-chemical and fate properties that are key parameters for different types of polymer products*.

Recommendation 2: *Consider prevailing technical limitations of available tools, test methods and models for polymer risk assessment*.

Recommendation 3: *Maintain the CF4Polymers as a 'living', flexible framework, and review and update it in line with emerging knowledge on how it can efficiently and effectively support polymer risk assessment.*

Recommendation 4: *Expand the knowledge base to (1) substantiate the polymers of low concern concept and (2) to identify under which conditions the presence of specific structural alerts or physico-chemical properties could be an indicator of environmental or human health hazard concerns*. Particularly, there is only weak evidence that anionic or amphoteric and water absorbing polymers might generally have a relevant hazard potential.

Recommendation 5: *Develop environmentally relevant models, methods and/or criteria to assess (bio)degradation to improve the reliability of exposure and fate assessments important to the risk assessment of polymers*.

1.2 The aim and scope of the present ECETOC TR No. 133-3

The present *ECETOC TR No. 133-3 Case Studies Putting the CF4Polymers into practice* concludes the TR No. 133 series. Seven case studies (Table Intro-1) were selected from the diverse universe of polymers to further evaluate both the usefulness of the CF4Polymers (ECETOC TR No. 133-1) for the safety assessment of different

types of polymers and the information on the applicability of tools, methods and models for the hazard and risk assessment of polymers presented in ECETOC TR No. 133-2. Thereby, the seven case studies were also intended to provide insight to address and/or refine the five recommendations identified in the previous reports (see Box 2 above):

- **Case Study 1 – polycarboxylates, polyacrylates and polymethacrylates**: Focus is on poly(acrylic/maleic acid) copolymers (P-AA/MA) and on linear poly(acrylic acid) homopolymers (P-AA). The selected intended uses are in household laundry detergents and additionally, for P-AA, in personal care products, i.e. consumer uses with down-the-drain release. For comparison, poly(methyl methacrylate) (PMMA) and ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA) are also considered.
- **Case Study 2 – cationic polymers**: Focus is on polyquaternium-6 (PQ-6) and polyquaternium-10 (PQ-10). The selected intended uses include use of PQ-6 as flocculant during wastewater treatment and use of PQ-6 and PQ-10 in conditioning shampoos. As relevant and available, the case study also considers information on other polyquaterniums.
- **Case Study 3 – polyolefins:** Focus is on polypropylene while also considering low-density polyethylene (LD-PE), linear low-density polyethylene (LLD-PE), and high-density polyethylene (HD-PE). The selected intended use is as food contact material for fatty food (olive oil bottle), while also referring to use in medical devices and cosmetic packaging.
- **Case Study 4 - bisphenol-A diglycidylether (BADGE) polymers (BADGE epoxy resins**): Focus is on solid BADGE epoxy resins. These are used exclusively in closed industrial settings, i.e. for the preparation of solvent-based and powder coatings.
- **Case Study 5 - polyetherols (PEOLs; or polyether polyols):** PEOLs are used exclusively in closed industrial settings where they usually undergo further reactions with methylene diphenyl diisocyanate and toluene diisocyanate to form foams that are used in e.g. mattresses and insulation boards. For example, when reacted with diisocyanates, PEOLs form polyurethanes, which are used in different product applications such as flexible and rigid foams, and in Coatings, Adhesives, Sealants & Elastomer systems that are used in industrial and professional settings.
- **Case Study 6 – surfactant polymers**: Focus is on linear alcohol ethoxylates (AEs), which have wide dispersive consumer uses in household and personal care products, including those with down-the-drain release. The selected intended use is in household laundry detergents. Further, industrial use of AEs for the manufacturing of water-based dispersions and textile, leather, and paper is considered.
- **Case Study 7 – selected professional and consumer uses of polyurethane and polyurea**: Whereas the other case studies start out from a specific (chemical) type of polymer, Case Study 7 shows how different intended uses of the same types of polymers should be considered for exposure assessment. Focus is on use of polyurethane and polyurea for microencapsulations of agricultural / horticultural products and fragrances. Further, professional paint applications of these same polymers are considered.

Clearly, the seven case studies only cover a small fraction of the seemingly infinite world of polymers. Nonetheless, they cover a broad spectrum of polymer chemistries, including polymers that are considered to have some hazardous properties, and those that do not.

Table Intro-1: ECETOC TR No. 133-3: Seven case studies putting the CF4Polymers into practice

Case study	Polymers considered	Intended uses considered	Polymer component considered	Steps of CF4Polymers in focus of case study [a]	Aspects considered
1	**Polycarboxylates:** Polyacrylate homopolymer (P-AA); polyacrylic / maleic acid copolymer (P-AA/MA) Further: PMMA and EPPAA	*P-AA & P-AA/MA*: Laundry detergents; additionally, for P-AA: personal care products (down-the-drain release) *PMMA*: Acrylic paints *EPPAA*: Coating products, waterless inks	Polymeric substance NIAS and IAS also likely relevant	Run through all steps of the CF4Polymers	ENV & HH
2	**Cationic polymers**: Polyquaternium 6 (PQ-6) and PQ-10; other PQs, as relevant	*PQ-6 and PQ-10*: Consumer use in shampoo and conditioner *PQ-6*: Flocculant in wastewater treatment plants	Polymeric substance	Run through all steps of the CF4Polymers Also: discuss evidence to group PQ6 and PQ10, respectively	ENV & HH
3	**Polyolefins**: Polypropylene Also: low-, linear-low- and high-density polyethylenes	Consumer use in food contact materials (fatty food: olive oil bottle)	Focus: LMW components (NIAS & IAS) & show: polymeric substance is inert	Run through all steps of the CF4Polymers Focus: (Step 3) polymer component strategy and (Steps 5 & 6) exposure assessment → Migration of LMW components	HH
4	**BADGE polymers:** (LMW and HMW); BADGE monomer / prepolymer and oligomers	Industrial use: Solvent-based coatings and powder coatings There is no consumer or professional exposure	Monomer, oligomer, LMW polymer, HMW polymer	(Step 2) polymer identification (Step) 4 grouping approach evaluation	Focus: HH; also: ENV
5	**Polyetherols (PEOLs)**	Industrial use: Usually reacts further with TDI/MDI → foams	Polymeric substances (NLPs until PEOLs with 18,000 Da)	(Step 2) polymer identification (Step) 4 grouping approach evaluation	ENV & HH
6	**Surfactant polymers:** Alcohol ethoxylates (AEs)	Consumer use: Laundry detergents (down-the-drain release) Industrial use: Water-based dispersions, textile, leather	Polymeric substances (over a range of AEs)	Run through all steps of the CF4Polymers Inform on opportunities for (Step 4) grouping	ENV & HH
7	**Selected intended uses of polyurethanes and polyureas**	Microencapsulations (horticultural / agricultural, fragrances) Professional paint application	Polymeric substance as part of an article	(Steps 5 & 6) exposure assessment: How do different intended professionals / consumer uses affect exposure assessment?	Focus: ENV; also: HH

Footnote to Table Intro-1:

Note: It is not the purpose of the case studies to perform a hazard and risk assessment for any specific polymer. Instead, the case studies serve to illustrate how the CF4Polymers could be used for polymer hazard and risk assessment, while critically assessing its scientific usefulness and comprehensiveness.

Abbreviations: AE: Alcohol ethoxylate, BADGE: Bisphenol-A diglycidylether, Da: Dalton, ENV: Environmental hazard, exposure and risk assessment; EPPAA: Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer, HH: Human health hazard, exposure and risk assessment; HMW: High molecular weight, IAS: Intentionally added substances; LMW: Low molecular weight, MDI: Methylene diphenyl diisocyanate, NIAS: Non-intentionally added substances, NLP: No-longer polymers, P-AA: Polyacrylate homopolymer; P-AA/MA: Polyacrylic / maleic acid copolymer; PEOL: Polyetherol, PMMA: Poly(methyl methacrylate), PQ: Polyquaternium, TDI: Toluene diisocyanate.

It is important to note that it is not the purpose of the case studies to perform a hazard and risk assessment for any specific polymer. Instead, the seven case studies serve to illustrate how the CF4Polymers *can be used* for polymer hazard and risk assessment while critically assessing its scientific usefulness and comprehensiveness. The case studies serve to investigate if the CF4Polymers is applicable to different types of polymers and/or different types of intended uses. They serve to identify if steps of the CF4Polymers need to be amended, refined or expanded to enhance applicability for any particular type of polymer. To focus the case studies, they are restricted to a specific life cycle stage of the polymer product (reflected in *CF4Polymers (Step 1) problem formulation*). Nonetheless, polymer products can change their form during different stages of their life cycle so that distinct hazard and risk assessment processes may be necessary during different life cycle stages.

The case studies include polymers with wide dispersive consumer use that have been submitted to (extensive) hazard and risk assessment on account of such use. These are P-AA/MA and P-AA (Case Study 1) and AEs (Case Study 6), and to a lesser extent also PQ-6 (Case Study 2). Since these polymers are (relatively) data rich, the respective case studies address all eight steps of the CF4Polymers for a selected use type.

As regards physico-chemical properties, the case studies include polymers that are considered as 'polymers of low concern' or 'reduced regulatory requirements polymers' in different jurisdictions in which legislation for the notification / registration of polymers is in force, including USA, Canada, Australia (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021). Polymers of low concern are "*those deemed to have insignificant environmental and human health impacts. Therefore, these polymers should have reduced regulatory requirements*" (OECD, 2009). Physico-chemical properties to determine polymers of low concern include low proportion of LMW compounds within the polymer product, high molecular weight of the polymer, and absence / low content of reactive functional groups (see Section 4.1 in ECETOC TR No. 133-1 for further discussion of the polymers of low concern concept). As the case studies will show, the polyolefins (Case Study 3) and polyurethane / polyurea (Case Study 7) typically fulfil the criteria for polymers of low concern.

The case studies also include polymers that have specific physico-chemical properties that have traditionally been considered as indicating potential hazard concerns, e.g. cationicity (Case Study 2 – cationic polymers), reactivity (Case Study 4 – BADGE polymers), and surface tension (Case Study 6 – surfactant polymers). For these types of polymers, the specific properties of the given variant determine if it does, or does not, fulfil the criteria for polymers of low concern / reduced regulatory requirements polymers.

Hence, fit-for-purpose polymer identification is indispensable for a meaningful hazard and risk assessment. Therefore, all case studies include details on *CF4Polymers (Step 2) polymer identification*. As relevant, such details include standard chemical descriptors, structural and morphological descriptors as well as physico-chemical and screening level fate properties. Regarding standard chemical descriptors, Chemical Abstract Service (CAS) registry numbers and names are presented, while also critically discussing their limitations for the identification of polymers. All information presented for (Step 1) polymer identification is also further evaluated in view of identifying those physico-chemical properties that are 'key' for the fit-for-purpose identification of the given type of polymer and/or that might be indicative of specific hazard concerns.

CF4Polymers (Step 3) polymer component strategy is considered in all case studies since this step is unique to polymer risk assessment, as compared to the risk assessment of mono-constituent substances. Further, Case Study 3 (polyolefins) was selected to specifically focus on the potential of LMW constituents of polymer products to migrate from the polymer matrix and on a (theoretical) hazard and risk assessment of these LMW constituents.

CF4Polymers (Step 4) grouping approach evaluation is expected to play an important role in streamlining efforts to conduct a meaningful risk assessment of polymers. Three case studies were selected and designed to focus on the grouping of polymers:

- Case Study 4 (BADGE polymers): The grouping and hazard characterisation is founded on properties of the BADGE monomer/prepolymer.
- Case Study 5 (PEOLs): The grouping and hazard characterisation focuses on the corresponding oligomers.
- Case Study 6 (surfactant polymers): The grouping and hazard characterisation is conducted across a broad range of similar AEs that only differ by carbon-chain length and degree of ethoxylation (and hence molecular weight).

These three case studies serve to enhance the understanding of how different types of polymers may be grouped together to streamline subsequent testing needs. Thereby, the present report also advances the outline of the (Step 4) grouping approach evaluation included in the ECETOC TR No. 133-1 CF4Polymers. Specifically, a three-Criteria approach is introduced to define and justify polymer similarity. The rationale for, and details of the three-Criteria approach are presented and discussed in Section 1.3 below.

Generally, it is hypothesised that the respective polymers have the same – or less – hazard properties than the underlying monomers (Case Study 4 - BADGE polymers) or oligomers (Case Study 5 - PEOLs). Box 3, Table Intro-2 and Figure Intro-1 present the definitions for polymers, oligomers, and no-longer polymers (NLPs), also as compared to substances of unknown or variable composition, complex reaction products and biological materials (UVCBs). While polymers may have some resemblances with UVCBs, they are not themselves UVCBs.

Box 3: Definitions of polymers ('3n+1 rule' and '50% rule'), oligomers, no-longer polymers and UVCBs

A **polymer** comprises *"(a) a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or another reactant; (b) less than a simple weight majority of molecules of the same molecular weight"* (Article 3(5) of the European Union (EU) *Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals* (REACH; EP and Council, 2006)).

This definition is also known as the '**3n+1 rule**'. In the context of this definition, a 'monomer unit' means the reacted form of a monomer substance in a polymer (EP and Council, 2006; ECHA, 2012a, 2017b).

The European Chemicals Agency (ECHA, 2012a) has provided further explanations on the REACH definition of polymer:

"In accordance with REACH (Article 3(5)), a polymer is defined as a substance meeting the following criteria: (a) over 50 percent of the weight for that substance consists of polymer molecules […]; and (b) the amount of polymer molecules presenting the same molecular weight must be less than 50 weight percent of the substance."

This definition is also known as the '**50% rule**'.

An **oligomer** contains less than three monomer units, which are covalently bound to at least one other monomer unit or another reactant, and thus does not fulfil the '3n+1 rule', and/or it does not fulfil the '50% rule'.

No-longer polymers (NLPs): Before the 7th amendment of Directive 67/548/EEC (Council, 1967) was adopted in 1992 (Council, 1992), the EU definition for polymers differed from the OECD definition (http://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm). Upon implementation of the 7th amendment (Council, 1992), a number of substances which had been considered to be polymers under the European Inventory of Existing Commercial Chemical Substances (EINECS) were no longer considered as such. These substances were called NLPs and mainly included alkoxylated substances, oligomeric reaction products, oligomers from one monomer only, dimers and trimers, and polymer-like substances containing ≥ 50 weight% of species with the same molecular weight (ECB, 2007).

When the EU REACH Regulation entered into force, the no-longer polymers had to be registered as phase-in substances (Article 12 of the REACH Regulation).

Since the list of NLPs comprises a number of oligomers, NLP is often used as synonymous to oligomeric substances.

A **substance of unknown or variable composition, complex reaction products or biological material (UVCB**) is "*a substance that cannot be sufficiently identified by its chemical composition, because (1) the number of constituents is relatively large and/or (2) the composition is, to a significant part, unknown and/or (3) the variability of composition is relatively large or poorly predictable"* (ECHA, 2012b).

While polymers may have properties that resemble those of UVCBs, they are not UVCBs (Table Intro-2).

Table Intro-2: Comparison of polymers, no-longer polymers (NLPs) and substances of unknown or variable composition, complex reaction products or biological material (UVCBs)

Type of substance	**Polymer**	**NLP**	**UVCB**
Reference for definition	**As defined under the EU REACH Regulation and in OECD (2009)**	**As defined following Council (1992) and ECB (2007) [1]**	**As defined under the EU REACH Regulation**
Reactants / monomers	Reactants/monomers known [3]	Reactants/monomers known [3]	Constituents partly unknown
Exact composition	Exact composition variable, but generally known [4]	Exact composition variable, but generally known [3]	Exact composition variable and generally unknown
Molecular weight	Molecular weight distribution [5]	Molecular weight distribution	Molecular weight distribution random and partly unknown
3n+1 and 50% rules [2]	Fulfils 3n+1 and 50% rules	Does not fulfil 3n+1 or 50% rules	Does not fulfil 3n+1 or 50% rules
Regulatory status under the EU REACH Regulation	So far not registered (fall 2021)	Registered	Registered

Footnote to Table Intro-2:

[1] See Box 3 above for further details on the definition of NLPs.

[2] In accordance with Article 3(5) of the EU REACH Regulation (EP and Council, 2006) and the subsequent guidance implemented in ECHA (2012a, 2017a).

[3] Some polymers and NLPs are produced from starting materials which can include UVCBs.

[4] 'Generally known' with respect not only to monomers and other reactants but also other IAS and to a lesser extent NIAS.

[5] Most polymers have near Gaussian distributions of molecular weights (with certain deviations, some can also be bimodal) and the compounds within the distributions are basically the same chemistry, just different sizes. The molecular weight distributions for many synthetic polymers can be predicted using probability generating functions (see e.g. Sarmoria et al., 2012). The same structures occurring in NLPs can be part of the (oligomeric) LMW constituents of the corresponding polymer product.

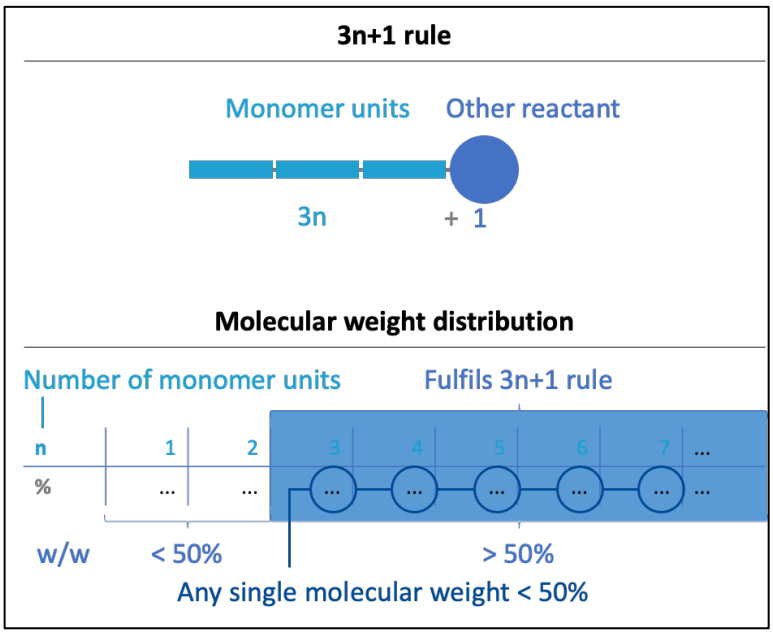


Figure Intro-1: Definition of polymers: '3n+1' rule and '50% rule' under the EU REACH Regulation

Footnote to Figure Intro-1: (Figure provided by ECETOC Polymers TF member company)

Following the provisions of the EU REACH Regulation (EP and Council, 2006):

A **polymer** is a substance consisting of molecules characterised by the **sequence** of one or more types of **monomer units**. Such molecules must be distributed over **a range of molecular weights**. Differences in the molecular weight are primarily attributable to **differences in the numbers of monomer units**.

'3n+1 rule': A '**polymer molecule**' is a molecule that contains a **sequence of at least 3 monomer units**, which are covalently bound to at least **one other monomer unit** or other reactant.

'50% rule': **Over 50%** of the weight for that substance consists of **polymer molecules**. The amount of polymer molecules presenting the **same molecular weight** must be **< 50 weight %** of the substance.

As regards *CF4Polymers (Step 5) determination of exposure scenarios* and *(Step 6) exposure characterisation*, the case studies cover wide dispersive consumer uses, occupational uses in closed industrial settings, and professional uses. Similarly, the case studies cover unintentional and intentional releases into the environment, including exposures to the aquatic, sediment and soil compartments. In this regard, Case Study 1 (polycarboxylates), Case Study 2 (cationic polymers) and Case Study 6 (surfactant polymers) cover down-the-drain release of consumer products and Case Study 7 (professional use of polyurethane and polyurea) the intentional application of microencapsulated agricultural and horticultural products to land as well as down-the-drain release of microencapsulated fragrance as release scenarios with potential for environmental concern.

For *CF4Polymers (Step 7) hazard assessment*, the case studies include publicly available ecological and toxicological data, while also considering unpublished company data, as relevant. These data are reviewed in view of identifying relevant endpoints and in view of establishing the applicability of the respective methods and models for the assessment of the respective types of polymers.

As regards *CF4Polymers (Step 8) risk characterisation*, the case studies do not aim at performing a risk assessment for any particular polymer. Therefore, these sections of the case studies generally only present high-level conclusions on risk characterisation, while further discussing the applicability of the CF4Polymers for the given type of polymer. An overarching discussion of the applicability of the CF4Polymers is provided after the seven case studies in Section 9.1.

The abundance of information collated for the seven case studies is also further evaluated to enhance the understanding on the applicability and/or technical limitations of the corresponding tools, test methods, and models for polymer hazard and risk assessment, i.e. for a re-appraisal of the evidence presented in the ECETOC TR No. 133-2. While details on the applicability of tools, methods and models are provided in the respective case studies, an overarching discussion thereof is provided in Section 9.2. The suggestions made in ECETOC TR No. 133-2 as to how specific TGs might be adapted to facilitate the testing of polymers are revisited based upon the evidence collated for the present case studies.

1.3 Outline of a flexible approach for the grouping of polymers

1.3.1 Rationale for a grouping approach specifically for polymers

As described in the ECETOC (2019) TR No. 133-1: "*Step 4 of the CF4Polymers, grouping approach evaluation, includes the identification of structurally and/or biologically similar polymers… for which data are available that are potentially relevant for read-across. This approach follows the general approach for substance grouping and read-across as described in the OECD Guidance Document on grouping of chemicals (OECD, 2014) and the European Chemicals Agency (ECHA) Read-Across Assessment Framework [RAAF] (ECHA, 2017c). The identification of structural and/or biological similarity (and hence polymer grouping and read-across) should be based on an understanding of the fundamental relationship between key parameters of relevance for the given type of polymer (at the given life cycle stage(s)) and may also include a certain biological aspect (e.g. bioavailability and/or a specific (eco)toxicological endpoint). As applicable, such key parameters can include structural and/or morphological descriptors as well as physico-chemical and screening-level fate properties and may inform on environmental and human health hazard potential.*"

Hence, the grouping approach suggested by the ECETOC Polymers TF in 2019 follows internationally agreed grouping concepts. In the present TR No. 133-3, it has been further advanced to better scope the complexity and versatility of polymers. Definitions going beyond the internationally agreed grouping concept have been introduced. A central role has been assigned to the term 'hazard similarity' (called 'biological similarity' in TR No. 133-1) that forms a central element of the grouping of polymers (Section 1.3.2). It is the overarching aim of the polymer grouping approach to define 'hazard similarity' of different polymers and, consequently, the final group. Generally, polymer groups based on similar hazards can be expected to contain many more members than categories for non-polymer substances. The reason is the building block nature of polymer chemistry. Related polymers are often homologues manufactured from the same starting materials and similar processes, leading to a large number of similar structures. But even if few of the building blocks are different, such chemical variation in a small part of a macromolecule does usually not lead to differences in physico-chemical or biological properties.

Following the OECD and ECHA grouping approach, substances, whose physico-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, may be considered as a group, or 'class' of substances, or unique substance. Application of the grouping concept requires that physico-chemical properties, environmental fate, environmental effects and/or human health effects may be predicted from data for source substance(s) within the group by interpolation to other substances within the group, i.e. the target substances (read-across approach). This avoids the need to test every substance for every endpoint (ECHA, 2008, 2013, 2017c).

The approach below avoids unnecessary limitation of the boundary of substances within a polymer domain to simply polymers that meet the OECD polymer definition. In so doing it broadens the availability of source substances and renders available a greater resource of hazard data thereby reducing the need for unnecessary testing. The reason for this extension from the internationally agreed grouping concept developed for non-polymeric substances is that, when the polymer grouping approach is applied, a 'group' can, by definition, only contain polymers. Indeed, polymers are generally not considered together with non-polymeric substances in regulatory settings. However, the definition of a polymer has been established for regulatory purposes, applying boundaries (3n+1 rule; 50% rule; Box 3) that are not founded on science-based thresholds. There may be substances that do not fulfil the definition of a polymer but whose properties are all very close to those of the polymers within the given group. This mainly refers to the corresponding oligomeric NLPs (Box 3) or the monomeric units of the polymers. Therefore, the grouping approach for polymers comprises both polymers (source and target substances) and substances that do not meet the definition for polymer as source substances that lie outside the actual group as defined by regulatory means.

The polymer grouping approach proposed by the ECETOC Polymers TF allows to significantly simplify the data requirements for polymer hazard and risk assessment and gives rise to a pragmatic and reasonable description of the substance identity for polymers. In the present report, the polymer grouping approach is exemplified in three case studies, i.e. Case Study 4 (BADGE polymers), Case Study 5 (PEOLs), and Case Study 6 (surfactant polymers; specifically AEs). Notably (and as shown in all three case studies), application of the grouping approach requires sufficient hazard data density for (the) key endpoint(s) and benefits from a continuum of properties both across the given group of polymers as well as towards and across the corresponding non-polymeric substances. The applicability of the polymer grouping approach to other types of polymers needs to be explored on a case-by-case basis. It has been designed to be flexible so that it can be adapted for the polymers under investigation, as required.

1.3.2 Enhancement of the five sub-steps of CF4Polymers (Step 4) grouping approach evaluation by three Criteria to define hazard similarity

In the ECETOC TR No. 133-1, the CF4Polymers Step 4 (grouping approach evaluation) has been subdivided into five steps. Step 4.1 includes expert judgement to identify key parameters of the potential group; Step 4.2 expert judgement to determine similarity, i.e. the potential for grouping; Step 4.3 the definition of the hypothesis for grouping; Step 4.4 the identification of all available relevant (eco)toxicological data; and Step 4.5 the justification of the grouping (Figure Intro-2; see also Appendix 1).

The grouping approach for polymers presented here enhances the outline of Steps 4.1 to 4.5 by introducing a three-Criteria approach to defining and justifying polymer similarity. Specifically, similarity is based upon (Criterion 1) chemical nature; (Criterion 2) physico-chemical property/ies; and most importantly (Criterion 3) ecological and toxicological properties (Figure Intro-3, Panels A and B).

This three-Criteria approach builds upon the following rationale: Polymer chemistry is marked out by a set of building blocks (e.g. monomers, initiator molecules, repeating units) that can be arranged in a very similar manner, over and over again. While the specific chemical structure may differ between different variants of polymers that are all composed of the same building blocks, the corresponding relevant physico-chemical and ecological and toxicological properties will not change – or at least not significantly. In addition, polymers are usually mixtures or homologues of the same building blocks. This drives the tremendous variety of polymer chemistry and gives rise to the challenges encountered when identifying and characterising polymers.

Nonetheless, different polymers that were produced using the same building blocks will, in the vast majority of instances, be very similar with an ever-varying, marginally different structure and corresponding properties.

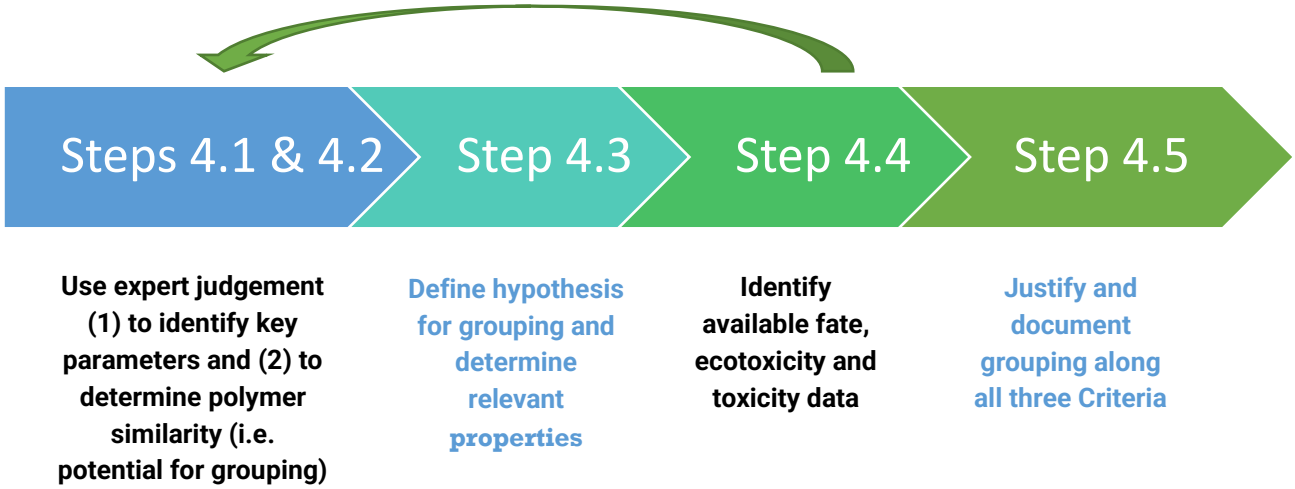


Figure Intro-2: Illustration of the stepwise grouping approach described in Step 4 (grouping approach evaluation) of the CF4Polymers (ECETOC TR No. 133-1)

Footnote to Figure Intro-2: This sequence of steps is not necessarily passed through in a consecutive order, e.g. the (Step 4.1) identification of key parameters and the (Step 4.2) determination of polymer similarity are closely interlinked with the (Step 4.3) definition of the hypothesis for grouping. Similarly, the (Step 4.4) identification of fate, ecotoxicity and toxicity data is a pre-requisite to determine 'hazard similarity' in Step 4.2 and critical to verify the hypothesis in Step 4.3. Therefore, there may be an iterative step back from 4.4 to the beginning in Step 4.1 & 4.2.

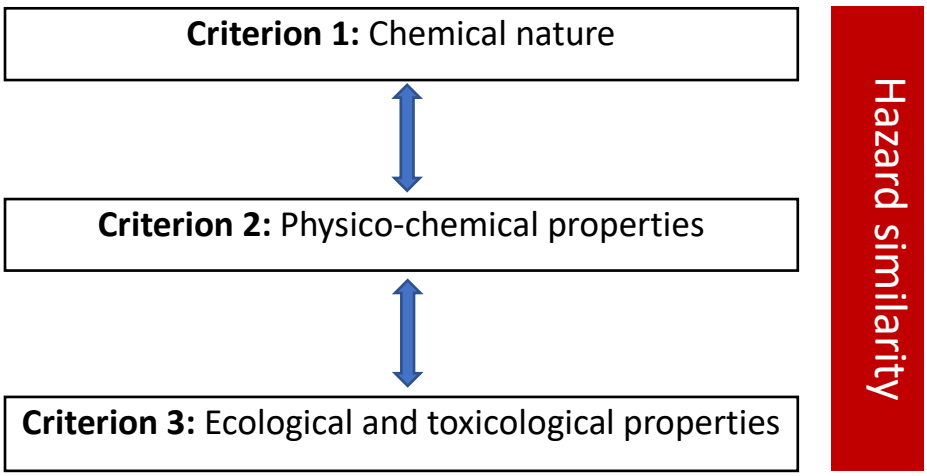


Figure Intro-3 – Panel A: Three Criteria to enhance Step 4 (grouping approach evaluation) of the CF4Polymers as described in ECETOC TR No. 133-1

Footnote to Figure Intro-3 – Panel A: This graphic presents the basic principle for polymer grouping following three Criteria and visualises the balancing of aspects represented in therein. All Criteria serve to establish hazard similarity of the group (see text for details). (Figure provided by ECETOC Polymers TF member company)

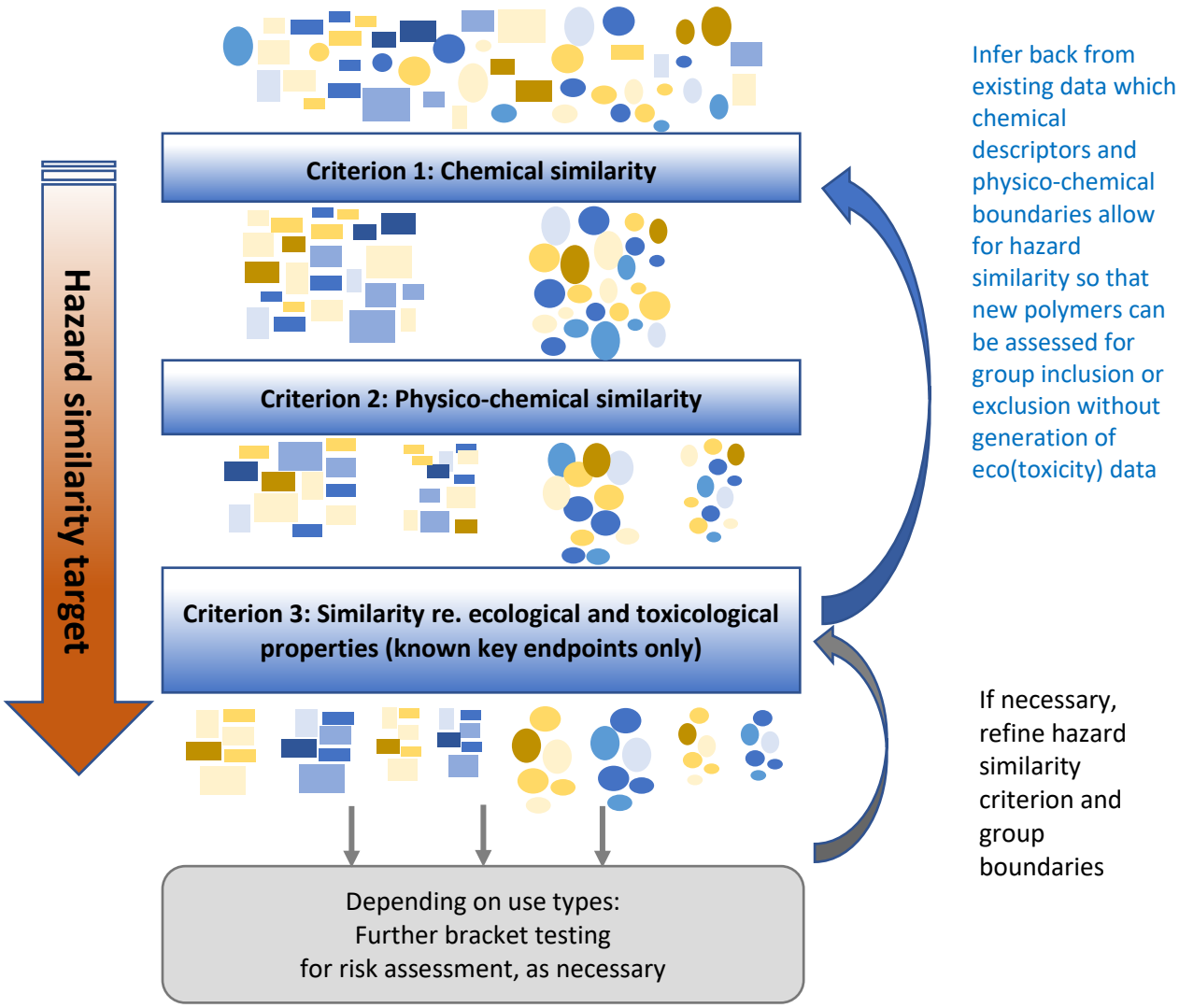


Figure Intro-3 – Panel B: Further details on the three Criteria to enhance Step 4 (grouping approach evaluation) of the CF4Polymers as described in ECETOC (2019) TR No. 133-1

Footnote to Figure Intro-3 – Panel B: This graphic presents the basic principle for polymer grouping following three Criteria and visualises the balancing of aspects represented in therein. All Criteria serve to establish hazard similarity of the group (see text for details). In this example, group boundaries are round vs. box for Criterion 1, large vs. small for Criterion 2 and blue vs. yellow for Criterion 3.

The three Criteria of the grouping approach were designed to reflect this similarity. All three Criteria correspond with each other, and they are critical for the full description of the polymer group. The properties of each criterion also define the content and the boundary of the group. If the defined group is understood as one 'substance' (in a regulatory context), the content and boundaries of the three Criteria can serve as descriptors for substance identity. Criterion 3 addresses hazard properties as the overarching and driving property for building and defining the entire group and finally for risk assessment as implemented in chemical legislations in all (major) jurisdictions. Nonetheless, all three Criteria are indispensable to describe the *hazard similarity* of the group. Hazard similarity is taken as the central element and the ultimate goal when defining and justifying the polymer group.

Against this background, Criterion 1 serves to define the chemical nature of the polymers of interest, i.e. the chemical space describing the group. For example, one starts out with a *generic* group encompassing all polymers that are of general interest and narrows this group down step-by-step in view of establishing one or more *meaningful* groups (Figure Intro-4 and Figure Intro-5, Panel A and B). Within the polymer grouping approach, the stepwise narrowing down of a particular group is described as different iterations until a final group is identified.

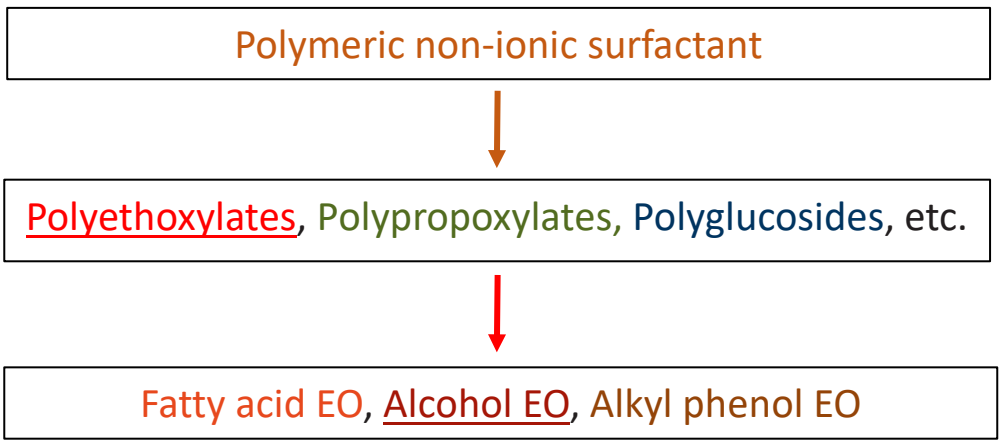


Figure Intro-4: Example of the grouping of alcohol ethoxylates along (Criterion 1) chemical nature, towards a final group

Footnote to Figure Intro-4: In this example, the relevant polymers for grouping are polymeric non-ionic surfactants (Criterion 1 – chemical nature). These polymers for grouping are further subdivided until a final group is reached. This final group has been defined based upon relevant (Criterion 2) physico-chemical properties and (Criterion 3) ecological and toxicological properties and fulfils the premise of hazard similarity. For further details on the grouping of alcohol ethoxylates, see case study 6 (surfactant polymers).

Abbreviation: EO: Ethoxylate(s).

Importantly, Criterion 1 includes the identification of *common key features* of all members of the (preliminary) group. Common key feature can be structural elements of the polymer (building blocks), substances (e.g. residual monomers) or structural descriptors (e.g. shape and size; see Glossary for further details on the definition for common key feature). When defining the preliminary group in Criterion 1 (chemical nature), hazard similarity as the final, overarching justification of the grouping already needs to be reflected. The common key features are key to the hazard and risk assessment of the members of the given group of polymers, and they are identified based upon common hypothesised relevant hazard properties.

Therefore, the Criterion 1 definition of the preliminary group is further substantiated in Criterion 2 by identifying relevant physico-chemical properties and in Criterion 3 by hypothesising relevant hazard properties. Again, the respective Criterion 2 physico-chemical properties are drivers of the Criterion 3 relevant ecological and toxicological properties. The relevant hazard properties need to reflect the main hazards of the given group, and their identification may consider common modes-of-action for the endpoint under consideration. While the relevant hazard properties can differ in their *extent* (i.e. severity) between group members, the extent needs to be predictable across the group (e.g. by following a certain trend).

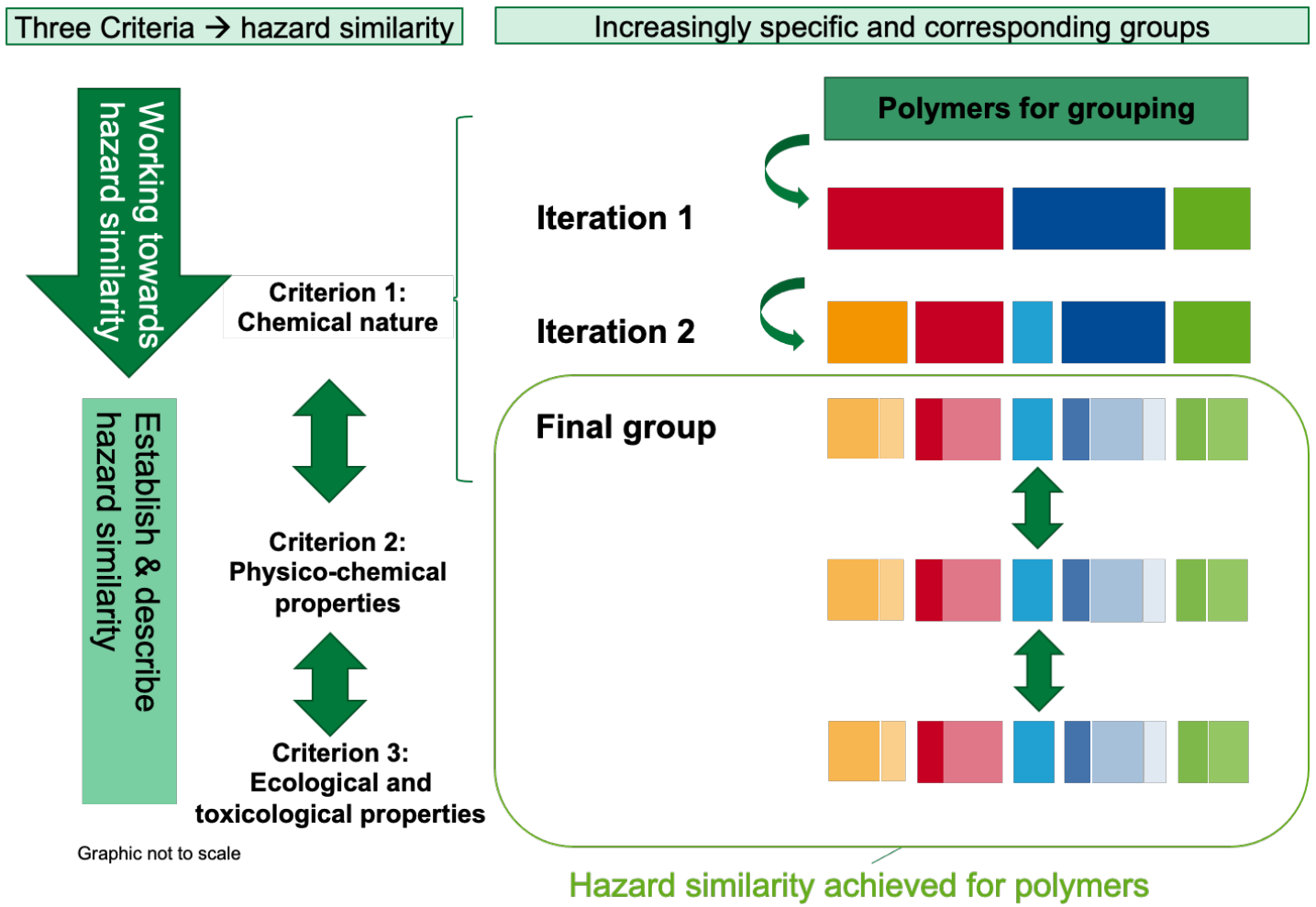


Figure Intro-5 – Panel A: Basic principle of polymer grouping and balancing of aspects represented in Criteria 1-3: The determination of all three Criteria serves to establish hazard similarity of all group members

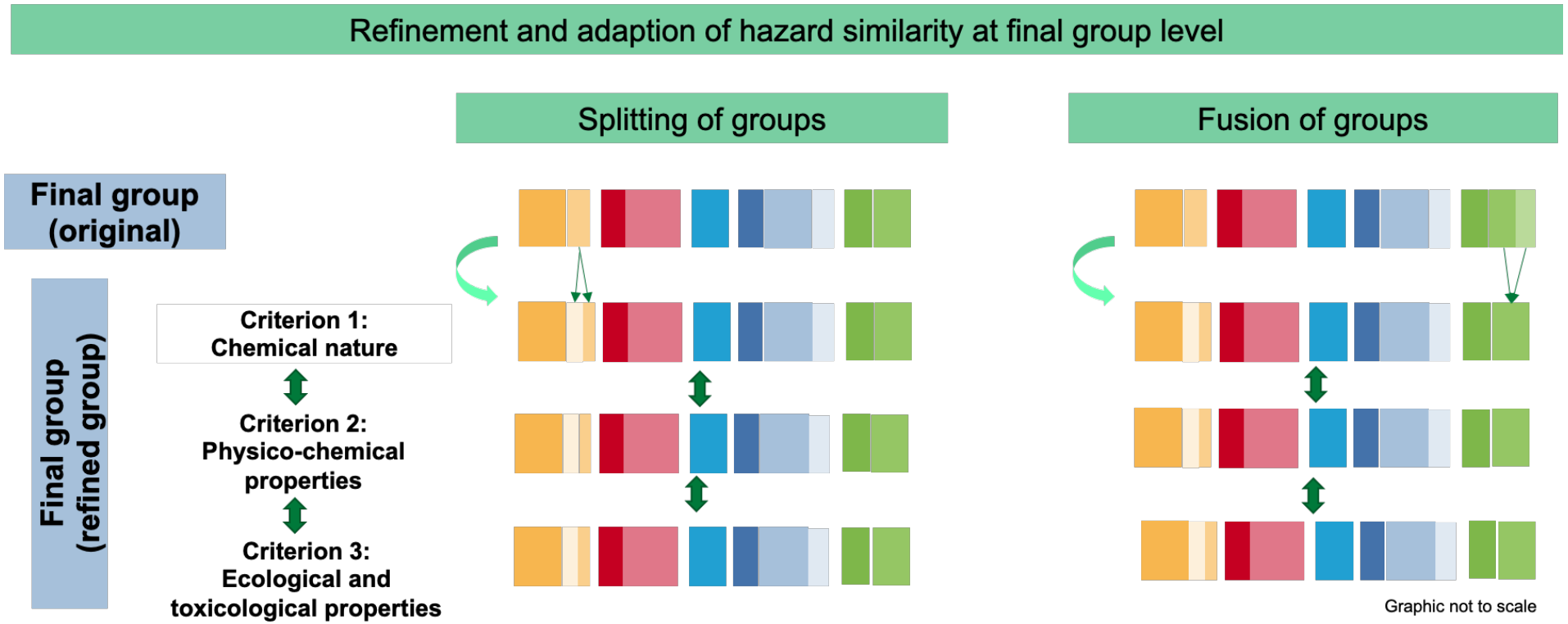


Figure Intro-5 – Panel B: Ongoing refinement and adaptation of the final groups to reflect new knowledge as it becomes available; see text for further explanation

Footnote to Figure Intro-5 – Panels A and B: In these not-to-scale graphics, the different colours reflect different preliminary / final groups as well as a continuum of the extent of different (common) properties within each final group. The different colours indicate different groups as identified along the process. On the level of the final groups, different colours and also different shades of the same colours refer to different groups. However, as groups highlighted by different shades of the same colours are defined rather late in the process, they are more similar to each other than to groups of other colours. Note that the grouping concept is intended to be flexible. Certain steps may not be useful for all types of polymers, and some types of polymers may benefit from adding other aspects of grouping. (Figures provided by ECETOC Polymers TF member company)

In Steps 4.1. and 4.2. of the CF4 Polymers, expert judgement is applied for an initial identification of the key parameters as needed for the three Criteria and for an initial determination of the similarity of the polymers. Taken together, the efforts on Steps 4.1 and 4.2 provide an initial assessment along the three Criteria to establish the potential for grouping.

After a (preliminary) completion of the three Criteria in Steps 4.1 and 4.2 of the CF4Polymers, the hypothesis for the final group needs to be defined and a relevant grouping approach needs to be determined (Step 4.3). To support the hypothesis (as well as the selection of the relevant hazard properties in Criterion 3), Step 4.4 focuses on the identification of all available environmental fate, ecotoxicity and toxicity data. Hence, Step 4.1-4.4 are closely interlinked and are not necessarily followed in a strictly consecutive order. Taken together, these four steps serve to first hypothesise relevant hazard properties and then confirm that these are indeed the 'key' hazard properties. Thereby, it is either confirmed that all members of the preliminary group fulfil the premise of hazard similarity, or it is established that an iterative step is necessary. This iterative step may include the subdivision of the preliminary group into more than one distinct sub-groups or the merging of preliminary groups. Ultimately, the final groupings need to fulfil the premise of hazard similarity. This iterative step may also be conducted as a maintenance step if new knowledge comes to light that justifies further sub-division (see also Section 1.3.3 for the level of similarity that needs to be achieved and maintained for any given final group). Finally, in Step 4.5, the outcome of the Step 4.1-4.4 grouping is justified and documented.

Possibly, in Step 4.4 information for (Criterion 3) ecological and toxicological properties is not readily available from the very beginning for all key endpoints, or not for a sufficient number of polymers being representative for the range intended to be grouped. Therefore, Step 4.1 - Step 4.3 are applied in a flexible manner forming a preliminary group. Any missing relevant data that are needed to justify the final group in Step 4.3 (including relevant Criterion 3 hazard data) are then generated based on use and fate properties (see ECETOC TR No. 133-2). Once these new data become available (Step 4.4), all steps can be completed, and the final group can be justified and documented (Step 4.5).

Criterion 1 to 3, as well as an ongoing refinement and adaptation step ('maintenance step'), are proposed as the principal elements for polymer grouping. Once the final groups are assigned, justified, and documented, new polymers may come up that need to be assigned to one of the pre-defined final groups. As the three Criteria correspond with each other and are interdependent in their properties, the new polymer can be assigned to one of the final groups based on the definitions and boundary definitions determined in Criterion 1 and Criterion 2. In case the new polymer cannot be allocated to any of the existing final groups, a new final group may need to be identified and justified along the five-step approach.

Finally, it is important to note that, just as the entire CF4Polymers has been designed to be flexible and non-prescriptive, the polymer grouping approach described here should be viewed as a flexible framework. Certain steps of the grouping approach may be of higher or lower importance for some types of polymers, whereas other types of polymers may benefit from adding specific aspects to the grouping that are more particular to their chemistry and are not described here.

1.3.3 Level of similarity

An important part of the polymer grouping approach is to describe the level of similarity that is needed to achieve confidence on similarity of the final group. There is no one-way-fits-all or simple answer, rather

similarity needs to be established on a case-by-case basis (see Figure Intro-6 for general guidance). The principle of hazard similarity assumes the identification of relevant hazard properties for the specific group.

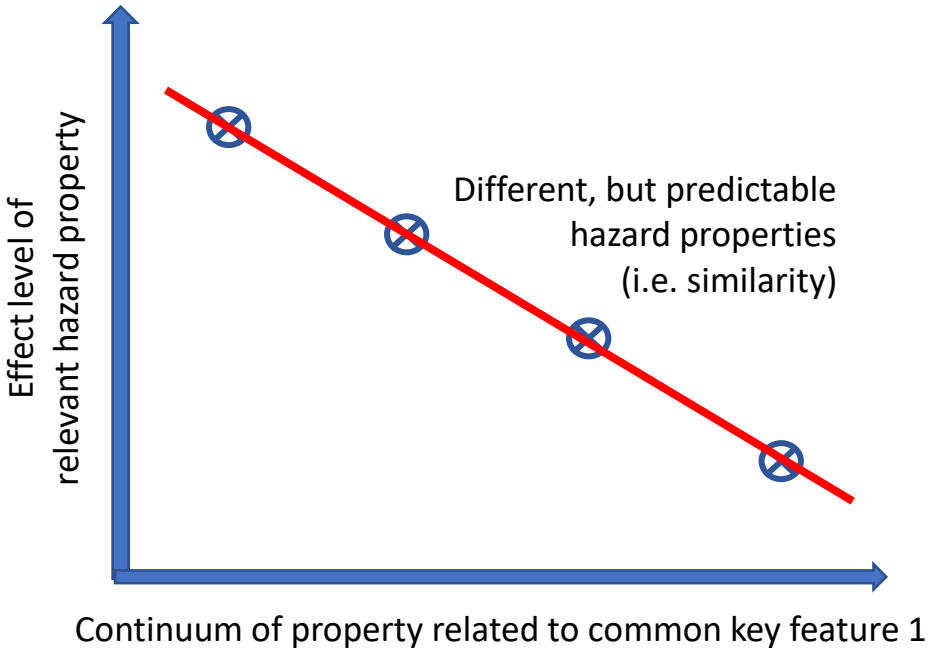


Figure Intro-6: Visualisation of the final group that fulfils the premise of hazard similarity

Footnote to Figure Intro-6: The effect level of relevant hazards properties of group members from one end of the group do not necessarily have to be the same as those for group members at the other end. However, the relevant hazard properties *as such* (e.g. acute oral toxicity) need to be the same for the entire group, and there needs to be a *continuum* of the effect level for the relevant hazard property from one end to the other. A continuum and predictivity of the relevant hazard property should be established and justified. (Figure provided by ECETOC Polymers TF member company.)

These relevant hazard properties are characteristic for that group and determine the Criterion 3 ecotoxicological and toxicological properties, while retaining consistency with both Criterion 1 (chemical nature) and Criterion 2 (physico-chemical properties). Consequently, it is hypothesised that hazard properties can be reliably predicted based upon a combination of all three Criteria. Further, if hazard properties vary between group members, they do so in a regular pattern or trend that relates to and can be explained in terms of differences in Criterion 1 and 2 properties. Nonetheless, the relevant hazard properties as such need to be the same for the entire group (e.g. acute oral toxicity). Similarly, there should be a continuum of the effect level for the relevant hazard property from one end to the other. In the event of newly generated data being inconsistent with the predicted relationship between Criterion 1 and 2 properties and predicted hazard properties the polymer grouping may necessitate revision (Section 1.3.2; Figure Intro-5, Panel B). This would be the case if, e.g., some group members are assigned H372 (causes damage to organs through prolonged / repeated exposure) but other group members no H-class in accordance with the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS; United Nations, 2019) that has been implemented in *EU Regulation No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures* (CLP; EP and Council, 2008).

1.3.4 Bracket testing

CF4Polymers Step 4.4 includes the identification of available ecotoxicity and toxicity data. There may be cases where additional data are not readily available for the preliminary group and the generation of targeted, use-specific data on one or more relevant hazard properties is deemed appropriate. To cover the variety of polymers, so-called bracket testing can be applied when additional endpoint data are required to characterise the hazards of a group of polymers. When bracket testing is applied, few different test materials out of the group are selected for testing and subsequent read-across of the properties across the group members. This requires selecting those test materials which are at the boundaries and in the middle of the group in terms of chemical nature and physico-chemical properties, so that the read-across relies on interpolation and not extrapolation. The number of test items in the bracket test necessary to adequately represent the entire group of polymers will depend upon the range and consistency of Criterion 1 and 2 properties and the available data on effects within the polymer group as well as the concordance of the findings of any bracket testing.

1.3.5 Data matrix

For better evaluation of the polymer grouping approach, the common key feature(s) as well as the corresponding relevant hazard property/ies can be visualised in a data matrix, e.g. using a spreadsheet or graph (Figure Intro-7). The number of matrices and dimensions needed therein is dependent on the number of relevant hazard property/ies and/or common key feature(s) identified. Using such data matrices, the consistency and predictability of the relevant hazard properties along the common key feature can be assessed and documented.

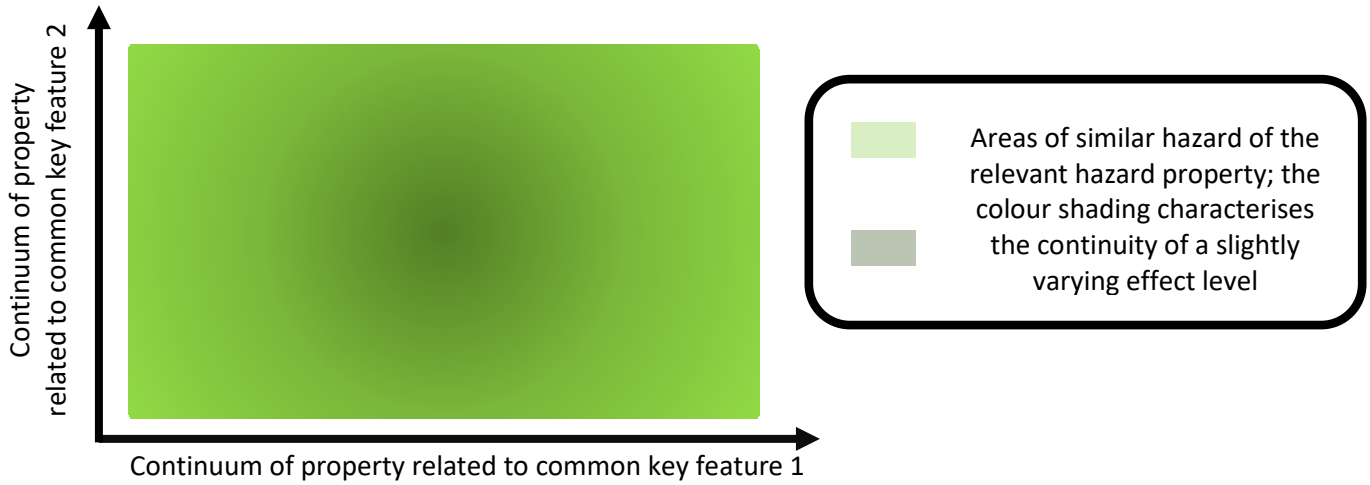


Figure Intro-7: Example of data matrix to visualize the continuity and predictability of the relevant hazard properties related to different common key features (Figure provided by ECETOC Polymers TF member company)

1.3.6 Risk characterisation for the final group

The CF4Polymers outlined in ECETOC TR No. 133-1 includes a step for risk characterisation (i.e. Step 8). As described in this general approach for the grouping of polymers, the final polymer group, with its hazard

similarity between group members, also needs to be submitted to a risk characterisation associated with a relevant intended use and hence potential for exposure (Figure Intro-8). This is a pivotal and important element that is superior to the simple application of hazard properties for polymer safety assessment. Just as has been described for the polymer grouping approach as such, the risk characterisation for the final group is founded on the common key feature and relevant hazard properties are again central. Depending upon the level of protection required i.e. the margin of safety between the level of predicted exposure and the derived no-effect level or predicted no-effect concentration, it may be necessary to subdivide the final category so as to further refine the exposure or hazard assessment. Importantly, such a sub-division for the purpose of risk assessment needs to be undertaken on case-by case and in a flexible manner. Other reasons for more than one risk assessment may be different uses or properties. However, the final decision on the number of individual risk assessments may also be driven by the margin of safety needed to demonstrate safe and sustainable use.

1.4 Summary of aim and scope of present ECETOC TR No. 133-3

In the present *ECETOC TR No. 133-3* that concludes the TR No. 133 series, seven case studies were selected to further evaluate (1) the usefulness of the CF4Polymers (ECETOC TR No. 133-1) for the safety assessment of different types of polymers and (2) the information on the applicability of tools, methods and models for the hazard and risk assessment of polymers presented in ECETOC TR No. 133-2.

Accordingly, the evidence from the seven case studies, that are presented below in Sections 2-8, shall be used in the overarching discussion (Section 9) order to

- Section 9.1: Confirm the applicability of the CF4Polymers (ECETOC TR No. 133-1) or to identify the need to update it
- Section 9.2: Provide further evidence on the applicability of tools, methods, and models for polymer risk assessment (ECETOC TR No. 133-2)
- Section 9.3: Revisit the five recommendations to promote the hazard and risk assessment of polymers as spelled out in ECETOC TR No. 133-1 and 133-2 (Box 2).

Importantly, it is not the purpose of the case studies to perform a hazard and risk assessment for any specific polymer. Also, the case studies do not describe how any specific legal requirements should be met.

The ECETOC TR No. 133 series describe how polymer risk assessment can be undertaken, regardless of the underlying motivation and/or legal requirements. Thereby, the CF4Polymers can both be applied for research, product stewardship and in regulatory settings. There may be regulatory settings requiring more or less knowledge than outlined in the CF4Polymers. Evidently, such regulatory requirements take precedence if the risk assessment is conducted to fulfil the respective legal obligations. In such cases, the CF4Polymers may provide insight that facilitates adaptations of traditional testing approaches implemented in current legislation.

Finally, the evidence presented in the ECETOC TR No. 133 series shall by no means be considered ‘final’. It reflects current experience and knowledge and shall be adapted, amended and refined as new evidence on the process of polymer hazard and risk assessment becomes available. Therefore, ECETOC has mandated an *ad-hoc* committee to follow up such new insight and proactively update the TR No. 133 series to keep abreast of the state-of-the-art within this domain.

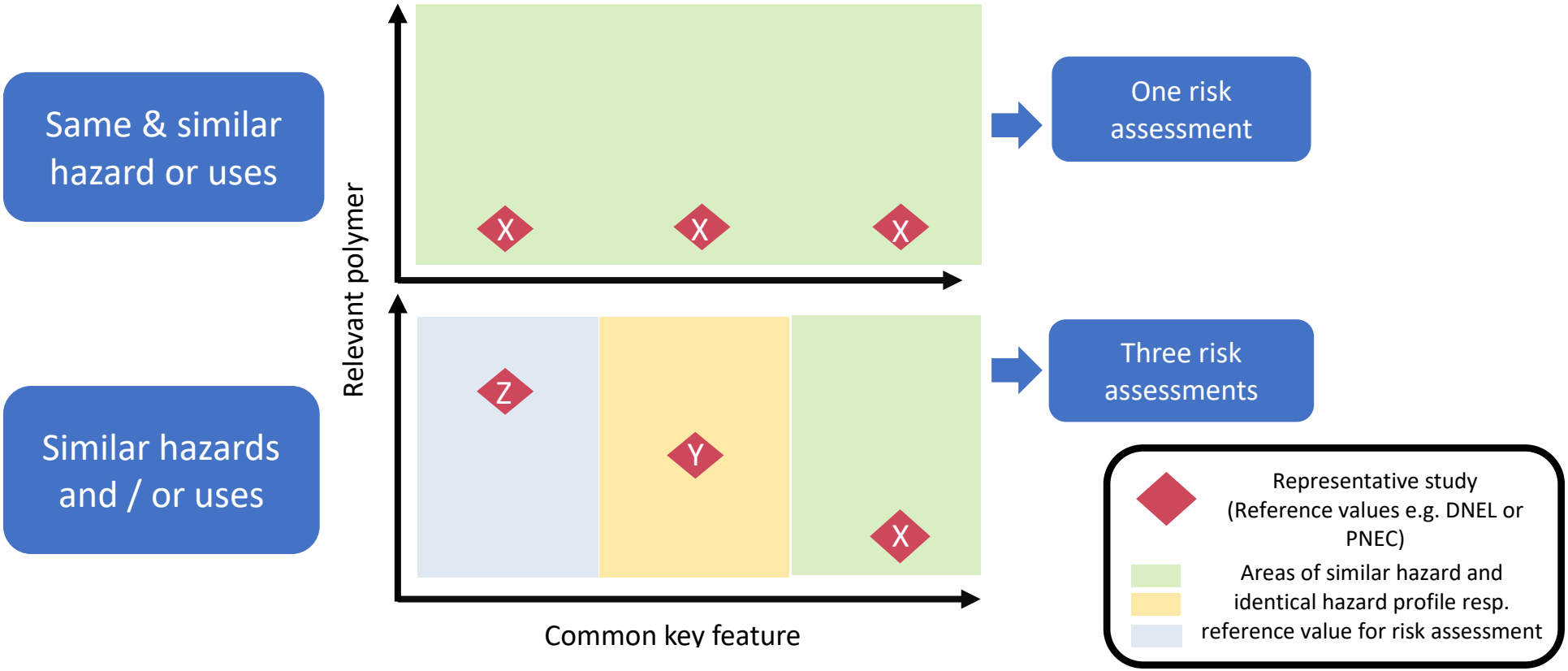


Figure Intro-8: Schematic illustration for risk assessment based on relevant hazard properties and common key component

Footnote to Figure Intro-8: Upper part of figure: The hazard of the final polymer group may be very similar. The corresponding derived no effect level or predicted no effect concentration is deemed sufficient for risk assessment. Lower part of figure: In case the relevant hazard property is similar but too distinct for risk assessment (or the use), one may subgroup the polymer group for the purpose of risk assessment. (Figure provided by ECETOC Polymers TF member company)

Abbreviations: DNEL: Derived no effect level; PNEC: Predicted no effect concentration.

[a] For example, molecular weight, monomer degree, charge density, morphology, etc.); depending on the polymer type, one, two or more common key features may be used to characterise the polymer.

2. CASE STUDY 1: POLYCARBOXYLATES, POLYACRYLATES, POLYMETHACRYLATES

2.1 Introduction

2.1.1 Scope and outline of Case Study 1

Polycarboxylates, polyacrylates, and polymethacrylates are polymers with a carbon-carbon backbone. Polycarboxylates are produced by polymerisation of carboxylic acid anhydrides, and polyacrylates and polymethacrylates by polymerisation of esters based on acrylic and methacrylic acids, respectively. Polycarboxylates, polyacrylates, and polymethacrylates can be linear or cross-linked, and they cover a wide molecular weight range.

This case study focuses on *polyacrylic acid-maleic acid copolymers (P-AA/MA)* and linear *polyacrylic acid homopolymers (P-AA)*. Since P-AA/MA and P-AA are widely used in multiple personal, home care, and industry applications, they have undergone extensive hazard and risk assessment and thus are relatively data rich. Already in 1993, ECETOC published the Joint Assessment of Commodity Chemicals Report No. 23 on polycarboxylate polymers as used in detergents (ECETOC, 1993). Further, for both P-AA/MA and P-AA, assessments from the Human and Environmental Risk Assessment (HERA) project that was jointly funded by the International Association for Soaps, Detergents and Maintenance Products (AISE) and the European Chemical Industry Council (Cefic) were published in 2014 (HERA, 2014a, b).

This case study aims to take P-AA/MA and P-AA through all steps of the CF4Polymers (as described in ECETOC TR No. 133-1) to evaluate its suitability to perform a (theoretical) risk assessment for these types of polymers. Consumer use in laundry detergents and additionally, for P-AA, in personal care products was selected as intended use. The selected exposure scenarios focus on environmental exposure on account of the down-the-drain release while also considering potential consumer exposure by use of the final products containing P-AA/MA and P-AA.

Further, for some parts of this case study, reference is made to the polymethacrylate *poly(methyl methacrylate) (PMMA)*, which is also frequently used in personal care products, and to a LMW polyacrylate copolymer, *ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA)*. EPPAA is used in coatings and waterless inks, and it is a data rich polymer, also since it had been registered under the European Union (EU) *Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals* (REACH; EP and Council, 2006).

The comprehensive database presented in this case study is also further evaluated to enhance an understanding of the suitability of standardised tools, test methods, and models (as described in ECETOC TR No. 133-2) for the assessment of polycarboxylates, polyacrylates and polymethacrylates.

2.1.2 Definition, structural considerations and uses

Different definitions for polycarboxylates and polyacrylates can be found in the literature. Below, the rationale applied by the ECETOC Polymers TF is outlined.

2.1.2.1 Polycarboxylates

Polycarboxylates are anionic, linear polymers with a carbon-carbon backbone and multiple carboxylate functional groups (COOH) that result from the polymerisation of monounsaturated carboxylic acids. Polycarboxylates are identified based on the monomers used in their synthesis. The carboxylic acids include e.g. acrylic acid (i.e. prop-2-enoic acid), methacrylic acid (i.e. 2-methylprop-2-enoic acid), and maleic acid (i.e. cis-butenedioic acid). Carboxylates may be homopolymers or copolymers, which can be composed of a sequence of (the same or different) carboxylic acids. Carboxylate copolymers can also be crosslinked with allyl ethers of linear or cyclic monomers such as pentaerythritol, propene, or sucrose. Polycarboxylates are often associated with cations to form salts of polycarboxylates. Thus, P-AA/MA are copolymers of acrylic acid and maleic acid as well as their sodium salts, and linear P-AA are homopolymers of acrylic acid as well as their sodium salts (Figure CS1.1, Panels A and B).

Polycarboxylates are often used as scale control agents in detergents, as their properties allow sequestration of cations that could otherwise react with anionic surfactants and form unwanted precipitates when washing with those detergents. They can therefore be considered water softeners and can be found in domestic and industrial cleaning formulations. Further, when adsorbed to larger scale crystals, polycarboxylates can prevent both aggregation and deposition of scale onto surfaces.

2.1.2.2 Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are structurally similar polymers that result from the polymerisation of acrylate and methacrylate monomers, which are esters based on the structures of acrylic and methacrylic acids, respectively. Polymerisation occurs through the C=C bond present in the acrylate or methacrylate group. Examples of monomers include methyl acrylate, ethyl acrylate, butyl acrylate, 2-ethylhexyl acrylate, trimethylolpropane triacrylate, pentaerythritol tetraacrylate, as well as the methacrylate counterparts of all of these monomers and many other alkyl, aryl and alkylaryl esters of (meth-)acrylic acid.

Similar to polycarboxylates, polyacrylates include a carbon-carbon backbone. However, instead of –COOH functional groups, they include –COOR ester groups, where R corresponds to the alkyl/aryl/alkylaryl chain of the monomers. The properties of the resulting polymer are heavily influenced by the –R side chain originating from the respective ester monomers. Many polyacrylates are transparent, elastic and resistant to e.g. mechanical forces, and as such they are commonly present in products where these properties are useful. Examples include e.g. cosmetics products (e.g. nail polish), coatings and inks (as rheological agents), 3D printing, medical devices, and implants. Specific polyacrylates are also commonly used in textile industry because of their durability, softness and resistance to discoloration. Low glass-transition temperature polyacrylates can be used as adhesive products.

A well-known example of a polymethacrylate is PMMA, which has the structural formula $[CH_2C(CH_3)(CO_2CH_3)]_n$. Accordingly, PMMA includes a backbone resulting from the methacrylate groups of the monomers and -$COOCH_3$ functional groups that are derived from the methyl groups of methyl methacrylates (methacrylic acid methyl esters) (Figure CS1.1, Panel C). Similarly, a polymer of ethyl acrylate would include -$COOCH_2CH_3$ functional groups, a butyl acrylate polymer would have -$COOCH_2CH_2CH_2CH_3$ groups, etc.

PMMA, as a transparent thermoplastic, has a wide range of uses, including acrylic paints, dentures, furniture (as a replacement for glass), optical fibres, artificial nails and many others.

It should be noted that copolymers manufactured from both carboxylic acids and acrylate esters exist as well, i.e. resulting in structures combining polycarboxylate and poly (meth)acrylate repeat units.

Figure CS1.1 – Panel A: P-AA/MA

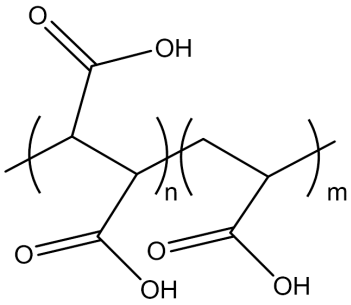


Figure CS1.2 – Panel B: P-AA

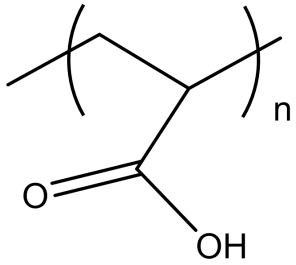


Figure CS1.1 – Panel C: PMMA

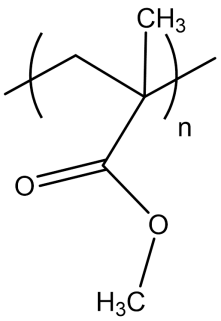


Figure CS1.2 – Panel D: EPPAA

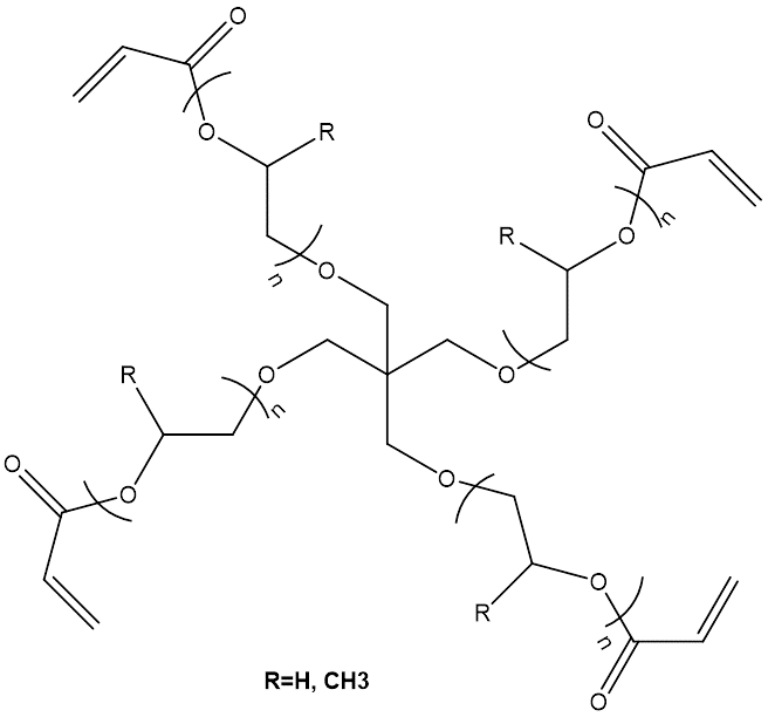


Figure CS1.1: Chemical structure of polycarboxylates, polymethacrylates, polyacrylates considered in Case Study 1 (Panel A: Polyacrylic / maleic acid copolymer (P-AA/MA); Panel B: Polyacrylate homopolymer (P-AA); Panel C: Poly(methyl methacrylate) (PMMA); Panel D: Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA))

2.1.2.3 Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA)

Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer (EPPAA) is produced via a reaction of 4 moles ethoxylated and 1 mole propoxylated pentaerythritol and acrylic acid. The polymerisation results from an esterification reaction (alcohol groups from alkoxylated pentaerythritol and acrylic acid) and an etherification reaction (double links from acrylic acid). EPPAA is therefore a copolymer of two repeating monomer units, i.e. alkoxylated pentaerythritol and acrylic acid (Figure CS1.1, Panel D – see preceding page).

EPPAA is used in coatings and waterless inks.

2.1.3 Synthesis

Polycarboxylates, polyacrylates, and polymethacrylates are manufactured by different chemical processes. Acrylic and carboxylic monomers polymerise exothermally and are stabilised using hindered phenolic inhibitor additives at a level appropriate to the anticipated storage temperatures and duration of storage.

The polymerisation of acrylate and methacrylate esters is often achieved by free-radical, head-to-tail chain propagation using free-radical initiators such as azo compounds, peroxides and hydroperoxides; also, in some cases photochemical and radiation-initiated polymerisations are possible (Slone, 2010).

Industrial polymerisation processes include simple bulk polymerisation, solution polymerisation (using a co-solvent), emulsion polymerisation (using water, a surfactant and a water-soluble initiator), suspension polymerisation (monomers dispersed in water droplets and stabilised through protective colloids or suspending agents), graft polymerisation (attachment to a pre-existing polymer backbone of similar or different composition), and ultraviolet (UV) photocuring, among others.

Current polyacrylates are often emulsion polymers that are obtained by emulsification of the acrylic monomers and polymerisation in small droplets. These droplets are then stabilised in aqueous media by addition of surfactants whereby the size of the polyacrylate particles can also be controlled.

PMMA is manufactured in many different forms including thermoplastic sheets (i.e. acrylic or acrylic glass), beads or extrusion polymers for moulding into articles (vehicle lights), suspension or solution resins for use in the manufacture of inks and coatings, etc. The PMMA manufacturing process includes free radical polymerisation. PMMA beads are also manufactured for use in medical devices and in cosmetic products with different size of the PMMA spheres depending on the specific intended use.

2.2 Case Study 1: CF4Polymers (Step 1) Problem formulation

This case study focuses on P-AA/MA and P-AA in final formulations that are intended for consumer use (laundry detergents and additionally, for P-AA, personal care products). The relevant life cycle is towards the end-of-life, i.e. the down-the drain-release of P-AA/MA and P-AA. Therefore, the case study focuses on environmental exposure assessment with freshwater and sediment as predominant environmental compartments, while also considering the terrestrial compartment as well as the behaviour of P-AA/MA and P-AA in wastewater treatment plants (WWTPs).

Second, potential human exposure to the final formulation via the dermal, as well as inhalation and/ or oral, routes of exposure is considered since many P-AA/MA and P-AA are likely to become bioavailable externally

(e.g. at the skin) and also may be taken up via ingestion. Here, the protection goal addresses the individual consumer.

For some steps of the case study, reference is also made to PMMA as transparent thermoplastic used in acrylic paints and to EPPAA used in coatings and waterless inks. Again, there may be some release into the aquatic and terrestrial compartments, and consumer exposure may occur via the dermal and oral routes of exposure (or, at very low levels, via inhalation).

2.3 Case Study 1: CF4Polymers (Step 2) Polymer identification

2.3.1 Step 2.1: Identification of the polymeric substance

2.3.1.1 Standard chemical descriptors and molecular weight

Introductory notes

CAS registry numbers: Polymers including polycarboxylates, polyacrylates and polymethacrylates are routinely identified by Chemical Abstract Service (CAS) registry numbers. However, polymers that share the same common or International Union of Pure and Applied Chemistry (IUPAC) name generally have multiple CAS numbers since CAS numbers sometimes take account of differences in the manufacturing process, particularly if the same polymer can be synthesised out of different starting materials. Different variants of a polymer (as regards e.g. (median) molecular weight, molecular weight distribution and/or physical form) can be subsumed under one CAS number. Relying on CAS numbers alone therefore misses opportunities to glean valuable knowledge, such as the form of a polymer at key life-cycle stages or molecular weight distribution ranges used to make specific consumer products.

Sector-specific descriptors and additional information: Sector-specific manufacturers and downstream users have provided additional polymer descriptors. For example, the cosmetic and personal care industry uses the International Nomenclature of Cosmetic Ingredient (INCI) system to describe and name cosmetic and personal care ingredients (https://www.personalcarecouncil.org/resources/inci/). The INCI system assigns an INCI name and unique identifying code (Unique Monograph ID Number; MonoID) to polymeric ingredients following a standardised approach. It is important to note that INCI names also represent polymers which have ranges of physico-chemical properties, but additional information is provided on the physico-chemical properties of raw material and formulated ingredients. Also, in the INCI databases, standardised, well-defined ingredient functions have been assigned to polymer INCI names and MonoIDs. Functions relate to key product attributes that result in part from the physico-chemical properties of the raw material polymers supplied by manufacturers. For example, the desired rheology of a finished product is influenced by the use of certain molecular weights/chain lengths. Functions also reflect downstream modifications to polymers resulting from formulation processes. For example, a solid raw material may be solubilised or molten into a product, or a polymer's properties may be designed to change by altering e.g. the pH of the matrix of the formulated material. The INCI databases therefore include additional information regarding downstream and upstream polymer properties (Table CS1.1).

Table CS1.1: Polymeric cosmetic ingredients that are polycarboxylates, polyacrylates and polymethacrylates: INCI descriptors (used with permission from PCPC, USA), CAS numbers and frequency of use as per US FDA (2021) VCRP (used with permission obtained under the US Freedom of Information Act)

INCI name	INCI MonoID	CAS number(s)	Ingredient functions (assigned by INCI)	US FDA VCRP count (frequency of use)
Carbomer	5092	9003-01-4; 9007-16-3; 9007-17-4; 9062-04-8; 76050-42-5	Emulsion stabilizers	7,510
			Viscosity increasing agents	
Acrylates/C10-30 alkyl acrylate crosspolymer	4663	Not available	Emulsion stabilizers	4,055
			Viscosity increasing agents	
Acrylates copolymer	52	25035-69-2; 25035-88-5; 25212-88-8; 25685-29-4; 26300-51-6; 159666-35-0	Adhesives	3,363
			Artificial nail builders	
			Binders	
			Dispersing agents	
			Film formers	
			Hair fixatives	
			Skin conditioning agents	
Sodium polyacrylate	6285	9003-04-7; 25549-84-2	Absorbents	1,209
			Emulsion stabilizers	
			Film formers	
			Hair fixatives	
			Skin conditioning agents	
			Viscosity increasing agents	
Polymethyl methacrylate (PMMA)	5111	9011-14-7	Bulking agents	1,041
			Film formers	
Styrene/acrylates copolymer	3088	9010-92-8; 25034-86-0; 25085-34-1; 27306-39-4	Film formers	523
			Opacifying agents	
Methyl methacrylate crosspolymer	5159	25777-71-3	Bulking agents	499
			Film formers	
			Viscosity increasing agents	
Methyl methacrylate/glycol dimethacrylate crosspolymer	12530	25777-71-3	Film formers	499
Acrylates/octylacrylamide copolymer	5100	129702-02-9	Film formers	353
Acrylates/octylacrylamide copolymer	5100	129702-02-9	Hair fixatives	353
Sodium acrylate/sodium acryloyldimethyl taurate copolymer	17390	37350-42-8; 77019-71-7; 136903-34-9	Anticaking agents	260
			Dispersing agents	
			Emulsion stabilizers	
			Film formers	
			Opacifying agents	
			Viscosity increasing agents	
Octylacrylamide/acrylates /butylamino-ethyl methacrylate copolymer	1781	70801-07-9	Film formers	234
			Hair fixatives	

INCI name	INCI MonoID	CAS number(s)	Ingredient functions (assigned by INCI)	US FDA VCRP count (frequency of use)
Sodium carbomer	6050	73298-57-4; 1401207-41-7	Emulsion stabilizers Film formers Viscosity increasing agents	202
Sodium acrylates copolymer	6613	25549-84-2	Binders Film formers Viscosity increasing agents	233
Acrylates/dimethicone copolymer	10082	Not available	Anticaking agents Binders Film formers	135
Polyacrylic acid (P-AA)	2402	9003-01-4	Binders Emulsion stabilizers Film formers Viscosity increasing agents	131
Styrene/acrylates/ammonium methacrylate copolymer	3087	Not available	Dispersing agents Film formers	126
Lauryl methacrylate/glycol dimethacrylate crosspolymer	10384	Not available	Film formers Hair fixatives	120
Polyacrylamido methyl propane sulfonic acid	3730	27119-07-9	Film formers Dispersing agents	116
Acrylates/beheneth-25 methacrylate copolymer	12077	Not available	Viscosity increasing agents	110

Footnote to Table CS1.1: Abbreviations: CAS: Chemical Abstract Service; FDA: Food and Drug Administration; INCI: International Nomenclature Cosmetic Ingredient; MonoID: Monograph ID number; PCPC: Personal Care Products Council; VCRP: Voluntary Cosmetics Reporting Program; US: United States.

It is common practice for in-use personal care ingredients to be aligned with an existing INCI name or to be assigned a new INCI name, following the product labelling requirements implemented in Article 19(1)g of the EU *Regulation (EC) No 1223/2009 on cosmetic products* (EP and Council, 2009). A similar practice is also favoured by the United States (US) Food and Drug Administration (FDA). Likewise, ingredient functions (for an INCI name) are reported by companies. This provides additional useful information for the industry. Of note, one INCI name can have multiple reported functions. This is because an INCI name can cover a wide array of polymers that may have, for example, different chain length distributions/average chain lengths. Also, formulation processes alter polymer function e.g. in the course of polymer-polymer/polymer-substance interactions and due to delivery systems. For example, polymers can wrap around surfactants to form complex micelles, which can impact a polymer's properties relative to the raw material. However, the functions described for the INCI polymer are proposed at the time of initial submission. Therefore, all functions described under a given INCI name may not be relevant for all actual marketed products.

A review of available INCI names reveals a relatively high number of entries related to polymers with a carbon-carbon backbone. The US FDA oversees the Voluntary Cosmetic Reporting Program (VCRP; https://www.fda.gov/cosmetics/voluntary-cosmetic-registration-program). The VCRP tracks the number of unique cosmetic formulations an ingredient is used in (expressed as VCRP counts), allowing assessors to

prioritise resources and efforts. Table CS1.1 outlines the most widely used polymeric cosmetic ingredients that are polycarboxylates, polyacrylates and polymethacrylates (defined here as those with at least 100 VCRP counts).

Generally, the molecular weight and physical form of polycarboxylates, polyacrylates and polymethacrylates can vary greatly depending upon the manufacturing conditions and intended application.

P-AA/MA and P-AA

P-AA/MA copolymers and their sodium salts (that are mainly used in home care products, but only very rarely in personal care products) have the CAS No. 52255-49-9 (unless they contain chain transfer agents). They cover products with mean molecular weights ranging from approx. 12,000 to 100,000 Dalton (Da; g/mol), with the many commercial P-AA/MA copolymers used for laundry detergents having a mean molecular weight of approx. 70,000 Da (HERA, 2014b). Other polycarboxylates, for example P-AA/MA copolymers using chain transfer agents such as phosphorous acid, may have molecular weights down to below 2,000 Da.

Poly(acrylic acid) homopolymers (P-AA) have the INCI MonoID 2402 and different CAS numbers including CAS No. 9003-01-4, 9007-16-3, 9007-17-4, and 9062-04-8, and they can be identified via the IUPAC name '*2-propenoic acid, homopolymer'*. The overall group of linear P-AA homopolymers and their sodium salts covers products with molecular weights ranging from 1,000 to 78,000 Da, with the P-AAs typically used in detergents having a molecular weight of approx. 4,500 Da (HERA, 2014a).

The typical molecular weight distribution (polymer dispersity) is 10 for P-AA/MA (HERA, 2014b) and approx. 2 for P-AA (HERA, 2014a) – with higher polydispersity indices indicating broader molecular weight distribution, and their melting point lies above 150 °C.

PMMA

PMMA has the INCI MonoID 5111, and it is assigned one single CAS number, i.e. CAS No. 9011-14-7. Nonetheless, the molecular weight and physical form of PMMA varies greatly depending upon the manufacturing conditions and formulation of intended application. On account of the respective physico-chemical properties, different variants of PMMA can exhibit different functions in finished cosmetic and personal care products (e.g. bulking agents or film formers; Table CS1.1). Further, the substances that are used to aid the polymerisation process, to stabilise PMMA and to enable its further processing, as well as the polymerisation process itself, can vary between different manufacturers and between different variants of PMMA. Therefore, the final PMMA will vary greatly depending on the manufacturing process and IAS used. Since none of this is reflected in the CAS number, this conventional descriptor is insufficient to describe the technical properties of varied forms of PMMA placed on the market. Hence, the value chain uses additional specifications to describe the variants.

EPPAA

EPPAA has the IUPAC name '*reaction products of (1 mole) pentaerythritol ethoxylated and propoxylated (4:1) with 2-propenoic acid (4 moles)*'; the CAS No. 144086-02-2; and the EC No. 604-394-0. EPPAA is composed of several constituents with varying degrees of alkoxylation. It is a clear, colourless liquid and has a molecular weight < 2,000 Da.

2.3.1.2 Acid dissociation constant

P-AA/MA and P-AA

P-AA/MA and P-AA are weak polyelectrolytes deriving from polycarboxylic acids. Their apparent dissociation is not a constant, but a function of the pH of the solution or the degree of ionisation. The apparent acid ionisation constant (K_a) follows the equation

$$pK_a = pH + n \log[(1 - \alpha)/\alpha]$$

where pK_a is the negative base-10 logarithm of K_a, n is a constant for a given titration, and α is the degree of neutralisation (Gregor et al., 1955; Spencer, 1962).

Thus, P-AA chains (and similarly P-AA/MA chains) contain carboxyl groups which dissociate as the pH of the solution increases. P-AA macromolecules are characterised by a pK_a = 4.5. This implies that, at pH > 4.5, dissociated –COO groups are expected to be more frequent than undissociated –COOH groups, whereas almost all carboxylic groups are dissociated at pH = 9 (Wiśniewska and Chibowski, 2005).

P-AA and P-AA/MA are generally used in neutralised form (pH 6-8) as their sodium salts (HERA, 2014a, b).

PMMA and EPPAA

As compared to P-AA/MA and P-AA, PMMA and EPPAA are (meth-)acrylic acid ester polymers that do not undergo dissociation. Therefore, pK_a is not considered a relevant property for PMMA and EPPAA.

2.3.1.3 Solubility in water

Polycarboxylates (P-AA/MA and P-AA) and polyacrylates

For both P-AA/MA and P-AA, water solubility exceeds 400 g/L at 20°C (HERA, 2014a, b). Further, P-AA is a brittle material at room temperature, capable of absorbing large amounts of water (Slone, 2010). It is important to note that the water solubility of P-AA/MA (and other polycarboxylates on account of their anionicity) appears heavily dependent on the water hardness and the test concentrations (HERA, 2014b).

Generally, polycarboxylates can be very water-soluble, and their degree of hydrophilicity is linked to the density of the carboxylate groups attached to the carbon-carbon backbone. *Vice versa*, polycarboxylates are often insoluble in organic solvents, such as alcohols or hydrocarbons (Opgenorth, 1992).

Many polyacrylates are a lot less water-soluble than their polycarboxylate counterparts as they include ester groups with carbon chains of varying length and hydrophilicity instead of carboxylate groups. Polyacrylates with longer side chains tend to be more hydrophobic and thus more soluble in hydrocarbons.

PMMA

PMMA is hydrophobic due to its hydrophobic hydrocarbon chain and methyl side chains and only moderately polar $-COOCH_3$ endings. The water insolubility of PMMA (< 1 mg/L; http://ampolymer.com/SDSPDF/PolymethylMethacrylateSDS.pdf) allows its use in waterproofing solutions.

EPPAA

EPPAA is moderately water soluble (1,388 mg/L at 20°C as determined in an OECD TG 105 study with methodological adaptations following OECD TG 123; https://echa.europa.eu/registration-dossier/-/registered-dossier/15998).

2.3.1.4 n-Octanol/water partition coefficient

P-AA/MA and P-AA

Since P-AA/MA and P-AA are both hydrophilic, they are expected to have low n-octanol/water partition coefficients (log K_{ow}).

PMMA

The ECETOC Polymers TF is unaware of any measured log K_{ow} values for PMMA; however, this polymer lacks water solubility and is known to exhibit lipophilic behaviour.

EPPAA

Measured log K_{ow} values ranged from 1.73 to 3.11 in an OECD TG 117 study, indicating moderate lipophilicity (https://echa.europa.eu/registration-dossier/-/registered-dossier/15998).

2.3.1.5 Adsorption/desorption and organic carbon/water partition coefficient

Many polycarboxylates and polyacrylates tend to attach to solid phases. The adsorption/desorption distribution coefficient (K_d) for different environmental compartments (soil, sediments, activated sludge) was determined for a radiolabelled P-AA with an average molecular weight of 16,100 Da (HERA, 2014a). K_d values ranged from 27 L/kg in soil to 1,825 L/kg in activated sludge. The organic carbon normalised adsorption coefficient (K_{oc}) can be estimated as approx. 4,900 L/kg based on the K_d for activated sludge (divided by 0.37, i.e. the fraction of organic carbon in activated sludge). A similar pattern was observed for a radiolabelled P-AA/MA for which K_d values ranged from 90 L/kg in sediments to 15,714 L/kg in activated sludge (HERA, 2014b), though wider ranges were noted for such data; again, by a similar approach, a K_{oc} of approx. 40,000 L/kg can be estimated from the activated sludge K_d. Due to these properties, P-AA and P-AA/MA will adsorb to activated sludge and precipitate thereby facilitating their elimination in WWTPs and their potential presence in the soil compartment.

2.3.1.6 Surface tension

Anionic polymers such as P-AA and sodium salt of P-AA or polycarboxylate copolymers are not expected to fall under the surfactant category implemented in the context of the EU Detergents Regulation (EP and Council, 2004a), where the 'international trade tariff value' of 45 mN/m reduction in surface tension is referred to in order to identify surfactants (European Commission, 2018); see Section 7.3.1.9 in Case Study 6 on surfactant polymers for a discussion of criteria and threshold values to determine surface-active properties.

2.3.1.7 Glass transition temperature and density

Glass transition temperature and density are further physico-chemical properties that are potentially relevant for polycarboxylates, polyacrylates and polymethacrylates but that were not specifically addressed in the ECETOC (2020) TR No. 133-2 on the applicability of tools, methods and models for polymer risk assessment. Notably, however, glass transition temperature and density are relevant from a technical point of view, but only have an indirect impact on human health hazard assessment (e.g. by resulting in difficulties in applying materials that are solid at room temperature to *in vitro* and environmental test systems).

The glass transition temperature range can vary widely for acrylic and methacrylic ester polymers. For example, butyl acrylate homopolymers have a glass transition temperature of -54 °C whereas that of P-AA is

103 °C (Slone, 2010). Below the respective glass transition temperature, the respective polymers exhibit segmental rigidity and take on a rigid, glass-like form. Generally, the glass transition temperature of acrylate and methacrylate monomers tends to increase with decreasing length and increasing hydrophilicity, thereby also increasing the elasticity of the resulting polymers. A common way of fine-tuning polycarboxylate and polyacrylate properties is to copolymerise two or more different monomers with different glass-transition temperatures. This will ultimately determine the hardness of the polymer film.

EPPAA is a clear, colourless liquid at 20°C and therefore has a low glass transition temperature. Its relative density was measured as 1.139 at 20°C (https://echa.europa.eu/registration-dossier/-/registered-dossier/15998).

2.3.1.8 Analytical verification of polymer concentrations in environmental media

Both cold analytical methods (liquid chromatography and mass spectrometry) and quantification methods using radiolabelled material have been developed for well and moderately water-soluble polymers, such as P-AA/MA, P-AA and EPPAA, as well as for other polycarboxylates and polyacrylates. Method development and validation is more challenging for insoluble polymers (e.g. PMMA) and for polymers with variable or partly unknown composition.

2.3.2 Step 2.2: Identification of additives

A broad spectrum of IAS can be used in the manufacture of polycarboxylates, polyacrylates and polymethacrylates both to regulate the polymerisation process (including radical initiators, promotors, transfer agents, and reversible fragmentation agents) and aid in their downstream processing and prolong service-life (including UV stabilisers, dispersants, emulsifiers, coalescent agents, thickeners, biocides, impact modifiers, etc.).

Polycarboxylates and polyacrylates can be present in different forms (Section 2.1.3).

2.3.3 Step 2.3: Identification of NIAS

P-AA/MA and/or P-AA may include residual monomers as NIAS. PMMA is a solid which can contain varying, but generally very low, amounts of residual methyl methacrylate. For example, Pemberton and Lohmann (2014) reported that emulsion polymerised PMMA contain 0.01-0.05% residual monomer, and solution polymerised PMMA contain 0.1-0.9% residual monomer. In some cases, the polymer might contain trace levels of the polymerisation by-products acrylic acid and esters monomers.

EPPAA may include residual monomers and oligomers. Notably, however, EPPAA itself is an LMW polymer which is close to the transition to an oligomer (see Box 3 in Section 1.2).

2.4 Case Study 1: CF4Polymers (Step 3) Polymer component strategy

In a regular safety assessment, additives for example might have to be considered as well, but in this purely illustrative case study, focus is on the polymeric substances, i.e. P-AA/MA and P-AA as well as PMMA and EPPAA.

2.5 Case Study 1: CF4Polymers (Step 4) Grouping approach evaluation

This case study does not discuss the CF4Polymers (Step 4) grouping approach evaluation.

2.6 Case Study 1: CF4Polymers (Step 5) Determination of exposure scenarios

Polycarboxylates and polyacrylates are used in a broad range of applications (Section 2.1.2). In some applications, they are used in high volumes; for other applications, volumes of use may be lower, and a more physico-chemically and functionally diverse polymer palette may be relevant. Due to their wide dispersive use, a long list of life cycle stages and human and environmental exposure scenarios may need to be considered during the risk assessment of any given polycarboxylate or polyacrylate. These may include manufacturing and formulation steps, industrial and professional uses, and wide dispersive use by consumers (also leading to down-the-drain release).

This case study focuses on consumer use of the polycarboxylates P-AA/MA and P-AA in laundry detergents and additionally, for P-AA, in personal care products (i.e. in the final products). Generally, laundry detergents and personal care products are diluted with water before or during use; further, P-AA/MA and P-AA have medium to high solubility in water (Section 2.3.1.3) so that they may be present in the aqueous compartments. Upon disposal via down-the-drain release, P-AA/MA and P-AA used in laundry detergents and (for P-AA) personal care products are found predominantly in the wastewater, so that they reach WWTPs and subsequently, potentially, freshwater, the terrestrial compartment and seawater. With respect to human exposure assessment, the general population, including sensitive subpopulations such as children and elderly, are relevant target populations. Exposure to humans is most likely via the dermal route of exposure but may also occur at very low levels via the oral or inhalation routes.

Accordingly, relevant exposure categories for P-AA/MA and P-AA include:

- Chemical Product Category (PC35) *Washing and cleaning products* (ECHA, 2015)
- Environmental Release Category (ERC2) *Formulation into mixture* (ECHA, 2015)
- Environmental Release Category (ERC8a/b) *Wide-spread use of non-reactive / reactive processing aid (no inclusion into or onto article, indoor)* (ECHA, 2015)

PMMA and methacrylate-based copolymers are extremely resistant to biotic and abiotic degradation (Kaplan et al., 1979) leading to their use in a wide range of applications demanding long service life. PMMA acrylic sheeting is used as a substitute for glass in safety and security glazing, panels, signs and illuminated light displays and liquid-crystal displays (LCDs). Copolymers and modified polymers based upon methyl methacrylate are used for coating and impregnation resins to give colour fastness and weather-resistance properties to latex paints, road-marking and industrial paints, powder coatings and inks, lacquer resins and stoving enamels. Methacrylate polymers are used pharmaceutical (drug delivery systems), biomedical (bone cement and substitutes), dental (false teeth and orthodontics), optical (intraocular lenses), solar panels, sensor technology, battery electrolytes, nanotechnology, viscosity modifiers, pneumatic actuation, molecular separation and a wide range of consumer products (household appliances, sanitary ware and furniture). Due to the extreme resistance of PMMA and methacrylate-based copolymers to biotic and abiotic degradation

they do are not biodegradable and do not bioaccumulate. Therefore, PMMA is not considered further in (Step 6) exposure characterisation (Section 2.7).

Regarding exposure scenarios for EPPAA, this copolymer is manufactured and used in closed batch processes; it is used in the polymer industry and in formulations for waterless inks and coatings, as a chemical cross-linking agent (intermediate).

2.7 Case Study 1: CF4Polymers (Step 6) Exposure characterisation

2.7.1 Release of polycarboxylates and polyacrylates

Environmental releases can be expected from the use of P-AA/MA and P-AA in laundry detergents and (for P-AA) in personal care products via down-the-drain release so that they reach WWTPs. Therein, many polycarboxylates (as well as polyacrylates) possess a strong potential for adsorbing to solid particles. After sewage treatment, P-AA/MA and P-AA may reach the freshwater compartment in low concentrations, and possibly the terrestrial compartment upon sewage sludge application onto land. Ultimately, P-AA/MA and P-AA have also been shown to reach the marine compartment. In natural waters, P-AA/MA and P-AA may form precipitates with cations such as calcium ions (HERA, 2014a, b).

2.7.2 Environmental fate assessment

2.7.2.1 (Bio)degradation assessment

Aerobic biodegradation in activated sludge / semi-continuous activated sludge

The biodegradation of polycarboxylates in activated sludge / semi-continuous activated sludge is often slow (and limited to some LMW variants), and a fraction is likely to remain adsorbed onto WWTP sludge. An abundance of (screening and simulation) biodegradation data in activated sludge / semi-continuous activated sludge is available for one type of polycarboxylate, i.e. linear P-AA, and limited data for P-AA/MA (Table CS1.2).

Figure CS1.2 relates the biodegradability of P-AA or P-AA/MA in activated sludge (measured by CO_2 evolution in OECD TG 301B studies) to the molecular weight of the respective P-AA or P-AA/MA (with the latter measured both using chain labelling and carboxyl labelling). There is no apparent correlation between CO_2 evolution and molecular weight. By comparison, the data from OECD TG 302A studies using semi-continuous activated sludge show a correlation between the removal of dissolved organic carbon (DOC) and molecular weight of the P-AA and P-AA/MA considered (Figure CS1.3). The ECETOC Polymers TF identified that methods relying on the measurement of O_2 consumption and CO_2 generation are more suitable for the characterisation of degradation (see ECETOC TR No. 133-2). It is assumed that sorption to sludge solids could contribute to differences in the removals observed in the different studies.

Similarly, when tested in activated sludge simulation tests (OECD TG 303A), there is a fairly good correlation between DOC removal and molecular weight of the P-AA / P-AA/MA (R^2 = 0.8) (Figure CS1.4). DOC removal is mainly attributable to sorption processes, and most likely, the molecular weight (i.e. size) of the polymers impacts sorption mechanistically.

Table CS1.2: Biodegradation and elimination data publicly available for polycarboxylates and polyacrylates

Polymer name / description	M_n (Da)	Biodegradation screening [a1-2] & simulation [b] in activated sludge	Inherent biodegradation in SCAS [c]	Freshwater [d1]	Sediment [d2]	Sludge-treated soil [d3]	Reference
P-AA	1,000	[a1] 43% CO_2; 90 days [b] 9 % / 24 % DOC for C_{inf} 15 / 10	45% DOC; 7 days; elimination: 9-24% [h]	20% CO_2 135 days	58% CO_2 135 days	35% CO_2 165 days	[e]
P-AA	2,000	[a1] 19% CO_2; 90 days [b] 13 % / 24 % DOC for C_{inf} 18 / 10	16 & 21% DOC; 7 days; 12% DOC; 25 days elimination: 3-18% [h]	10-19% CO_2 90-135 days	37% CO_2 135 days	11% CO_2 165 days	
P-AA	3,400		22-40% DOC; 7 days				[f]
P-AA	4,500	[a1] 9% CO_2; 30-90 days [b] 55% / 76% [b1] DOC	40% DOC; 7 days; elimination: 27% / 98% without / with $FeCl_3$	10 % CO_2 31 days	6% CO_2 106 days	7% CO_2 81 days	[e]
P-AA-sodium	4,500	15.6%; 42 days 55% DOC	37.5% DOC 98% with $FeCl_3$				[n]
Resin polymer composed primarily of styrene & acrylic acid	4,500 - 6,000	[a2] 2.64%; 60 days	92-97% sorbed to solids (K_{oc}: 1060)				[g]
P-AA	9,400		40%				[h]
P-AA	10,000	[a1] 17% CO_2; 90 days	58%; 7 days	7% CO_2 135 days	12% CO_2 135 days	5% CO_2 165 days	[e]
P-AA/MA	12,000	[a1] 39% / 13% CO_2; 90 days [l] [b] 71% / 80% DOC for C_{inf} 15 / 30	83%; elimination: 70% / 96% without /with $FeCl_3$	21%/31% CO_2 90 days [l]	41%/6% CO_2 100 days [l]	32%/10% CO_2 165 days [l]	[i]
P-AA	15,000		58% DOC; 7 days				[f]
P-AA	23,000		48%				[h]
Polymer emulsion prepared from styrene & several acrylate monomers, incl. methacrylic acid	50,000 - 60,000	[a2] 0.85%; 60 days	96-99% sorbed to solids (K_{oc}: 2730)				[g]
P-AA/MA	50,000-60,000	[b] 93% DOC for C_{inf} 15	95% DOC; 7 days				[i]
P-AA/MA	60,000		93% / 85%; 7 / 8 days				[i]
P-AA	60,000		93%				[k]
P-AA/MA	70,000	[a1] 13% / 18% CO_2; 90 days [l] [b] > 94% DOC	95%; elimination: 82% without $FeCl_3$	12%; 100 days [m]	11% / 13% CO_2; 100 days [l]	8% / 11% CO_2; 165 days [l]	[i]
P-AA	78,000		Elimination: 78%				[h2]
P-AA	111,000		81%				[h]
P-AA	152,000		95%				[h]
P-AA	215,000		95%				[h]

Footnote to Table CS1.2: see next page

Footnote to Table CS1.2:

Abbreviations: Da: Dalton; DOC: Dissolved organic carbon; C_{inf}: Influent concentration (mg/L); K_{oc}: Organic carbon/water partition coefficient; M_n: Number-average molecular weight; P-AA: homopolymer of acrylic acid; P-AA/MA: copolymer of acrylic/maleic acid; SCAS: Semi-continuous activated sludge.

[a1] CO_2 evolution after contact with activated sludge for 30-90 days / [a2] OECD TG 301B (modified Sturm test): CO_2 evolution in activated sludge within x days

[b] OECD TG 303A (activated sludge simulation test): CO_2 evolution or relative DOC removal (C_{inf} in mg/L) within x days

[b1] Wastewater treatment simulation test (testing protocol not specified)

[c] OECD TG 302A (inherent biodegradability: modified semi-continuous activated sludge test): relative DOC removal within x days (at least six weeks)

[d1-3] CO_2 evolution test using: [d1] river water; [d2] river water and sediment; [d3] sludge-treated soil: relative CO_2 evolution within x days

[e] Opgenorth (1992) and/or ECETOC (1993) and/or HERA (2014a) citing unpublished studies by Procter & Gamble

[f] HERA (2014a)

[g] Jop et al. (1997)

[h] ECETOC (1993) citing unpublished studies by Unilever; or [h2] citing unpublished studies by Henkel Laboratory

[i] Opgenorth (1992) and/or ECETOC (1993) and/or HERA (2014b) citing unpublished studies by Procter & Gamble

[k] Opgenorth (1992)

[l] Chain labelled / carboxyl labelled

[m] Chain labelled

[n] Hamilton et al. (1996)

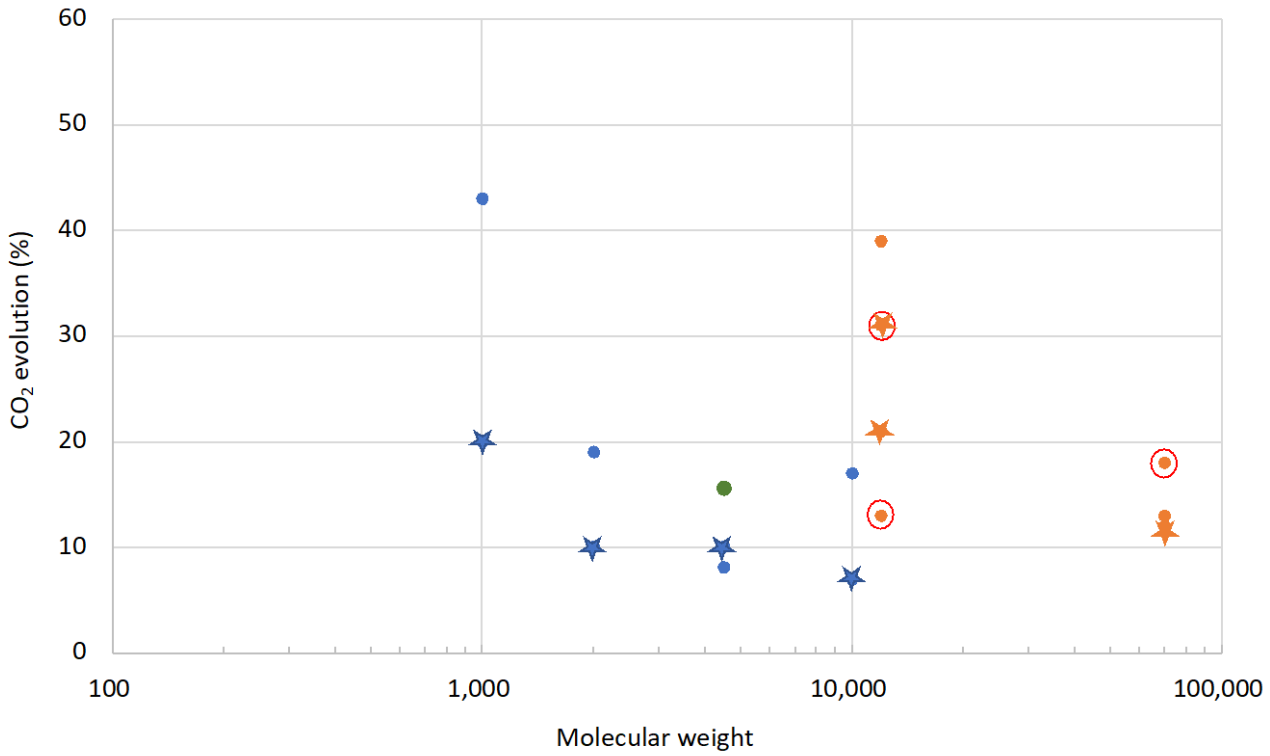


Figure CS1.2: OECD TG 301B - modified Sturm test / CO_2 evolution test: Biodegradation of P-AA and P-AA/MA in activated sludge and freshwater (measured as maximum CO_2 evolution; see Table CS1.2 for timepoints) as compared to molecular weight (data adapted from HERA, 2014a, b)

Footnote to Figure CS1.2: Colour legend: Blue: Biodegradation of poly(acrylic acid) homopolymer (P-AA), adapted from studies by Procter & Gamble; green: Biodegradation of P-AA, adapted from Hamilton et al. (1996); all studies all cited in HERA (2014a); brown: Biodegradation of poly(acrylic/maleic acid) copolymer (P-AA/MA), adapted from studies by Procter & Gamble; all cited in HERA (2014b); brown data points with red circle: Measurement after carboxyl radiolabelling; brown datapoints without red circle: Measurement after chain radiolabelling.

Dots: Measurement in activated sludge; stars: Measurement in freshwater.

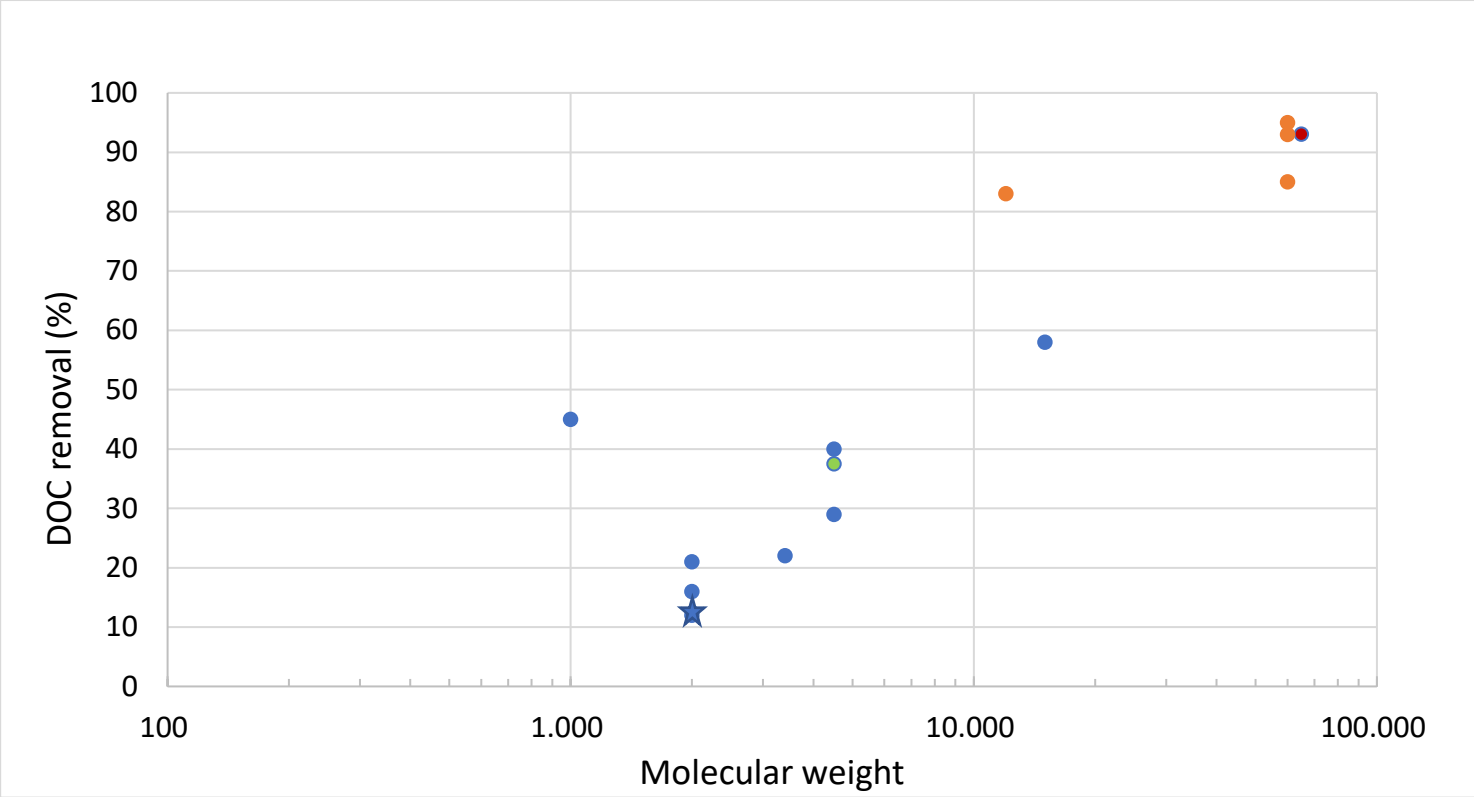


Figure CS1.3: OECD TG 302A - inherent biodegradability: modified semi-continuous activated sludge test: Biodegradation and elimination of P-AA and P-AA/MA in semi-continuous active sludge (measured as relative DOC / ^{14}C removal within (generally) 7 days) as compared to molecular weight

Footnote to Figure CS1.3: Different entries for the same-sized poly(acrylic acid) homopolymer (P-AA) or poly(acrylic/maleic acid) copolymer (P-AA/MA) relate to different studies. Generally, dissolved organic carbon (DOC) / ^{14}C removal was measured after 7-8 days, the star indicates measurement after 25 days.

Colour legend: Blue: Biodegradation of P-AA, adapted from studies by Procter & Gamble as cited in HERA (2014a); green: Biodegradation of P-AA, adapted from Hamilton et al. (1996) as cited in HERA (2014a); brown: Biodegradation of P-AA/MA, adapted from studies by Procter & Gamble as cited in HERA (2014b); red: Biodegradation of P-AA/MA, adapted from Opgenorth (1992).

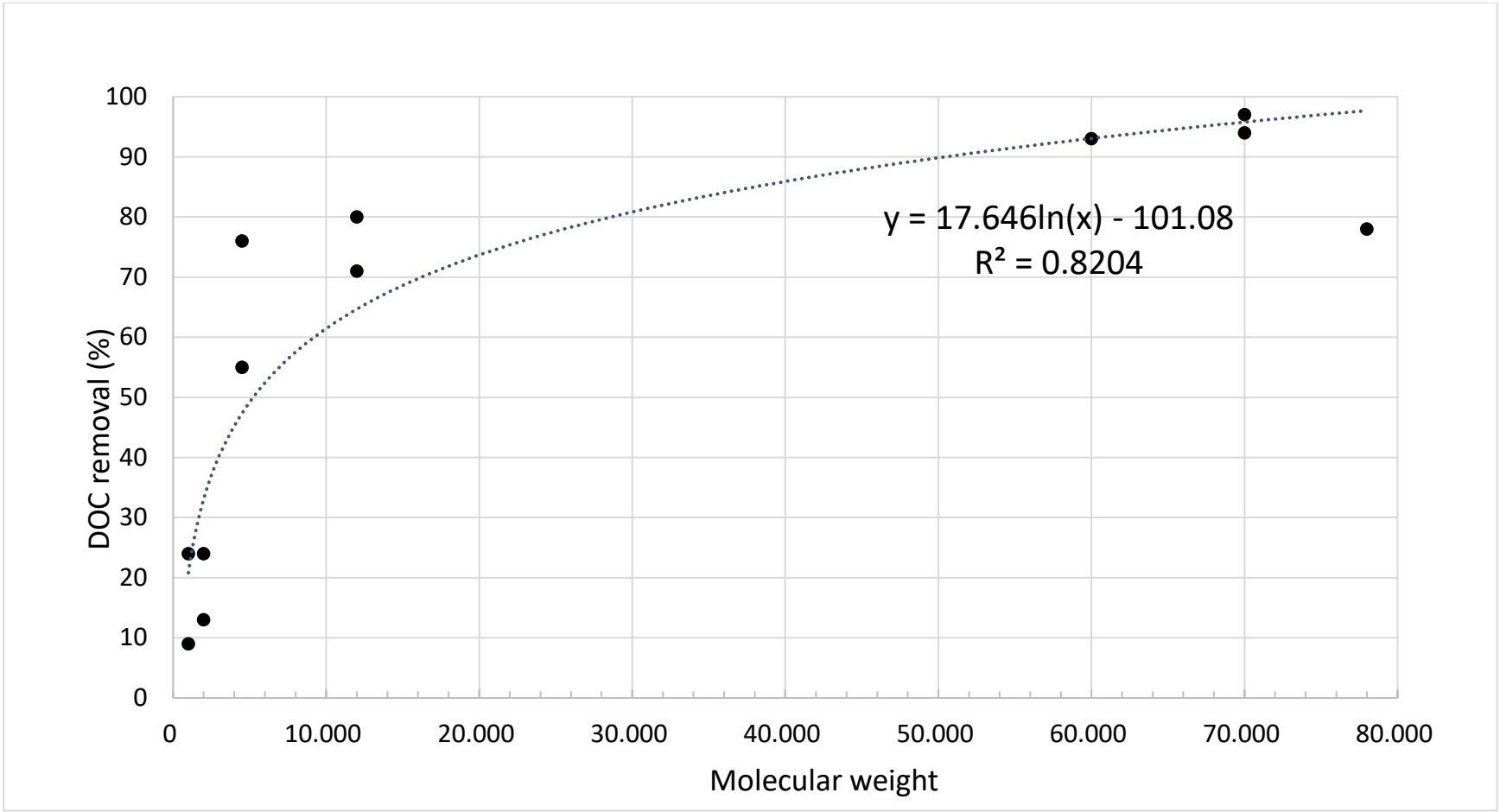


Figure CS1.4: OECD TG 303A - activated sludge simulation test: Biodegradation and elimination of P-AA and P-AA/MA in activated sludge (relative DOC / ^{14}C removal) as compared to molecular weight

Footnote to Figure CS1.4: Abbreviations: DOC: Dissolved organic carbon; P-AA: Poly(acrylic acid) homopolymer; P-AA/MA: Poly(acrylic/maleic acid) copolymer.

Data adapted from HERA (2014a, b) citing studies by Procter & Gamble and Hamilton et al. (1996). Data are generally derived from (OECD TG 303A) activated sludge simulation test; one data-point for 4,500 Da P-AA-sodium from wastewater treatment simulation test (testing protocol not specified). Different entries for the same-sized P-AA or P-AA/MA relate to different studies.

Biodegradability tests utilising freshwater / sediment as the test matrix

The few data available for linear P-AA show even more limited biodegradation in freshwater than in activated sludge, that again decreases with increasing molecular weight (Figure CS1.2). The highest reported biodegradation in freshwater was for a 1,000-Da P-AA, i.e. 20-43% CO_2 evolution within 135 days (HERA, 2014a).

Biodegradation in sediment also decreases with increasing molecular weight. Again, the highest biodegradation value reported was for a 1,000-Da P-AA, i.e. 58% CO_2 evolution within 135 days (HERA, 2014a). Sediment biodegradation values were a bit higher than those for soil (see below) implying that linear P-AA biodegrades somewhat faster in sediment than in soil (Figure CS1.5).

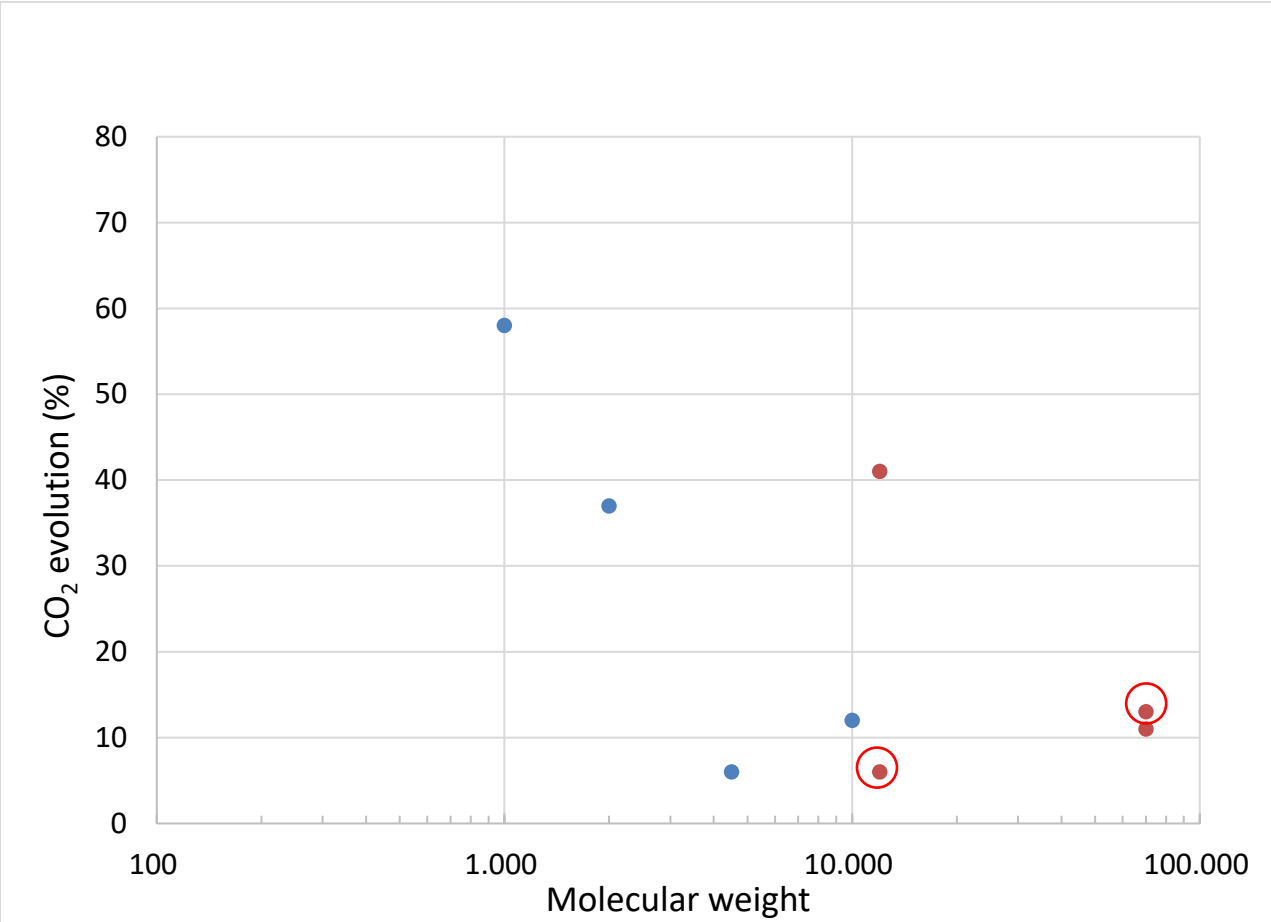


Figure CS1.5: CO_2 evolution test: Biodegradation of P-AA and P-AA/MA in sediment as compared to molecular weight

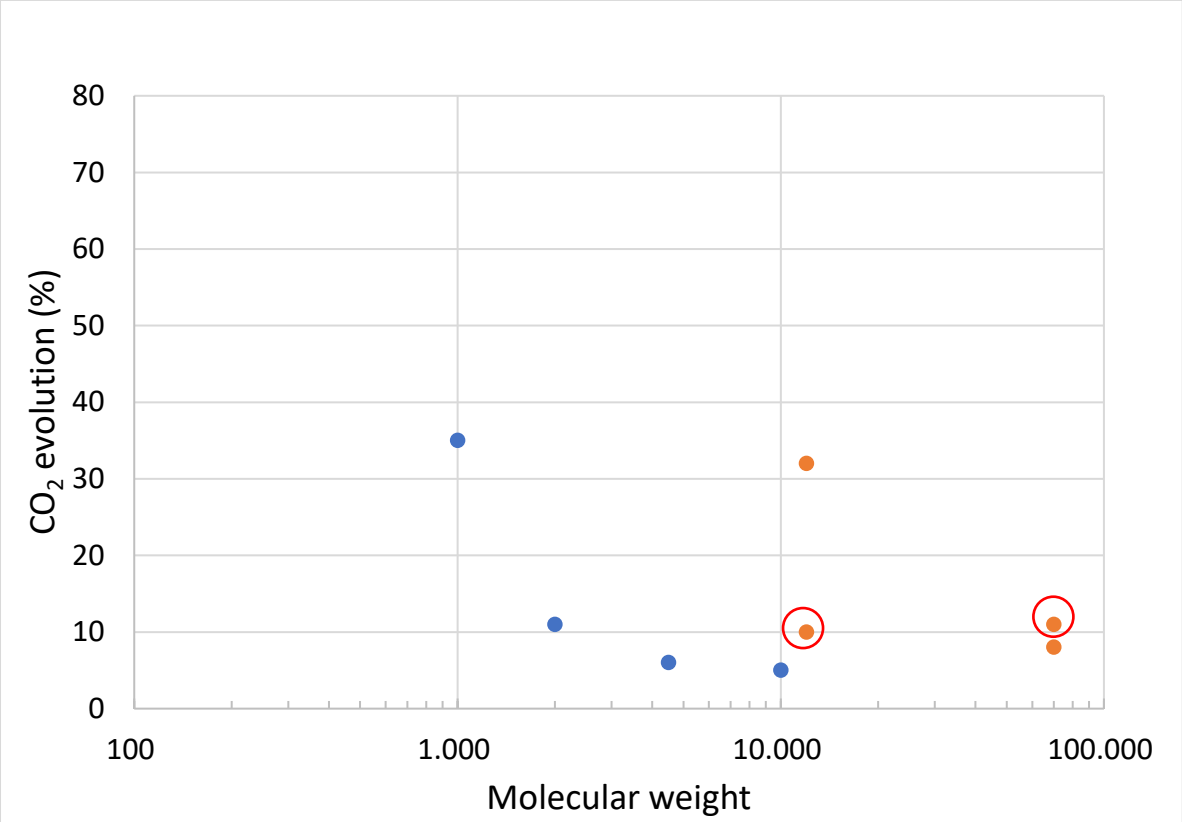
Footnote to Figure CS1.5: Colour legend: Blue: Biodegradation of poly(acrylic acid) homopolymer (P-AA), adapted from HERA (2014a) citing studies by Procter & Gamble; brown: Biodegradation of poly(acrylic/maleic acid) copolymer (P-AA/MA), adapted from HERA (2014b) citing studies by Procter & Gamble.

Data for P-AA/MA: Red circle: Measurement after carboxyl radiolabelling; no red circle: Measurement after chain radiolabelling.

For EPPAA, read-across was applied using biodegradation data available from an analogue with lower molecular weight (i.e. ethoxylated pentaerythritol and acrylic acid oligomer; CAS No. 51728-26-8) that showed 27% O_2 uptake after 28 days in OECD TG 301F.

Biodegradability tests utilising soil as the test matrix

The few data available for linear P-AA show limited biodegradation in sludge-treated soil, decreasing with increasing molecular weight. Again, the highest biodegradation value reported was for a 1,000-Da P-AA, i.e. 35% CO_2 evolution within 165 days (HERA, 2014a) (Figure CS1.6).



Figures CS1.6: CO_2 evolution test: Biodegradation of P-AA and P-AA/MA in sludge-treated soil as compared to molecular weight

Footnote to Figure CS1.6: Colour legend: Blue: Biodegradation of poly(acrylic acid) homopolymer (P-AA), adapted from HERA (2014a) citing studies by Procter & Gamble; brown: Biodegradation of poly(acrylic/maleic acid) copolymer (P-AA/MA), adapted from HERA (2014b) citing studies by Procter & Gamble.

Data for P-AA/MA: Red circle: Measurement after carboxyl radiolabelling; no red circle: Measurement after chain radiolabelling.

Further research work is recommended to enhance the understanding of the final fate of polycarboxylates in the terrestrial and aquatic compartments over time (e.g. formation of non-extractable residues). Specifically, the development of analytical methods that enable measurements in these compartments appears as a pertinent research need.

Anaerobic biodegradation

Very limited data on anaerobic biodegradation profiles of this type of polymers (P-AA and P-AA/MA) indicated low anaerobic biodegradation potential. For example, HERA (2014a) reported that no data on anaerobic biodegradation were available for P-AA and only one study for the copolymer P-AA/MA (70,000 Da) indicating approx. 3% mineralisation to CO_2. HERA (2014b) reported on the anaerobic biodegradability of P-AA/MA (70,000 Da), investigated by incubation of radiolabelled P-AA/MA in a mixture of digester sludge, indicating a

biodegradability extent of 11-16%. Thus, in the context of the HERA risk assessment, no anaerobic degradation of PAA or P-AA/MA was assumed.

Abiotic degradation

Under typical environmental conditions, polycarboxylates and polyacrylates are generally stable to photodegradation and chemical degradation. PMMA and acrylic acid homopolymers are highly resistant to photodegradation since they are transparent to most of the solar spectrum. This resistance can decrease when UV-absorbing monomers such as styrene are integrated into the polymer backbone, whereas other UV-absorbing substances that are not covalently bound can improve the UV-stability of acrylate homopolymers (Slone, 2010).

Polyacrylates and polymethacrylates are also generally highly resistant to hydrolysis at environmentally relevant pH values. However, when these polymers are exposed to very acidic or alkaline conditions, they can hydrolyse to poly(acrylic acid) and the alcohol(s) corresponding to their side-chain. Longer side-chains are generally related to a higher hydrolysis resistance; for example, poly(butyl acrylate) is more resistant to hydrolysis than poly(ethyl acrylate), which is more resistant than poly(methyl acrylate) (Slone, 2010).

2.7.2.2 Bioaccumulation assessment

In a regulatory setting, it is generally accepted that molecules with molecular weights > 1,000 Da have a low likelihood of becoming systemically bioavailable (see e.g. EFSA, 2008a; US EPA, 2013; Section 3.7.1.1 in ECETOC (2019) TR No. 133-1 and Section 4.2.1 in ECETOC (2020) TR No. 133-2). Therefore, the higher-molecular weight polycarboxylates and polyacrylates are unlikely to pass cell membranes to any significant degree. As is further explained in HERA (2014a, b) for both P-AA and P-AA/MA: "*Mechanisms for uptake of charged molecules are ion pumps or ion channels. These are effective for small charged cations but have not been described for polymers carrying multiple negative charges. Likewise there is no evidence of transmembrane transport modes involving carriers or endocytosis playing a significant role in xenobiotic bioaccumulation*."

Further, most polycarboxylates can be expected to be readily eliminated from organisms due to their hydrophilicity. Taken together polycarboxylates are unlikely to bioaccumulate significantly (Opgenorth, 1992; HERA, 2014a, b).

EPPAA is also considered to have a low potential for bioaccumulation based on its moderate lipophilicity (Section 2.3.1.4; see ECETOC (2011) for correlation between lipophilicity and potential for bioaccumulation).

2.7.3 Environmental exposure assessment

The use of P-AA/MA and P-AA in consumer products, in particular laundry-related products, indicates that the dominant environmental exposure route from this use will be down-the-drain emission to wastewater. Based on the available environmental fate data (Table CS1.2), both P-AA/MA and P-AA will sorb to sewage sludge and be eliminated from wastewater to varying degrees. Degradation during anaerobic digestion of sewage sludge is not expected to occur (Opgenorth, 1992). Therefore, two major environmental pathways need to be considered in the exposure assessment, i.e. wastewater effluent discharge to freshwater and the application of sludge to agricultural soil. Considering these pathways, predicted environmental concentrations (PECs) should be calculated in freshwater, sediment, and sludge-amended agricultural soil. Lysimeter investigations of sludge-amended soil determined that P-AA/MA and P-AA are largely immobile and that the small mobile

fraction is biodegradable (Opgenorth, 1992). Therefore, it is not necessary to estimate ground water PECs or to consider agricultural run-off in the freshwater.

P-AA/MA and P-AA are highly soluble, while EPPAA is moderately soluble. Therefore, the exposure models EUSES (European Union System for the Evaluation of Substances) and iSTREEM (in-stream exposure model) described in Table 5 of Section 5.1 of ECETOC TR No. 133-2 (ECETOC, 2020) can be used for the environmental exposure assessment of these polymers. Preferably, EUSES should be used as it is a multi-media model and can estimate freshwater, sediment, and soil PECs. iSTREEM is a single media model (freshwater) and would need to be paired with other single-media exposure models to estimate PECs in all relevant environmental media. As compared to P-AA/MA, P-AA or EPPAA, PMMA is poorly soluble and would likely require a different exposure modelling strategy, for example use of SimpleBox4nano, nanoDUFLOW or the proposed iSTREEM framework by Holmes et al. (2020), while considering a different set of key physico-chemical parameters (e.g., density, particle size).

Four environmental exposure assessments pertaining to either P-AA or P-AA/MA have been identified (Table CS1.3). Opgenorth (1992) conducted a simple local environmental exposure assessment of P-AA/MA (70,000 Da) in surface water and soil for Germany, and HERA (2014a, b) applied EUSES to calculate PECs for surface water, sediment and soil of both P-AA and P-AA/MA. Thus, the findings from the Opgenorth modelling approach are comparable to the local PEC reported by HERA. Opgenorth (1992) and HERA (2014b) reported similar local PEC for the freshwater compartment (0.05 mg/L vs 0.049 mg/mL), whereas the local PEC for P-AA/MA in soil reported in HERA (2014b) (35.2 mg/kg) was higher than the corresponding value in Opgenorth (1992) (13-27 mg/kg). This is likely partly due to more conservative assumptions regarding sewage sludge application to soil applied in the HERA report (see Table CS1.3 for further data).

In the same approach, but applied to P-AA, HERA (2014a) estimated PECs for all relevant environmental compartments (Table CS1.3). At the time of writing the HERA report, there were no other comparable environmental exposure estimates for Europe. More recently, DeLeo et al. (2020) conducted a US-wide down-the-drain assessment of P-AA/MA and P-AA in cleaning products using the US EPA Exposure and Fate Assessment Screening Tool (E-FAST) model (https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014). Since E-FAST only predicts surface water concentrations (on a national basis for compounds with down-the-drain disposal), DeLeo et al. (2020) did not conduct a terrestrial exposure assessment. While the results of the assessment are not quantitatively relevant for Europe, the study provides further proof-of-concept for the prediction of polycarboxylates concentrations in relevant environmental media (e.g. PEC in WWTP effluent estimated by HERA (2014a) and DeLeo et al. (2020): 0.65 and 0.57 mg/L, respectively; see Table CS1.3 for further data).

Table CS1.3: Predicted environmental concentrations of polycarboxylates

Polymer	M_n (Da)	Region	Model	Key assumptions	Compartment	PEC [1]	Reference
P-AA/MA (copolymer of acrylic/ maleic acid)	70 000	Germany	Generic local-scale environmental exposure algorithms	• 0.31 kg/capita/year emission • 300 L/capita/day wastewater generation • 90% WWTP elimination • No degradation in anaerobic digestor • 3 years of sludge application to agricultural soil	Activated sludge	2.9 mg/L	Opgenorth (1992)
					Freshwater	0.05 mg/L	
					Soil	13 - 27 mg/kg	
					WWTP effluent	0.26 mg/L	
	12 000 – 70 000	European Union	EUSES	• 33,000 tonnes/year emission • 89% WWTP elimination • K_d for activated sludge, soil, and sediment: 15, 714, 407 and 90 L/kg, respectively • No degradation in anaerobic digestor • 10 years of sludge application to agricultural soil, 3 tonnes/hectare	Freshwater	0.035 mg/L [2] 0.049 mg/L [3]	HERA (2014b)
					Sediment	38.8 mg/kgwwt [2] 45.4 mg/kgwwt [3]	
					Soil	26.8 mg/kgwwt [2, 4] 35.2 mg/kgwwt [3, 4]	
					WWTP effluent	0.15 mg/L	
	12 000 – 70 000	USA	E-FAST	• 55 000 tons per annum emission • 89% WWTP elimination	Surface water	0.02 mg/L [5] 0.13 mg/L [6]	DeLeo et al. (2020)
					WWTP effluent	0.13 mg/L	
P-AA (homo-polymer of acrylic acid)	1 000 – 15 000	European Union	EUSES	• 21 000 tons per annum emission • 25% WWTP elimination • K_d for activated sludge, soil, and sediment: 1,825, 27, and 54 L/kg, respectively • No degradation in anaerobic digestor • 10 years of sludge application to agricultural soil, 3 tonnes/hectare	Freshwater	0.043 mg/L [2] 0.11 mg/L [3]	HERA (2014a)
					Sediment	4.88 mg/kgwwt [2] 11.6 mg/kgwwt [3]	
					Soil	0.47 mg/kgwwt [2] 4.37 mg/kgwwt [3]	
					WWTP effluent	0.65 mg/L	
	1 000 – 15 000	USA	E-FAST	• 34,551 tonnes/year emission • 25% WWTP elimination	Surface water	0.07 mg/L [5] 0.57 mg/L [6]	DeLeo et al. (2020)
					WWTP effluent	0.57 mg/L	

Footnote to Table CS1.3: Abbreviations: kgwwt: kilogram wet weight; PEC: Predicted environmental concentration; WWTP = wastewater treatment plant.

[1] Water solubility of both P-AA/MA and P-AA recorded as > 400 g/L (HERA, 2014a, b). [2] $PEC_{regional}$ (i.e. regional background concentration of generic standard environment at steady-state). [3] PEC_{local} (i.e. the emission of a WWTP into a spatially limited local environment in addition to $PEC_{regional}$ background concentration).

[4] The ECETOC Polymers TF maintains the view that these two values were mistakenly reversed in HERA (2014b). It does not make sense for the regional PEC to be greater than the local PEC given their equations. Therefore, they are reported here opposite to how they appear in the HERA report.
[5] 90th percentile PEC based on national harmonic mean flow in the USA. [6] 90th percentile PEC based on national low flow conditions (i.e., 7 consecutive days of lowest flow over a 10-year period) in the USA.

2.8 Case Study 1: CF4Polymers (Step 7) Hazard assessment

2.8.1 Ecotoxicity assessment

2.8.1.1 Ecotoxicity data for P-AA and P-AA/MA

Acute and chronic aquatic toxicity

Aquatic toxicity data addressing mostly P-AA, but also P-AA/MA, are available for all three aquatic trophic levels, i.e. algae, freshwater invertebrates and fish (Opgenorth, 1992; ECETOC, 1993; HERA, 2014a, b; Duis et al., 2021).

With respect to acute aquatic toxicity, a 4,500-Da P-AA homopolymer was found to be slightly harmful to daphnids (48-hour EC_{50}[1] > 200 mg/L) and fish (96-hour LC_{50}[2] > 1,000 mg/L for *Lepomis macrochirus*). Similarly, chronic aquatic toxicity was relatively low in algae (*Desmodesmus subspicatus;* 96-hour ErC_{10}[3] = 180 mg/L); daphnids (21-day no observed effect concentration (NOEC) ranging from 5.6 to 450 mg/L); and fish (*Pimephales promelas*; 32-day NOEC = 56 mg/L); Table CS1.4, referring to data from HERA (2014a) and Opgenorth (1992).

Other P-AA homopolymers with lower molecular weight (1,000-2,500 Da) and higher molecular weight (8,000-78,000 Da) showed similar low aquatic toxicity in daphnids or fish. By comparison, toxicity to algae was a bit higher for those P-AA having higher molecular weight (72-hour EC_{50} = 40 and 44 mg/L for P-AA with 8,000 Da and 78,000 Da, respectively; 96-hour NOEC = 32.8 mg/L for P-AA with 78,000-Da; as compared to 72-hour ErC_{10} = 180 mg/L for the 4,500-Da P-AA) (Table CS1.4). However, this database is not sufficiently comprehensive to conclude on any correlation between molecular weight and potential for toxicity to algae. Several activated sludge respiration inhibition studies were conducted with P-AA of molecular weight varying from 1,000 Da to 15,000 Da (Duis et al., 2021); EC_{50} values were generally higher than the maximum tested concentrations (3-hour EC_{50} > 100 mg/L or EC_{50} > 1,000 mg/L), indicating low potential for toxicity to WWTP microorganisms (data not shown in Table CS1.4).

The water solubility and precipitation behaviour of P-AA/MA in the presence of ions with 2+ charge (e.g. ubiquitous Ca^{2+} and Mg^{2+}) can greatly affect the outcome of chronic aquatic toxicity studies (with water solubility further appearing dependent on water hardness and test concentrations (Section 2.3.1.3)). This also explains the large variability of 21-day NOECs (1.3-350 mg/L; Table CS1.4) observed in the studies using daphnids (Opgenorth, 1992; see HERA (2014b) for further discussion). Also, HERA (2014b) reported that P-AA/MA forms insoluble precipitation products at low concentrations and that these insoluble products may potentially cause secondary adverse effects which result in low NOECs (HERA, 2014b).

[1] EC_x: Effective concentration required to achieve x% effect change from the control
[2] LC_x: Concentration required to achieve x% change in lethality from the control
[3] ErC_x: Effective concentration inducing x% reduction in growth rate (algae) as compared to controls

Table CS1.4: Ecotoxicity data publicly available for polycarboxylates and polyacrylates

Polymer type	Molecular weight (Da)	Acute aquatic toxicity (mg/L)	Chronic aquatic toxicity (mg/L)	Sediment toxicity (mg/kgdw)	Terrestrial toxicity (mg/kgdw)	Reference
P(AA)	1,000	*Daphnia* LC/EC_{50} (48 hours) > 200 Fish LC/EC_{50} (96 hours) > 200				HERA (2014a)
P(AA)	1,200	Fish LC/EC_{50} (96 hours) > 500				
P(AA)	2,000	*Daphnia* LC/EC_{50} (48 hours) > 200 Fish LC/EC_{50} (96 hours) > 200				
P(AA)	2,500	Fish LC/EC_{50} (96 hours) > 500				
P(AA)	4,500	*Daphnia* EC_{50} (48 hours) > 200 Fish LC_{50} (96 hours) > 200	Algae EC_{10} (96 hours) 180 *Daphnia* NOEC (21 days) > 1,000; 5.6 [a]; 450 [a]; 58 [a]; 12 [a] Fish NOEC (28 days) > 450 [a] Fish early life stage NOEC (32 days) 56 [a]	Sediment organisms EC_0 > 4,500 [a]	Earthworms EC_0 (14 days) 1,000 [a] Plants EC_0 225 [a] Soil microorganisms, C- and N- transformation EC_{10} (28 days) > 2500 [a]	Opgenorth (1992) [a] HERA (2014a)
P(AA)	8,000	Fish LC/EC_{50} (96 hours) > 500 Algae EC_{50} (72 hours) 40				HERA (2014a)
P(AA)	10,000	Fish LC/EC_{50} (96 hours) > 1,000				
P(AA)	15,000	Fish LC/EC_{50} (96 hours) > 1,000				
P(AA-MA)	70,000	*Daphnia* EC_{50} (48 hours) > 200 Fish LC_{50} (96 hours) > 200	Algae EC_{10} (96 hours) 32 - > 200 *Daphnia* NOEC (21 days) 1.3-350 Fish NOEC (42 days) 40			Opgenorth (1992)
P(AA)	78,000	*Daphnia* LC/EC_{50} (24 hours) 276 Fish LC/EC_{50} (96 hours) > 400 Algae EC_{50} (96 hours) 44	Algae NOEC (96 hours) 32.8		Earthworms EC_0 (14 days) 1,000 Plants NOEC (21 days) 1,000	HERA (2014a)

Footnote to Table CS1.4:

Abbreviations: Da: Dalton; EC_x: Concentration required to achieve x% effect change from the control; kgdw: Kilogram dry weight; LC_x: Concentration required to achieve x% change in lethality from the control; NOEC/: No observed effect concentration; P(AA): homopolymer of acrylic acid; P(AA-MA): copolymer of acrylic/maleic acid.

Toxicity to sediment-dwelling organisms and to terrestrial organisms

Similar to the low aquatic toxicity potential of the 4,500-Da P-AA, this homopolymer elicited only negligible toxicity to sediment-dwelling organisms (*Chironomus riparius*: 96-hour EC_0 > 4,500 mg/ kg dry weight (kgdw)) or to terrestrial organisms, i.e. earthworm (*Eisenia foetida*: 14-day EC_0 = 1,000 mg/kgdw; nitrogen transformation 28-day EC_{10} > 2,500 mg/kgdw). In addition, terrestrial toxicity data are available for the 78,000-Da linear P-AA, which again yielded a low 14-day EC_0 of 1,000 mg/kgdw (Table CS1.4).

For P-AA/MA, HERA (2014b) recorded that experimental sediment toxicity data were unavailable. Therefore, HERA applied the equilibrium partitioning method using data from aquatic species to derive a sediment predicted no effect concentration (PNEC) for P-AA/MA, yielding a sediment PNEC of 536 mg/kg wet weight. HERA (2014b) noted that the equilibrium partitioning method has some limitations, but that the results were considered sufficiently conservative to be comparable to experimental data.

Summary ecotoxicity data for P-AA and P-AA/MA

Taken together, despite high water solubility (> 400 g/L; Section 2.3.1.3), P-AA and P-AA/MA do not seem to pose a significant hazard to the environment. No clear relationship between molecular weight of P-AA or P-AA/MA and ecotoxicity potential is evident. Notably, however, experimental soil and sediment toxicity data are unavailable for P-AA/MA. It can be expected that most P-AA and P-AA/MA generally possess low ecological hazard and, if they meet respective molecular weight requirements, that they also fulfil the criteria for polymers of low concern (ECCC and HC, 2018).

2.8.1.2 Ecotoxicity data for PMMA

The ECETOC Polymers TF is unaware of robust ecotoxicity data for PMMA.

2.8.1.3 Ecotoxicity data for EPPAA

In an acute toxicity study using fish (*Danio rerio*), EPPAA was found to elicit acute aquatic toxicity (96-hour LC_{50} = 7.9 mg/L). The further ecotoxicological evaluation of EPPAA included read-across following the analogue approach (Glossary) using ethoxylated pentaerythritol and acrylic acid oligomer (CAS No. 51728-26-8; similar structure, although not propoxylated) as source substance. For this oligomer, acute aquatic toxicity data are available for all trophic levels. The analogue oligomer presented similar aquatic toxicity to fish (*D. rerio*: 96-hour LC_{50} = 1.76 mg/L) as EPPAA. Other aquatic organisms were less sensitive than fish to the analogue substance, according to results obtained with aquatic invertebrates (*D. magna*: 48-hour EC_{50} = 90.94 mg/L), algae (*Pseudokirchneriella subcapitata*: 72-hour ErC_{50} > 100 mg/L) and aquatic microorganisms (3-hour EC_{50} > 100 mg/L; OECD TG 209).

Based on these experimental data, aquatic exposure to the ethoxylated pentaerythritol and acrylic acid oligomer is likely to lead to some degree of environmental hazard, in particular to fish. Therefore, the read-across to EPPAA also indicates likely aquatic toxicity potential of this polymer.

2.8.2 Human health hazard assessment

2.8.2.1 Toxicity data for P-AA and P-AA/MA

As presented and discussed in HERA (2014a), P-AA homopolymers are of low acute toxicity to the rat (LD_{50}[4] > 5,000 mg/kg body weight (bw)/day); they are not irritating to the rabbit skin and, at the most, slightly irritating to the rabbit eye. Further, P-AA has no sensitising potential. In a 91-day inhalation toxicity study using rats, P-AA elicited mild, reversible pulmonary irritation (NOEC = 0.2 mg/m^3). HERA (2014a) assessed this finding as local particle effect owing to the physical properties of the respirable dust. There was neither evidence for *in vitro* or *in vivo* genotoxic potential of P-AA, nor for developmental and reproductive toxicity in the rat. Based upon the available data, HERA (2014a) concluded that exposure to P-AA does not imply any particular human health hazard.

For P-AA/MA, HERA (2014b) generally reported the same low acute toxicity as well as absence of skin or eye irritation, skin sensitisation, *in vitro* and *in vivo* genotoxic potential and developmental and reproductive toxicity in the rat. In a 91-day inhalation toxicity study using rats, mild, reversible pulmonary irritation was also recorded upon exposure to P-AA/MA (NOEC = 0.1 mg/m^3), and again, HERA (2014b) assessed this finding as a non-substance-related particle effect (HERA, 2014b).

Opgenorth (1992) reported that salts of linear polyacrylic acids are of low toxicity and that the available dataset for higher molecular weight, slightly crosslinked polyacrylates, which are used as thickeners in cosmetics, also gives no indication of specific toxic properties.

To supplement the database for P-AA and P-AA/MA, Appendix CS1-A summarises data from the Cosmetic Ingredients Review (CIR) Expert Panel report on acrylates copolymers (CIR, 2018). Hence, these data do not relate to the linear P-AA homopolymer or to P-AA/MA. Consistently, the data from CIR (2018) summarised in Appendix CS1-A show that acrylates copolymers do not possess systemic toxicity potential, that they are not skin irritants or skin sensitisers, but that they may be eye irritants (depending on the monomers used).

2.8.2.2 Toxicity data for PMMA

The below examples demonstrate that different variants of PMMA can be manufactured to have broadly different properties and technical uses, with different molecular weights, physico-chemical properties and residual levels of IAS/NIAS.

The US FDA has performed a safety assessment of PMMA for use in medical devices, which included human and animal data (US FDA, 2002a, b). Based thereupon, the US FDA approved the use of PMMA in diagnostic contact lenses and orthopaedic devices as Class II medical devices. Class II medical devices require pre-market notification and hence adherence to the *International Standardization Organisation (ISO) 10993 Standards Series on the Biological Evaluation of Medical Devices* (US FDA, 2020); see also Appendix C3-A2 for details on the ISO 10993 standard series.

Following the US FDA approval, PMMA uses in diagnostic contact lenses and orthopaedic devices are listed in the US Code of Federal Regulations (CFR), Volume 8, Title 21 (*Food and Drugs*; 21 CFR); https://www.ecfr.gov/cgi-bin/ECFR?SID=cc7a19ecd123c4c16408cd1a1cc65c5a&mc=true&page=browse:

[4] LD_{50}: Dose required to achieve 50% change in lethality from the control

- CFR 21, Part 886 (ophthalmic devices), Section 1385: PMMA diagnostic contact lens – "*a device that is a curved shell of PMMA intended to be applied for a short period of time directly on the globe or cornea of the eye for diagnosis or therapy of intraocular abnormalities*"
- CFR 21, Part 888 (orthopaedic devices), Section 3027: PMMA bone cement – "*a device intended to be implanted that is made from methyl methacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene. The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone*"

On account of the safety assessment by the US FDA, the CIR expert panel safety assessment of PMMA and related ingredients (Becker et al., 2011) and the CIR (2018) report on acrylates copolymers concluded that there was no need to review systemic toxicity data on PMMA applied to the skin via cosmetic products as the safety of this route of exposure could be extrapolated from data on use of PMMA as medical devices, which were likely to yield much higher exposures (Becker et al., 2011; CIR, 2018). With respect to local effects, PMMA was mildly irritating in rabbit eyes whereas it was not irritating to the rabbit skin and not irritating or sensitising in a human repeated insult patch test (Becker et al., 2011; CIR, 2018).

Pemberton and Lohmann (2014) investigated how residual methyl methacrylate monomers contribute to the skin sensitisation potential of PMMA. The risk of induction of contact allergy in consumers was determined using a method based upon the exposure-based quantitative risk assessment approach developed for fragrance ingredients (Api et al., 2008). Twenty-four-hour continuous exposure was assumed as worst-case scenario based upon the quantitative determination of monomer migration into simulants. The 'no expected sensitisation induction level' was based on the threshold to induction of sensitisation (EC3: Estimated concentration needed to produce a stimulation index of 3 in the LLNA (OECD TG 429)) in the local lymph node assay (LLNA; OECD TG 429). Application of default and chemical-specific adjustment factors resulted in a very high margin of safety of 10,000 for *induction* of allergic contact dermatitis in consumers handling polymers under selected conservative exposure conditions. Pemberton and Lohmann (2014) concluded that, although data to derive a risk characterisation ratio for *elicitation* of allergic contact dermatitis were unavailable, that ratio was likely to be lower than that for induction.

2.8.2.3 Toxicity data for EPPAA

See summary at https://echa.europa.eu/registration-dossier/-/registered-dossier/15998.

Skin and eye irritation: EPPAA did not elicit skin irritation or corrosion in rabbits. In three rabbit eye irritation studies, EPPAA instillation caused reversible effects on cornea, iris and conjunctivae so that EPPAA is classified as Category 2 eye irritant.

Skin sensitisation: Experimental data for EPPAA are unavailable. Read-across from a guinea pig maximisation test for an analogue substance indicated absence of skin sensitisation properties.

Acute toxicity: An acute oral toxicity study showed 40% mortality in rats treated with 5,000 mg/kg bw EPPAA. Data on acute toxicity upon inhalation or dermal exposure are unavailable.

Repeated-dose toxicity: In an oral 28-day repeated toxicity study (OECD TG 407), EPPAA caused stomach irritation in rats upon gavage administration of ≥ 200 mg/kg bw/day. Accordingly, the no observed adverse effect level (NOAEL) for systemic effects was determined to be 80 mg/kg bw/day.

Genotoxicity: In an Ames test (OECD TG 471), EPPAA did not show any mutagenic potential either with or without metabolic activation (S9 liver fraction). An *in vitro* mammalian cell gene mutation test (OECD TG 476) assessing EPPAA was inconclusive without S9 and negative with S9. An *in vivo* micronucleus using rats (oral route of exposure) yielded negative results for EPPAA. Based on a weight of evidence evaluation of all three studies, EPPAA was not considered to be mutagenic, and no classification for genotoxicity was required for EPPAA.

Developmental and reproduction toxicity: A reproduction/developmental toxicity screening study (OECD TG 421) using rats indicated no adverse effects on reproduction or development caused by EPPAA at doses up to 80 mg/kg bw/day.

2.9 Case Study 1: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for P-AA/MA, P-AA, PMMA or EPPAA. Instead, it has served to evaluate if the CF4Polymers is generally applicable to polycarboxylates, polyacrylates and polymethacrylates and if the collated information provides further insight on the applicability of tools, test methods and models for the physico-chemical characterisation and toxicity / ecotoxicity testing of these polymers. Generally, the case study has confirmed both the usefulness of the CF4Polymers (ECETOC TR No. 133-1) and the validity of the information on the applicability of tools, methods and models (ECETOC TR No. 133-2) for the assessment of polycarboxylates, polyacrylates and polymethacrylates.

Specific polycarboxylates, such as P-AA and P-AA/MA that are being used in consumer products with wide dispersive use (laundry detergents, personal care products), have been submitted to extensive hazard and risk assessment. These polycarboxylates are (fairly) data rich. The database covering the entire spectrum of relevant ecological and toxicological endpoints confirms that these polymers can be submitted to the battery of test methods that is relevant for hazard and risk assessment. Specifically, these polymers are water soluble so that poor solubility does not pose any problems when submitting them to ecological and/or toxicological test methods.

Nonetheless, as complex polymer products, they do pose the 'usual' challenges during analytical assessment. For example, the molecular weight of polycarboxylates is best expressed as mean value (together with the minimum and maximum values). Their apparent acid dissociation is not a constant, but a function of the pH of the solution or the degree of ionisation. In some cases, adsorption of the test material to the test flasks may impair its availability at the test system. Also, the water solubility and precipitation behaviour of P-AA/MA in the presence of ions with 2+ charge (e.g. ubiquitous Ca^{2+} and Mg^{2+}) can greatly affect the outcome of chronic aquatic toxicity studies (with water solubility further appearing dependent on water hardness and test concentrations.

As regards environmental fate, there is a fairly good correlation between dissolved organic carbon removal and molecular weight of the different P-AA / P-AA/MA. Additionally, it can be expected that most P-AA and P-AA/MA generally possess low ecological hazard and, if they meet respective molecular weight requirements, that they also fulfil the criteria for polymers of low concern.

3. CASE STUDY 2: CATIONIC POLYMERS

3.1 Introduction

3.1.1 Scope and outline of Case Study 2

Cationic polymers are polymers that contain "*net positively charged atom(s) or associated group(s) of atoms covalently linked to the polymer molecule. This includes, but is not limited to phosphonium, sulfonium, and ammonium cations*" (US EPA, 1997). Nitrogen groups (e.g. quaternary nitrogen atoms (Jaeger et al., 2010)) are the most common cause of cationicity in polymers, and available data show that aquatic toxicity is related to the charge density of the polymer (US EPA, 2015). Many cationic polymers are also water soluble, or otherwise dispersible in water, and thus may be present in the aquatic compartments. Due to these properties, cationic polymers are regarded as posing a hazard concern towards aquatic species. Specifically, cationic polymers will sorb to surfaces, and strongly to any negatively charged surfaces. Hence, the mechanism of aquatic toxicity is assumed to be via sorption to respiratory surfaces e.g. those present in gills (Muir et al., 1997; Pereira et al., 2018). At the same time, this sorptive capacity is believed to mitigate exposure as the cationic polymers will also sorb to particles thereby reducing the fraction that is (externally or systemically) bioavailable to living aquatic organisms (Boethling and Nabholz, 1997). Taken together, the toxicity mechanisms of cationic polymers such as polyquaterniums (i.e. polycationic polymers used in the personal care industry that all share the presence of quaternary ammonium functional groups (Cumming, 2008)) are not yet fully understood. Work is ongoing in the Cefic Long-Range Research Initiative (LRI) ECO46 project *Improved Aquatic Toxicity Testing and Assessment of Polymers* (iTAP; http://cefic-lri.org/projects/eco-46-improved-aquatic-testing-and-assessment-of-cationic-polymers-itap/) to elucidate these.

This case study on cationic polymers focuses on polyamines with the INCI names polyquaternium-6 (PQ-6) and polyquaternium-10 (PQ-10). PQ-6 is a poly diallyldimethyl-ammonium chloride (DADMAC) polymer with wide dispersive use, for which reason it is relatively data rich as compared to other cationic polymers. The intended uses of PQ-6 addressed in this case study are use in conditioning shampoos, i.e. personal care products with down-the-drain release and use as flocculant in water and WWTPs (the bulk of PQ-6 use). PQ-10 is a cationic hydroxyethyl cellulose with fairly comprehensive database. PQ-10 is generally used in personal care products, and again, use in conditioning shampoos was selected as intended use for the case study.

This case study covers all steps of the CF4Polymers to evaluate its suitability to perform a (theoretical) risk assessment for PQ-6 and PQ-10. This serves to provide an overview of the state-of-the-science hazard and risk assessment of cationic polymers. Focus is on environmental exposure and hazard assessment while also referring to aspects of relevance for human exposure and hazard assessment. To supplement the human health toxicity database, reference is also made to toxicity data available for other polyquaterniums (PQ-7, PQ-11, PQ-22, PQ-28, PQ-39 and PQ-47). Finally, this case study also serves to illustrate the suitability, or need for adaptation, of standardised tools, test methods, and models for the hazard and exposure assessment of cationic polymers.

3.1.2 Structural considerations, manufacture and use of cationic polymers

Cationic polymers typically have carbon, silicon, or natural (e.g. polysaccharide) backbones, and they comprise a wide range of molecular weights. Importantly, cationic polymers contain a net positively charged atom, e.g. quaternary ammonium, phosphonium or sulfonium. Alternatively, they contain groups that are anticipated to become cationic in water, e.g. primary, secondary and tertiary aliphatic amines (US EPA, 1997).

Cationic polymers can have different properties and functionalisations ranging from designed pharmacodynamic properties, over cosmetic properties, to sorptive properties as flocculants for wastewater treatment. They can be designed for an intended function, e.g. by the addition of a specific functional group, or different functional groups, and/or by the embedding of additives to enable a specific performance as relevant for the intended use. Thus, cationic polymers are very versatile and cover thousands of different compounds, which are used in a broad range of products and processes. The global production volume of cationic polymers comprises millions of tonnes per year, with the exact numbers being very dynamic and rising overall; https://www.prof-research.com/Polymer/Cationic-Polymer-Market?limit=50.

The manufacturing route for PQ-6 involves the reaction of two equivalents of the allyl chloride DADMAC with dimethylamine, for which reason PQ-6 is also known as poly(DADMAC). PQ-6 is used in a broad variety of applications: As per the Substances in Preparations in Nordic Countries (SPIN) database, PQ-6 is used in 73 different preparations, with the highest proportion (as regards tonnage) being as flocculant in WWTPs (http://www.spin2000.net/spinmyphp/; accessed 19 March 2021). Notably, PQ-7 (CAS No. 26590-05-6), which is referred to in Section 3.8.2 (human health hazard assessment) is also a poly(DADMAC). When used as flocculants in WWTPs, poly(DADMAC)s contribute to charge neutralisation and act as promoters for anionic retention aids.

PQ-10 is manufactured by reacting hydroxyethyl cellulose with trimethylammonium substituted epoxide. Therefore, PQ-10 is a trimethylammonium-modified hydroxyethyl cellulose polymer. PQ-10 is ultimately derived from cellulose (either cotton or wood pulp), which is a natural, renewable resource (Elder, 1988). PQ-10 is primarily used in personal care products as substantive deposition aid (conditioner, thickener, emollient) at concentrations of 0.1-5%.

3.2 Case Study 2: CF4Polymers (Step 1) Problem formulation

This case study focuses on consumer use of conditioning shampoo containing PQ-6 or PQ-10 and on the use of PQ-6 as flocculant in WWTPs. Accordingly, the case study serves to show which parameters relating to physico-chemical, exposure-related, ecotoxicological and toxicological properties are relevant for a (theoretical) risk characterisation. In practice, such a risk characterisation would be conducted to determine e.g. the acceptable level of risk for the environment (PQ-6) and/or human health (PQ-6 and PQ-10). The environmental target populations for assessment are predominantly aquatic populations, but also sediment-dwelling and terrestrial populations. Human target populations are both workers that may come into contact with PQ-6 and PQ-10 during the manufacture and formulation into products as well as the individual consumers that use these formulations and as such may also include sensitive subpopulations such as children. Professional users may also be relevant for hazard and risk assessment of PQ-6 and PQ-10 but are not considered in this case study.

3.3 Case Study 2: CF4Polymers (Step 2) Polymer identification

3.3.1 Step 2.1: Identification of the polymeric substance

3.3.1.1 Standard chemical descriptors

Polyquaternium is the INCI name (see Section 2.3.1.1 for details) for polycationic polymers used in the personal care industry that all share the presence of quaternary ammonium functional groups (Cumming, 2008).

PQ-6 has the CAS name '*2-propen-1-aminium, N,N-dimethyl-N-2-propen-1-yl-, chloride (1:1), homopolymer*'. The main CAS number used for PQ-6 is CAS No. 26062-79-3 (see e.g. ECCC and HC, 2020).

Polyquaternium-10 is the INCI name for a group of cationic hydroxyethyl cellulose polymers primarily used in personal care products as substantive deposition aids. PQ-10 has the CAS name '*cellulose, 2-(2-hydroxy-3-(trimethylammonium) propoxy)ethyl ether, chloride*'. PQ-10 has four CAS numbers, i.e. CAS No. 68610-92-4, CAS No. 53568-66-4, CAS No. 54351-50-7, and CAS No. 55353-19-0.

For a broad variety of polyquaterniums that are used in cosmetics, Appendix 1 in Cumming (2008) presents the CAS name and number, formula, structure and function. Of note, the CAS numbers for polyquaterniums come with huge variations and may reflect different synthesis methods.

3.3.1.2 Structural and morphological descriptors

PQ-6 is a colourless to light yellow viscous solution / suspension with solid levels in the range of 10-50% (ECCC and HC, 2020).

PQ-10 is manufactured as a white or off-white powder that is subsequently formulated into aqueous consumer products at levels ranging from ≤ 0.1% to 5% (https://online.personalcarecouncil.org/jsp/CIRList.jsp?id=376).

3.3.1.3 Weight-average and number-average molecular weight

The grades of PQ-6 supplied to the personal care industry typically have high weight-average molecular weight (M_w) of approx. 150,000 Da. Grades of PQ-6 with M_w values as low as 15,000 Da are available depending on the product use, whereas for other PQ-6, the M_w may even attain 1 million Da (Bolto and Gregory, 2007; Cumming, 2007, 2008; Fevola, 2013; Lubrizol, 2017). Similarly, the PQ-6 that are used as flocculants in wastewater treatment are of high molecular weight (HMW) (e.g. 90,000 Da to 597,000 Da as used in the Cefic LRI iTAP project).

PQ-10 have average molecular weights that generally range from 250,000 Da to approx. 1,000,000 Da (see e.g. Marcelo et al., 2007; Gao et al., 2009; Cumming et al., 2011a).

3.3.1.4 Charge density

The charge density of cationic polymers is based on the proportional weight of the amine-nitrogen present in the polymer chain (Boethling and Nabholz, 1997; Cumming, 2008). There are two indirect methods to measure charge density, i.e. polyelectrolyte/charge titration (Cumming, 2008) and measurement of the Total Kjeldahl

Nitrogen (%TKN; Kimberly and Roberts, 1905). Polyelectrolyte/charge titrations can be carried out with an automatic titrator combined with a particle charge detector (Saveyn et al., 2008). While both methods are valid to measure the charge density of PQ-6 and PQ-10, they both also have limitations e.g. with respect to precision.

The charge density for PQ-6 ranges between 5.8 and 6.2 mEq./g depending upon the size and weight of the material (e.g. Cumming, 2008). This corresponds to a functional group equivalent weight (FGEW) of 162 Da for some commonly used PQ-6 with molecular weight range of approx. 15,000-150,000 Da.

For PQ-10, the charge density is typically measured as %TKN. PQ-10 has trimethylammonium substitution levels between 0.4-2.2 %TKN. This corresponds to 0.3-1.1 mEq./g (Cumming, 2008; Table CS2.1) or a FGEW of 500 to 2000 Da for a PQ-10 with 250-1,600 kDa.

Notably, cationic density, unless extremely low, prevents a polymer from being considered as 'polymer of low concern' in those jurisdictions in which legislation for the registration or notification of polymers is in force (Section 1.2). This is justified by concerns for aquatic toxicity. Specific cationic polymers may nonetheless meet the criteria for polymers of low concern. These are:

- *"Cationic or potentially cationic polymers that are solids, are neither water soluble nor dispersible in water, are only to be used in the solid phase, and are not excluded from exemption by other factors; and*
- *Cationic or potentially cationic polymers with low cationic density (the percent of cationic or potentially cationic species with respect to the overall weight of polymer) which would not be excluded from the exemption by other factors.*

For a polymer to be considered to have low cationic density, the concentration of cationic functional groups is limited to a FGEW of ≥ 5,000 Da" (US EPA, 1997; similar provisions in: Canada, 2005, 2021; Australian Government, 2019).

Hence, on account of their moderate to high charge density (FGEW well below 5,000 Da), PQ-6 and PQ-10 do not meet the criteria for polymers of low concern implemented e.g. in the USA, Canada, and Australia.

3.3.1.5 Acid dissociation constant

The acid dissociation constant is not relevant for the quaternary ammonium chlorides since they are salts.

3.3.1.6 Solubility in water

PQ-6 has high water solubility (see e.g. Amjad, 2002; ECCC and HC, 2020; https://www.irochemical.com/product/Daily-Chemicals/Polyquaternium-6.htm#:~:text=It%20is%20clear%20to%20light,and%20good%20water%20solution%20stability.

PQ-10 is soluble in water as per safety data sheet (see e.g. for the PQ-10 UCARE™ Polymer JR-30M: https://www.dow.com/en-us/pdp.ucare-polymer-jr-30m.084958z.html).

A review of the available water solubility data is under preparation within the Cefic LRI iTAP project (personal communication from Hans Sanderson, Aarhus University, Denmark). Generally, water solubility of the polyquaterniums is difficult to measure also due to a lack of analytical tools that are suitable for these charged polymers. Further, the exact solubility may vary between different types of e.g. PQ-6 and PQ-10, respectively.

Table CS2.1: Summary of environmental fate and aquatic toxicity data for different polyquaternium-10 variants (published data and unpublished Task Force member company data; used with permission)

	Molecular weight (average)	Viscosity as 2% aqueous solution	Charge density	Kjeldahl nitrogen	K_d value	Biodegradation screening	Predicted WWTP removal	48-h EC_{50} *Daphnia*	72-h $EC_{10/50}$ algae (*Chlorella sp12)*	96-h EC_{50} fish
Unit	Da	mPa *s	mEq./g	%TKN	L/kg		%	mg/L	mg/L	mg/L
Reference	[a] or noted	[b]	[c]	[b]	See below	[f]	[g]	[h]	[d]	See below
UCARE JR125	250,000	75-125	High (0.9)	1.5-2.2	359 (humic acid) [d, e] 10,000 (sludge solids) [m]		13	-	EC_{50} = 0.04	1.2 [i]
UCARE JR400	400,000	300-500	High (1.2)	1.5-2.2	440 (humic acid) [d, e] 10,000 (sludge solids) [m]	31 % DOC 64 days	13	34-48	EC_{10} = 0.013 EC_{50} = 0.05	2.1 [i] 2.4 [k]
UCARE JR30M	1,000,000 [n]	25,000-35,000	High (1.0)	1.5-2.2	634 (humic acid) [d, e] 10,000 (sludge solids) [m]		16	-	EC_{10} = 0.002 EC_{50} = 0.05	1.5 [i]
UCARE LR400	400,000	300-500	Low (0.6)	0.8-1.1	Not available			-	Not available	64 [i]
UCARE LK	400,000	300-500	Low (0.3)	0.4-0.6	Not available			-	Not available	100 [i] > 120 [l]
UCARE LR30M	1,000,000	25,000-35,000	Low (0.4)	0.8-1.1	10,000 (sludge solids) [m]			-	Not available	66 [i]

Footnote to Table CS2.1:

Abbreviations: %TKN: Total Kjeldahl Nitrogen; Da: Dalton; DOC: Dissolved organic carbon; EC_{50}: Concentration required to achieve 50% effect change from the control; K_d value: Adsorption/desorption distribution coefficient; mEq./g: Milli equivalent/gram; mPa * s: Millipascal seconds; WWTP: Wastewater treatment plant.

[a] Unpublished Company data, estimated based on viscosity information; [b] Siebert et al. (1990); [c] Cumming et al. (2010); [d] Cumming (2008); [e] Cumming et al. (2011a); [f] Unpublished Company data; inherent primary biodegradability, pre-adapted sludge (OECD TG 302B); [g] Cumming et al. (2011b); [h] Unpublished Company data (1981) using *Daphnia magna*; [i] Cumming et al. (2008) using *Gambusia holbrooki*; [k] Unpublished Company data (1981) using *Pimephales promelas* (Fathead minnow); [l] Unpublished Company data (1999); using rainbow trout, flow-through exposure; [m] Unpublished data (2021) American Cleaning Institute, Adsorption Isotherms by Activated Sludge; used with permission; [n] Gao et al. (2009).

3.3.1.7 n-Octanol/water partition coefficient

The ECETOC Polymers TF is unaware of a suitable methodology to measure the n-octanol/water partition coefficient (log K_{ow}) of cationic polymers such as PQ-6 or PQ-10. At the same time, the TF maintains the view that this parameter is neither relevant to predict the bioaccumulation of PQ-6 or PQ-10 nor relevant for environmental risk assessment modelling approaches. Both have HMW preventing diffusion through the membranes, and hence low absorption potential, and they are further very sorptive due to their cationicity. For these reasons, PQ-6 and PQ-10 are unlikely to become systemically bioavailable, and thus will not bioaccumulate (Section 3.7.1.3).

3.3.1.8 Adsorption/desorption and organic carbon/water partition coefficient

Humic acid is a component of the high and diverse organic matter content of sewage sludge, and it is used as substrate to measure the sorption behaviour of compounds for which fate in WWTPs is relevant.

Cumming et al. (2011a) described sorption to humic acid (where this humic acid is employed as a surrogate for WWTP biosolids) of selected polyquaterniums (i.e. PQ-6, PQ-10, PQ-11, PQ-28, PQ-55) and of a cationic surfactant. The sorption of PQ-10, PQ-28 and PQ-55 used in cosmetics with a charge density in the range of 0.7 to 11 mEq./g was less extensive than that exhibited by PQ-6 used in water treatment with a higher charge density of 5 mEq./g and also less extensive than that of the cationic surfactant (Cummings et al., 2011a).

The measured adsorption/desorption distribution coefficient (K_d) was 2,200 L/kg in humic acid for a 50,000 Da variant of PQ-6 (5.8 mEq./g). Lower K_d values were measured for three PQ-10 with molecular weights of 250,000 Da, 400,000 Da, and approx. 1,000,000 Da, and high charge density (1.5-2.2 %TKN or 0.3-1.1 mEq./g), i.e. 359, 440 and 634 L/kg in humic acid, respectively (Marcelo et al., 2007; Gao et al., 2009; Cummings, 2008; Cummings et al., 2011a) .

Considering there are uncertainties about the relevance of the partitioning to humid acid to inform on the partitioning to sludge solids in WWTP, four PQ-10 were identified for further study of their adsorption potential to activated sludge solids. The K_d values (sludge solids) were estimated to be 10,000 and 7,000 L/kg based on the quantification limit in the water, indicative of strong adsorption potential to sludge solids (Table CS2.1).

The current information provides insights into uncertainties in using K_d values in humic acid to characterise distribution in WWTP.

3.3.1.9 Surface tension

PQ-6 or PQ-10 do not have relevant surface-active properties.

3.3.1.10 Analytical verification of polyquaternium concentrations in environmental media

Mass spectrometry-based methods to verify the concentrations of polyquaterniums in (experimental or natural) environmental media at relevant limits of quantification are currently unavailable. Therefore, test results are evaluated based upon nominal concentrations. However, since polyquaterniums can adsorb to surfaces and precipitate out of solution, the effective exposures may be much lower than the nominal concentrations, thereby potentially leading to erroneous conclusions on the actual concentrations at which effects are absent. Substantial pre-work is needed to ensure bioavailability and stability of the test materials within the test systems. Variations in test setups (e.g., solution preparation, water quality parameters) may

greatly affect the effect concentrations and hence also the test results. The ongoing Cefic LRI project iTAP (Section 3.1.1) is exploring appropriate test design procedures and necessary pre-work for aquatic toxicity tests.

The Cefic LRI project iTAP is also engaged in developing cold analytical (mass spectrometry) approaches. While significant methodological challenges need to be addressed to develop such robust and sensitive analytical methods, these are expected to become available in the future (personal communication from Hans Sanderson, Aarhus University, Denmark).

An indirect colorimetric approach following the phenol method as described by Dubois et al. (1956) and Kanzaki and Berger (1959) supports the verification of PQ-10 concentrations. However, the method has limitations in quantifying low concentrations especially in matrices with a background colour.

3.3.2 Step 2.2: Identification of additives

The 'as produced' PQ-6 and PQ-10 do not contain additives. Selected PQ10 polymer products may contain low levels of glyoxal (CAS No. 107-22-2), as an additive for dispersibility.

3.3.3 Step 2.3: Identification of NIAS and/or residual substances (monomers)

The 'as produced' PQ-6 generally has very low contents of unreacted monomers, oligomeric substances and/or impurities (e.g. < 1% for the unreacted monomers). The most important complexity to consider is that PQ-6 has different molecular weight groups.

Impurities of PQ-10 include sodium salts (e.g. acetate, chloride), nitrate, water and isopropanol at levels below 1.5%.

3.4 Case Study 2: CF4Polymers (Step 3) Polymer component strategy

This case study is restricted to the polymeric substance.

3.5 Case Study 2: CF4Polymers (Step 4) Grouping approach evaluation

This case study does not focus on (Step 4) grouping approach evaluation. However, at the end of the case study, high level conclusions on opportunities to group (different types of) polyquaterniums shall be drawn from the presented data.

3.6 Case Study 2: CF4Polymers (Step 5) Determination of exposure scenarios

3.6.1 Environmental exposure scenarios

ECCC and HC (2020) provide a detailed description of uses and release pathways for polyamines.

3.6.1.1 Use of PQ-6 as flocculant in WWTPs

When PQ-6 are used as flocculants in WWTPs to promote the separation of solids from liquids, they are directly dosed to water. Due to this direct dosing and further considering the functionality of PQ-6 in stimulating the flocculation of suspended matter, release into the environment cannot be excluded. The specific route of release into the environment is highly dependent on the fate and partitioning processes in the WWTPs.

If generic exposure categories are unavailable for the specific use of PQ-6 as flocculant in WWTPs, the description of the exposure scenario should consider e.g. whether the polyquaternium is used in primary and/or secondary clarifiers, the dosing practice (continuous feed vs dosing frequency), and whether the polyquaternium is emitted bound to suspended solids or as 'free polymer'.

3.6.1.2 Use of PQ-6 and PQ-10 in personal care products

In personal care products, PQ-6 and PQ-10 are used mainly in conditioning shampoos. The different PQ-6 variants are manufactured as solutions and the different PQ-10 in the form of powders. Both are diluted during the formulation, which is performed at industrial sites (so that local emissions may occur). After consumer use, the conditioning shampoos containing PQ-6 or PQ-10 are emitted to the sewer via down-the-drain release. This is considered a wide-dispersive use leading to continuous emissions to the WWTP. Release rates into the WWTP in support of Tier 1 exposure assessment (as per EU REACH Regulation; EP and Council, 2006) can be estimated by use of the Cosmetics Europe Specific environmental release categories (SpERCs) developed for low viscosity liquids (https://cosmeticseurope.eu/cosmetics-industry/cosmetics-industry-and-reach/). Once emitted to wastewater, the environmental behaviour of PQ-6 and PQ-10 greatly depend on their partitioning and fate properties (Section 3.3.1.7 and Section 3.7.1).

3.6.2 Human exposure scenarios

In personal care products, PQ-6 and PQ-10 are used mainly in conditioning shampoos, typical use levels in shampoos have been described to be < 1% up to 10% (Becker et al., 2012). As a result, potential consumer exposure is to the scalp, hair, skin as well as eyes. Use of PQ-6 and PQ-10 in cosmetics is documented in the respective CIR Expert Panel reports on safety assessment of these polyquaterniums as used in cosmetics, i.e. CIR (2020) for PQ-6 and CIR (1988) for PQ-10. Downstream users need to evaluate for the total levels of glyoxal that may be used in personal care formulations containing PQ-10.

Further, PQ-6 is widely used as coagulant and flocculent in wastewater treatment, for sludge dewatering and as coagulant in drinking water purification (Duis et al., 2021). Workers in WWTPs are generally trained and

advised to safely handle chemicals including PQ-6 following the safety measures described in the safety data sheets.

Commercially available cationic water treatment flocculants containing poly(DADMAC)s (e.g. PQ-6 or PQ-7) are certified by the National Sanitation Foundation (NSF) International (https://www.nsf.org) to meet the *NSF/American National Standards Institute (ANSI) Standard 60: Drinking water treatment chemicals – health effects* (https://www.nsf.org/knowledge-library/nsf-ansi-standard-60-drinking-water-treatment-chemicals-health-effects). Following these specifications, the residual monomer concentration is less than one percent of the mixture, and – when used according to the manufacturer's dosing rate – any monomer in the finished product is below the maximum level allowed for drinking water standards.

The US Army Public Health Command (USAPHC) conducted a preliminary assessment of possible effects on environmental quality and human health from the use of commercially available water treatment chemicals some of them containing poly(DADMAC). When used according to the manufacturer's guidelines, the chemicals were found to pose little to no risk as they were almost completely removed from the finished water after completion of the recycling process. The USAPHC concluded that disposal of unused product and sludge from the intended application should follow pertinent guidelines (USAPHC, 2014).

3.7 Case Study 2: CF4Polymers (Step 6) Exposure characterisation

3.7.1 Environmental fate assessment for polyquaterniums

Overall, limited environmental fate data are publicly available for polyquaterniums (see e.g. recent reviews by ECCC and HC (2020) and Duis et al. (2021)). Due to their cationic properties, sorption (to any type of – especially negatively charged – particles and surfaces) is expected to play an important role in the environmental fate of PQ-6 and PQ-10.

3.7.1.1 (Bio)degradation assessment

Taken together, PQ-6 polymers are expected to be stable in the water, sediment and soil compartments (ECCC and HC, 2020). It is important to note that use of humic acid from different sources may affect the outcome of biodegradation testing (personal communication by Hans Sanderson, Aarhus University, Denmark).

(Bio)degradation assessment of PQ-6

Historical data (likely to be Klimisch reliability 2 (Klimisch et al., 1997)) indicate that PQ-6 is neither readily biodegradable (test method not reported) nor inherently biodegradable in an OECD TG 302 study (ECCC and HC, 2020) (Table CS2.2). Information to assess the biodegradation potential of PQ-6 in sediments is unavailable (ECCC and HC, 2020). However, it is generally expected to be (even) slower than in water (or soil), where aerobic conditions favour biodegradation.

As further denoted by ECCC and HC (2020) abiotic degradation of PQ-6 is also not expected*: "While hydrolysis information for the two poly(DADMAC) polymers was not identified, hydrolytic stability is expected since they are used for coagulation, flocculation and other products where they would be formulated with water. Padhye et al. (2011) have investigated the interactions of ozone with poly(DADMAC) during water treatment at water and wastewater utilities. The study results show that contact with ozone releases N-nitrosodimethylamine (…) but not at significant concentrations."*

Table CS2.2: Summary of publicly available fate and ecotoxicity data for polyquaternium-6 (PQ-6)

Property	K_d value	Predicted WWTP removal	Biodegradability	48-hour acute invertebrate toxicity	7-day chronic invertebrate toxicity	96-hour acute fish toxicity	30-day chronic fish toxicity
Unit	**L/kg**			**mg/L**	**mg/L**	**mg/L**	**mg/L**
Test results	2,200 [1]	38% [2]	Not readily biodegradable (method not reported) [3] Not inherently biodegradable (OECD TG 302) [3]	*D. magna*, immobilisation [4] EC_{50} = 0.075 / 2.1 NOEL = 0.50 / < 0.059 *Ceriodaphnia*, mortality [5] EC_{50} = 0.32 / 0.54 / 0.51 / 0.77 [6]	*Ceriodaphnia* [5] EC_{20} (reproduction) = 0.0042 EC_{50} = 0.014	*P. promelas*, mortality [4] LC_{50} = 0.22 / 0.26 NOEL = 0.11 / ≤ 0.10 *O. mykiss*, mortality [4] LC_{50} = 0.066 / 0.077 NOEL = 0.043 / ≤ 0.059 *S. namaycush*, mortality [7] LC_{50} = 2.08	*S. namaycush*, survival and growth [5] NOEC = 0.5 LOEC = 1.0 mg/L

Footnote to Table CS2.2:

Abbreviations: $EC_{20/50}$: Concentration required to achieve 20/50% effect change from the control; K_d: Adsorption / desorption coefficient; LC_{50}: Concentration required to achieve 50% change in lethality from the control; LOEC Lowest observed effect concentration; NOEC/NOEL: No observed effect concentration / level; WWTP: Wastewater treatment plant.

[1] Cumming et al. (2011a) for a 50,000 Da variant of PQ-6.

[2] Cumming et al. (2011b) for a 50,000 Da variant of PQ-6.

[3] ECCC and HC (2020); data on physico-chemical properties and/or trade names of the respective tested PQ-6 unavailable.

[4] US Environmental Protection Agency ECOTOX knowledge base; available at: https://cfpub.epa.gov/ecotox/; data on physico-chemical properties and/or trade names of the respective tested PQ-6 unavailable.

[5] DeRosemond and Liber (2004); testing MagnaFloc™ 368 (Ciba Specialty Chemical; Suffock VA, USA).

[6] Tested without pH adjustment / after adjustment to pH 3 / after adjustment to pH 11 / after adjustment to pH 11 and filtering through membrane filters (0.45 µm pore size).

[7] Liber et al. (2005); testing MagnaFloc™ 368 (Ciba Specialty Chemical).

(Bio)degradation of PQ-10

Due to their high molecular weight, PQ-10 are generally not expected to meet the criteria for being readily biodegradable. However, inherent primary biodegradability (31% DOC removal at 64 days) was recorded for the PQ-10 variant UCARE JR30M (approx. 1'000,000 Da; high charge density) when tested in OECD TG 302B with pre-adapted sludge (unpublished company data; Table CS2.1).

3.7.1.2 Fate in WWTPs

High cationic charge density polyamines with often high molecular weight are widely used as primary coagulants in water treatment applications as well as in WWTPs mainly to improve the processes of sludge thickening and dewatering. As discussed in ECCC and HC (2020), cationic polymers are likely to leave treatment facilities with the dewatered biosolids rather than in the treated effluent. Similarly, Boethling and Nabholz (1997) applied a generic WWTP removal rate of 90% under the US EPA Toxic Substances Control Act Program for cationic polymers with number average molecular weight (M_n) > 1,000 Da (PQ-6 and PQ-10 fall under this molecular weight category) when actual data were unavailable. Boethling and Nabholz based this generic value on the assumption that polymers partition mainly to the solid phase and that 90% represents a typical WWTP removal level for solids. By contrast, for a PQ-6 with 50,000 Da, the estimated removal in WWTP was approx. 38% based on a K_d of 2,200 L/kg in humic acid (Cumming et al., 2011a, b), which is lower than expected from consideration on the polymer function, as well as from the greater sorption observed in sludge solids (K_d values) that were recently determined for other PQs (Table CS2.1). The ability to extend the data available for this PQ-6 to PQ-6 variants with higher molecular weight, as used in personal care products and water treatment, is unclear at this time.

Further research work is recommended to determine whether molecular weight, in addition to cationic charge, is a relevant driver for the fate (and aquatic effects) of members of the group of PQ-6.

Using K_d values obtained in humic acid (Cumming et al., 2011a) and flow rate data from a local municipal WWTP in Southeast Queensland, Australia, Cumming et al. (2011b) predicted the WWTP removal efficiencies of three PQ-10 with molecular weight ranging from 250,000 Da to approx. 1,000,000 Da to be as low as 13-16% (Table CS2.1). Adsorption to sludge solids was 10-fold greater than the reported adsorption to humic acid alone, and led to much greater predicted WWTP removal efficiencies (e.g. up to 70% for K_d = 10,000 L/kg) of the polymers, based on the model by Cumming et al. (2011b). Since K_d is the dominant parameter affecting the prediction of removal efficiency (Cumming et al., 2011b), these findings suggest that more work is needed to characterise the sorption of polyquaterniums (both PQ-6 and PQ-10) to WWTP sludge solids at more realistic exposure levels (lower dose) to more predict their fate in wastewater treatment and release to receiving waters as a component of effluent more accurately.

There are indications that fate in WWTPs is strongly influenced by sorptive processes, as evidenced by adsorption/desorption on sludge solids for PQ-10 or in association with the primary function of water flocculants.

3.7.1.3 Bioaccumulation assessment

Both the HMW and sorptive properties limit uptake and passage of polyquaterniums through biological membranes. Therefore, systemic bioavailability and bioaccumulation potential are expected to be low (Murgatroyd et al., 1996; Arnot et al., 2009; see also Section 4.2.1 in ECETOC (2020) TR No. 133-2).

3.7.2 Environmental exposure assessment

The conventional exposure models are generally not applicable for polyquaterniums. First, the exposure models usually require input of the effective concentrations. However, these are generally unavailable for polyquaterniums since it is difficult, if not impossible, to analytically verify polyquaternium concentrations in environmental media (Section 3.3.1.10). Further, current evidence indicates that it is the sorptive properties of polyquaterniums that are relevant for hazard and risk assessment, leading to effects on the outside of the test organisms (Section 3.8.1.1). Such exposure scenarios are usually not covered by the domains of conventional exposure models so that these models might not be valid for the assessment of polyquaterniums (see Section 5.1 of ECETOC TR No. 133-2 for a detailed discussion of the applicability of conventional environmental exposure models for polymers).

Due to these limitations, the environmental exposure assessment of polyquaterniums is usually based on qualitative assumptions rather than on verifiable quantifications. Such assumptions will consider e.g. that, on account of their sorptive properties, polyquaterniums will rather be present in the sediment and soil than in the water column. ECCC and HC (2020) followed a weight of evidence approach evaluating all available information to derive a conclusion on the environmental exposure assessment for PQ-6. In this regard, ECCC and HC (2020) considered that the desired properties of PQ-6 when used as flocculant are also indicative of its environmental behaviour.

3.8 Case Study 2: CF4Polymers (Step 7) Hazard assessment

3.8.1 Conceptual framework for polymer ecotoxicity assessment

The subsections below have been structured following the tiers of the Conceptual Framework for Polymer Ecotoxicity Assessment described in Section 6.4 of the ECETOC TR No. 133-2.

3.8.1.1 Tier 0: Identification of ecotoxicity testing needs and of relevant environmental compartment(s)

Polyquaterniums are a type of cationic polymer that is typically prioritised for environmental review due to reported effects on aquatic species (Rowland et al., 2000; Cumming, 2008; Cumming et al., 2008). A number of polymer properties need to be considered when preparing aquatic toxicity studies (or any other ecotoxicity study) for the assessment of polyquaterniums. Some of these issues are also relevant for the testing of other types of polymers (for further details; see website of the iTAP project: http://cefic-lri.org/projects/eco-46-improved-aquatic-testing-and-assessment-of-cationic-polymers-itap/).

Generally, polyquaternium polymers cover a broad range of polymer backbone, molecular weights and cationic charge (Cumming, 2008); thus, a review of polymer characteristics is warranted in the review of testing information and evaluation of testing strategies.

Water solubility

Water solubility is a key parameter affecting the ready availability of polymers in aqueous media and hence their aquatic toxicity potential. The design of an aquatic toxicity study needs to consider whether the polymer of interest is (at least) poorly water soluble, not soluble, or particulate. In this regard, it may be difficult to

precisely determine the water solubility of complex and variable polymer products, so that it may rather be denoted as range of water solubilities of its different constituents. Generally, PQ-6 and PQ-10 are water soluble (Section 3.3.1.6). Nonetheless, they might not be distributed homogeneously in aqueous media on account of their propensity to sorb to particles.

Modes-of-action of aquatic toxicity and mitigation of toxicity

The modes-of-action by which polyquaterniums elicit aquatic toxicity, while not yet being fully understood, are not related to systemic narcotic effects (see Veith and Broderius (1990) for review of narcotic modes-of-action of aquatic toxicity). Cationic polymers sorb to surfaces and strongly to anionic surfaces, thus their mechanism of aquatic toxicity is assumed to be via sorption e.g. to fish gills, daphnids, and algal cells. There, cationic polymers have the potential to elicit physical hazards e.g. by preventing oxygen exchange on the gills, causing physical entrapment (Muir et al., 1997). Physical effects have also been described for an acrylamide-acrylic acid copolymer (Liber et al., 2005).

Polycationic and amphoteric polymers may exhibit artificially high toxicity in standard aquatic hazard testing media (e.g. as described in the OECD TGs) that usually have a low total organic content than surfaces waters (US EPA, 2013).

More recently, Salinas et al. (2020) showed that the acute toxicity of cationic polymers (with different molecular weights and charge densities) to *Daphnia magna* and *Raphidocelis subcapitata* (*Pseudokirchneriella subcapitata*) varied by more than 10-fold in response to slight changes in total organic content and water hardness, although both parameters were maintained within OECD TG limits. Salinas et al. recommended that the laboratory water should be standardised at the lowest biologically tolerable hardness and total organic carbon at a reliably measurable level (> 1 to < 2 mg/L) to reduce variability and increase the reliability of the determination of the baseline aquatic toxicity of cationic polymers (Salinas et al., 2020).

The modes-of-action of polyquaternium aquatic toxicity and opportunities to reflect these in aquatic toxicity test methods (including possibly necessary test method adaptations to allow investigating physical hazards) are being addressed by the ongoing Cefic LRI project iTAP (Section 3.1.1).

Quantitative structure activity relationship (QSAR) modelling - molecular weight and charge density

As relevant, the identification of ecotoxicity testing needs should preferably include the performance of QSAR modelling. The US EPA developed a structure activity relationship for cationic polymers supporting the prediction of acute effects to aquatic species. To account for higher total organic content and DOC in surface water than in testing media, a mitigation factor is calculated on the basis of overall charge density, calculated as percent amine nitrogen (%A-N), for the polymer (US EPA, 2013).

Sanderson et al. (2020) have suggested models that predict the molecular weight and charge density of cationic polymers as useful for estimating their aquatic toxicity potential. In this regard, novel fragment-based two- and three-dimensional hologram QSARs may prove relevant in determining these properties and may then be used to derive hypotheses about toxic mechanisms and to guide experimental test designs (Sanderson et al., 2020, 2021). It is especially the HMW cationic polymers that are expected to exert surface effects on aquatic species. Nonetheless, it has not yet been possible to establish a molecular weight limit for toxicity as some of the cationic polymers with molecular weight above 1 million Da have been reported to exert toxicity to aquatic organisms (Sanderson et al., 2021). It is expected that the ongoing Cefic LRI project iTAP (Section 3.1.1) will provide further insight on whether molecular weight is a relevant driver for aquatic effects of (different types of) polyquaterniums.

3.8.1.2 Tier 1: Screening for acute ecotoxicological effects

Appendix Table CS2-A.1 provides a general overview of publicly available ecotoxicity data for polyquaternium-1, -6, -10, -11, -15, -28, -32, -33, -42 and -55. All these data relate to aquatic toxicity studies. The ECETOC Polymers TF is unaware of ecotoxicological assessments of cationic polymers using sediment-dwelling organisms or terrestrial organisms.

Tables CS2.2 and CS2.1 summarise aquatic toxicity data that are publicly available for PQ-6 and PQ-10 products, respectively. For PQ-6, the acute aquatic toxicity studies using invertebrates (*Daphnia* and *Ceriodaphnia*) and fish generally yielded EC_{50}/LC_{50} values below 1 mg/L. Aquatic toxicity studies on PQ-10 were performed on the polymer product; however, the additive glyoxal (Section 3.3.2) is not expected to contribute to the identified hazard on the basis of its low aquatic toxicity[5] and presence at low levels. Acute toxicity to fish was observed in the range of 1-10 mg/L; the few available data on acute aquatic toxicity on algae indicate more pronounced effects (≤ 1 mg/L) but no aquatic toxicity for effects on daphnids or fish. Generally, charge density has been observed to affect the acute ecotoxicity potential of PQ-10s (Cumming et al., 2011a), with lower EC/LC_X observed for the PQ-10s with higher charge density.

3.8.1.3 Higher-tier follow-up of ecotoxicological screening

Similar to the classification for acute aquatic toxicity, the few chronic aquatic toxicity studies that are available for PQ-6 indicate effects on invertebrates at NOEC or $EC_x \leq 0.1$ mg/L and chronic effects (NOEC) on fish in the range of 0.1 to 1 mg/L. The ECETOC Polymers TF is unaware of chronic aquatic toxicity studies for PQ-10.

3.8.2 Human health hazard assessments

Polyquaternium-6: In unpublished human health toxicity studies, PQ-6 was not found to elicit acute oral or inhalation toxicity in rats, or acute dermal toxicity in rabbits. Also, it was not an acute skin irritant in rabbits, and further elicited no or only slight eye irritation in two rabbit eye irritation tests. In a human repeated insult patch test, PQ-6 was not a skin sensitiser or skin irritant, and it further was not photoallergic in humans. In a 28-day repeated dose toxicity feeding study using rabbits, reduced body weight gain, increased water consumption, and decreased diet efficiency were recorded in the high-dose group (10,000 ppm) so that a no effect level of 3,300 ppm (corresponding to 280 mg/kg/day) was set. In a 90-day repeated dose dermal toxicity study using rabbits, the only effects observed were slight skin irritation whereas there was no evidence for systemic toxicity (Table CS2.3).

[5] As summarised on the ECHA dissemination portal (https://echa.europa.eu/registration-dossier/-/registered-dossier/16112), glyoxal (CAS No. 107-22-2), has no classification for aquatic toxicity.

Table CS2.3: Human health toxicity data on polyquaternium-6 (molecular weight range: 15,000-150,000 Da; Task Force member company data; used with permission)

Endpoint	Route	Species	Doses	Dilution	Results	Conclusion
Acute toxicity	Oral	Albino rat	2.15, 3.16, 4.46, 6.81, 10.0, 14.7 g/kg bw	Not reported	LD_{50} = 8.71 g/kg	No acute oral toxicity
	Dermal	Rabbit	2.15, 4.64, 10.0, 21.5 g/kg bw	8%	LD_{50} > 21.5 g/kg	No acute dermal toxicity
	Inhalation	Rats	0,2mg/L	Aerosol (vehicle distilled water; 1:1) admin. into animals' breathing zone	All animals: survival at the end of 14 days	No acute inhalation toxicity
Eye irritation	Ocular	Rabbit	0.1 mL	Neat/undiluted	Slightly irritating; slight conjunctival injection and moderate clear colour-less discharge in all 6 eyes at 15 min and 2 h; 2 of 6 eyes: still very slight injection at 24 h but disappeared at 48 h; other 4 eyes: normal at 24 h.	Slightly eye irritant
	Ocular	Rabbit	0.1 mL	Neat/undiluted	No signs of eye irritation	Not eye irritant
Skin irritation	Dermal	Rabbit	0.5 mL	Neat/undiluted	Two abraded test sites: very slight erythema for 5 days when dressings were removed 24 hours after treatment. Other four abraded sites and all intact sites: no irritation at 24 hours or during the two-week observation period.	Not skin irritant
	Dermal	Rabbit	0.5 mL	Neat/undiluted	No signs of skin irritation	Not skin irritant
HRIPT	Dermal	Human	0.1 mL/cm^2	Neat	No irritation and sensitization reported	Not skin irritant Not skin sensitizer
Photoallergy	Dermal	Human	Neat	Not Applicable	No evidence of contact irritation, sensitisation or photoallergy	Non photoallergic
28-day repeated dose study	Oral	Rabbit	40% solution; diet: 0, 330, 1,000, 3,300, 10,000 ppm	40%	m & f: 10,000 ppm: reduced body weight gain, increased water consumption, decreased diet efficiency. The maximum no-effect dosage: 3,300 ppm for m (280 mg/kg bw/day) and f (295 mg/kg bw/day).	NOEL 280 mg/kg/day
90-day repeated dose study	Dermal	Rabbit	40% solution applied topically to 10 m & 10 f; 0.25, 0.75, 2.25 mL/kg bw/day	40%	The intact skin treated with the test substance did not show irritation during the study, the abraded skin showed varying amounts of erythema and oedema observed along the lines of abrasion. No evidence of systemic toxicity was observed in all groups.	Slightly skin irritant

Footnote to Table CS2.3:

Abbreviations: bw: Body weight; Da: Dalton; f: Female; h: Hour(s); HRIPT: Human repeated insult patch test; LD_{50}: Dose required to achieve 50% change in lethality from the control; m: Male; NOEL: No observed effect level.

Polyquaternium-10: The human health toxicity potential of PQ-10 products has been extensively reviewed by Becker et al. (2012). As concluded by Becker et al., PQ-10 has at most only a low potential to penetrate the stratum corneum, but it is adsorbed by keratinous surfaces. PQ-10 does not have acute oral toxicity potential. Similarly, dermal toxicity and skin irritation studies as well as eye irritation studies using mostly rabbits (but also rats) indicated, at most, only a slight skin and eye irritation potential (and only at test concentrations that exceed those used in cosmetic products). In humans, PQ-10 was not a skin irritant. Finally, PQ-10 did not elicit genotoxicity *in vitro* (either with and without metabolic activation) or *in vivo* (Table CS2.4; data adapted from Becker et al. (2012), as well as Task Force company data, used with permission). The low levels of glyoxal that may be present in PQ-10 products are not expected to have contributed to the observed effects[6]. In its opinion on glyoxal, the Scientific Committee on Consumer Products (SCCP) concluded that "*any risk to consumers when glyoxal is present up to 100 ppm in cosmetic products is considered to be negligible*" (SCCP, 2005).

For comparative reasons, available human health toxicity data for further polyquaterniums are briefly summarised below:

The human health toxicity potential of polyquaternium-7, which is a poly(DADMAC) just as PQ-6, has been reviewed by CIR (1995). The only adverse effects were mild skin irritation in humans and minimal skin irritation in rabbits, that were both observed upon application of 8% dilutions, whereas only 0.1-5% of PQ-7 are typically added to personal care products (Appendix Table CS2-A.2; adapted from CIR, 1995).

The human health toxicity potential of polyquaternium-11, a quaternised copolymer of vinylpyrrolidone and di-methylamine ethyl methacrylate, has been reviewed by CIR (1983). The only adverse effect recorded was in a 24-hour single insult skin patch test, where 1 of 19 subjects showed slight skin irritation upon exposure to 9.5% polyquaternium-11 in water, i.e. at a concentration that again exceeds the concentration at which polyquaterniums are used in personal care products (CIR, 1983).

The CIR expert panel also reviewed the human health toxicity data available for different trimoniums, e.g. polyquaternium-28 and polyquaternium-47, which are quaternary ammonium salts wherein three of the four substituents on the nitrogen atoms that comprise the quaternary ammonium moiety are methyl groups (Becker et al., 2012). The CIR Expert Panel noted data gaps for some of the trimoniums, but assessed the overall available data as being sufficient to support a safety assessment for the entire group, considering similar structural activity relationships, functions in cosmetics, and cosmetic product usage. Mild skin or eye irritation was recorded for some trimoniums, but again only at higher concentrations. Therefore, the CIR expert panel concluded that trimoniums were safe in the present practices of use and concentration when formulated to be non-irritating (Becker et al., 2012; see also Appendix Table CS2-A.3 with the data for polyquaternium-28 and polyquaternium-47; adapted from Becker et al., 2012).

[6] As summarised on the ECHA dissemination portal (https://echa.europa.eu/registration-dossier/-/registered-dossier/16112), glyoxal (CAS No. 107-22-2) has no acute toxicity concern when applied orally or dermally but is considered to be harmful if inhaled. In *in vivo* rabbit studies, glyoxal was found to be a skin irritant and to cause serious eye damage. Glyoxal (40%) consistently elicited skin sensitisation in a guinea pig maximization test, in further Buehler studies and in a LLNA. Glyoxal possesses *in vitro* mutagenic/genotoxic potential but is not classified for carcinogenicity or reproductive toxicity based on the available study data. Further, it is pointed out on the ECHA dissemination portal that positive *in vivo* genotoxicity results exist, which are restricted to the pyloric mucosa of the stomach and to the liver and which were induced at high dose levels of glyoxal (50 mg/kg bw).

The SCCP (2005), in its opinion on glyoxal, appears to have considered (widely) the same studies as those summarised on the ECHA dissemination portal.

Table CS2.4: Human health toxicity data for polyquaternium-10 (PQ-10; molecular weight typically > 100,000 Da; data adapted from Becker et al. (2012) as well as Task Force member company data; used with permission)

Species	Doses and exposure	Dilution /dose level	Study results	Reference
Oral toxicity; acute and repeated dose				
Rat	Acute: 16 g/kg bw	Not reported	LD_{50} > 16 g/kg bw: Not toxic	[a]
Rat	Acute: 16, 8, 2 g/kg bw	Not reported	LD_{50} = 13.1 g/kg bw. Gross pathology: stomachs distended 3-4x normal size, filled with chemical, walls paper thing, pylorus white, scattered haemorrhages; intestines distended, chemical filled, sections slightly yellow and pink; lungs, kidneys, adrenals changed	[b]
Rat (Sprague Dawley)	90-day: 0%, 0.45%, 1.8%, 4.5% (3.5% after 15 days)		Time-weighted average intake: m: 0, 326, 1292, 2735; f: 0, 358, 1427, 3066 (mg/kg bw/day) NOAEL (m & f): 1.8% (m: 1292 & f: 1427 mg/kg bw/day) - based upon equivocal changes in few clinical chemistry and urinalysis parameters	[b]
Dermal toxicity; acute and repeated dose				
Rat	2g/kg bw	0.5%	LD_{50} > 2 g/kg bw: Not toxic	[b]
Rabbit	4 g/kg bw	Not reported	LD_{50} > 4.0 g/kg bw; material weighted onto Vinylite wrap and moistened with water: Slightly toxic	[b]
	4 g/kg bw	Not reported	LD_{50} > 4.0 g/kg bw of material moistened with water	[b]
	21-day: 1%	1%	Non-toxic	[a]
Eye irritation				
Rabbit	Single application of different PQ-10 grades	Application of approx. 100 mg powder into one eye / animal; and instillation of 0.5 mL of 2%, or 5%, or 10% suspension in H_2O into the other eye of the respective animals	Not eye irritant	[b]

Species	Doses and exposure	Dilution /dose level	Study results	Reference
Skin irritation				
Rabbit	Single application	10 µL of 2% in H_2O	Not skin irritant (only slight effects observed)	[a]
		10 µL of 5% or 10% in H_2O	Not skin irritant	[a]
Human	21 days	5% dilution in H_2O	Not skin irritant	[a]
Genotoxicity and mutagenicity				
S. typhi-murium	10-2000 mg/plate; with and without liver S9 metabolic activation		No mutagenicity; with or without metabolic activation	[a]
CHO Cells	2.0-2.8 mg/mL; with and without liver S9 metabolic activation		No chromosome aberration; with or without metabolic activation	[a]
Swiss albino mice	0.125-0.4 g/kg bw (intraperitoneal application)		Negative in *in vivo* micronucleus assay: did not induce increase in bone marrow polychromatic erythrocytes	[a]

Footnote to Table CS2.4:

Abbreviations: bw: Body weight; CHO: Chinese Hamster Ovary; Da: Dalton; f: Female; LD_{50}: Dose required to achieve 50% change in lethality from the control; m: Male; NOAEL: No observed adverse effect level; PQ: Polyquaternium.

References: [a] Becker et al. (2012) – also referring to unpublished company data; [b] Task Force member company data, used with permission.

Finally, the CIR expert panel reviewed the human health toxicity data available for polyquaternium-22 (a copolymer of acrylic acid and dimethyldiallyl ammonium chloride) and polyquaternium-39 (a copolymer of the two aforementioned monomers and acrylamide) (Johnson et al., 2016). The overall evidence indicated no signs of systemic or local toxicity (Appendix Table CS2-A.4; adapted from Johnson et al., 2016).

3.9 Case Study 2: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for any specific cationic polymer. Instead, it has served to evaluate if the CF4Polymers is generally applicable to cationic polymers (taking the examples of PQ-6 and PQ-10) and if the collated information provides further insight on the applicability of tools, test methods and models for the physico-chemical characterisation and toxicity / ecotoxicity testing of these polymers. Generally, the case study has confirmed the usefulness of the CF4Polymers (ECETOC TR No. 133-1): The CF4Polymers is sufficiently flexible to account for specific testing and/or modelling needs that are determined by the type of polymer.

Overall, the case study has also illustrated complexities involved in the hazard and risk assessment of cationic polymers (and many other polymers). Any hazard and risk assessment of a polymer needs to be preceded by a fit-for-purpose identification of the given polymer. In this regard, CAS numbers are generally not sufficiently precise, since one single CAS number can include different polymers (Section 2.3.1.1). Further, many of the conventional analytical tools and test methods to assess physico-chemical properties are not readily applicable for polyquaterniums, which are complex polymer products covering a (more or less) broad molecular weight range. While the ECETOC Polymers TF is unaware of any suitable methodology to measure the n-octanol/water partition coefficient of cationic polymers, the TF also maintains the view that this parameter is not relevant for fit-for-purpose identification, or hazard and risk assessment of these polymers. By contrast, charge density is a relevant parameter – and key property for cationic polymers, but also here the available methods have shortcomings with respect to precision of the measurement.

Once the fit-for-purpose characterisation of the polymer has been completed and fate, ecotoxicity and/or human health toxicity testing needs have been identified, it needs to be decided if and how the test method may need to be adapted to account for specificities of the (cationic) polymer. It needs to be ensured that the test result is not merely a function of a poorly designed test that does not take into account the special features of these materials. For example, the design of aquatic toxicity tests to investigate cationic polymers needs to consider the total organic content and water hardness of the laboratory water used for the testing. According to the state-of-the-science, polyquaterniums are unlikely to be present in the water column (since they tend to sorb to particles) but will rather be present in the sewage sludge, sediment and sludge-treated soil; further, the biodegradability of many polyquaterniums is low, but they are unlikely to bioaccumulate. Knowledge gaps prevail for how to apply fate and exposure models for these materials.

Opportunities to group and/or sub-group cationic polymers to streamline ecotoxicity and toxicity testing are currently limited by prevailing knowledge gaps. Cationic polymers have different backbones, charge densities, molecular weights, additives, portions of monomers residuals, etc., all sometimes within the same CAS number or CAS name. Since there are so many cationic polymers with vastly different properties, it is difficult to assign them to specific (sub-)groups. There are currently uncertainties about the key polymer characteristics supporting a group amongst the many different cationic polymers. As regards ecotoxicological

endpoints, the publicly available data are sparse for many polyquaterniums, which further impairs their (sub-)grouping in deciding which properties to use for the grouping. However, polyquaterniums generally show aquatic toxicity potential, which is assumed to be caused by physical effects. As regards human health toxicity endpoints, the data available for a broad spectrum of chemically diverse polyquaterniums consistently indicate that their systemic bioavailability is likely to be low on account of their HMW and that they thus do not exhibit systemic toxicity potential. By contrast, some polyquaterniums exhibited potential for mild local irritation, which however was mostly recorded at concentrations exceeding realistic human exposures.

The case study did reveal some evidence to support grouping to streamline registration / notification needs for different types of the same (or similar) polyquaterniums. For example, with respect to ecological endpoints, there is some indication that the K_d of different variants of PQ-10 increases with increasing charge density and that PQ-10 with high charge vs low charge exhibit different aquatic toxicity potential.

Further investigations are recommended to explore how the charge density of different types of polyquaterniums may be correlated with environmental fate, ecotoxicological and toxicological endpoints. This may serve to develop fate models and /or reveal opportunities to group polyquaterniums – also across different chemistries.

4. CASE STUDY 3: POLYOLEFINS

4.1 Introduction

4.1.1 Scope of Case Study 3

Polyolefins are polyethylene and polypropylene thermoplastics that are mainly produced from oil and natural gas. They have widespread and diverse use in a broad variety of consumer products and medicinal products (Section 4.1.2). Focus of this case study is on the use of polypropylene in food contact materials (FCMs) (Box 4), and specifically in olive oil bottles, i.e. an FCM for fatty food. Further, this case study refers to different polyethylenes and considers the use of polyolefins in medical devices (Box 4).

It is important to note that this case study is different from the other case studies in this report in that it does not only refer to scientific evidence of relevance to fill in the eight steps of the CF4Polymers for polyolefins, but also considers the current EU and US legislation that applies to plastic FCMs and medical devices, respectively. This is because FCMs and medical devices uses are regulated by specific and highly demanding end-use legislation rather than only driven by general product safety considerations. Therefore, this case study is not limited to the application of the CF4Polymers to polyolefins, but also compares the CF4Polymers approach to the more formalised assessment approaches as implemented in the applicable legislation and associated guidance (Section 4.1.4).

The polyolefins considered in this case study are HMW polymeric substances that fulfil the criteria for ‘polymers of low concern’ or ‘reduced regulatory requirements polymers’ in different jurisdictions in which legislation for the notification / registration of polymers is in force, including USA, Canada, and Australia (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021). Some other, more flexible grades of polyolefins are of lower molecular weight but are not the focus of this case study.

Polyolefins generally include low levels of intentionally added substances (IAS, i.e. additives) and non-intentionally added substances (NIAS) (Section 4.1.3). Nevertheless, due to the sensitive use, the CF4Polymers (Step 3) polymer component strategy is one focus of this case study. The case study shall show how the LMW compounds of polypropylene should be considered during polymer hazard and risk assessment in compliance with the applicable legislation – and/or following the steps of the CF4Polymers. This case study includes a detailed presentation of CF4Polymers (Step 5) determination of exposure scenarios and (Step 6) exposure characterisation to describe how the potential of LMW compounds to migrate from the polymer matrix can be determined during exposure assessment, and then followed up during (Step 7) hazard assessment and (Step 8) risk characterisation. Since use of polyolefins in FCMs or medical devices are intended uses of high relevance for consumers, this case study addresses those components of the CF4Polymers that are related to human health hazard and risk assessment. Environmental exposure, hazard and risk assessment are out of scope.

The type of food and the type of FCM (e.g. presence of further types of polymers) may affect the spectrum of expected migrants from the intended product use. The intended use of polypropylene in olive oil bottles reflects a potential ‘worst-case scenario’ since the migration of hydrophobic LMW compounds from the polymer matrix may be enhanced in the presence of the fatty food.

Box 4: Intended use of polyolefins: Food contact materials and medical devices

Food contact materials include (1) food packaging; and (2) food contact articles, e.g. kitchenware and food production equipment. Food contact materials may consist entirely or partially of polyolefins (or other polymers). Similarly, different types of **packaging of cosmetics and pharmaceutical substances** may contain polymers. The applications of polymers in packaging include traditional polymeric packaging, but also (e.g. for food) polymeric biodegradable packaging, polymeric active packaging, polymeric coatings in metal-can food packaging and seals and closures for glass and ceramic containers.

Medical device is an umbrella term for any apparatus, appliance, software, material, or other article with intended use to support human health and welfare with no or subordinate pharmaceutical function (e.g. diagnosis, prevention, monitoring of diseases) (International Standardisation Organisation (ISO) 10993-1)[7]. There are over 500,000 types of medical devices and *in vitro* diagnostic medical devices on the EU market. Some medical devices are entirely or partially made of polymers. Examples of medical devices are contact lenses, x-ray machines, pacemakers, breast implants, hip replacements, and sticking plasters. *In vitro* diagnostic medical devices, which are used to assess biological samples, include human immunodeficiency virus blood tests, pregnancy tests, and blood sugar monitoring systems for diabetics (http://ec.europa.eu/growth/content/new-eu-rules-medical-devices-enhance-patient-safety-and-modernise-public-health-0_en). Thus, human exposure to medical devices ranges from indirect contact (diagnostics) to very intimate direct contact (e.g. implants) and from short-term exposures to long-term exposures.

4.1.2 Overview of polyolefins and their major applications

Polyolefins are broadly grouped into four major families, which are determined by the monomer used for their production (ethylene versus propylene) and the density of the final polymer as key physical property. The density of the final polyolefin is primarily dependent on the selected process of polymerisation (Sharpe, 2015; https://www.plasticseurope.org/en/about-plastics/what-are-plastics/large-family/polyolefins).

Low-density polyethylene (LD-PE): LD-PE is a highly branched polyethylene. Because of this high ramification, LD-PE has low density (approx. 910-940 kg/m^3) as well as lower hardness, stiffness and strength than HD-PE, but higher ductility (Bayer et al., 2017). LD-PE is reasonably flexible and tough and can withstand temperatures of 80 °C continuously and 95 °C for short periods. LD-PE is typically used for cling film, carrier bags, agricultural film, milk carton coating, electrical cable coating, and heavy-duty industrial bags.

Linear low-density polyethylene (LLD-PE): LLD-PE is a substantially linear polyethylene, with significant numbers of short branches, commonly made by copolymerisation of ethylene with longer-chain olefins. LLD-PE has similar density as LD-PE (900-930 kg/m^3), but higher tensile strength and higher impact and puncture resistance. LLD-PE is very flexible and elongates under stress. It can be used to make thinner films and is unaffected by common solvents. However, LLD-PE is not as easy to process as LD-PE. Main applications of LLD-PE are stretch film, industrial packaging film, thin-walled containers, as well as medium and small heavy-duty bags.

High-density polyethylene (HD-PE): Although the density of HD-PE (940-970 kg/m^3) is only marginally higher than that of LD-PE, it has little branching, giving it stronger intermolecular forces and tensile strength than LD-

[7] Since standards are periodically subject to revision as necessitated by emerging knowledge, the reader is referred to https://www.iso.org/standards.html as reference to all ISO standards included in this report to ensure the consideration of the most recent version of the respective document.

PE has. It is also harder and can withstand slightly higher temperatures (120 °C for short periods). It is used in crates and boxes, bottles (for food products, detergent, cosmetics), food containers, toys, petrol tanks, industrial wrapping and film, pipes, and houseware.

Polypropylene: Polypropylene is generally linear, and it is the polyolefin with the lowest density (890-910 kg/m^3). Compared to polyethylene, it has superior mechanical strength and thermal resistance, but less chemical resistance. Polypropylene is normally tough and flexible, especially when ethylene is incorporated as co-monomer (in block or randomly) into the polypropylene chain. Polypropylenes are used in food packaging including fatty food (e.g., oil bottles, yoghurt and margarine pots, wrappers for sweets and snacks), microwave-proof containers, but also in many more applications, for example carpet fibres, garden furniture, medical packaging and devices, luggage, appliances, and pipes.

Polypropylene is the most important polyolefin and represents about 20% of the plastics market (PlasticsEurope, 2020). Since polypropylene is tough and flexible, especially when copolymerised with ethylene, it can be used as an engineering plastic. The properties of polypropylene depend on its molecular weight, molecular weight distribution, crystallinity, and the type and proportion of co-monomer, if used. The properties of polypropylene are also dependent on its tacticity. Polypropylene is isotactic when all methyl groups are oriented on one side of the carbon backbone, but it can also be syndiotactic when the methyl groups are on both sides of the chain, or atactic when they are randomly distributed.

4.1.3 LMW components of polyolefins

The polypropylenes considered in this case study are generally of HMW, and they may include low levels of IAS and NIAS. IAS can be intentionally added to the FCM at any step of the supply chain, and they have a specific function. Depending on the type of polymer and type of application, the IAS that polypropylenes may contain include antioxidants, antistatic agents, lubricants, processing aids and nucleating agents. Antioxidants are required during preparation to prevent degradation. Further, polypropylenes in particular tend to be too ‘sticky’ to be machinable. Therefore, lubricants, slip agents and antiblocking agents are added to facilitate their further processing. These additives intentionally migrate to the surface of the polymer product thereby reducing its ‘stickiness’. Other additives (e.g. stabilisers) stay inside the polymer product where they serve to maintain specific product properties (e.g. stability). Some polyethylenes also need additives, depending on specific physico-chemical properties (e.g. melting point) and intended use, as well as transition down the value chain. As a rule, additives will only be present in the polyolefin polymer product at small quantities (with the possible exception of fillers that might be present in higher volumes).

NIAS are impurities or reaction intermediates formed during the production process, or decomposition or reaction products (Article 3(9) of the Plastics Regulation (European Commission, 2011); see also European Commission (2013a); Section 4.1.4). Sometimes, the same substance can be considered as IAS or NIAS. For example, when oligomers are used as prepolymers, they are considered IAS. However, when they are not intentionally added but are part of the manufactured polymer (a sub-product of polymerisation), they should be considered NIAS.

While the polypropylene matrix is considered as inert, the embedded IAS and NIAS can potentially migrate from the FCM during the use phase. Therefore, it must be ensured that they do not pose a human health or environmental concern.

4.1.4 Legal provisions implemented for the LMW components of polyolefins when used in food contact materials, other packaging or medical devices

The major EU legislation that is applicable to polyolefins when used in FCMs is:

- *Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food* (FCM Regulation; EP and Council, 2004b)
- *Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food* (Plastics Regulation; European Commission, 2011)

The European Food Safety Authority (EFSA) is the authority implementing the FCM legislation, and it issues the associated guidance. In the EU, only additives that have been assessed by the EFSA and that are included in the Union list of authorised substances in Annex I of the Plastics Regulation, and its amendments, may be used in FCMs. Since additives are generally chemical substances, any new additive also needs to fulfil the provisions of the respective applicable chemical legislation. In the EU, this is the REACH Regulation (EP and Council, 2006).

The Union list of authorised substances (also called Positive List) includes monomers (or other starting substances), additives (excluding colorants), polymer production aids (excluding solvents), and macromolecules obtained from microbial fermentation. Substances that are included in the Positive List are authorised to be used in the manufacture of plastics. Notably, the list does not include solvents, colorants or polymerisation aids (e.g. catalysts, initiators, transfer agents), for which reason such IAS are also called 'non-listed substances' (NLS).

Since NLS, but also NIAS, are not included in the Positive List, the manufacturer must perform a risk assessment based on internationally recognised principles (as per Article 19 of the Plastics Regulation (European Commission, 2011)). Therefore, NIAS, and specifically the oligomers that may migrate from the polypropylene matrix, are in the focus of this case study.

Finally, all components of a plastic have to comply with the general safety requirements set out in Article 3 of the overarching FCM Regulation (EP and Council, 2004b).

Appendix CS3-A.1 presents and discusses further details of the EU and US legislation for FCMs, and additionally refers to the corresponding legal requirements for packaging of cosmetics and pharmaceuticals. Also, Appendix CS3-A.1 lists guidance published by different industry associations to support industry in performing the risk assessment of IAS (and specifically NLS that also have not been authorised under another legislation) and NIAS in line with the FCM Regulation (EP and Council, 2004b) and the Plastics Regulation (European Commission, 2011). The approaches for the risk assessment of NLS and/or NIAS described in these guidance documents are widely concordant. Important aspects of these risk assessment approaches for IAS, NLS, and NIAS are considered below in CF4Polymers Steps 5-8 (Sections 4.6-4.9).

To complement the overview of legislation that is applicable to FCMs and other packaging, Appendix CS3-A.2 summarises the EU legislation and ISO standards of relevance for the risk assessment of medical devices. Notably, the CF4Polymers as presented in ECETOC TR No. 133-1 was not developed with medicinal applications in mind (e.g. intravenous, subcutaneous routes of application, implantation of medical devices) and thus might not be applicable for all cases of medicinal applications (ECETOC, 2019). In general, FCM-approved materials will be used in medical devices (so that the risk assessment performed for the FCM can be considered for the evaluation of medical devices), but there may be exceptions. Also, a polypropylene that is

used both in FCM and in medical devices may have toxicity data for the medical device that go beyond those collated for the assessment of the FCM.

4.2 Case Study 3: CF4Polymers (Step 1) Problem formulation

This case study passes a (theoretical) polypropylene homopolymer that shall be used in olive oil bottles through the CF4Polymer. It covers human health hazard assessment, addressing the safety protection of the individual (i.e. the consumer). The entire polymer product is considered, i.e. the polymeric substance, IAS (additives), and NIAS. Manufacturing, compounding, end of life and environmental aspects are out of scope of this illustrative case study.

Since additives may only be used in FCM if their use has been approved (Section 4.1.4), the additives present in the polypropylene will already have undergone comprehensive hazard and risk assessment in the context of the applicable FCM legislation. For this reason, the following sections will only consider the polypropylene polymer and all further LMW compounds that may potentially migrate from the polymer matrix. These will be considered since humans might be exposed to these substances when consuming food that was packaged in FCM containing the polypropylene. Such LMW compounds that are not additives mainly include oligomers, but to a lesser extent also catalyst residues, and antioxidant degradation products.

Notably, even if the polypropylene were not a FCM grade material, any hitherto unassessed additives would be identified in CF4Polymers (Step 3) polymer component strategy and then submitted to (Step 7) hazard assessment.

4.3 Case Study 3: CF4Polymers (Step 2) Polymer identification

4.3.1 Step 2.1: Identification of the polymeric substance

Polypropylene homopolymers have the chemical formula $(C_3H_6)_n$ and the CAS No. 9003-07-0. They are comprised of linked propylene monomers and do not contain substituted monomer units unless < 2%.

Table CS3.1 provides an overview of the physico-chemical properties of (a theoretical) polypropylene as well as of its catalysation and transformation processes. For comparison, this same information is also provided for (theoretical) LD-PE, LLD-PE, and HD-PE. The polypropylene homopolymer has a linear structure, its molecular weight is > 10,000 Da, and its density 890-910 kg/m^3.

The melting temperature of the polypropylene homopolymers is 140-165 °C. Hence, it is a solid at room temperature. Generally, polypropylene is produced in pelleted form for transportation to downstream users, where it can be moulded or extruded into any number of different shapes. Bottles can be made via blow moulding and films produced through blown film extrusion. As such, the polypropylene homopolymer is also not water soluble, it does not dissociate, and it is not charged: Cationicity and surface tension are not relevant for this polypropylene (or other polyolefins). Also, the polypropylene (just as all other polyolefins) does not have any reactive functional groups or critical chemical elements in it (i.e. heavy metals or fluorine).

Table CS3.1: Polymerisation and physico-chemical characterisation of four exemplary polyolefins

Polyolefin	Monomer	Copolymer	Branching	Catalytic system [a]	Transformation process [b]	Type of additives	Level of IAS [c]	Molecular weight	Density	Melting temperature [e]	Melt flow index [d]	Tacticity
							[ppm]	[g/mol]	[kg/m^3]	[°C]	[g/10 min]	
Low-density polyethylene	Ethylene	Homo-polymer	Long chain branching	Metallocene, Ziegler Natta, Phillips	Blown film (milk bottle coating, carrier bags, cling film); injection moulding (housewares, toys, containers caps); pipe extrusion	None	0	> 10^4	910-940	110-120	0.25-8	Not relevant for polyethylenes
Linear low-density polyethylene	Ethylene	Butane/ hexene/ octene	Short chain branching		Injection moulding (household lids, thin wall containers); blown films	Antioxidant, processing aid, antiblocking agent	2000-5000	> 10^4	900-930	100-118	1-30	
High-density polyethylene	Ethylene	Hexene or butane	Limited / no branching	Metallocene, Ziegler Natta, Phillips	Injection /blow moulding (containers, bottles); blown film (packaging); optional: pasteurisation or sterilisation		< 2000	> 10^4	940-970	129-133	0.7-5	
Polypropylene	Propylene	Here: homo-polymer [f]	Linear	Ziegler Natta, Metallocene	Cast film, injection moulding (containers, film)	Antioxidant, acid scavenger, antiblocking agent, nucleating agent	3000-6000	> 10^4	890-910	140 -165	8-70	Isotactic / syndio-tactic, atactic

Footnote to Table CS3.1:

This table does not cover the full range of polyolefins, but rather provides a representative overview of the major polyolefins used in food contact materials; data adapted from PlasticsEurope oligomer study (PlasticsEurope, 2016). All of these polyolefins include oligomers. By contrast, polyolefins do not include reactive functional groups, nor heavy metals or fluorine. Also, cationicity and surface tension are not relevant properties for polyolefins.

[a] Catalytic system as used for the production of the polymers (and that will determine the structure of the polymer).

[b] Transformation relates to the further processing of the polymer product.

[c] Intentionally added substances (IAS); as added to polymer during production.

Footnote continued on next page: bullets [d], [e], [f]

Footnote to Table CS3.1 continued:

[d] The melt flow index is a key characteristic directly related to the ability for a polymer to flow. It corresponds to the time required for 10 grams of a molten plastic to flow through a die of a specific diameter and length under a pressure applied by a defined weight and at a given temperature. The conditions used depend on the type of polymer, the molecular weight range and the molecular structure (e.g., branched or non-branched). The melt flow index of a specific grade is usually reported on the technical data sheet. The methods and conditions are described in the International Standard Organisation (ISO) 1133 and the American Society for Testing and Materials (ASTM) Standard D1238.

[e] Differential scanning calorimetry peak.

[f] Polypropylene copolymers may contain butene or ethylene.

The polypropylene selected for this case study is isotactic with an isotactic index between 85% and 95% (data not shown). While tacticity is a relevant descriptor for polyolefins, this property rather addresses technical aspects (e.g. stickiness impeding machinability), but not human health issues. Similarly, glass transition temperature and density (Table CS3.1) are relevant from a technical point of view, but only have an indirect impact on human health hazard assessment (e.g. by posing technical difficulties during *in vitro* testing). Also, the viscosity / melt-flow index (Table CS3.1) is used to differentiate different types of process and application but is of limited relevance from a safety point of view (while it might have some effect on migration potential and limit of use).

Taken together, the polymeric substance (polypropylene) is inert and does not become systemically bioavailable even upon ingestion since it is HMW (> 10,000 Da). Therefore, polypropylene (just as other polyolefins) typically fulfils the criteria for ‘polymers of low concern’ or ‘reduced regulatory requirements polymers’ (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021).

4.3.2 Step 2.2: Identification of additives

The polypropylene for use in olive oil bottles contains antioxidants, acid scavengers, and antiblocking agents. Further, it includes catalyst residuals as NLS. The fraction of all of these IAS in the polypropylene can be determined, typically 3,000-6,000 ppm (Table CS3.1), since they have been ‘intentionally added’. Also, when oligomers present in the final polymer product have been used as prepolymers, they are considered IAS.

Generally, all IAS are only present in the polypropylene polymer product at very low levels.

4.3.3 Step 2.3: Identification of NIAS

The polypropylene includes propylene monomers, incomplete products of polymerisation (oligomers), and breakdown products of IAS (e.g. oxidised antioxidants, which, however, are not considered in this case study (Section 4.4.)). In contrast to the known fraction of the IAS (Section 4.3.2), the exact fraction of these NIAS is not fully known prior to the risk assessment. Its determination is addressed in CF4Polymers (Step 6) exposure characterisation (Section 4.7).

Generally, also any NIAS are only present in the polypropylene polymer product at very low levels.

4.4 Case Study 3: CF4Polymers (Step 3) Polymer component strategy

This case study considers the polymeric substance (polypropylene), the IAS and the NIAS (including oligomers).

4.5 Case Study 3: CF4Polymers (Step 4) Grouping approach evaluation

While this case study is not looking into justifying the basis for grouping, such a grouping approach could be considered based upon the type of polyolefin polymeric substance. There could also be subgrouping based on the use of co-monomers which may be useful from a regulatory standpoint. There is also the possibility that, instead of splitting into subgroups, there could be merging of polymers into one large polyolefin approach. Examples are that other polyolefins might be sufficiently similar for grouping such as ethylene propylene copolymers, or even ethylene polymers. The grouping would be accomplished based on the polymers' physico-chemical properties, which would show that all group members are equally inert and that they are comprised of similar hydrocarbon chemistry. However, for the assessment of specific applications such as FCMs, it would have to be considered that low density vs high density polymers could have different rates of migration of NIAS.

Subgrouping of polyolefins by e.g. branching, stereometric structure does not appear relevant for human safety assessment because these properties are generally not drivers of human health toxicity.

Notably, Section 4.8 (CF4Polymers (Step 7) hazard assessment) refers to opportunities to group the identified *oligomers* (that may migrate from the polymer product) into categories (OECD, 2014; ECHA, 2008, 2013, 2017c) based on their chemical class (olefins, aldehydes, ketones, etc.) for subsequent read-across.

4.6 Case Study 3: CF4Polymers (Step 5) Determination of exposure scenarios

The consumer safety assessment of polypropylene in food contact applications considers uses by the general population with a focus on oral exposure. Depending on their composition, properties and use, packaging materials (i.e. FCM) can transfer constituents to the packed products (i.e. food; here: olive oil). Therefore, the further steps of this case study focus on the oligomers and their potential to migrate from the olive oil bottle. Evidently, in practice, the consumer safety of all components of the FCM is assessed (Section 4.1.4).

This case study considers the conservative assumption of 100% migration and exposure to the oligomers. However, in the presence of application-specific migration data, this conservative approach should be further refined.

4.7 Case Study 3: CF4Polymers (Step 6) Exposure characterisation

The CF4Polymers (Step 6) exposure characterisation begins by identifying the spectrum of potentially relevant oligomers present in the polypropylene. Generally, this spectrum is not well-known. Therefore, it is advisable

to first collect information on those substances that are used for the manufacture of the polypropylene, including the conditions of processing and use. This information can help predict which types of oligomers (and other NIAS) are likely present in the polypropylene and might migrate therefrom, for selection of appropriate analytical methods.

4.7.1 Assessment of release (migration) of oligomers from polymer matrix

The spectrum of oligomers present in a polymer product can be characterised by different methods that all follow the same basic principles, i.e. (1) extraction of the oligomers and (2) identification of the oligomers. The oligomers can be extracted, e.g. using dichloromethane; alternatively, they can be obtained by performing migration studies in ethanol. Analytical methodologies employed for the identification of oligomers include e.g. purge and trap gas chromatography, head space gas chromatography, followed by flame ionisation detection and mass spectroscopy, and/or two-dimensional gas chromatography (see e.g. PlasticsEurope, 2016; Sanchis et al., 2017; Testoni and Mingozzi, 2019). These methodologies are suitable for the identification of oligomers with a molecular weight up to 1,000 Da (a threshold to roughly distinguish oligomers from polymers (OECD, 2009)). Nonetheless, it can be very time consuming and elaborate to qualify and quantify) the most important peaks from amongst the abundance of peaks that may be recorded during chromatographical analysis.

The oligomers that may be present in the selected polypropylene homopolymer include linear and branched alkanes and alkenes (PlasticsEurope, 2016).

Once the spectrum of relevant oligomers has been characterised, their migration level from the polypropylene can be derived from (1) worst-case calculations (modelling assuming 100% migration); (2) migration calculation models (diffusion models); or (3) migration studies using food simulants (experimental data); or (4) migration studies using actual food (rarely done due to analytical challenges due to the food matrix). The worst-case '100% migration' calculation does not consider that the migration rate of a substance is a function of its physico-chemical properties, the intrinsic characteristics of the plastic and the food, and/or the duration and conditions of the contact (e.g. temperature of the food). By contrast, migration studies serve to determine both the spectrum of migrants and their migration levels from plastics into food under typical conditions of use.

In a research project on the determination of the migration of oligomers from polyolefins commissioned by PlasticsEurope, migration tests were carried out using standard conditions, both 10% and 95% ethanol for 10 days at 40 °C and 60 °C. Based on the determined concentration levels of extractable oligomers in the plastics, the migration levels into food were estimated through migration modelling for the scenarios 10 days at 25 °C, 40 °C and 60 °C with the partitioning coefficients reflecting use of 10% and 95% ethanol, respectively. The results from the migration modelling were then compared to the findings from the migration tests. These showed an overall good agreement confirming the validity of the modelling approach (PlasticsEurope, 2016).

Exposure modelling is most extensively used for the evaluation of FCMs, where a well-articulated framework for the safety assessment of additives has been adopted. For other end use regulations, different frameworks and approaches have been developed. For example, biocompatibility testing takes precedence for the safety assessment of medical devices (Appendix CS3-A.2). Also, different approaches are taken in different jurisdictions for exposure modelling related to FCMs. Within the EU, migration testing into real food and food simulants is combined with a theoretical concept of a 'Euro-cube paradigm' (Section 4.7.2) to achieve a simplistic, conservative estimate of consumer exposure.

In this context, the Plastics Regulation (European Commission, 2011) has laid down specific migration limits (SMLs) for specific authorised substances (i.e. IAS), which are included in the Positive List (Section 4.1.4). A SML is "*the maximum permitted amount of a given substance released from a material or article into food or food simulants*" (Article 3(13) of the Plastics Regulation). If a SML is not specified and no other restrictions apply for the particular substance, a generic SML of 60 mg/kg food is applied (Article 11(2) of the Plastics Regulation). These migration levels are a function of consumer exposure to the respective material. All components of the polypropylene that exceed the SMLs (or generic SMLs) in food or food simulant should be identified for subsequent exposure, hazard and risk assessment. By contrast, if the SML or generic SML is undercut, the corresponding exposure is so limited that further assessment can generally be waived (Article 13 of the Plastics Regulation). In addition, a generic *detection* limit of 0.01 mg/kg food applies to substances included in the Positive List (Annex I of the Plastics Regulation) reflecting the analytical detection limit.

Generally, migration limits, and other limits, may differ e.g. between different food types, and also between different end use legislations. Due to these differences, the CF4Polymers does not include any migration limits or similar pre-determined safety levels. However, the CF4Polymers has been designed flexibly and can be adapted to meet the requirements of end-use legislation (e.g. toys, medical devices, FCM).

Notably, a comprehensive characterisation and quantification of all oligomers or other NIAS that can migrate from the polymer matrix (or non-polymer FCM) is often hindered by analytical capabilities, including a lack of reference standard materials. The best available technology needs to be determined on a case-by-case basis, while taking note of the state-of-the-science.

4.7.2 Exposure calculations: Estimated daily intake

Once the oligomers (or other NIAS) have been tentatively identified and (semi)-quantified, the next step of the exposure assessment includes calculating the dose that individuals in exposed populations can take up, i.e. the so-called estimated daily intake (mg/person/day). This calculation relates the oligomer migration data (Section 4.7.1) with data on the amount of food (and water) that are consumed by the average consumer as well as information on the types and shapes of packaging that are used for the food (and water). In addition, potential exposures to the given substance from other sources (e.g. toys, cosmetics, food additives) may need to be considered, but was not in scope of this case study.

Regulators have provided default values to assess the exposure to plastic components in the absence of real data (European Commission, 2001; EFSA, 2016). For food consumption and packaging use, the default (worst-case) assumption applied in the EU is that every day an adult person consumes 1 kg of food (packaged in a 1 dm^3 cube of the same FCM with a surface of 6 dm^2 (European Commission, 2001, 2011)). In the present case study, this implies consumption of 1 kg olive oil in a polypropylene bottle per day. This worst-case assumption, which is also called the 'Euro-cube paradigm', is currently under review by EFSA to introduce different levels of consumption for adults, children and toddlers (EFSA, 2016). EFSA also provides a database to facilitate further refinements regarding the amount of food consumed; see http://www.efsa.europa.eu/en/food-consumption/comprehensive-database. In the USA, the US FDA applies food type distribution factors based on the market share of different FCM packaging materials (US FDA, 2007).

In contrast to this very conservative approach that does not reflect realistic exposure scenarios, higher-tier exposure models (e.g. probabilistic dietary exposure models) can be used instead (Section 4.7.3). However, such models require the availability of detailed information, and thus are usually applied for specific end uses.

Taken together, the levels of oligomers (or other NIAS, or IAS) that can migrate from the polypropylene matrix are very low, and the degree of migration is also very low.

4.7.3 Higher-tier models to estimate daily intake

The FACET (*Flavours, Additives and Food Contact Material Exposure Task*) software tool and (2) the MATRIX calculation tool are examples for higher-tier consumer exposure assessment tools that have been developed to refine exposure calculations for components of FCMs. Both models have been developed using data from a limited set of polymers (that does include polyolefins) and therefore can only be used to model the migration of LMW components from these specific polymers.

Some further details on FACET and MATRIX are provided below. Notably, however, it was not the purpose of this case study to evaluate the applicability of these models.

FACET (https://cordis.europa.eu/project/rcn/87815/factsheet/en) was a project funded under the 7th EU Research Framework Programme that aimed at developing a new tool to estimate exposure to substances migrating from food contact packaging as well as food additives and flavourings. The FACET software tool allows modelling exposure to such substances on a country base for the EU population. The probabilistic exposure results are based on comprehensive pan-European food consumption and food packaging data encrypted in the software.

For this purpose, the FACET model combines the following information inputs:

- Food consumption (as recorded in national dietary surveys)
- Structure, size and market share of the various FCMs used for each food (industry data)
- Composition of each component used in the FCM: identity of substances, concentration range, probability of presence in the FCM (industry data)
- Contact conditions (range of temperature and time) during conditioning, storage and use of the packed food product (industry data)

Since all relevant data is encrypted in the FACET software, the user only has to run a 'pre-population' (once per country) to calculate the levels of substance migration into food and can then proceed to the actual exposure calculation. The big advantage of this approach is that it allows an exposure calculation across the consumer's complete diet (per country, per dietary survey) without requiring extensive knowledge on the use and composition of all FCMs in all packaging sectors, a level of expertise that is likely unrealistic for any user.

The MATRIX project (https://matrixcalculation.eu/matrix/accounts.nsf/home.xsp) was jointly initiated, financed and supported by Food Contact Additives-Cefic (FCA-Cefic), the European Plastic Converters, Flexible Packaging Europe, and PlasticsEurope (PlasticsEurope, 2014). Within the project, generic levels of migration into food were derived for specific plastic packaging materials.

The Matrix Project derived country data sets for Germany, France, Italy, Spain and United Kingdom with the respective packaging surface to which consumers are exposed per plastic material group and per consumed food and the respective calculation of levels of interest. Plastics material groups can be assessed on a country base to define the level where identified migrants need to be submitted to further risk assessment.

4.8 Case Study 3: CF4Polymers (Step 7) Hazard assessment

The HMW polypropylene considered in this case study fulfils the criteria for 'polymers of low concern' or 'reduced regulatory requirements polymers' (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021; see also Sections 4.1.1 and 4.3.1). Therefore, ecotoxicity and toxicity tests are not usually required for safety assessment of the HMW polypropylene (or other HMW polyolefins).

As regards safety assessment of the LMW components, the Positive List (European Commission, 2011; Section 4.1.4) can be used to screen for relevant IAS, and the respective SMLs defined therein can be used to check if the amounts migrating are below the allowable levels. If testing is deemed necessary, the workflow 'Polymer human health hazard assessment' outlined in Figure 7 of the ECETOC (2020) TR No. 133-2 works well with LMW substances that are of commercial interest such as IAS, where traditional approaches to substance testing can be applied.

By contrast, toxicity testing of oligomers and other NIAS that may migrate in low amounts from the FCM is oftentimes not feasible since it is technically not possible to isolate or synthesise the respective test materials in sufficient quantities to enable such testing. (Such technical limitations may also impair the validation of toxicity test methods specifically for NIAS.) To account for these limitations, an approach for the hazard assessment of oligomers is suggested that avoids (higher tier) testing:

Once the spectrum of oligomers has been identified for the polymer sample (Section 4.7), a grouping approach can be used to combine types of oligomers into categories based on their chemical class (e.g. olefins, aldehydes, ketones) (OECD, 2014; ECHA, 2008, 2013, 2017c). As oligomers may exist as regular mono-constituent substances, they may have already been assessed under the respective applicable chemical legislation so that data may be available therefrom. Therefore, read-across to data from other oligomers of the same category may be an efficient approach to fill any prevailing data gaps (PlasticsEurope, 2016).

For data-poor substances, for which no read-across information is available, assessments should begin by determining the threshold of toxicological concern, e.g. following the guidance by Kroes et al. (2004) and EFSA (2019). In cases where a concern cannot be excluded on the basis of existing information, read-across or the threshold of toxicological concern assessment, testing to complete the toxicological profile of the given oligomer(s) should generally focus on *in silico* predictions (using e.g. QSARs and computational toxicology) and *in vitro* high-throughput assays (Severin et al., 2017; Schilter et al., 2019; Van Bossuyt et al., 2019).

Notably, technical limitations rendering toxicity testing of oligomers challenging are not considered in the EFSA (2008a) *Note for guidance for the preparation of an application for the safety assessment of a substance used in plastic food contact materials,* as this guidance has been developed with IAS in mind. The testing battery presented therein depends on to the anticipated level of migration of the substance from the FCM and of its toxicological nature:

Migration < 0.05 mg/kg of food/food simulant: At least two genotoxicity tests (i.e. bacterial reverse mutation assay (OECD TG 471) and *in vitro* mammalian cell micronucleus test (OECD TG 487); in case of positive results obtained from these tests, further *in vivo* genotoxicity tests may be required.

Migration 0.05-5 mg/kg of food/food simulant: In addition to the above, 90-day oral toxicity data and data to demonstrate the absence of potential for accumulation in humans.

Migration > 5 mg/kg of food/food simulant: In addition to all above, adsorption, distribution, metabolism, elimination (ADME) data, as well as data on reproduction (in one species), and developmental toxicity (normally in two species), and long-term toxicity/carcinogenicity (normally in two species).

For relevant studies, the NOAEL (mg/kg bw/day) is determined as point-of-departure for the subsequent (Step 8) risk characterisation.

Within the CF4Polymers, the (Step 7) hazard assessment does not prescribe any specific test methods, but instead describes what may be considered to determine the need for testing in a scientific approach. As the example of the EFSA (2008a) guidance shows, there may be regulatory settings requiring more or less knowledge than outlined in the CF4Polymers. Evidently, such regulatory requirements take precedence for the risk assessment conducted to fulfil the respective legal obligations. Nonetheless, the technical challenges in conducting higher-tier testing remain.

4.9 Case Study 3: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

Once all relevant information on the potential exposure and hazard of the oligomers, as relevant (LMW) components of the polypropylene, has been collected, generated or modelled, the final step of the risk assessment (i.e. risk characterisation) is performed.

This section of Case Study 3 describes general issues to be considered for the risk characterisation of the polypropylene used in olive oil bottles (or other polyolefins used in FCM). Therefore, this case study concludes by summarising the outline for risk characterisation implemented in the context of the EU FCM legislation:

The risk characterisation should consider that the SMLs, which are denoted in the Positive List (European Commission, 2011), or the generic SML of 60 mg/kg food (Article 11(2) of the Plastics Regulation), in case a specific SML is unavailable, may not be exceeded (Section 4.7.1). Also, the risk characterisation should consider any further restrictions included in the Positive List, such as "*not to be used for articles in contact with fatty foods*".

During risk characterisation, the estimated daily intake (Section 4.7.2) is compared to the maximum tolerable daily intake.

Alternatively, the calculated (worst-case or modelling) or measured migration level into the food can be compared to a self-derived SML (or acceptable migration limit) or threshold of toxicological concern:

(Self-derived) SML (mg/kg food) = 60 (kg bw/person) * tolerable daily intake / 1 kg food /day.

In this formula, the weight of a person and the amount of packed food consumed by day have been established by convention.

As long as the estimated daily intake is below the tolerable daily intake, or the migration level under the typical condition of use is below the self-derived SML, the use of the substance in the defined plastics materials, taking into account the defined use conditions, is considered safe for consumer health.

For example, in the research project on the determination of the migration of oligomers from polyolefins commissioned by PlasticsEurope (Section 4.7.1) the potential migration levels of the oligomers from the plastics to food, and the corresponding potential for dietary exposure, were below any toxicological level of

concern, even for the highly conservative assumption of lifelong daily consumption of 1 kg of food out of the same packaging material. Tolerable daily intake levels derived for the oligomers were consistently above 1 mg/kg bw/day and hence sufficiently high to not be exceeded if the maximum allowed overall migration limit of 60 mg/kg food was respected (PlasticsEurope, 2016). PlasticsEurope (2016) concluded that consumer exposures to the oligomers from the polyolefin plastics food packaging under typical conditions of use are not a safety concern to human health.

This case study exemplifies the diverging assessment approaches in in different regulatory setups. These setups often represent an amalgam between scientific consideration, simplification and policy decisions, and approaches which are purely determined by risk assessment needs and the state of the science. In the context of food contact assessments, exposure assessment is the area being influenced most by simplification and policy decisions.

5. CASE STUDY 4: BADGE POLYMERS

5.1 Introduction

5.1.1 Scope and outline of Case Study 4

This case study addresses bisphenol-A diglycidylether (BADGE) oligomers and polymers (also called BADGE epoxy resins) as well as the underlying BADGE monomer/prepolymer. The industrial use of solid BADGE epoxy resins in powder coatings for metallic substrates is considered. Indeed, solid BADGE epoxy resins are exclusively used in industrial settings, for the production of solvent-based coatings (can coatings) and powder coatings (mostly for metallic substrates as corrosion protection primer (pipelines, reinforcing bars, boilers) or as decorative coatings for interiors). (Hence, solid BADGE epoxy resins are used for formulation and application before curing.)

Solid BADGE epoxy resins include oligomers and polymers covering a broad molecular weight range up to > 30,000 Da for ultra-HMW BADGE epoxy resins (Danish EPA, 2012). **This case study considers the BADGE monomer/prepolymer (M_n 359 Da) and solid BADGE epoxy resins that cover the molecular weight range from M_n 969 Da to 3,211 Da.** Importantly, liquid BADGE epoxy resins (with M_n < 969) are out of scope of this case study.

Commonalities of all BADGE epoxy resins include a backbone with identical BADGE monomer/prepolymer sequence, terminal reactive (epoxide) groups, and an LMW fraction consisting of BADGE monomers/prepolymers. Taken together, BADGE epoxy resins may be LMW polymers, and they generally have both reactive functional groups and LMW constituents. All of these properties have been identified as potential drivers for toxicity of polymers (ECETOC, 2019).

Focus of the case study is on Steps 2-4 and 7 of the CF4Polymers. All components of the solid BADGE epoxy resins (i.e. the BADGE monomer/prepolymer, oligomers and polymers) are being considered in line with the (Step 3) polymer component strategy. After a fit-for-purpose (Step 2) polymer identification, the main focus is to apply (Step 4) grouping approach evaluation to the BADGE epoxy resins. This grouping follows the three-Criteria grouping approach described in Section 1.3. As a starting point, the BADGE epoxy resins are subgrouped making use of the criteria to identify 'polymers of low concern' or 'reduced regulatory requirements polymers' that have been implemented in different jurisdictions in which legislation for the registration or notification of polymers is in force (e.g., US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021); see Section 1.2 for further details on the polymers of low concern concept.

Following the polymers of low concern criteria, the criteria applied in this case study for the subgrouping of BADGE epoxy resins include (1) proportion of LMW compounds within the polymer product; (2) molecular weight of the polymer; and (3) content of reactive functional groups.

Further, this case study considers lower-tier toxicity and ecotoxicity data that have been gathered for two types of BADGE epoxy resins. The outcomes of the grouping and the lower-tier (eco)toxicological assessments are evaluated to derive preliminary conclusions for

- The establishment of criteria and thresholds to distinguish BADGE epoxy resin grades (also named 'type' by the man-of-the-art) that present a hazard concern from those that do not; and

- The need for specific higher-tier toxicity testing ((Step 7) hazard assessment). Generally, focus is on human health hazard assessment (i.e. worker protection), but some aspects of environmental hazard assessment are also considered.

In parallel, this case study discusses evidence on the applicability of tools and test methods for the measurement of specific physico-chemical and (eco)toxicological properties of BADGE epoxy resins (or limitations thereof) – as a follow up to the evidence presented in the ECETOC TR No. 133-2 (ECETOC, 2020).

5.1.2 Production and use of BADGE epoxy resins

BADGE epoxy resins can be obtained by two different processes (Gupta and Kumar, 1987), i.e.

1. By polymerisation of bisphenol-A with epichlorohydrin via the so-called Taffy process.

These BADGE epoxy resins are bisphenol A-epichlorohydrin copolymers. The reaction of bisphenol-A with epichlorohydrin produces the BADGE prepolymer (that may include BADGE monomers and BADGE oligomers with 1 or 2 repeat units (n = 1 or 2)) and BADGE epoxy resins. During this reaction, the monomers bisphenol A and epichlorohydrin are fully consumed and are no longer present at the end of the polymerisation reaction (beyond residual traces).

2. By polymerisation of bisphenol-A with BADGE via the so-called advancement (AVA) process.

These BADGE epoxy resins are BADGE bisphenol A copolymers. Again, the monomer bisphenol A is fully consumed during the reaction and is no longer present at the end of the polymerisation reaction (beyond residual traces). By comparison, the BADGE monomer as well as BADGE oligomers (n = 1 or 2) may still be present in the LMW fraction of these BADGE epoxy resins.

The processing conditions (Taffy process vs AVA process) are very much alike (i.e. normal pressure, temperature approx. 150-160°C) with the main difference being the starting materials. Regardless of the underlying polymerisation process, the resulting BADGE epoxy resins are widely the same – while the AVA process allows to produce higher molecular weight polymers (further discussed in Section 5.3.1.1).

Solid BADGE epoxy resins are manufactured and processed at industrial facilities only. Hence, they are also only delivered to industrial facilities. The delivery form of solid BADGE epoxy resins consists of flakes with low dustiness. BADGE epoxy resins are used in combination with epoxy resin hardeners and various formulation components (e.g., additives, pigments) for further processing as solvent-based coatings or, via extrusion, as powder coatings. Solvent-borne liquid coatings using BADGE epoxy resins are mostly used for can coating applications, whereas powder coatings are mostly used for metallic substrates as corrosion protection primer (pipelines, reinforcing bars, boilers) or as decorative coatings for interiors.

Since the solid BADGE epoxy resins, just as other thermoset polymer formulations, are cured[8] at the end of the processing (to become part of articles), potential human exposure to the lower molecular weight solid

[8] *Thermosets* are synthetic polymers that can be changed into substantially infusible products when cured by heat, by crosslinking by reaction of functional groups, or by radiation. Thermosets retain their defined form in the intended applications (or during use) (ECETOC, 2019). *Curing* refers to the chemical process of converting a prepolymer or a polymer into a polymer of higher molar mass and then into a network. It is achieved by the induction of chemical reactions which might or might not require mixing with a chemical curing agent (IUPAC, 1997).

epoxy resins in scope of this case study is limited to transfer of the substance or mixture and the downstream processing steps of mixing/formulation, application, and curing. For all these industrial tasks, stringent risk management measures are in place to ensure worker protection as well as environmental protection. Cured solvent- and powder-based coatings are indeed part of industrial, technical equipment as well as consumer articles, but the solid BADGE epoxy resins have been converted to a highly three-dimensional crosslinked polymer product with different physico-chemical and hazard properties and no potential for consumer or professional exposure. Such cured thermoset polymers are out of scope of this case study.

Taken together, there are no intended professional or consumer uses of solid BADGE epoxy resins.

5.2 Case Study 4: CF4Polymers (Step 1) Problem formulation

This case study addresses the BADGE monomer/prepolymer as well as four grades ('types') of solid BADGE epoxy resins.

Different solid BADGE epoxy resin grades are referred to as 'types' of resins in the technical literature. While the resin type is neither scientifically defined nor accurately agreed among manufacturers, it provides an approximate indication of the resin's molecular weight and related properties. BADGE epoxy resins considered in this case study are called Type 1, Type 2, Type 4, and Type 7, with higher molecular weight for higher type number (Table CS4.1).

Further, this case study considers the intended industrial use for the formulation of powder coatings to be used for metallic substrates. Accordingly, the protection goal includes a definition of the acceptable level of risk to safeguard the health of the individual worker. While this case study focuses on intrinsic hazards, the relevant test methods (e.g., skin and eye irritation tests) might not always enable a reliable distinction between intrinsic and physical hazards. Generally, focus is on human health hazard assessment (i.e. worker protection), but some aspects of environmental hazard assessment are also considered.

5.3 Case Study 4: CF4Polymers (Step 2) Polymer identification

5.3.1 Step 2.1: Identification of the polymeric substance

5.3.1.1 Standard chemical descriptors and chemical names

BADGE monomer/prepolymer

The BADGE monomer and the BADGE prepolymer, which also contains oligomers (n = 1 or 2), has the CAS No. 1675-54-3 and the EC No. 216-823-5. A typical BADGE commercial product contains approx. 83% of the BADGE monomer (60-100%) with the rest of the composition to sum up to 100% being covered by BADGE oligomers.

BADGE has the chemical name *2-{[4-(2-{4-[(oxiran-2-yl)methoxy]phenyl}propan-2-yl)phenoxy]methyl}oxirane*.

Table CS4.1: Molecular weight and components of BADGE non-polymeric substances and BADGE polymers

Property	BADGE monomer / pre-polymer	BADGE epoxy resins			
		Type 1	Type 2	Type 4	Type 7
Physical state	Slightly viscous	Solid			
Number average molecular weight (M_n; Da)	359	969	1079	1476	3211
Weight average molecular weight (M_w; Da)	379	1931	2269	3085	9702
Polydispersity (no unit)	1.057	1.992	2.104	2.090	3.021
Presence of phenolic epoxide groups on polymeric substance					
Functional group equivalent weight (g/Eq.)	183-189	450-465	570-480	714-752	1695-1885
Epoxy index (Eq./kg)	5.30-5.45	2.15-2.22	1.68-1.75	1.33-1.40	0.53-0.59
Component distribution, as measured by gel permeation chromatography (% surf.)					
BADGE (n = 0; M_n: 340 Da)	83	13	10	7	1.4
Monochlorohydrin of BADGE	4.4	1.6	1.5	1.4	1.1
BADGE oligomer (n = 1; M_n: 625 Da)	11.5	2.6	2.0	1.4	2.7
BADGE oligomer (n = 2; M_n: 909 Da)	1.4	19.1	16.4	12.2	3.1
BADGE polymer (n = 3; M_n: 1193 Da) [b]	< 1%	20.4	18.7	15.0	91.7
BADGE polymer (n > 3) [b]	< 1%	43.6	51.4	63.3	
Sum of the above (% surf.)	*100*	*100*	*100*	*100*	*100*
Water extraction (ppm) [a]					
BADGE monomer		31	3		0.5
BADGE dimer		< 0.5	Not detected		Not detected

Footnote to Table CS4.1:

Abbreviations: % surf.: peak surface percent; BADGE: Bisphenol-A diglycidylether; Da: Dalton; n: Number of repeat units.

[a] A fraction of the respective BADGE epoxy resin was ground to fine powder as worst-case scenario (usually BADGE solid resins are delivered as flakes); results expressed in ppm of residual BADGE after extraction at 30 °C for 20 hours.

[b] As per ECHA (2017b), a polymer molecule is a "*molecule that contains a sequence of at least 3 monomer units, which are covalently bound to at least one other monomer unit or other reactant*".

BADGE oligomers and BADGE epoxy resins

Depending on the manufacturing process (Taffy vs AVA; Section 5.1.2) and starting materials, BADGE epoxy resins have two different CAS identifiers.

1. BADGE epoxy resins obtained by polymerisation of bisphenol-A with epichlorohydrin via the Taffy process have the CAS No. 25068-38-6 (but currently no EC No.).

2. BADGE epoxy resins obtained by polymerisation of BADGE with bisphenol-A via the AVA process have the CAS No. 25036-25-3 and the EC No. 607-500-3.

The chemical name of these BADGE epoxy resins is *4,4'-isopropylidenediphenol, oligomeric reaction product with 1-chloro-2,3-epoxypropane* (or: *4,4'-isopropylidenediphenol, polymer with 2-{[4-(2-{4-[(oxiran-2-yl)methoxy]phenyl} propan-2-yl)phenoxy]methyl}oxirane*).

It is important to note that, regardless of the starting materials, the resulting substances can range from BADGE oligomers to lower and higher molecular weight BADGE epoxy resins. Since the CAS identifiers do not provide information on the molecular weight, both CAS No. 25068-38-6 and CAS No. 25036-25-3, that describe the same types of final polymer products, may include BADGE monomers/prepolymers and lower and higher molecular weight BADGE oligomers.

5.3.1.2 Structural and morphological descriptors

Figure CS4.1 presents the chemical structure of BADGE epoxy resins. Epoxy resins are linear polymeric substances, which differ only in the number of BADGE links in the chain and in the fraction of unreacted BADGE. The BADGE monomer/prepolymer is slightly viscous, whereas the lower and higher molecular weight BADGE epoxy resins considered in this case study are solid resins (Table CS4.1).

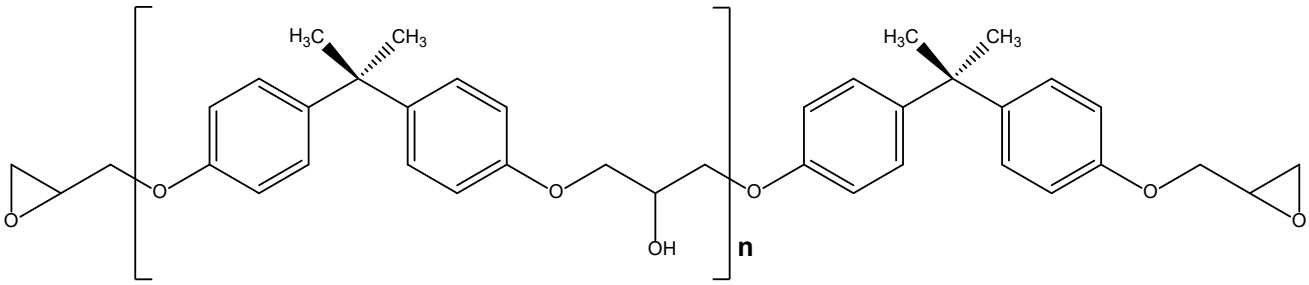


Figure CS4.1: Chemical structure of bisphenol-A diglycidylether (BADGE) epoxy resins (n = number of repeat units)

Solid epoxy resins are typically delivered in the form of flakes (thickness 1-2 mm / diameter 5-8 mm) with low dustiness. Dust formation can occur upon transfer or processing operations and therefore requires suitable risk management measures, e.g. ventilation and respiratory protection.

Presence of LMW constituents

Table CS4.1 presents the proportion of the different LMW constituents of Type 1, Type 2, Type 4, and Type 7 BADGE epoxy resins as determined via gel permeation chromatography (GPC). Generally, the LMW fraction consists of BADGE (n=0) and of BADGE oligomers (n=1 or 2). The ratio of the LMW fraction decreases with increasing molecular weight of the polymer (Table CS4.1; Figure CS4.2). Type 1 BADGE epoxy resin includes 13% BADGE, 2.6% oligomer (n=1), and 19.1% oligomer (n=2). By comparison, Type 4 includes 7% BADGE, 1.4% oligomer (n=1), and 12.2% oligomer (n=2), whereas the largest Type 7 BADGE epoxy resin only includes 1.4% BADGE, 2.7% oligomer (n=1), and 3.1% oligomer (n=2) (Table CS4.1).

Importantly, neither bisphenol A (a monomer for BADGE epoxy resins regardless of the polymerisation procedure (Section 5.1.2)) nor epichlorohydrin (a monomer for BADGE epoxy resins produced by the Taffy process) are detectable via GPC at a limit of detection of 1% (and generally the residual epichlorohydrin is present in concentrations below 5 ppm).

Hence, bisphenol A and epichlorohydrin do not form part of the LMW constituents of the Type 1, Type 2, Type 4, or Type 7 BADGE epoxy resins.

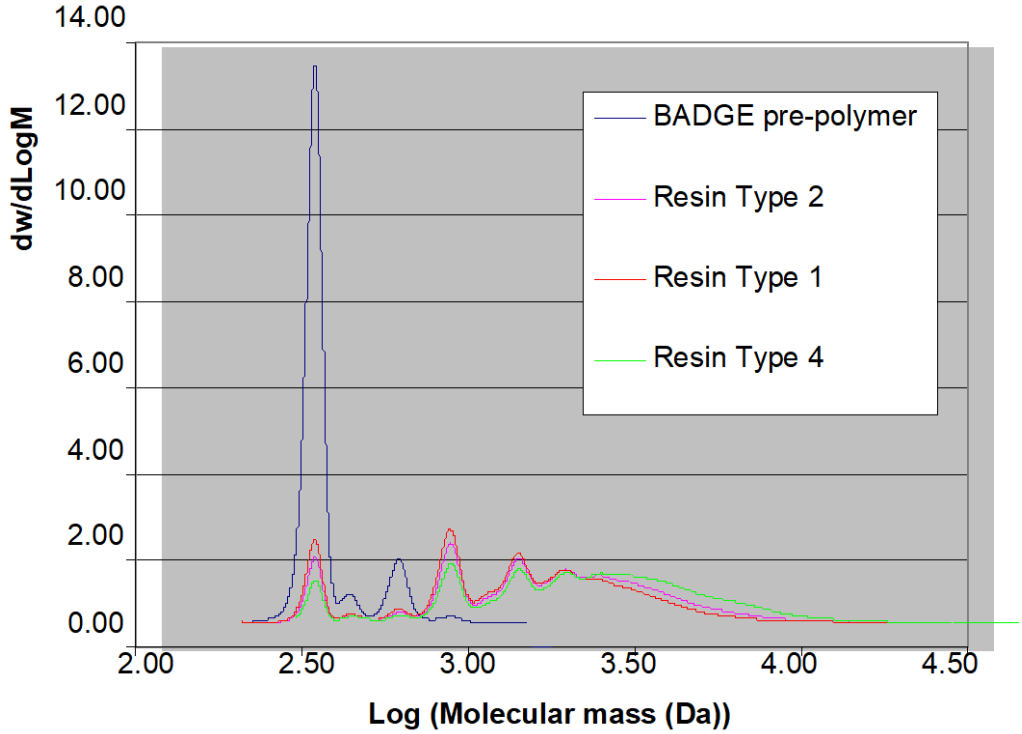


Figure CS4.2: Comparison of gel permeation chromatograms for bisphenol-A diglycidylether (BADGE) prepolymer versus solid Type 1, Type 2 and Type 4 BADGE epoxy resins (dw/dLogM: differential weight fraction)

Presence of reactive functional groups

The FGEW of resident cationic or reactive functional groups is the weight of the polymer that contains one equivalent weight (one mole) of a particular functional group (US EPA, 1997; Canada, 2005). In those jurisdictions in which specific legislation for the registration or notification of polymers is in force, polymers containing moderate- or high-concern reactive functional groups do not qualify as polymers of low concern (Section 5.1.1) if each reactive functional group has a FGEW below 1,000 and 5,000 g/Eq., respectively. Epoxides are considered 'moderate-concern' reactive functional groups (US EPA, 1997; Canada, 2005). Thereby, BADGE epoxy resins cannot be assessed as being of 'low concern' if the FGEW undercuts 1,000 g/Eq. See Section 4.3 of the ECETOC No. TR 133-1 (ECETOC, 2019) for a further discussion of the identification and evaluation of reactive functional groups.

Type 1, Type 2 and Type 4 BADGE epoxy resins have FGEW values below 1,000 g/Eq., whereas Type 7 with the highest molecular weight has a FGEW above 1,000 g/Eq. (i.e. 1,695-1,885 g/Eq.) (Table CS4.1).

The epoxy index (equivalent (Eq.)/unit mass), that is inversely correlated with the FGEW, is a further important parameter to evaluate the properties of epoxy resins. The epoxy index is defined as "*moles of epoxy groups per 100 g of epoxy resins. This index can be used for calculating the amounts of cross-linking reagent needed in the epoxy resin formula and determining the curing degree of epoxy resins*" (Li et al., 2007). The epoxy index increases with increasing fraction of BADGE monomer/prepolymer in different epoxy resin types (Figure CS4.3).

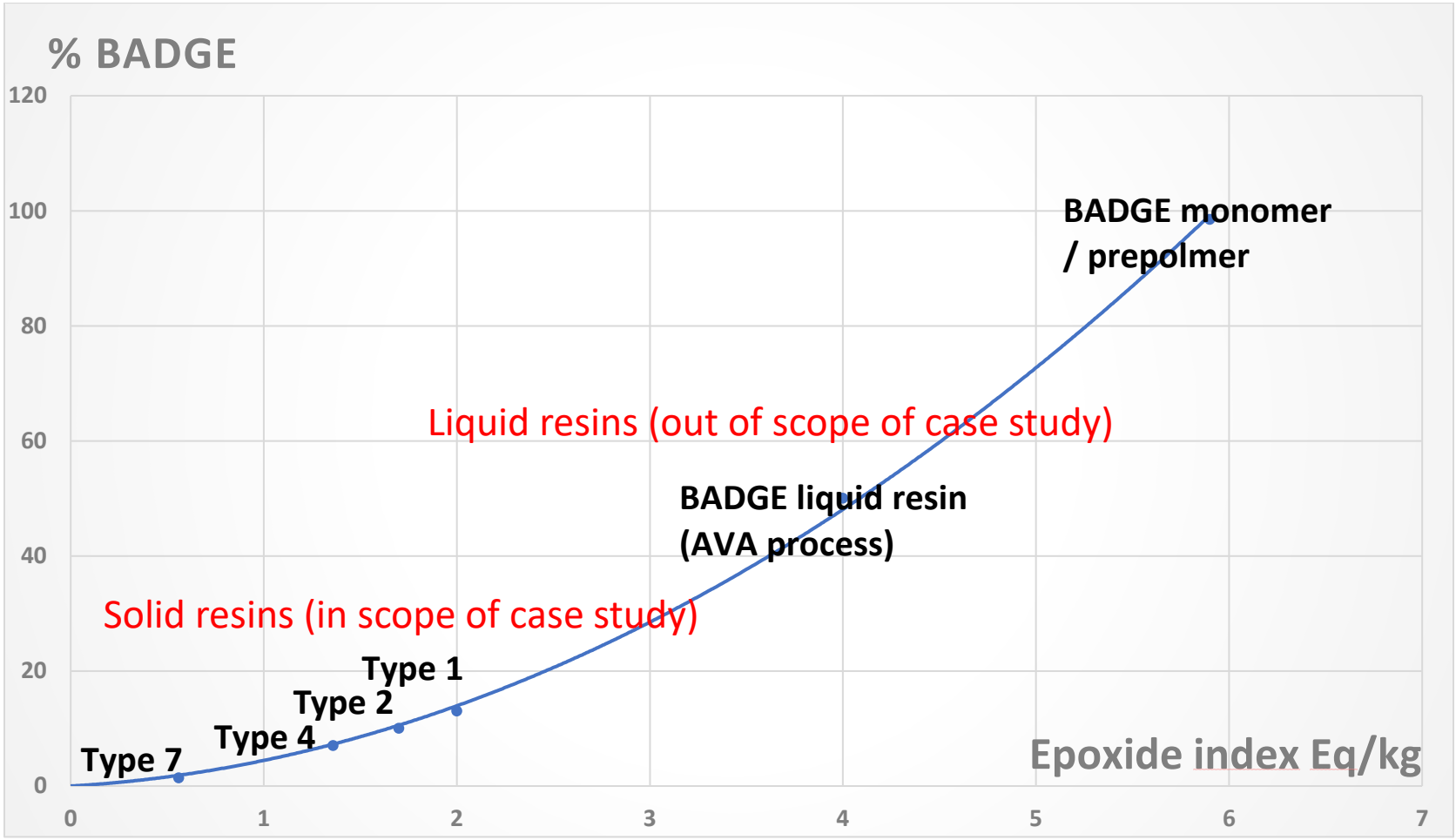


Figure CS4.3: Epoxy resins: Bisphenol-A diglycidylether (BADGE) content versus epoxide index (equivalent/kg; Eq./kg)

5.3.1.3 Molecular weight and solubility in water

The molecular weights (M_n and M_w) of the BADGE monomer/prepolymer, and Type 1, Type 2, Type 4 and Type 7 BADGE epoxy resins are presented in Table CS4.1. Specifically, the M_n ranges from 359 Da for BADGE to 969 Da, 1,079 Da, and 1,476 Da for Type 1, Type 2, and Type 4, respectively, whereas Type 7 with the highest molecular weight has a M_n of 3,211 Da.

The BADGE monomer/prepolymer has a polydispersity index > 1, and the BADGE epoxy resins have polydispersity indices ranging from approx. 2 (for Type 1, Type 2 and Type 4) to approx. 3 (for Type 7), which is reflected in the increasingly broad molecular weight distribution of these resins.

Generally, the epoxy resin LMW constituents / oligomers can well be assessed by GPC (OECD TG 118) using a refractive index detector and tetrahydrofuran as solvent. The oligomers are well separated and identified, which is very useful for the overall identification of the polymer's LMW constituents. By comparison, the higher molecular weight and/or cured (polymeric) constituents are not well separated above an M_n of approx. 1,000 Da, i.e. they cannot be assigned to discrete peaks, but are rather combined to a very broad band. Nonetheless, this does not impair applicability of GPC for epoxy resins, since distinct peak identification is not needed for subsequent hazard and risk assessment of the higher molecular weight range components that are unlikely to become systemically bioavailable. The average molecular weight and content below 500 Da and 1,000 Da can still be determined accurately for such HMW epoxy resins.

Neither the BADGE monomer/prepolymer, nor the BADGE epoxy resins are water soluble. Solubility in water (OECD TG 105) is 6.9 mg/L for the BADGE monomer/prepolymer and < 2 mg/L (limit of quantification) for both Type 1 and Type 2 BADGE epoxy resins (data not shown).

Table CS4.1 also presents water extractability data for Type 1, Type 2 and Type 7 BADGE epoxy resins (assessed using a company-internal method). To test for water extraction (at 30 °C for 20 hours), a sample of the respective BADGE epoxy resin was ground to fine powder. This represents a worst-case scenario since BADGE epoxy resins are usually delivered as flakes (Section 5.1.2). Overall, water extraction of all BADGE epoxy resins is very low and further decreases with decreasing LMW fraction. Only a tiny fraction of the few percent of BADGE monomer included in the solid epoxy resins was released upon water extraction showing that the BADGE monomer is firmly trapped in the polymer matrix, which considerably hinders its physical availability. Also, it was only possible to extract the BADGE (epoxy) monomer, whereas the oligomers were not water extractable.

5.3.1.4 Partition coefficients, and surface tension

The BADGE prepolymer has an n-octanol/water partition coefficient (log K_{ow}) of 3.242.

The BADGE epoxy resin (CAS No. 25036-25-3) has a log K_{ow} of 3.84 as per RPS BKH Consultants B.V. (2002).

For the BADGE epoxy resin (CAS No. 25068-38-6) log K_{ow} values of 3.26 ± 0.52 and 3.242 ± 0.324 have been recorded at 25 °C and pH 7 as per Danish EPA (2012) where these data are cited as "*ECHA, European Chemicals Agency, public dossier (2012A): Dossiers data on 25068-38-6 with public access. Visited 17. September, 2012*". The ECETOC Polymers TF has been unable to trace back the respective values on the

current ECHA dissemination portal (https://echa.europa.eu/substance-information/-/substanceinfo/100.131.204; accessed 9 February 2021).

For the liquid BADGE epoxy resin (CAS No. 25068-38-6; water solubility 6.9 ± 1.5 mg/L), Danish EPA (2012) has further recorded a surface tension of 58.7-58.9 mN/m (20 °C; tested concentration not recorded by the Danish EPA), and it has stated: "*As the surface tension is lower than 60 mN/m, test substance should be regarded as a surface active material*" (Danish EPA, 2012). Notably, this is one of the examples for the lack of suitability of the 60 mN/m value (Council, 2008) to identify substances with technically and biologically relevant surface tension effects. The ECETOC Polymers TF questions the 60 mN/m threshold, suggesting instead a cut-off value of 45 mN/m to identify polymers with surfactant properties, which is concordant with the International Trade tariff threshold to determine surface active properties; https://ec.europa.eu/docsroom/documents/19522/attachments/1/translations/en/renditions/native; see also Section 7.3.1.9 of the present report.

Applying the 45 mN/m threshold, the CAS No. 25068-38-6 BADGE epoxy resin is not a surface-active material.

Generally, the ECETOC Polymers TF maintains the view that partition coefficients and surface tension (as well as dissociation constants) are not relevant physico-chemical properties for BADGE epoxy resins since they are generally solid materials that do not dissociate and are not soluble in water.

5.3.2 Step 2.2: Identification of additives

Additives, solvents, etc., are not required for BADGE polymers. Also, any catalysts are eliminated upon washing of the resins.

5.3.3 Step 2.3: Identification of NIAS and/or residual substances (monomers)

Solid BADGE polymer epoxy resins only contain a variable amount of residual BADGE monomer/prepolymer (Table CS4.1: 1.4%-13%), but no other NIAS.

5.4 Case Study 4: CF4Polymers (Step 3) Polymer component strategy

This case study on BADGE epoxy resins considers all components of these polymer products, i.e. the BADGE monomer/prepolymer and the BADGE polymers. BADGE epoxy resins have no constituents that are unrelated to BADGE.

5.5 Case Study 4: CF4Polymers (Step 4) Grouping approach evaluation

In this section, the three-Criteria grouping approach for polymers, outlined in Section 1.3, is applied for the BADGE monomer/prepolymer and the Type 1, Type 2, Type 4 and Type 7 BADGE epoxy resins (i.e. polymers that consist entirely of BADGE).

In each criterion, it is strived to subgroup the BADGE epoxy resins by common properties. For this subgrouping, those properties and thresholds were selected and applied that have been implemented in different jurisdictions to distinguish polymers of low concern from polymers requiring registration or notification (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021), and that appear to be relevant properties for BADGE epoxy resins.

Importantly, focus is on properties that may be relevant for human health hazard assessment. This includes properties that may increase the likelihood for external or systemic bioavailability (i.e. presence of extractable LMW constituents and/or of LMW polymeric substances; see Sections 3.6.1 and 3.7.1.1 in ECETOC (2019) TR No. 133-1) and/or that may be drivers for intrinsic toxicity (i.e. presence of reactive functional groups). It is hypothesised that, if bioavailable substances (LMW constituents or LMW polymeric substances) are hazardous, then the concentration and exposure conditions determine if the polymer product is hazardous. Accordingly, the subgrouping should aim at identifying subgroups of BADGE epoxy resins that share the same hazard range (e.g. hazard classification).

5.5.1 Criterion 1: Initial grouping according to chemical nature and common key constituent

All BADGE polymers considered here are composed entirely of BADGE repeat units. They have no further major constituents. Similarly, the BADGE monomer/prepolymer has no constituents that are unrelated to BADGE. Hence, it is hypothesised that the common key feature (here: common key constituent) is BADGE. Hence, all polymer products in this group should have BADGE (as residual monomers / prepolymers), whereas polymer products that do not include BADGE are not included in the group. Further subgrouping of the BADGE epoxy resins is possible by the fraction of LMW constituents (and hence BADGE) present in the BADGE epoxy resins (Criterion 2; Section 5.5.2).

5.5.2 Criterion 2: Further grouping and subgrouping by similar key properties

Following the criteria implemented for the identification of polymers of low concern, the further subgrouping of the BADGE polymers is undertaken by (1) fraction of LMW components; (2) the molecular weight of the polymeric substance; and (3) the amount of reactive functional groups.

5.5.2.1 Subgrouping by fraction of LMW constituents

As per US EPA (1997) and Canada (2005, 2021), a polymer may qualify as polymer of low concern if it includes:

- **< 10%** components with M_n **< 500 Da**; and
- **< 25%** components with M_n **< 1,000 Da**.

These thresholds were followed to subgroup the BADGE epoxy resins by the fraction of LMW constituents:

The BADGE monomer (molecule) has a M_n of 340 Da, the BADGE oligomer (n=1) a M_n of 625 Da, and the BADGE oligomer (n=2) a M_n of 909 Da. Hence, those BADGE epoxy resins that have < 10% monomers (including monochlorohydrin of BADGE) and < 25% monomers and oligomers (n=1 and n=2), respectively, can be subgrouped into one group.

Accordingly, Type 1 and Type 2 that both have ≥ 10% BADGE monomers and ≥ 25% monomers and oligomers with n=1 or n=2 (Table CS4.1) are subgrouped into one subgroup. In this subgroup, the amount of LMW constituents may pose a concern for bioavailability and hence toxicity elicited by the BADGE monomer (Section 5.5.4). Type 4 and Type 7 that have < 10% BADGE monomers and < 25% monomers and oligomers with n=1 or n=2 (Table CS4.1) are subgrouped into a group where the amount of LMW constituents does not pose such a concern.

Importantly, these considerations assume the 'worst-case scenario', i.e. that all of the LMW constituents present in the respective BADGE epoxy resins would migrate to the surface of the polymer matrix and hence become physically available – and thus also externally and internally bioavailable. By contrast, the water extraction data available for Type 1, Type 2 and Type 7 indicate that only a minor fraction of the BADGE is extractable at 30 °C within 20 hours.

5.5.2.2 Subgrouping by molecular weight of the polymeric substance

The US EPA (1997) and Canada (2005) guidance list a M_n threshold of < 1,000 Da to identify LMW polymers that may become systemically bioavailable (for further details, see Section 4.2 of the ECETOC TR No. 133-1). Based thereupon, the BADGE epoxy resins can be subgrouped as either having M_n < 1,000 Da or M_n ≥ 1,000 Da.

Type 1 BADGE epoxy resin has M_n of 969 Da, which is just below the 1,000 Da threshold, whereas the M_n of Type 2 BADGE epoxy resin is just above this threshold (1,079 Da). By contrast, Type 4 and Type 7 BADGE epoxy resins have M_n further above 1,000 Da (1,476 and 3,211 Da) indicating absence of systemic bioavailability and no LMW polymer.

Accordingly, Type 1 is subgrouped into a group where the size of the polymeric substance may pose a concern for external and internal bioavailability – and hence intrinsic toxicity caused by any hazard potential of the polymeric substance; Type 2 is subgrouped into a group that is just above the threshold for such a concern; and Type 4 and Type 7 are subgrouped into a group that does not pose such a concern.

5.5.2.3 Subgrouping by amount of reactive functional groups (FGEW)

The US EPA (1997) and Canada (2005) guidance indicate that epoxides are moderate-concern reactive functional groups and indicate FGEW < 1,000 g/Eq. as the threshold to identify a concern for reactivity. Based thereupon, the BADGE epoxy resins can be subgrouped as either having FGEW < 1,000 g/Eq. or FGEW ≥ 1,000 g/Eq.

The BADGE monomer/prepolymer and the Type 1, Type 2, and Type 4 BADGE epoxy resins have FGEW < 1,000 g/Eq. By contrast, Type 7 has FGEW 1,695-1,885 g/Eq. indicating absence of concern for reactivity.

Accordingly, Type 1, Type 2 and Type 4 are subgrouped into a group where the amount of reactive functional groups present on the polymeric substance may pose a concern for intrinsic toxicity. Type 7 is subgrouped into a group that does not pose such a concern.

5.5.3 Summary of the Criterion 1 and Criterion 2 subgrouping

The combination of (1) LMW fraction (≥ 10% components with Mn < 500 Da = concern); (2) M_n of the polymeric substance (M_n < 1,000 Da = concern) & (3) FGEW (FGEW < 1,000 g/Eq. = concern) yields the matrix presented in Table CS4.2.

This matrix implies that, for Type 1 and Type 2 BADGE epoxy resins, the LMW fraction (i.e. presence of BADGE), the amount of reactive functional groups, and – at least for Type 1 – the rather small size of the potentially bioavailable polymer might all be drivers of toxicity. For Type 4 BADGE epoxy resins, the amount of reactive functional groups might be a relevant driver of toxicity, but to a lesser extent than for Type 2. For Type 7 BADGE epoxy resins, LMW fraction, M_n of polymeric substance and presence of reactive functional groups do not constitute 'properties of concern'.

Table CS4.2: Summary of Layer 1 and Layer 2 subgrouping of BADGE epoxy resins (Type 1, Type 2, Type 4 and Type 7)

Parameter	LMW fraction	M_n of the polymeric substance	FGEW
Threshold for concern	***≥ 10% / ≥ 25% components with M_n < 500 Da / < 1,000 Da***	***M_n < 1,000 Da***	***FGEW < 1,000 g/Eq.***
Type 1	**Concern**	**Concern**	**Concern**
Type 2	**Concern**	No concern, but close to threshold	**Concern**
Type 4	No concern	No concern	**Concern**
Type 7	No concern	No concern	No concern

Footnote to Table CS4.2:
Abbreviations: BADGE: Bisphenol-A diglycidylether; Da: Dalton; FGEW: Functional group equivalent weight: LMW: Low molecular weight; M_n: Number average molecular weight.

5.5.4 Criterion 3: Further grouping and subgrouping by hazard similarity

5.5.4.1 Grouping by hazard similarity – the hazard of the BADGE monomer as common key constituent

As per Criterion 1 of the grouping approach evaluation, the BADGE monomer/prepolymer is the common key constituent (Glossary), i.e. the constituent within the polymer product, which is present in every member of the group of solid BADGE polymers. The BADGE monomer/prepolymer has clear potential for external and systemic bioavailability on account of its low M_n of 359 Da. The potential for bioavailability of BADGE is also supported by its water extractability: Even though the water extractability of BADGE is low (and further decreases with decreasing LMW fraction), it is the only LMW constituent that is extractable at all (at 30 °C within 20 hours).

It is hypothesised that all members of the group of solid BADGE polymers have the same – or less – hazard properties as the BADGE monomer. Therefore, the hazard properties of BADGE are explored below.

The BADGE monomer (CAS No. 1675-54-3; EC No. 216-823-5) has been registered under the EU REACH Regulation (EP and Council, 2006) as manufactured or imported at ≥ 100,000 to < 1,000,000 tonnes per year (https://echa.europa.eu/substance-information/-/substanceinfo/100.015.294; accessed 9 February 2021). Thus, the BADGE monomer has a full dataset that can be used for its hazard assessment. Available studies of relevance for human health hazard assessment include an *in vivo* toxicokinetics study, acute oral, dermal and inhalation toxicity studies, *in vivo* skin and eye irritation studies, an *in vivo* skin sensitisation study (LLNA), sub-chronic oral and dermal toxicity studies (including neurotoxicological investigations), *in vitro* and *in vivo* genotoxicity studies, a two-generation reproductive toxicity study, a developmental toxicity study, as well as observational studies in humans. With respect to ecological endpoints, the BADGE monomer has been tested for (bio)degradability, bioaccumulation, aquatic and terrestrial toxicity.

With respect to repeated-dose toxicity endpoints, the endpoint summaries provided on the ECHA dissemination portal indicate that 90-day oral gavage administration of BADGE to Fischer 344 rats (OECD TG 408; reliability 1) resulted in slight body weight effects at 250 mg/kg/day and higher. Enlarged cecum was noted at necropsy in male rats receiving 250 mg/kg/day. Slight histopathologic changes were noted in the adrenal gland, cecum and kidney of male and/or female rats ingesting 250 mg/kg/day. A 3% decrease in body weight was noted in female rats at 50 mg/kg/day and a slight increase in cholesterol levels was noted which was considered to be not detrimental. Based thereupon, the NOAEL was considered to be 50 mg/kg/day. Further, in a dermal 90-day toxicity study using B6C3F1 mice (reliability 1), the only systemic toxicity was a slight decrease in body weights at 1,000 mg/kg/day. Thus, the NOAEL for systemic toxicity was considered to be 100 mg/kg/day. The NOEL for dermal effects in female rats was 10 mg/kg/day. In male rats a NOEL for dermal effects was not detected.

As an outcome of the comprehensive hazard assessment, the BADGE monomer has been assigned the following hazard classes / hazard statement codes as per EU CLP Regulation (EP and Council, 2008):

- Skin irritation 2 (causes skin irritation) / H315; at concentrations ≥ 5%
- Eye irritation 2 (causes eye irritation) / H319; at concentrations ≥ 5%

- Skin sensitisation 1 (may cause an allergic skin reaction) / H317
- Aquatic chronic toxicity 2 (toxic to aquatic life with long-lasting effects) / H411

In summary, the BADGE monomer is not classified for systemic toxicity in mammals. However, it may cause skin or eye irritation at concentrations ≥ 5% and/or allergic skin reactions, and it exhibits chronic toxicity to aquatic organisms.

5.5.4.2 Conclusions re. Criterion 3 hazard similarity

Since it is hypothesised that all members of the group of solid BADGE polymers have the same – or less – hazard properties as the BADGE monomer, they may exhibit skin irritation, eye irritation, and/or skin sensitisation (human health hazard properties) and/or chronic aquatic toxicity (environmental hazard properties). To support this hypothesis, Type 1 and Type 2 BADGE epoxy resins (i.e. those BADGE polymers with the lowest molecular weight and hence highest potential for systemic bioavailability and toxic potential) have been submitted to lower-tier testing. While the findings from the lower-tier testing do indicate some potential for skin irritation and skin sensitisation, the tested BADGE polymers generally exhibited either no or low effects. It has not yet been possible to identify structural reasons for any differences in skin irritation / skin sensitisation potential between Type 1 and Type 2 BADGE epoxy resins (Section 5.8.1). Aquatic toxicity screening of the water-insoluble BADGE polymers was not possible in aqueous solution, but only after addition of Tween 80 (Section 5.8.1). This has been evaluated as indicating absence of aquatic toxicity potential (Section 5.8.2). All other hazard endpoints are not considered relevant for the solid BADGE polymers since the BADGE monomer does not show other hazards and the BADGE polymers are unlikely to exhibit higher toxicity potential than BADGE on its own.

Taken together, the solid BADGE polymers that have been grouped together in this case study include 0-16% BADGE monomer/prepolymer, which is further firmly trapped in the polymer matrix and thus of low physical availability (Section 5.3.1.3). By comparison, the registered BADGE monomer contains more than 80% BADGE constituent (Table CS4.1), which is (clearly) not trapped in a matrix and thus has some potential to become externally bioavailable. Therefore, the solid BADGE polymers likely exhibit less skin and eye irritation, skin sensitisation, and aquatic toxicity potential than the registered BADGE monomer. Nonetheless, (minor) differences in hazard potential may also be present within the group of solid BADGE polymers. The paragraphs below outline how the Criterion 2 properties of the solid BADGE might provide further evidence to support the grouping, or even subgrouping, of solid BADGE polymers. (For recollection, the liquid BADGE epoxy resins are out of scope).

LMW fraction: Since it is hypothesised that the presence of the BADGE monomer/prepolymer is the toxicity driver for the solid BADGE polymers, any hazard potential may be dependent upon the proportion of free BADGE. Notably, however, the BADGE monomer is not very toxic to humans (see above). Therefore, it is possible that minor differences in the fraction of free BADGE present in different solid BADGE epoxy resins do not result in measurable differences in the resin's overall hazard potential. Additionally, the oligomers do equally carry epoxide groups which might cause a certain hazard potential by themselves, despite expected lower reactivity due to the larger molecules. This may impair opportunities to subgroup solid BADGE polymers by the fraction of free BADGE monomer.

M_n of the polymeric substance: In a regulatory setting, it is generally accepted that molecules with molecular weights > 1,000 Da have a low likelihood of becoming systemically bioavailable (see e.g. EFSA, 2008a; US EPA, 2013). With respect to the M_n of the different BADGE epoxy resins, it remains to be established if Type 1 with M_n < 1,000 Da exhibits different hazard properties than Type 2 (with M_n just above 1,000 Da) or Type 4 and Type 7 with higher M_n. Furthermore, in this context it might be informative to assess the molecular weight of the oligomeric components and the total contents of oligomers with molecular weight < 500 Da and < 1,000 Da.

Presence of reactive functional groups: With respect to the FGEW of the different BADGE epoxy resins, it remains to be established if Type 1, Type 2 and Type 4 with FGEW < 1,000 g/Eq., and hence potential for reactivity, exhibit different hazard properties than the Type 7 with FGEW > 1,000 g/Eq.

5.6 Case Study 4: CF4Polymers (Step 5) Determination of exposure scenarios

This case study does not focus on exposure assessment. (As a general rule, the degree of polymerisation is likely to impact the potential release of BADGE constituent / prepolymer and oligomers from the polymer matrix.)

For comprehensiveness, Table CS4.3 presents relevant exposure scenarios for BADGE epoxy resins. Since BADGE epoxy resins are exclusively used in industrial set-ups, the human population addressed in the hazard and risk assessment are workers in production sites.

Potential worker exposure may include exposure to powder dust (via the dermal and respiratory routes of exposure) for powder-based BADGE epoxy resin coatings. By comparison, worker exposure to solvent-borne liquid coatings could occur via the dermal route, but it is unlikely due to the high degree of automation of all processes.

Powder-based coatings: Since some residual dust exposure is not excluded upon powder coating manufacturing and application (in the order of magnitude of a few µg/m^3), in spite of powerful aspiration and ventilation systems, risk management measures are in place consisting of local exhaust ventilation as well as wearing personal protection equipment like masks, gloves and overall.

Solvent-borne can coatings: The manufacture and application of solvent-borne can coating proceeds with high level of isolation/containment because of the presence of solvents.

Waste management: For both powder-based coatings and solvent-borne can coatings, wastes (mainly due to accidental spillage and overspray) are incinerated by specialised service companies. Basically, powder coatings are applied to temperature-resistant substrates since the cure temperature is greater than 160°C. Therefore, suitable substrates for powder-based coatings are essentially metal with marginal use on glass and ceramic. All these materials are recycled at very high temperature, at which the powder coating is burned. Therefore, no release to the environment is expected from these technologies.

Table CS4.3: Exposure scenarios for bisphenol A diglycidylether (BADGE) epoxy resins

Activity	Process Category (PROC)	Environmental Release Category (ERC)
Industrial formulation of powder coatings (dry-blending, extrusion, flaking, grinding)	3, 8b, 14, 24	2
Industrial packaging of powder coatings	9	2
Industrial application of coatings: electrostatic application of powder to objects to be cross-linked at high temperature	7	6d
Solvent borne paint manufacturing and packaging	3, 8b, 9	2
Industrial automated application of liquid paints and cure	7	6d

Footnote to Table CS4.3:

Exposure scenarios as per ECHA (2015):

ERC2 Formulation into mixture

ERC6d Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)

PROC3 Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition

PROC7 Industrial spraying

PROC8b Transfer of substance or mixture (charging and discharging) at dedicated facilities

PROC9 Transfer of substance or mixture into small containers (dedicated filling line, including weighing)

PROC14 Tabletting, compression, extrusion, pelletisation, granulation

PROC24 High (mechanical) energy work-up of substances bound in /on materials and/or articles

5.7 Case Study 4: CF4Polymers (Step 6) Exposure characterisation

CF4Polymers (Step 6) exposure characterisation is not relevant for this case study, as it does not intend to perform exposure assessment.

5.8 Case Study 4: CF4Polymers (Step 7) Hazard assessment

5.8.1 Lower-tier toxicity and ecotoxicity assessment

To provide further scientific evidence to support the grouping (Section 5.5) and to assess the bioavailability of BADGE monomers/prepolymers in solid epoxy resins, this case study also considers data from lower-tier toxicity and ecotoxicity studies that were conducted for BADGE epoxy resins Type 1 and

Type 2. These are the solid epoxy resins with the lowest M_n and hence highest potential for toxicity (as compared to Type 4 and Type 7).

To determine if any toxic effects are attributable to either the free BADGE monomer/prepolymer or the polymeric substance itself, both Type 1 and Type 2 were tested both 'as produced', i.e. with the complete LMW fraction, and after purification by distillation (in a short-path evaporator at 250 °C and 0,05 mbar) to remove the BADGE monomers/prepolymers. GPC data confirmed that Type 1 and Type 2 before purification exhibited 15.7% and 9.9% BADGE, respectively, but only 0.2% and 0.1%, respectively, after purification (Table CS4.4; Figure CS4.4, Panels A and B for Type 1 and Type 2, respectively).

The lower-tier studies were selected to include those toxicological and ecotoxicological endpoints for which the BADGE monomer has hazard classifications (Section 5.5.3). Further, water solubility of the Type 1 and Type 2 resins was considered. It is hypothesised for subgrouping that the BADGE epoxy resins, that consist entirely of BADGE repeating units do not exhibit any 'new' toxicological or ecotoxicological properties that the BADGE monomer itself does not possess.

Specifically, the testing strategy included:

- **OECD TG 105**: Water solubility
- **OECD TG 202**: *Daphnia* sp. acute immobilisation test
- **OECD TG 439**: *In vitro* skin irritation: Reconstructed human epidermis test method using Episkin™ test tissue models (https://episkin.com/) and reduction of the tetrazolium salt MTT as indicating reduced cell viability (Mossmann, 1983; Faller et al., 2002)
- **OECD TG 429**: *In vivo* skin sensitisation: LLNA in mice (six female CBA/Ca mice/group)

Water solubility of the Type 1 resin (as produced and purified) as well as that of the Type 2 resin (as produced and purified) were below the limit of quantification (i.e. < 2 mg/L; Section 5.3.1.3). Hence, both resins are not soluble in water, which indicates low potential for aquatic toxicity.

With respect to the lower tier ecotoxicological testing (*Daphnia* acute immobilisation test), a 0.01% Tween 80 solution was used as a vehicle (since Type 1 and Type 2 are not soluble in aqueous solutions) in order to produce usable solutions. Indeed, extensive solubility work was needed to identify an appropriate dose preparation method, and the Tween 80 solutions still contained approx. 40% of settleable solids so that the test items were a mixture of substance in suspension and possibly a dissolved part.

Table CS4.4: Analytical data for the samples of Type 1 and 2 epoxy resins (as produced and purified) that were used in the lower-tier testing

Property	Type 1 as produced	Type 1 purified	Type 2 as produced	Type 2 purified
Physical state	Solid			
Number average molecular weight (M_n; Da)	928	1426	1174	1621
Weight average molecular weight (M_w; Da)	1575	1822	1990	2121
Polydispersity (no unit)	1.7	1.28	1.7	1.33
Epoxide groups content				
Functional group equivalent weight (g/Eq.)	455	725	581	840
Epoxy index (Eq./kg)	2.2	1.38	1.72	1.19
Component distribution, as measured by gel permeation chromatography (% surf.)				
BADGE (n = 0)	15.7	0.1	9.9	0.2
Monochlorohydrin of BADGE	0.8	< 0.1	0.6	< 0.1
BADGE oligomer (n = 1)	2.2	2.6	1.7	2.8
BADGE oligomer (n = 2)	21.3	25.6	16.2	17.9
BADGE polymers (n ≥ 3)	60.0	71.7	71.6	79.1

Footnote to Table CS4.4: See text for distinction between 'as produced' and 'purified' epoxy resins. Abbreviations: % surf.: peak surface percent; BADGE: Bisphenol-A diglycidylether; Da: Dalton; n: Number of repeat units.

All findings (EC_{50} obtained in 0.01% Tween 80 solution) greatly exceed the water solubility of the solid epoxy resin polymers, which was below the limit of detection (< 2 mg/L): For the purified Type 1 and Type 2 in 0.01% Tween 80 solution, EC_{50} values of 31.64 and 39.4 mg/L, respectively, were measured, and for the 'as produced' Type 1 and Type 2 in 0.01% Tween 80 solution, EC_{50} values of 6.51 and 12.97 mg/L, respectively. The ECETOC Polymers TF questions the relevance of these findings since the testing conditions do not reflect realistic exposure conditions. The water insolubility of the epoxy resins clearly shows that similar effects would not be observable in water (By contrast, chronic testing with daphnids may be considered without using Tween 80.)

The lower-tier toxicological testing (*in vitro* skin irritation and *in vivo* skin sensitisation) yielded the following findings (Table CS4.5).

- *Type 1 BADGE epoxy resin 'as produced'*: 'not skin irritant' and 'not skin sensitising'
- *Type 1 BADGE epoxy resin 'purified':* 'not skin irritant' but 'weak skin sensitising'
- *Type 2 BADGE epoxy resin 'as produced'* 'skin irritant' but 'not skin sensitising'
- *Type 2 BADGE epoxy resin 'purified'* 'not skin irritant' and 'not skin sensitising'

Figure CS4.4: Panel A

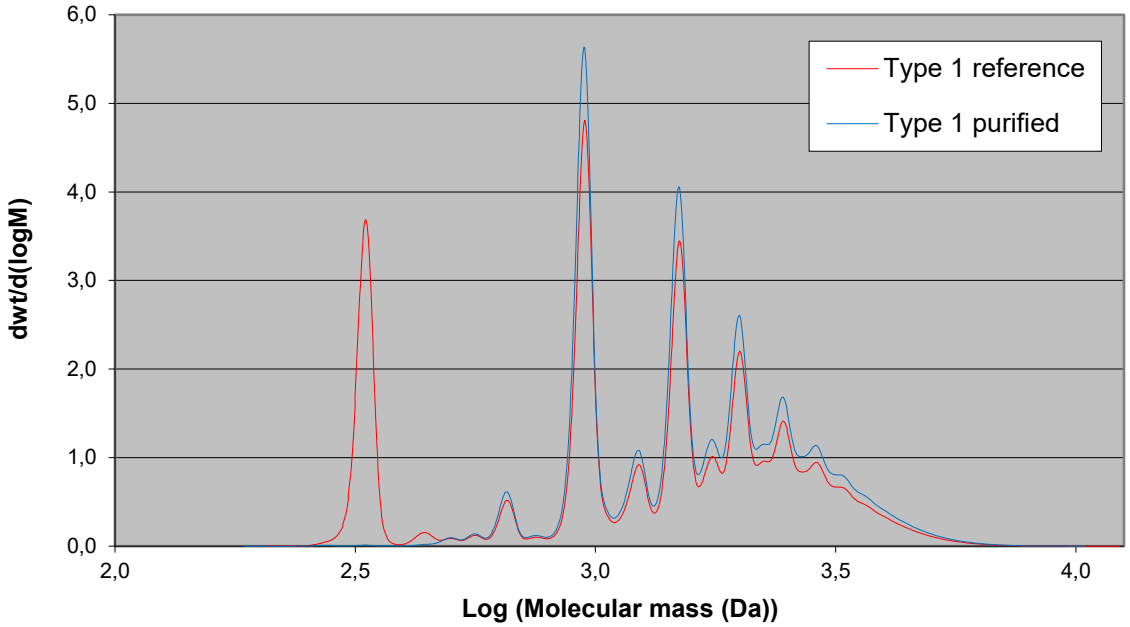


Figure CS4.4: Panel B

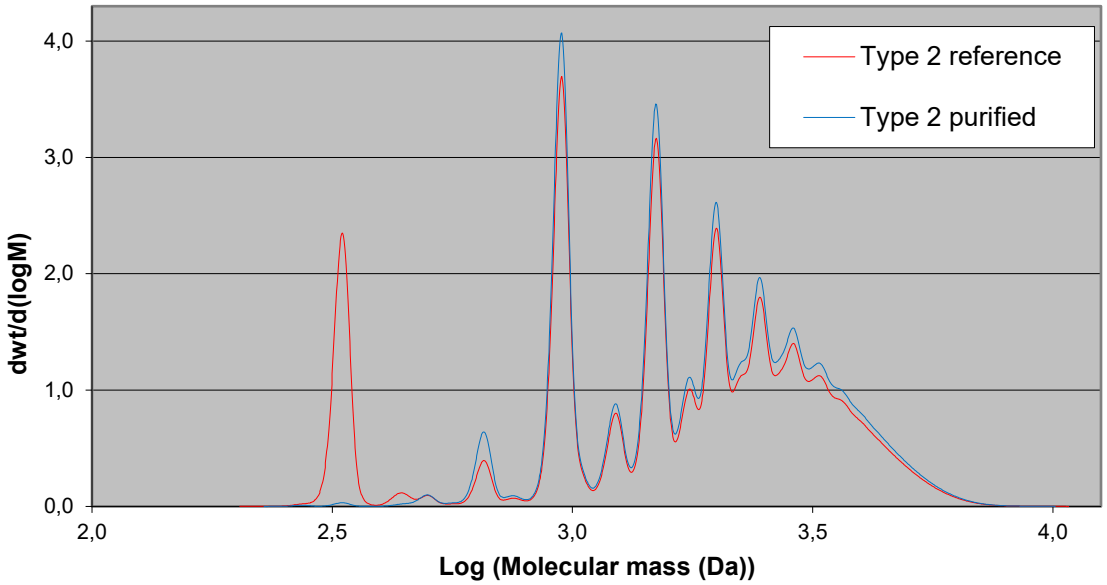


Figure CS4.4 – Panels A and B: Gel permeation chromatograms of Type 1 and Type 2 solid bisphenol-A diglycidylether (BADGE) epoxy resins with and without distillation of the BADGE monomers

Footnote to Figure CS4.4: Panel A: Type 1 BADGE epoxy resin; Panel B: Type 2 BADGE epoxy resin. The red curves relate to the epoxy resins before distillation and the blue curves to the epoxy resins after distillation (dwt/d(logM): differential weight fraction). Clearly, the peak at 2.5 log Da (corresponding to the BADGE monomer / prepolymer is no longer present / negligible after distillation.

Table CS4.5: Lower-tier toxicity and ecotoxicity data for bisphenol A diglycidylether (BADGE) monomer and 'as produced' and 'purified' Type 1 and Type 2 BADGE epoxy resins (unpublished Task Force member company data, used with permission)

	BADGE monomer	Type of BADGE epoxy resin			
		Type 1 'as produced'	Type 1 'purified'	Type 2 'as produced'	Type 2 'purified'
***In vitro* skin irritation (OECD TG 439) using Episkin™ tissue models; MTT reduction as measure of reduced cell viability**					
% Tissue viability Mean of 3 replicates ± SD	**Irritant**	78.56 ± 2.27 [a]	98.49 ± 2.46 [a]	**Skin irritant [b] 10.367 ± 0.50 [c]**	70.066 ± 0.48 [c]
***In vivo* skin sensitisation (OECD TG 429); LLNA - six female CBA/Ca mice/group**					
Mean SI for 15% / 30% / 60% w/v test item in MEK	0.9-11.8	1.03 / 1.27 **/** 1.60	1.06 / 1.74 / 3.28	1.20 / 1.57 / 1.79	1.23 / 1.70 / 1.92
EC3 value [d]	**Moderate sensitiser 5.7%**	Not applicable: No SI > 3	**Weak sensitiser 54.55%**	Not applicable: No SI > 3No SI > 3	Not applicable: No SI > 3No SI > 3
Water solubility (OECD TG 105)					
(mg/L)	6.9	< 2	< 2	< 2	< 2
Acute toxicity to *Daphnia magna* (OECD TG 202)					
EC_{50} (mg/L) [e]	1.8	6.51	31.64	12.97	39.4
LOEC (mg/L) [e]		9	10	9	10
NOEC (mg/L) [e]		5	5	5	5

Footnote to Table CS4.5: Abbreviations: EC3: Estimated concentration needed to elicit 3-fold increase in lymph node cell proliferative activity, i.e. to produce a stimulation index of 3; EC_{50}: Concentration required to achieve 50% effect change from the control; LLNA: Local lymph node assay; LOEC: Lowest observed effect concentration; MEK: Methyl ethyl ketone; MTT: A tetrazolium bromide; NOEC: No observed effect concentration; SD: Standard deviation; SI: Stimulation index; TG: Test guideline.

[a] Concurrent positive control (10 µL of 5% aqueous sodium dodecyl sulphate): 7.308 ± 0.13 % tissue viability (mean of 3 replicates). The concurrent negative control met the OECD TG 439 acceptance criteria.

[b] As per OECD TG 439, a substance is assessed as Skin Irritant Category 2 if it decreases cell viability ≤ 50%.

[c] Concurrent positive control (10 µL of 5% aqueous sodium dodecyl sulphate): 7.57 ± 0.46 % tissue viability (mean of 3 replicates). The concurrent negative control met the OECD TG 439 acceptance criteria.

[d] As per ECETOC TR No. 87 (*Contact sensitisation: Classification according to potency*), EC3 values between ≥ 1 and < 10 are evaluated as indicating moderate sensitisation and EC3 values between ≥ 10 and ≤ 100 as indicating weak sensitisation (ECETOC, 2003).

[e] Tween 80 was used as vehicle in order to produce a usable solution. Extensive solubility work was needed to identify an appropriate dose preparation method. All findings (EC_{50} in Tween 80) greatly exceed the water solubility of Type 1 and Type 2 BADGE epoxy resins, which was below the limit of detection (< 2 mg/L).

5.8.2 Evaluation of lower-tier toxicity and ecotoxicity testing and conclusions for hazard assessment

The only positive findings in the lower-tier toxicity tests were:

- 'Weak skin sensitisation' for the purified Type 1 BADGE epoxy resin that contains only residual amounts of free BADGE monomer, and
- 'Skin irritation' for the 'as produced' Type 2 BADGE epoxy resin that contains 11.3% free BADGE monomer.

Hence, while the (very limited) dataset is currently inconsistent with respect to skin irritation and skin sensitisation, it does point to an overall low local toxicity potential of the solid BADGE polymers.

It is not yet possible to determine if any skin sensitisation that may be elicited by solid BADGE polymers is rather caused by the BADGE monomer as common key constituent that is known to cause skin sensitisation, or rather by the BADGE oligomer / polymer itself with its free epoxide groups. (It is methodologically challenging to remove hazardous non-polymer components from BADGE polymers. Some of the effect may still have been caused by unintentional concentrations of more soluble components including residual monomers.)

Further research work is recommended to investigate if BADGE epoxy resins with even higher M_n than Type 2 that is just above the 1,000 Da threshold – and thereby also lower amounts of reactive functional groups – are, or are not, skin sensitisers. Similarly, further research work is recommended to investigate if the amount of LMW constituents, M_n of the polymeric substance, and amount of reactive functional groups are correlated with the skin irritation potential of BADGE epoxy resins.

While this case study does not aim at performing hazard or risk assessment for any specific solid BADGE polymer, the findings from the (Step 4) grouping approach evaluation and (Step 6) lower-tier toxicity and ecotoxicity testing allow drawing the following high-level conclusions:

- Since it is hypothesised that all members of the group of solid BADGE polymers have the same – or less – hazard properties as the BADGE monomer, they may exhibit skin irritation, eye irritation, and/or skin sensitisation (human health hazard properties) and/or chronic aquatic toxicity (environmental hazard properties). By contrast, they are unlikely to exhibit any other environmental or human health hazard properties.

- If the respective solid BADGE polymer is of too HMW to become systemically bioavailable and further does not include LMW constituents above the accepted levels (Section 5.5.2.1), such as is the case for Type 7, it is unlikely to pose a hazard concern.

- For those solid BADGE polymers that may become systemically bioavailable and/or that include LMW constituents above the accepted levels (Section 5.5.2.1), read-across from the data available for the BADGE monomer to fill data gaps for the solid BADGE polymers appears justifiable.

- If specific solid BADGE polymers were to be used for sensitive applications (which however is not the case), selected further testing may be recommendable to substantiate the available database.

Further, the findings from the lower-tier studies highlight, once again, that the applicability of *in vitro* studies or *in chemico* studies (such as the direct peptide reactivity assays), as well as *in vivo* studies, depends on key physico-chemical properties of the test material, and most importantly on its water solubility (see also Section 7.5 in ECETOC TR No. 133-2). Solubility can be facilitated by the selection of appropriate solvents / vehicles,

but their presence may also alter e.g. the particle size of the test material thereby potentially also creating artificial external / systemic bioavailability and hence environmentally irrelevant toxicity. Also, use of specific solvents does not reflect realistic exposure conditions, e.g. for aquatic toxicity testing, thereby calling into question the relevance of the test results. The case study also demonstrates that biological test systems with their inherent variability are not necessarily suited to reflect compositional differences between test materials, as analytical methodologies often are more sensitive and accurate.

5.9 Case Study 4: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for any specific BADGE epoxy resin (and, as such, did not consider release scenarios, exposure routes, etc.). Instead, it has served to evaluate if the ECETOC TR No. 133-1 CF4Polymers is generally applicable to BADGE epoxy resins and if the collated information provides further insight on the applicability of tools and test methods for the physico-chemical characterisation and toxicity / ecotoxicity testing of BADGE epoxy resins.

BADGE epoxy resins present an example that covers the chemical space of substances (monomers, prepolymers, oligomers) with a continuous transition to lower and higher molecular weight polymeric substances. The fit-for-purpose polymer identification has focussed on a comprehensive identification and relative quantification of all LMW constituents present in the polymer product; the M_n of the polymeric substance; the amount of reactive functional groups; as well as water solubility and water extractability. A pragmatic polymer fraction approach for polymer subgrouping has been applied, which also considered the presence and amount of reactive functional groups. Following the polymer fraction approach, a polymer could generally be defined as a mixture of an LMW fraction (that may include both non-polymeric as well as LMW oligomer constituents) and an HMW fraction that would have very low bioavailability.

The main part of the risk assessment would refer to the LMW fraction, which is bioavailable in the conditions of use. By contrast, the polymer matrix would mainly interfere with biological organisms via surface contact (and the LMW components that can migrate to the surface – unless the matrix hinders their physical availability). In this case study, a worst-case scenario has been applied assuming that the entire LMW fraction that is present in the polymer product may also become externally and systemically bioavailable It is currently unclear how much of the LMW fraction will become physically available, and hence potentially also externally and internally bioavailable, under different conditions of use. Presumably, the degree of release decreases with higher cross linking and molecular weight of the epoxy resins.

Further research work is merited to enhance an understanding of how the different ‘key’ properties (1) amount of BADGE; (2) amount of LMW polymeric substance; (3) amount of reactive functional group – in combination – might aggravate or attenuate the overall hazard potential of the respective BADGE epoxy resin.

While the present theoretical case study did not include exposure assessment, in practice, the risk assessment may need to consider use-specific exposure scenarios and risks. For example, if there is a risk of ingestion, the liposoluble fraction would need to be identified; or if the epoxy resins would be processed at high temperature, the distillate fraction may need to be identified, etc.

During hazard assessment, the soluble and insoluble fractions of the test item should be determined, especially if a major proportion of the test item is present as powder suspension. Clearly, the testing of solid

materials or partly soluble solid particle suspensions is more complex than the testing of true solutions, and existing test methods as used for soluble substances may need to be adapted to enable such testing (ECETOC, 2018; OECD, 2019).

The approach to consider the LMW fraction of the polymer for risk assessment requires an accurate definition of the relevant LMW fraction and hence also of the groups and subgroups that different members of the respective type of polymers should be assigned to in order to provide reliability and credibility to the grouping – and to the hazard and risk assessment.

In this regard, the present case study has made some suggestions for criteria that may need to be considered for the grouping and subgrouping of BADGE epoxy resins and it has provided first insight on relevant physico-chemical properties as well as potentially relevant hazard properties. Unsurprisingly, this insight has also served to reveal further research needs that have been identified above.

Beyond the BADGE epoxy resins considered in this case study (that consist entirely of BADGE), further work may be merited to consider a wider grouping of BADGE polymers with other epoxy polymers. For example, epoxy resins made of the prepolymer bisphenol-F diglycidylether (as common key constituent) could possibly form a larger group with epoxy resins having BADGE as common key constituent, since both common key constituents share many physico-chemical and (eco)toxicological properties.

6. CASE STUDY 5: POLYETHEROLS

6.1 Introduction

6.1.1 Scope and outline of Case Study 5

This case study addresses polyetherols (PEOLs), i.e. polymers which are based on initiator molecules which contain multiple hydroxyl or amino functional groups (Table CS5.1). During the production of PEOLs, the functional groups of the initiator molecules (synonyms: starter molecules or core molecules) are alkoxylated with propylene oxide (PO) and/or ethylene oxide (EO). Since the alkoxylation of the initiator molecules results in multiple free terminal hydroxyl groups, the overarching name for this type of compounds is polyols. PEOLs are polyether polyols. Further polyols, that are not included in this case study are e.g. polyester polyols, which are linked by carboxyl groups. The distinguishing features of polyols are the linkage-types between the initiator molecules and the ethoxy or propoxy repeating units. While PEOLs can be either ether-linked or amine-linked, focus of this case study is on the ether-linked PEOLs.

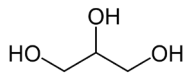
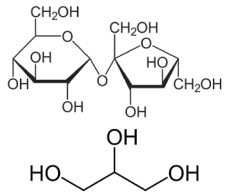
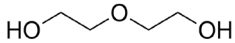
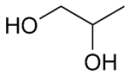
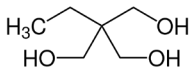
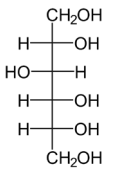
The intended use of the PEOLs considered in this case study is industrial use where the PEOLs undergo further reactions with methylene diphenyl diisocyanate and toluene diisocyanate to form foams that are used for the production of e.g. mattresses and insulation boards. In general, no consumer use or professional use is anticipated for PEOLs and subsequently exposure is also considered to be unlikely. Also, wide dispersive use of PEOLs is highly unlikely. PEOLs are mainly handled in a controlled, industrial setting, followed by further processing downstream of other polymers formed out of them, which is not considered in this case study. For example, when reacted with diisocyanates, PEOLs form polyurethanes, which are used in a number of product applications such as flexible and rigid foams, and in Coatings, Adhesives, Sealants & Elastomer systems that are used in industrial and professional settings.

Concerning worker exposure and environmental exposure, point sources must be considered. Under controlled industrial settings only low-level exposure is expected.

It is the aim of this case study to apply the CF4Polymers (Step 4) grouping approach evaluation presented in Section 1.3 to PEOLs. PEOLs are regarded as a group based on similar physical, chemical, ecotoxicological and toxicological properties, as well as based upon the types of chemistries for which they are used. During grouping, the oligomeric polyols will be used as source substances. The strategy for characterising and evaluating the hazard profile of the PEOLs is to rely on the information obtained from the oligomeric polyols in combination with basic data available for selected PEOLs. Opportunities shall be identified to apply read-across from the oligomeric polyols to fill data gaps for those PEOLs that have the same chemistries (i.e. initiator molecules, EO and PO).

With respect to (Step 3) polymer component strategy, focus is on the polymeric substances and on the oligomers that are generally present in PEOLs as one component of the different polyol constituents covering a certain molecular weight range.

Table CS5.1: Initiator molecules, chemical structure, alkoxylation variants and molecular weight ranges of PEOLs considered in case study

Initiator molecule (R1)	Chemical structure	Alkoxylation variants (repeating units)	Number-average molecular weight range (Da)
1,2,3-Propanetriol (i.e. glycerol)		EO PO EO-PO	**EO**: 300 (NLP) **PO**: 200-450 (NLP); 1,100-3,400 (polymers) **EO-PO**: 1,100-6,000 (polymers)
Saccharose / glycerol (mixture for co-initiated PEOLs)	 	PO EO-PO	**PO**: 400-630 (NLP) **EO-PO**: 600 (NLP)
Diethylene glycol (i.e. 2,2'-oxydiethanol)		EO-PO PO (only NLP)	**EO-PO**: 300 (NLP); 2,000 (polymer) **PO**: 280 (NLP)
Propane-1,2-diol (i.e. monopropylene glycol)		PO EO-PO	**PO**: 430 (NLP); 500-4,000 (polymers) **EO-PO**: 2,000-4,000 (polymers)
Propylidynetrimethanol (i.e. trimethylol propane)		EO PO EO-PO	**EO**: 170-280 (NLP); 700 (polymer) **PO**: 200-400 (NLP); 1,000-3,700 (polymer) **EO-PO**: 300 (NLP); 3,700 (polymer)
Glucitol (i.e. D-sorbitol)		PO EO-PO	**PO**: 400-550 (NLP); 800-2,000 (polymer) **EO-PO**: 6,000-18,000 (polymer)

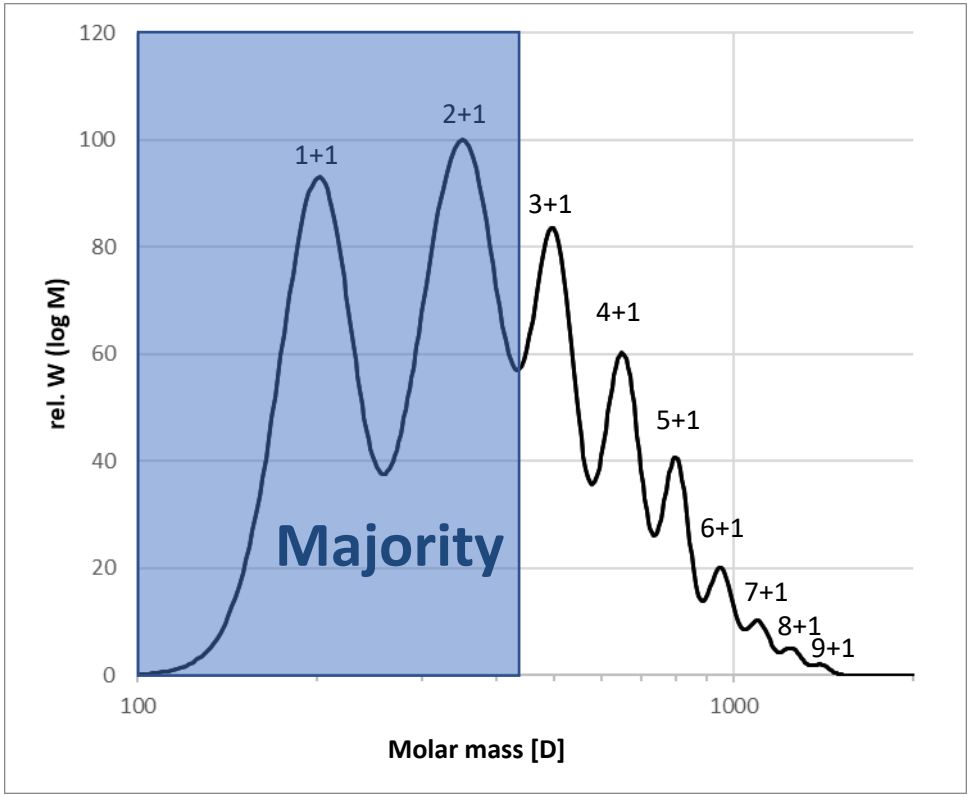
Footnote to Table CS5.1:

Abbreviations: Da: Dalton; EO: Ethylene oxide; NLP: No longer polymer; PEOL: Polyetherol; PO: Propylene oxide.

PEOLs can be either random polymers or block polymers.

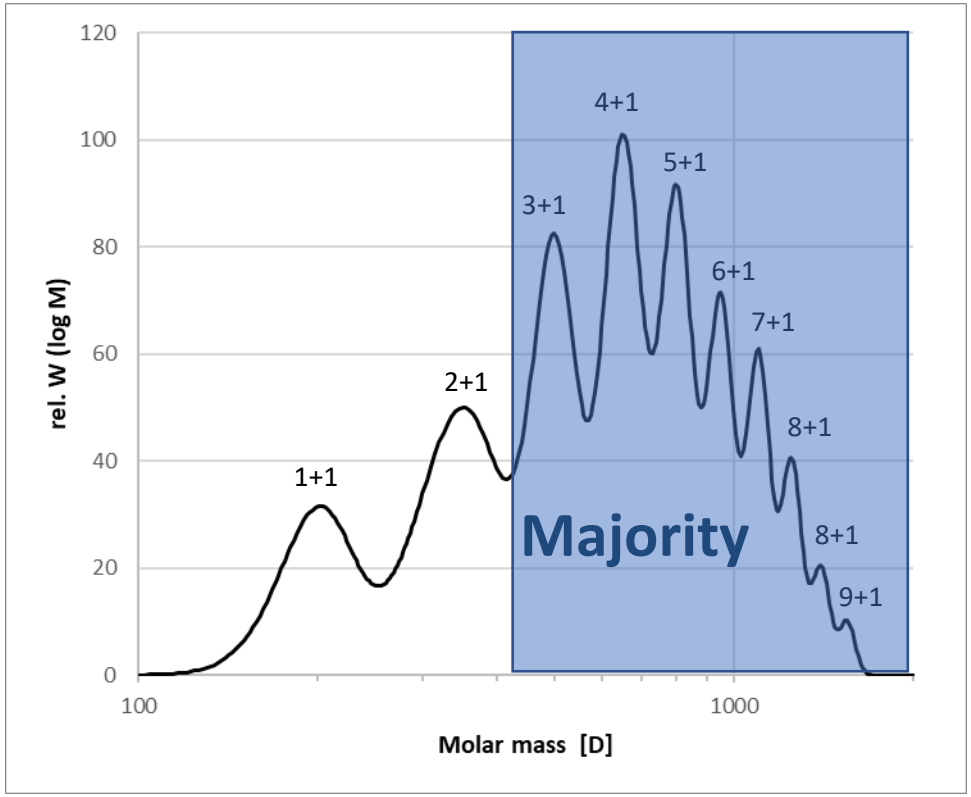
The alkoxylation of the initiator molecules results in molecules of varying chain lengths ranging from oligomeric polyols to polymeric polyols, i.e. PEOLs (Figure CS5.1). For each polyol, a certain molecular weight distribution is obtained. Nonetheless, the fraction of specific constituents (by molecular weight) present in any particular polyol may differ between producing facilities and even between batches produced in the same facility.

Oligomeric polyols (NLP)



Does not fulfil the polymer definition

Polymeric polyols (PEOLs)



Fulfils the polymer definition

Figure CS5.1: Schematic illustration of gel permeation chromatograms of oligomeric no-longer polymer (NLP) polyols and polymeric polyols (polyetherols (PEOLs)) resulting from alkoxylation of the initiator molecules and differentiation

Footnote to Figure CS5.1: X axis: Molar mass (D); Y axis (rel. W (log M)): relative mass fractions (in one molar mass interval).
The border between the blue and the white areas represents the threshold between those constituents of a PEOL that fulfil the criteria for a polymer (right hand side of each graph) and those that do not fulfil the criteria for a polymer (left-hand side of each graph).

6.1.2 Definition of oligomeric polyols vs PEOLs

Those polyols that do not fulfil the '3n+1 rule' or the '50% rule' (Box 3 in Section 1.2) are the smaller, oligomeric equivalents of the PEOLs, i.e. the oligomeric polyols. Since a number of oligomeric polyols are included in the list of NLPs, the terms NLP polyols and oligomeric polyols are used interchangeably in this case study. Generally, the NLP polyols have to undergo registration under the EU REACH Regulation (EP and Council, 2006), so that toxicological and ecotoxicological data have been generated, or are being generated, for them (Table Intro-2).

The PEOLs include those polyols, which do fulfil the '3n+1 rule' and therefore are regarded as polymers. The transition from NLP polyol to PEOL is continuous and outlines a shift from polyols with a lower degree of alkoxylation to polyols with a higher degree of alkoxylation, i.e. polyols where the majority of components fulfil the criteria of a polymer (Figure CS5.1).

6.1.3 Synthesis and use

A multitude of PEOLs are produced for custom-tailored uses in specialised applications (Section 6.1.1). Depending on their intended application, polyols of varying molecular weight, viscosity and reactivity can be formed. They are produced in industrial settings in closed systems and under controlled conditions due to the use of EO/PO as hazardous, volatile reactants.

Typically, the catalyst is first added to the initiating molecule, and then the monomers PO and/or EO are added in a polymerisation reaction until the desired degree of alkoxylation (chain length) and molecular weight are reached. Initiating molecules comprise sugar and aliphatic linear or branched molecules, e.g. glycerol, monopropylene glycol, diethylene glycol, propylidynetrimethanol, glucitol, and saccharose / glycerol (Table CS5.1; Figure CS5.2). Non-reacted PO and/or EO will be removed from the polyol. Such reactions yield PEOLs of a certain molecular weight range, i.e. polymer products with polyol constituents of different chain lengths.

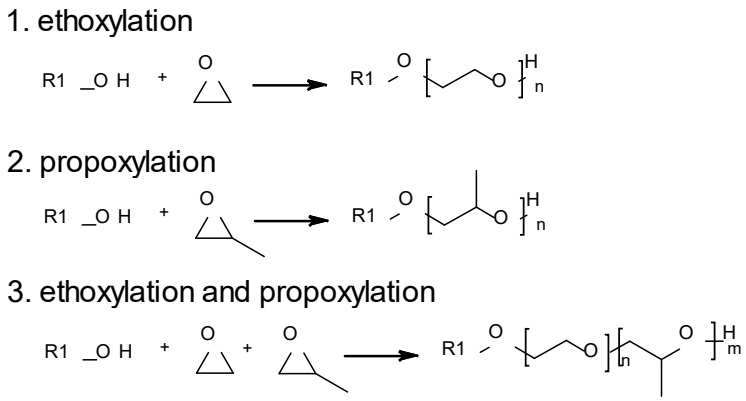


Figure CS5.2: Alkoxylation of the hydroxyl functional group of the initiator molecule with ethylene oxide (EO) or propylene oxide (PO): 1. Ethoxylation (EO) 2. Propoxylation (PO) 3. Ethoxylation and propoxylation (EO-PO)

Footnote to Figure CS5.2: n, m: Number of (different) repeat units; R1 = Initiator molecule.

Figure CS5.3 displays the propoxylation reaction of diethylene glycol as initiating molecule, resulting in propoxylated diethylene glycol, which is an NLP polyol. From this reaction, a wide range of propoxylated diethylene glycol constituents can be formed. For any oligomeric or polymeric polyol, the proportion of different polyol constituents (by chain length and hence molecular weight) may vary greatly, e.g. depending on the producing company or even depending on the given batch. In spite of this large variability, all samples would still be considered to be the 'same' substance (i.e. propoxylated diethylene glycol) and thus all have the same CAS number (i.e. CAS No. 9051-51-8). Thus, NLP polyols and PEOLs with high and low amounts of different constituents of varying degrees of alkoxylation can be found on the market.

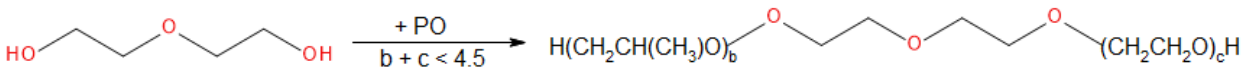


Figure CS5.3: Simplified propoxylation reaction of diethylene glycol to obtain the oligomeric polyol propoxylated diethylene glycol

6.2 Case Study 5: CF4Polymers (Step 1) Problem formulation

This case study considers industrial use of a PEOLs with different initiator molecules in closed industrial settings. Therefore, the protection goal relates to individual workers and the environment. Focus of the case study is on (Step 4) grouping approach evaluation to identify information needs for environmental and human health hazard assessment (intrinsic hazards). To support the grouping, the case study presents and discusses details on (Step 2) polymer identification and (Step 7) hazard assessment.

6.3 Case Study 5: CF4Polymers (Step 2) Polymer identification

6.3.1 Step 2.1: Identification of the polymeric substance

6.3.1.1 Standard chemical descriptors

Table CS5.1 lists the PEOLs in scope of this case study. Usually, the CAS name and the corresponding CAS number are used as chemical descriptors for PEOLs. PEOLs can either be random polymers or block polymers.

For example, PEOLs with the CAS No. 50658-23-6 and EC No. 701-310-5 have the CAS name '*ethanol, 2,2'-oxybis-, polymer with 2-methyloxirane and oxirane*'. However, this approach is not sufficiently specific for these (or many other) polymers when it comes to clear identification of hazardous products. CAS names describe only the starting materials or repeat units and do not discriminate e.g. different chains lengths or variations in composition such as proportion of initiator molecules/monomers.

6.3.1.2 Chemical name

Instead of CAS or IUPAC names, other chemical descriptors could be used to describe the chemical structure of the polymer. Taking the hypothetical example of Glyc(2) - EO(24) - PO(74), Glyc stands for the initiator molecule glycerol, EO / PO for the ethoxylated / propoxylated chains, and the numbers in brackets for the median of the relative fractions of the components of the distribution (i.e. amounting to 100%). However,

different naming conventions are possible. For example, the numbers in brackets could also indicate absolute numbers of the respective components. Alternatively, the numbers of moles might be indicated. Hence, the selected naming convention should be specified.

Nonetheless, the attempt to precisely define each PEOL, and to fully describe its composition, would lead to an almost infinite number of chemical identifiers. A pragmatic and still sufficiently precise approach to meet this challenge is warranted. Trade names and other commercial descriptors are supportive in this regard but are not chemical descriptors in the proper sense. Therefore, they should not be used on their own, but only together with a CAS number and a telling chemical descriptor, as described above. Taken together, considering the large variety of PEOLs (yielding an almost infinite number of any telling descriptor), it will likely remain challenging to find an approach that is both pragmatic and sufficiently precise for the respective objective of identity description.

6.3.1.3 Structural and morphological descriptors

The production of PEOLs, i.e. 'polyether polyols' results in structures with repeated ether bonds and two or more terminal hydroxyl groups. Due to the large variability of possible initiator molecules as well as of the number and order of the repetitive groups, a very large variety of PEOLs is possible and is indeed being marketed. Depending on the initiator molecule, PEOLs are either linear (which is mostly the case), or they have a branched structure (which is possible when the initiator molecules are either amines or alcohols with at least three functional groups).

6.3.1.4 Weight-average and number-average molecular weight

Due to their versatility, PEOLs cover a wide molecular weight range, i.e. LMW range approx. 500-800 Da, medium range 800-3,000 Da; and long chain and HMW up to 18,000 Da (Table CS5.1). The different molecular weight ranges determine the properties of PEOLs (e.g. size) and thus their use in a wide variety of applications. Also, depending on the production conditions, each PEOL may have a more or less broad molecular weight distribution.

6.3.1.5 Viscosity

The viscosity of different PEOLs covers a wide range from 100 mPa*s to 40,000 mPa*s (millipascal seconds) at 25 °C. Nonetheless, all PEOLs included in this case study are liquids at 20 °C (> 10,000 mPa*s, i.e. highly viscose liquids).

6.3.1.6 Solubility in water

All PEOLs included in this case study exhibit high to very high water solubility. Available water solubility data range from 1 g/L to 1,000 g/L at 20 °C.

6.3.1.7 n-Octanol/water partition coefficient

The n-octanol/water partition coefficients (log K_{ow}) of PEOLs are very low, and in most cases < 1 at 25 °C. Only a few PEOLs show a log K_{ow} value > 1 but in no case more than 2. These low log K_{ow} values are in line with the high water solubility.

6.3.1.8 Surface tension

Surface activity describes the ability of a substance to reduce the surface tension of water; see Section 7.3.1.9 in Case Study 6 on surfactant polymers for details on surface tension. There, it is also described that the ECETOC Polymers TF recommends applying a threshold of < 45 mN/m (European Commission, 2018; US Government, 2021), instead of < 60 mN/m (Council, 2008) for the identification of polymers with surfactant properties.

Surface-active potential has only been measured for few PEOLs, e.g. Glycerol-EO-PEOL (CAS No. 31694-55-0) and Diethylene glycol-EO-PO-PEOL (CAS No. 50658-23-6 / EC No. 701-310-5) (BASF SE; unpublished company data). These data show that the measured PEOLs do have the ability to reduce the surface tension of water, but in most cases only to a minor extent. The measured values generally range from 56-63 mN/m, i.e. they exceed the threshold of < 45 mN/m to determine surface activity. The only exception is the NLP *o*-1,2-diaminotoluene EO-PO (CAS No. 67800-94-6), which however is out of scope of the present case study (Table CS5.1), for which a surface tension of 43 mN/m was measured, so that it does undercut the threshold indicating surface activity.

6.3.1.9 Vapour pressure

Vapour pressures for the POELs included in this case study are low, and in most cases < 0.10 mbar at 20°C. The low vapour pressure stands in line with the (relatively) high molecular weight, which comes along with the polymeric nature of the PEOLs.

6.3.2 Step 2.2: Identification of additives

About half of the PEOLs included in this case study do not contain any additives at all, whereas the other half includes antioxidants. Generally, the content of an antioxidant in a PEOL is < 0.1% w/w. Additives are not considered in this case study and are therefore not further discussed here. However, due to their low content, they are not assumed to have a significant impact on the (hazard) properties of PEOLs.

6.3.3 Step 2.3: Identification of NIAS and/or residual substances

Oligomers are generally part of PEOLs. Apart from that, there are only few NIAS present in PEOLs (i.e. at most in the lower ppm range). The initiator molecules are completely reacted in the final product, especially in PEOLs with higher molecular weight. Similarly, reaction steps are implemented during the manufacture of PEOLs to ensure that EO and PO are completely consumed. Accordingly, the initiator molecules and EO / PO are no longer detectable in the final polymer products.

6.4 Case Study 5: CF4Polymers (Step 3) Polymer component strategy

Case Study 5 addressing PEOLs considers the polymeric substances as well as the oligomers that are part of PEOLs. The grouping approach presented in Section 6.5 uses the data that are available from the corresponding oligomeric polyols (Section 6.1.2) for the assessment of the polymeric polyols with higher molecular weight range, i.e. the PEOLs. For this reason, the oligomers contained in the PEOLs are *per se* included in the overall assessment.

Any additives or any further NIAS (especially EO /PO residues) present in the PEOLs (beyond the oligomers) may be considered in general cases of safety assessments but are out of scope of this case study.

6.5 Case Study 5: CF4Polymers (Step 4) Grouping approach evaluation

6.5.1 Premises and hypotheses for grouping

Following the three-Criteria grouping approach described in Section 1.3, polymers may be grouped together if they exhibit congruency of similarity along all three Criteria. Hence, PEOLs shall be grouped together on account of their similarity by chemical nature (Section 6.5.2), similarity by physico-chemical properties (Section 6.5.3) and hazard similarity (Section 6.5.4).

Further, it is hypothesised that data gaps for the group of PEOLs can be filled by read-across from the corresponding NLPs.

The alkoxylation of any given initiator molecule results in polyols with different chain lengths ranging from NLP polyols to PEOLs that each have a certain molecular weight distribution. The NLP polyols have to undergo registration under the EU REACH Regulation (EP and Council, 2006; Section 6.1.2). Therefore, a more extensive database has been generated, or is being generated, for the NLP polyols than for the polymeric PEOLs and is considered as an appropriate data source for a read-across approach.

Against this background, the strategy for characterising and evaluating the hazard profile of PEOLs relies on the available information for the corresponding oligomeric NLPs in combination with basic data available for selected PEOLs (Section 6.8).

The underlying assumption is that the chemistry of the initiator molecule and of the repeating units provide an indication for the physico-chemical and/or ecological / toxicological properties of the polyols. If the initiator molecule exhibits ecotoxicological and/or toxicological properties, these properties will likely diminish with increasing numbers of repeating units (i.e. increasing molecular weight). Similarly, higher systemic bioavailability (and hence higher potential to reach systemic target organs) is expected from the NLP polyols than from the PEOLs since the NLP polyols generally have lower molecular weight than the PEOLs.

The systemic bioavailability of a substance depends on its ability to cross cell membranes and reach its target organs or tissues. Most xenobiotics enter an organism via passive diffusion. Systemic bioavailability is driven by different physico-chemical properties of a substance, including molecular size, charge and solubility (Barratt, 1995; Lipinski et al., 2001; Williams et al., 2016). Importantly, however, systemic bioavailability does not *per se* indicate systemic toxicity, but only that the test material may reach target organs (see also Section 3.7.1.1 in ECETOC (2019) TR No. 133-1).

Taken together, if no systemic toxicity is observed for the NLP polyols (and first repeated dose toxicity studies that are becoming available do indicate this; data not shown), the corresponding PEOLs (which are based on the same/similar initiator molecule and alkoxylation but have longer chains and hence higher molecular weight and lower likelihood of becoming systemically bioavailable) are also not expected to exhibit systemic toxicity.

6.5.2 Grouping parameters

6.5.2.1 Criterion 1: Chemical nature

All PEOLs shall be grouped together in one group with potential subgrouping by initiator molecule.

PEOLs are manufactured in a polymerisation reaction by catalysed addition of the monomers PO and/or EO to an initiating molecule (Section 6.1.3). Their common key features are the initiator molecule and the chain produced by ethoxylation and/or propoxylation (Figure CS5.4).

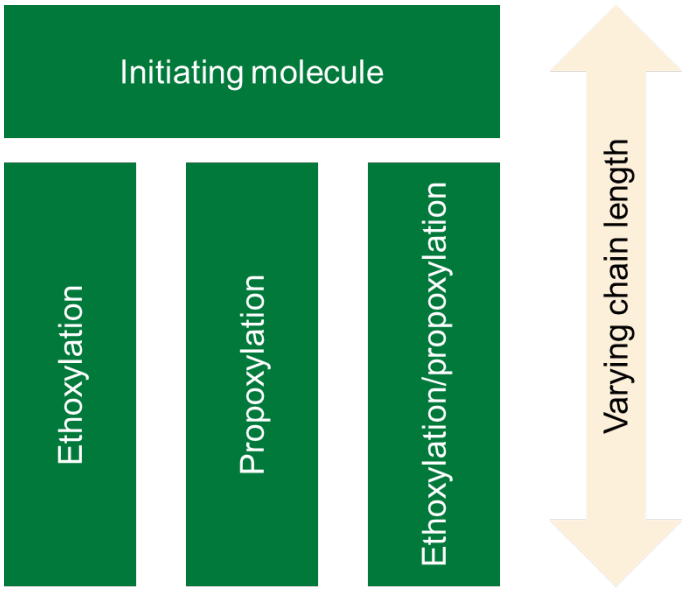


Figure CS5.4: Grouping approach evaluation for polyetherols (PEOLs): 'Criterion 1' grouping by initiating molecule and chain of ethoxylation and/or propoxylation and 'Criterion 2' grouping by molecular weight range

Footnote to Figure CS5.4: Graphical illustration of the (Criterion 1) common key components of the POEL for grouping: The initiating molecule (as applicable – see Table CS5.1) and the subsequent chain of ethoxylation and/or propoxylation and (Criterion 2) grouping by molecular weight range.

The same stands true for the NLP polyols, and indeed there is a continuum of chain length (and hence molecular weight distribution; Criterion 2) starting at the NLPs and continuing up to the polymeric size range. Following the provisions of the EU REACH Regulation and subsequent guidance, NLPs are not grouped together with the PEOL in this case study. The reason is that registration requirements are in force for the NLPs, whereas there are (currently) no registration requirements for the PEOLs. Nonetheless, the NLPs shall serve as data source to fill data gaps for PEOLs.

Taken together, the Criterion 1 borders of the group of PEOLs are (1) that they fulfil the '3n+1' rule (Section 6.1.2); (2) that they share the (same or similar) initiator molecule (Table CS5.1); and (3) that they have a chain produced by ethoxylation and/or propoxylation.

By comparison, the NLPs (as source substances for read-across) do not fulfil the '3n+1' rule, but they also have the (same or similar) initiator molecule and a chain produced by ethoxylation and/or propoxylation and therefore represent a conservative 'worse-case scenario'.

Of note, from a scientific perspective, PEOLs and NLPs could be grouped together in a wider group of polyether polyols – the 'does / does not fulfil the 3n+1 rule' is not a scientific, but a regulatory criterion. Still, motivated by regulatory needs, the source substances and target substances are not included in the same group (category) as per ECHA (2017c) in this case study.

6.5.2.2 Criterion 2: Physico-chemical properties

For PEOLs, relevant properties for Criterion 2 grouping include molecular weight range, water solubility and the n-octanol/water distribution coefficient. As described above for chemical nature (Criterion 1), the relevant (Criterion 2) physico-chemical properties also show a continuum within the group of PEOLs.

Both the type of initiator molecule and the chain lengths as common key feature (Criterion 1) determine the molecular weight distribution of PEOLs. The molecular weight range of the PEOLs that are grouped together in one group starts at rather low molecular weights of 500-800 Da and continues over a medium range of 800-3,000 Da up until long-chain and high molecular weight structures with a maximum of 18,000 Da (Section 6.3.1.4; Table CS5.1). The majority of PEOLs considered in this case study have a mean M_n in the range of 800-3,000 Da.

Water solubility of PEOLs is at least 1 g/L and typically much higher (Section 6.3.1.6). In line with this high water solubility, the corresponding n-octanol/water partition coefficients of the PEOLs are very low (log K_{ow} mostly < 1 at 25 °C and in no case > 2 (Section 6.3.1.7).

Taken together, the Criterion 2 borders of the group of PEOLs are (1) that their overall molecular weight range extends from 500 Da to 18,000 Da; and (2) that they have high water solubility and low log K_{ow}.

By comparison, the molecular weight of the NLPs ranges from 170 Da to 630 Da; all NLPs have high water solubility, and their log K_{ow} ranges from -3.6 to 2.3.

6.5.2.3 Criterion 3: Ecotoxicological and toxicological properties

Criterion 3 on hazard properties demands hazard similarity for all members of the group of PEOLs that fulfil the borders set out in Criterion 1 and Criterion 2. The following relevant hazard properties (that need to be similar to enable grouping) have been identified:

Relevant environmental hazard properties

Generally, robust, publicly available fate data for PEOLs are scarce. By comparison, some NLP polyols are readily biodegradable, whereas others are not (e.g. depending on their structure). Fate is not further considered for grouping.

NLP polyols are devoid of aquatic toxicity potential (generally up to the limit of 100 mg/L), and this is regarded an intrinsic property of the NLP polyols – since they do have the potential (1) to reach aquatic species on account of their high water solubility and (2) to become systemically bioavailable on account of their low molecular weight (Section 6.8.1). It is hypothesised that the corresponding PEOLs (which are based on the same/similar initiator molecule and alkoxylation but have longer chains and hence higher molecular weight) do not exhibit more pronounced toxicity than their lower molecular weight and shorter-chained NLP counterparts. Generally, since data from the NLP polyols did not raise concerns, only few studies have been performed for the corresponding PEOLs, which however also support this hypothesis (Section 6.8.1; Table CS5.2).

Based on the available data, the relevant Criterion 3 environmental hazard property for the group of PEOLs is therefore regarded as 'generally low to absent environmental hazard potential'.

The ECETOC Polymers TF is unaware of data from ecotoxicity studies using sediment-dwelling or terrestrial organisms for either NLP polyols or PEOLs (Section 6.8.1; Table CS5.2).

Relevant human health hazard properties

Potential for systemic bioavailability: As described by Lipinski et al. (2001), molecules with molecular weights < 500 Da are generally assumed to be sufficiently small to be absorbed by passive diffusion in the gastrointestinal tract. In a regulatory setting, it is generally accepted that molecules with molecular weights > 1,000 Da have a low likelihood of becoming systemically bioavailable (see e.g. EFSA, 2008a; US EPA, 2013). Similarly, the US EPA (1997) and Canada (2005) guidance list a M_n threshold of < 1,000 Da to identify LMW polymers that may become systemically bioavailable (see also Section 4.2 of the ECETOC TR No. 133-1).

Thus, the NLPs and the lower molecular weight PEOLs do have the potential to become systemically bioavailable, whereas it is unlikely that the higher molecular weight PEOLs have the potential to become systemically bioavailable. However, as described in Section 6.5.1, systemic bioavailability does not *per se* indicate systemic toxicity, but only that the test material may reach target organs.

Based on available data (Section 6.8.2), human health hazard potential of the PEOLs group is considered to be low to absent as regards both acute systemic toxicity and local toxicity. None of the PEOLs within the described borders of the group show indication for acute dermal toxicity, skin irritation, eye irritation, mutagenicity in bacteria or skin sensitisation. However, there are only limited toxicological data available for systemic toxicity endpoints. Based on the aforementioned assumptions and the overall low acute toxicity neither NLPs, nor PEOLs are expected to have the inherent potential to induce systemic toxicity.

Preliminary data indicate that glycerol- and propane-1,2-diol-started PEOLs of a certain molecular weight range (> 500 Da and < 2,000 Da) might elicit slightly more pronounced acute oral and inhalation toxicity. However, these preliminary data deserve further elaboration before reliable conclusions on their hazard properties and consequently their consideration in the grouping approach can be drawn. Within the other PEOL subgroups, there is a continuum of relevant hazard properties. Despite the deviation for acute oral and inhalation toxicity within the subgroup of the glycerol- and propane-1,2-diol-started PEOLs, this subgroup will be maintained in the larger group of PEOLs that are considered in this case study unless other hazards would in future trigger the need for separation of these group members.

Based on the available data, the relevant Criterion 3 human health hazard property for the group of PEOLs is therefore regarded as ‘generally low to absent human health hazard potential’ (Section 6.8.2; Table CS5.2). This is supported by the observation that also the lower molecular weight NLPs do not exhibit hazard potential – and the higher molecular weight PEOLs are generally not expected to be more toxic than their lower-molecular weight counterparts. Further data may become available in the future to further support this grouping hypothesis on hazard similarity and with respect to the glycerol- and propane-1,2-diol-started PEOLs (> 500 Da and < 2,000 Da).

Table CS5.2: Ecotoxicity and human health toxicity data available for oligomeric polyols and PEOLs

Initiator molecule	Alkoxylation	Number-average molecular weight (Da)	NLP / polymer	Acute aquatic toxicity (fish)	Acute aquatic toxicity (*Daphnia*)	Acute aquatic toxicity (algae)	Chronic aquatic toxicity (*Daphnia*)	Classification for any ecotoxicological hazard	Acute oral toxicity	Acute pulmonary / inhalation toxicity	Acute dermal toxicity	Skin irritation	Eye irritation	Skin sensitisation	Mutation (Ames test)	Classification for any human health hazard
1,2,3-Propanetriol (i.e. glycerol)	PO	200 - 450	NLP	x	x	x		None	x	PCLuS	x	x	x	x	x	None
		1100	Polymer							PCLuS						PCLuS neg.
		3400	Polymer							PCLuS						
	EO	300	NLP	x	x	x		None	x	PCLuS	x	x	x	x	x	None
	EO/PO	700	Polymer						x			x	x			None
		1100	Polymer						x							Cat 4
		1250	Polymer							PCLuS						PCLuS neg.
		3000	Polymer						x		x	x		x	x	None
		3500	Polymer							PCLuS						PCLuS neg.
		4400	Polymer	x				None	x			x	x			None
		4800	Polymer						x		x	x	x			None
		5000	Polymer							x						None
		6000	Polymer						x	PCLuS	x	x	x	x		None
Saccharose / glycerol	PO	500	NLP	x		x		None	x		x	x	x	x	x	None
		630	NLP						x							None
Diethylene glycol	EO/PO	260	NLP		x			None	x		x	x	x	x	x	None
Propane-1,2-diol (i.e. monopropylene glycol)	PO	400	NLP	x				None	x	PCLuS + x	x	x	x	x		None
		500	Polymer	x				None	x		x	x	x	x	x	Cat 4
		700	Polymer							PCLuS						PCLuS neg.
		1200	Polymer						x							Cat 4
		1500	Polymer							PCLuS + x						Cat 4
		2000	Polymer						x	PCLuS		x		x		None
		3000	Polymer							PCLuS						PCLuS neg.
		4000	Polymer						x	PCLuS						None
	EO/PO	2000	Polymer							PCLuS						PCLuS neg.

Initiator molecule	Alkoxylation	Number-average molecular weight (Da)	NLP / polymer	Acute aquatic toxicity (fish)	Acute aquatic toxicity (*Daphnia*)	Acute aquatic toxicity (algae)	Chronic aquatic toxicity (*Daphnia*)	Classification for any ecotoxicological hazard	Acute oral toxicity	Acute pulmonary / inhalation toxicity	Acute dermal toxicity	Skin irritation	Eye irritation	Skin sensitisation	Mutation (Ames test)	Classification for any human health hazard
Propane-1,2-diol (i.e. monopropylene glycol)	EO	4000	Polymer							PCLuS						PCLuS neg.
Propylidynetrimethanol (i.e. trimethylol propane)	PO	200-400	NLP	x	x	x		None	x		x	x	x	x	x	None
		1000	Polymer							PCLuS						PCLuS neg.
		2400	Polymer							PCLuS						
		3700	Polymer							PCLuS						
	EO	175-443	NLP	x	x	x	x	None	x		x	x	x	x	x	None
	EO/PO	3700	Polymer							PCLuS						PCLuS neg.
Sorbitol	PO	550	NLP	x	x	x	x	None	x						x	None
Sucrose	PO	400-1300	NLP	x	x	x		None	x		x	x	x	x	x	None
	EO/PO	444-1974	NLP		x			None	x		x	x	x	x	x	None

Footnote to Table CS5.2: This table includes sucrose-initiated NLPs that are not considered in Table CS5.1. PEOLs can be either random polymers or block polymers.

Cat.: Category of hazard classification; EO: Ethylene oxide; NLP: No longer polymer; PCLuS: Precision cut lung slices (*ex vivo* method; Hess et al., 2016); PO: Propylene oxide.

Ecotoxicity	Ecotoxicity endpoints; darker shading: Classification for any ecotoxicological hazard		
Toxicity	Human health toxicity endpoints; darker shading: Classification for any human health hazard		
NLP	Oligomeric polyol (NLP)		
Polymer	Polymeric polyol (PEOL)		
x	Data available, no hazard	PCLuS + x	Data from precision cut lung slices available & *in vivo* data available, no hazard
x	*In vivo* data available, leading to classification in Cat. 4	PCLuS + x	Data from precision cut lung slices available & *in vivo* data available, leading to classification in Cat. 4
PCLuS	Data from precision cut lung slices available, negative outcome		

Overall assessment on relevant hazard properties

Similar to observations in Criterion 1 and Criterion 2, there is also a continuum of Criterion 3 relevant hazard properties across the majority of group members of PEOLs, i.e. 'generally low to absent environmental and human health hazard potential' (Section 6.8; Table CS5.2). Due to the continuum of properties within all Criteria, data missing for specific PEOL group members can be interpolated from data for other PEOL group members. Similarly, read-across from the NLP polyols towards the polymeric PEOLs appears justifiable since they both share the same Criterion 1 common key constituents (except for the regulatory-driven fulfilment / non-fulfilment of the '3n+1 rule') and the same continuum of Criterion 2 physico-chemical properties and Criterion 3 hazard similarity.

6.6 Case Study 5: CF4Polymers (Step 5) Determination of exposure scenarios

Step 5 determination of exposure scenarios is not in the focus of Case Study 5 on PEOLs. Generally, PEOLs are used in an industrial setting with further downstream processing (which, however, is out of scope of the present case study (Section 6.1.1)).

Generally, the relevant environmental compartment considered for environmental hazard assessment is the aquatic compartment. For humans, i.e. workers, exposure would occur via the dermal route, if at all.

6.7 Case Study 5: CF4Polymers (Step 6) Exposure characterisation

Step 6 exposure characterisation is not in the focus of Case Study 5 on PEOLs. Generally, PEOLs are used in an industrial setting with further downstream processing. As the final group is deemed sufficiently similar, a general approach for exposure characterisation can be chosen in conjunction to the general grouping scheme (see Figures Intro-2 and Intro-3 in Section 1.3).

Generally, robust, publicly available fate data for PEOLs are scarce. By comparison, some NLP polyols are readily biodegradability, whereas others are not (e.g. depending on their structure). Fate is not further considered in this case study.

6.8 Case Study 5: CF4Polymers (Step 7) Hazard assessment

6.8.1 Environmental hazard assessment

The approach for the environmental assessment of PEOLs relies on the information obtained from the ether-linked NLP polyols in combination with basic data available for selected PEOLs. The ether-linked NLP polyols are characterised by a very low aquatic toxicity. This observation is independent of the test species: fish, *daphnia* and algae all are not susceptible to exposure to oligomeric polyols (Table CS5.2). However, the PEOLs are all highly water soluble (Section 6.3.1.6). Accordingly, the absence of aquatic toxicity is not due to a - potential - lack of exposure (as would be the case for insoluble or poorly soluble substances) but is an intrinsic

property of the PEOLs. The structural moieties of the NLP polyols are therefore considered to be of negligible aquatic toxicity. With increasing molecular size of the PEOLs, this already low to absent toxicity further decreases due to the decreasing bioavailability of the polymers.

On account of their physico-chemical properties, the aquatic compartments are most relevant for PEOLs (see also Figure 6 in ECETOC TR No. 133-2 describing the Conceptual Framework for Polymer Ecotoxicity Assessment). Therefore, (almost) all ecotoxicological data that are currently available for NLP polyols or PEOLs relate to aquatic toxicity potential. If information on the potential to induce adverse effects on sediment-dwelling and/or terrestrial organisms is deemed necessary, an equilibrium partitioning method that is based upon data for aquatic species can be applied for conservative predictions of the respective PNECs (see Section 2.8.1.1 in Case Study 1 and Section 7.7.3.2 in Case Study 6 for details).

Taken together, there is no concern pertaining to ecotoxicity or exposure of environmental organisms to the PEOLs. Hence, only few ecotoxicological data are available for PEOLs (data not shown). These data confirm the low toxicity of the PEOLs and thus the validity of the approach to rely on the data available for the NLP polyols when assessing the environmental hazard potential of PEOLs (that also underlies the (Step 4) grouping approach evaluation presented in Section 6.5). The read-across from data available for the oligomeric NLPs to fill data gaps for the PEOLs is therefore considered appropriate.

6.8.2 Human health hazard assessment

The approach for the human health hazard assessment of PEOLs relies on the information obtained from the NLP polyols in combination with basic data available for selected PEOLs (Table CS5.2). Where there is no hazard identified for the NLP polyols, no hazard is expected for PEOLs that have higher molecular weight, and hence less potential for bioavailability. Based on the data available for ether-linked NLP polyols, to date no hazard has been identified for these substances. This approach to rely on the available data for the NLP polyols when assessing the hazard potential of the PEOLs is further supported by basic data on local toxicity and *in vitro* toxicity data available for selected PEOLs (Table CS5.2). Based on the available data, NLP polyols and PEOLs generally show a low to complete absence of hazard potential concerning local toxicity or acute systemic toxicity, which is consistently observed for all NLP polyols and PEOLs that have been tested so far. None of the currently tested NLP polyols or PEOLs show acute *dermal* toxicity, skin irritation, eye irritation, or skin sensitisation. Exceptions are glycerol- and propane-1,2-diol-started PEOLs of a certain molecular weight range (> 500 Da and < 2,000 Da), where low to moderate acute oral toxicity and/or *in vitro* pulmonary / *in vivo* inhalation toxicity was observed (Table CS5.2). However, more information is needed to fully understand the underlying mode of action. Also, if prolonged exposures are expected, the need for repeated-dose toxicity studies may be considered on a case-by-case basis for those PEOLs which may become systemically bioavailable. For the majority of PEOLs, the observations regarding both local toxicity and acute systemic toxicity regardless of route of exposure are congruent to those obtained for the smaller NLP polyols. Therefore, it is concluded that it is appropriate to apply read-across from data available for the oligomeric NLPs to fill data gaps for the PEOLs.

6.9 Case Study 5: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for any specific PEOL (and, as such, did not consider release scenarios, exposure routes, etc.). Instead, it has served to evaluate if the ECETOC TR No. 133-1 CF4Polymers is generally applicable to PEOLs and if the collated information provides further insight on the applicability of tools and test methods for the physico-chemical characterisation and toxicity / ecotoxicity testing of PEOLs.

Focus of this case study has been the application of the general outline for CF4Polymers (Step 4) grouping approach evaluation, as described in Section 1.3, for PEOLs. The strategy for characterising and evaluating the hazard profile of PEOLs relies on the available information for the corresponding oligomeric NLPs in combination with basic data available for selected PEOLs (Section 6.8). Any ecotoxicological and/or toxicological properties that the initiator molecule exhibits will most likely diminish with increasing numbers of repeating units (i.e. increasing molecular weight). Similarly, higher systemic bioavailability (and hence higher potential for systemic toxicity) is expected from the lower molecular NLP polyols than from the PEOLs. Based on the available data, the relevant Criterion 3 human health hazard property for the group of PEOLs is regarded as ‘generally low to absent human health hazard potential’.

In conclusion, the updated grouping scheme described in Section 1.3 has turned out appropriate for the grouping of PEOLs. Further, the case study has shown that, as the hazard potential of PEOLs is low to absent and further considering that PEOLs are used in industrial settings only, there is no reason to assume that risks may arise from the use of PEOLs.

7. CASE STUDY 6: SURFACTANT POLYMERS

7.1 Introduction

7.1.1 Scope and outline of Case Study 6

This case study on surfactant polymers focuses on alcohol ethoxylates (AEs). AEs are surface active nonionic polyethers composed of a long-chain primary alcohol (hydrophobic moiety) reacted with ethylene oxide (EO) to form a hydrophilic (poly)oxyethylene moiety. This structure allows AEs to lower the surface tension of aqueous media they are dissolved in. AEs are excellent detergents, emulsifiers, and wetting agents; also, AEs are moderate foamers (ERASM, 2017a, b).

The naming convention for AEs (Cx-yEOn; see introduction to Section 7.3.1) describes the carbon chain length of the alcohol, that is typically 8-22 carbon atoms, and the average number of EO moles in the backbone, that may range from 1-50 units in length. AEs can either be linear or branched, saturated or unsaturated, natural or synthetic, and single moiety or complex mixtures (Kosswig, 1994; Talmage, 1994; HERA, 2009). For the commercially available AEs, the degree of branching and saturation as well as their chain length distribution varies by the feedstock source and by the method used to produce the alcohols.

As an example, this case study considers linear C12-15EO7, i.e. AEs with medium C-chain length and a medium degree of ethoxylation. These characteristics render C12-15EO7 very suitable for use in household detergents, and the selected intended use is consumer use of laundry detergents and cleaning agents. This polymer has a low vapour pressure. Thus, primary human exposure to C12-15EO7 is via the dermal route. Since laundry detergents and cleaning agents are down-the-drain applications, the predominant environmental exposure is to the aquatic compartment and to WWTPs, while exposure to the terrestrial compartment is also possible, via land applications of WWTP sludge.

Comparatively, this case study also considers AEs with high numbers of EO moieties, i.e. linear C16-18EO≥20. AEs with such high degrees of ethoxylation are rather used in industrial applications. The selected intended use of C16-18EO≥20 is for the manufacturing of water-based dispersions and for conditioning textile, leather, and paper.

Of note, in AEs, whose alcohols were produced via the synthetic ‘oxo-process’, a small percentage of the alkyl chains may have an internal methyl branching (so-called ‘essentially linear’ AEs); nonetheless, for improved readability these polymer products are also referred to as linear AEs in this report. AE polymers with a high degree of branching are not used in consumer products and are therefore not in scope of this case study.

Since AEs are the most produced nonionic surfactants and thus have proportionally extensive datasets (as compared to other types of polymers), they are well-suited for a case study to evaluate the applicability of the CF4Polymers. This case study aims to take C12-15EO7 and C16-18EO≥20 through all steps of the CF4Polymers to draw general conclusions regarding a theoretical risk characterisation. Notably, in line with the overarching goal of this ECETOC TR No. 133-3 (Section 1.1), it is not the aim to conduct a concrete risk characterisation for any specific AE.

An important focus of this case study is to apply the details of the CF4Polymers (Step 4) grouping approach evaluation (Section 1.3) to AEs. To facilitate the grouping, this part of the case study is not restricted to C12-15EO7 and C16-18EO≥20 but considers all linear AEs (and for human health endpoints additionally branched and unsaturated AEs) that are based on primary alcohols and have C = 8-18 and EO = 1-50. As the case study

will show, all of these AEs share the same mode-of-action regardless of C-chain length and/or degree of ethoxylation, i.e. they can all potentially elicit non-polar narcotic effects and surface tension-related effects.

7.1.2 Synthesis and use of alcohol ethoxylates

AEs can be synthesised either from bio-based (renewable) alcohol precursors (e.g. palm oil, palm kernel oil, coconut oil, tallow) or from fossil fuel (petroleum-based) alcohol sources. They are primarily produced from linear and essentially linear alcohols and to a lesser extent from linear random secondary alcohols from oleochemical or petrochemical feedstocks for detergent applications.

The respective alcohol is ethoxylated with EO (that is presently generally derived from fossil fuel sources). For detergent-range AEs, this reaction is normally catalysed by alkaline catalysts (potassium or sodium hydroxide) (ERASM, 2017a) followed by neutralisation with an acid (e.g. acetic acid or phosphoric acid) (Cowan-Ellsberry et al., 2014). Alternatively, acidic catalysts (e.g. boron trifluoride or zinc chloride) can be used for ethoxylation of AEs with medium C-chain length and medium degree of ethoxylation (ERASM, 2017a). Some more details on the synthesis of different AEs are provided in the Environmental Fact Sheets of the joint research platform *Environment and Health – Risk Assessment and Management* (ERASM) of the European detergents and surfactants industries; http://www.erasm.org/index.php/life-cycle-inventories-data/page-3.

AEs have been available commercially since the 1930s. Since AEs possess the typical structural characteristics of surface-active substances (Section 7.3.1.9), they are used as surfactants, as precursors to produce other types of surfactants (e.g. alcohol ethoxy sulphates), and as processing agents (Sasol, undated; Stepan, 2008; BASF SE, 2014; Evonik Corporation, 2017). The surface-active properties of AEs do not depend on the source of the alcohol precursor, but only on the structure (and chemistry) of the AE. AEs have many further desirable characteristics such as rapid biodegradation in the environment, low to moderate foaming ability, superior cleaning of man-made fibres, and tolerance of water hardness (HERA, 2009).

AEs are used in a wide variety of applications. Significant quantities of AEs are converted to alcohol ethoxy sulphates. The remaining AEs are used primarily in consumer products (e.g. household laundry detergents), but also in lesser quantities in household cleaners, institutional and industrial cleaners as well as in agricultural products, personal care products, and in the textile, paper and specific-process industries (Talmage, 1994; HERA, 2009).

The AEs that are commonly used in consumer products have linear carbon chains ranging from C8 to C18 and average EO chain lengths with 3-12 units (HERA, 2009), i.e. they have both a medium C-chain length and a medium degree of ethoxylation. AEs with less than 3 EO units do not meet the polymer definition (EP and Council, 2006; ECHA, 2012a, 2017b; see also Box 3 in Section 1.2). Typically, AEs with a molecular weight < 1,000 Da are used in down-the-drain applications since this facilitates their biodegradability, as desirable property at the end-of-life.

C12-15EO7 is used in personal care products (foaming agent in shampoos and bath gels), as wetting agent in detergents, laundry pre-spotters and hard surface cleaners as well as in the textile and leather industries. Further, it is used as surfactant intermediate, sulfonated to make sodium lauryl ether sulphate, used both in household and industrial products (ERASM, 2017a).

C16-18EO≥20 is used in chemical products for households and industries. Further, it is used as softener in textile and paper applications; as emulsifier for laundry detergents and cleaning agent for the home care / industrial and institutional cleaning industry; and as emulsifier for emulsion polymerisation. C16-18EO≥20 is not used in personal care products (ERASM, 2017b).

When AEs with high degrees of ethoxylation are used in industrial settings for water-based emulsion polymerisation, they form micelles that contain the polymerisation reaction of the preferred polymer, e.g. acrylate copolymers for coating applications. Micelle-forming properties are advantageous over foam-forming properties of the AEs in this use. General preferred properties for micelle formation of the substance in this process include high water solubility, and a mixture of polar emulsifier and its salts.

7.2 Case Study 6: CF4Polymers (Step 1) Problem formulation

This case study focuses on linear C12-15EO7 (consumer use) and linear C16-18EO≥20 (industrial use) representatives.

C12-15EO7 used in consumer laundry detergent with down-the-drain release

C12-15EO7 is a non-ionic surfactant AE with an average of 7 EO units. It is produced by the reaction of petroleum-based C12-15 fatty alcohols with EO. The ethoxylation reaction is catalysed by potassium hydroxide (ERASM, 2017a). The intermediate EO is industrially produced by direct oxidation of ethylene in the presence of silver catalysts (ERASM, 2017c).

The relevant life cycle stage is the final formulation containing C12-15EO7. The selected use scenario for C12-15EO7 is as surface-active agent in consumer laundry detergents and cleaning agents with down-the-drain release. The protection goals relate to consumers and the environment.

C16-18EO≥20 used as wetting agent in industrial settings

C16-18EO≥20 is produced by the reaction of C16-18 fatty alcohols derived from natural sources (preferably palm oil and tallow) with EO. The ethoxylation reaction for detergent-range AEs is catalysed by potassium hydroxide (ERASM, 2017b).

The relevant life cycle stage is the final article or formulation containing C16-18EO≥20. The selected use scenario for C16-18EO≥20 is as wetting agent in industrial settings for (1) the manufacturing of water-based dispersions; and (2) for the conditioning of textile, leather, and paper. The protection goals relate to workers and the environment.

Section 7.6 (CF4Polymers (Step 5) determination of exposure scenarios) presents further details on the exposure scenarios for C12-15EO7 and C16-18EO≥20.

7.3 Case Study 6: CF4Polymers (Step 2) Polymer identification

7.3.1 Step 2.1: Identification of the polymeric substance

AEs are defined by the basic structure Cx-yEOn (also expressed as Cx-yAEn). The C stands for the C-atoms in the (non-polar) hydrophobic alkyl chain part of the molecule and EO for the ethoxylated moieties in the (polar) hydrophilic part of the molecule. The subscript following the C indicates the number or range of carbon chain units. While this case study is restricted to linear AEs, the C denominator may generally cover both linear and branched C-chains. Also, the C-chains are usually mixtures of structurally related alkyl chains (e.g. distillation cuts). Similarly, the numbers of EO moieties may exhibit a broad statistical distribution curve (Figure CS6.1).

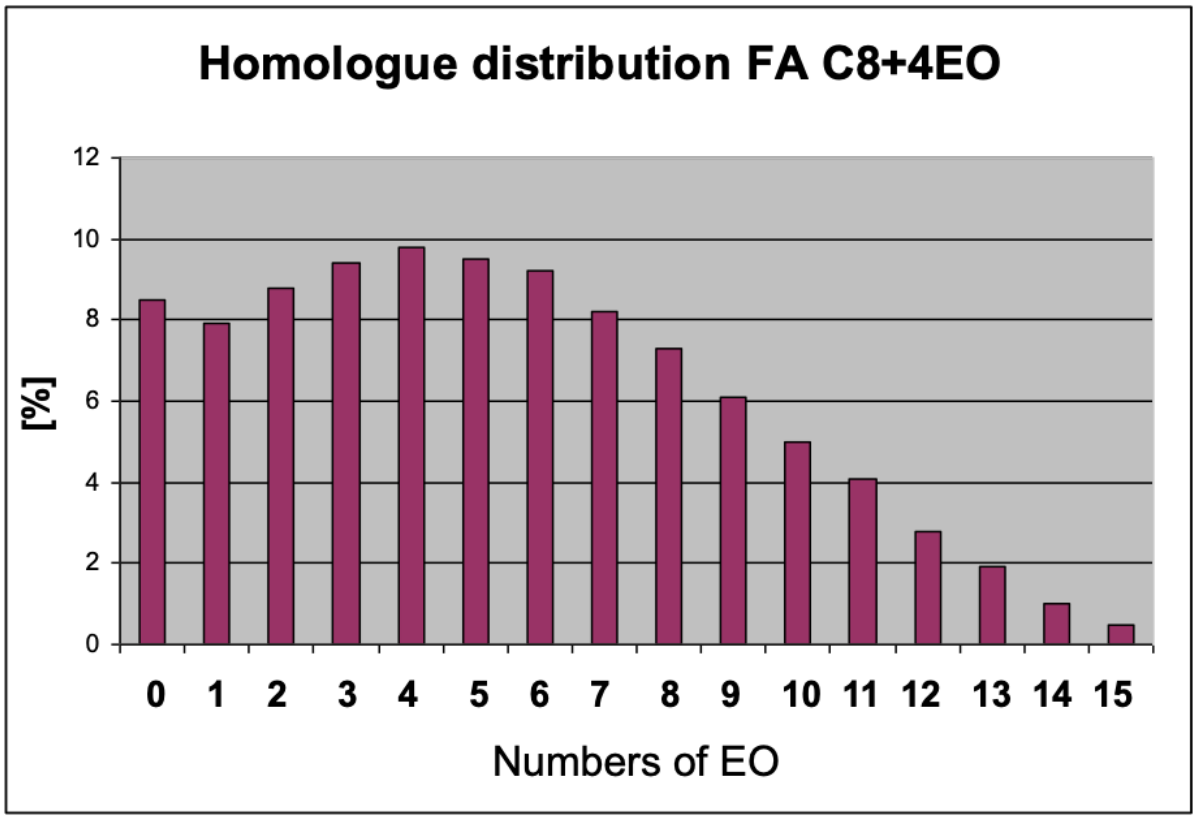


Figure CS6.1: Exemplary homologue distribution for an alcohol ethoxylate produced by reacting 1 mole C8 fatty alcohol (FA) with 4 moles ethylene oxide (EO)

Footnote to Figure CS6.1: Data derived from a gas chromatogram of a typical technical polymeric alcohol ethoxylate (AE) (unpublished ECETOC Polymers TF member company data). The AE is based on C8 alcohol that is reacted with four moles of EO. The 'as produced' technical AE includes different homologues that have the shown distribution of numbers of EO. The exact distribution depends on the type of catalysts used and the production process. Specific catalysts may yield more narrow distributions than shown here, i.e. distributions that are narrower around 4.

Thus, commercial AEs are generally mixtures consisting of several homologues differing in alkyl chain length and degree of ethoxylation (Wind et al., 2006). Depending on their manufacturing route, AEs are similar to UVCBs, and they include both NLPs (Glossary) and polymers. Accordingly, the AE names generally refer to median numbers of C-atoms and EO moieties.

7.3.1.1 Standard chemical descriptors

Although CAS and/or EC numbers are used as identifiers for AEs, these numbers are not sufficiently specific for the identification of AEs since they differentiate only between different alkyl chains, but do not consider the numbers of EO moieties. For example, CAS No. 68439-50-9 is defined as '*C12-14, ethoxylated*'. However, the physico-chemical and hazard properties of AEs depend on both, the length of the alkyl chain and the degree of ethoxylation. Therefore, in the context of hazard assessment, the average number of EO, or molar ratio of EO per fatty alcohol, or M_n should always be considered for the identification of an AE (Section 7.3.1.2).

7.3.1.2 Chemical name

In addition to the sometimes very complex IUPAC names (e.g. '*poly(oxy-1,2-ethanediyl), α-hexadecyl-ω-hydroxy-'* or '*isotridecanol, ethoxylated'*), simplified descriptions should be provided – and are mostly used – to describe the chemical structure of the given AE (e.g. '*alcohols, C12-14, ethoxylated (5EO)*'; or '*fatty AE, C12-14 + 5 EO'*). Similarly, trade names and other commercial descriptors are not useful on their own e.g. to support grouping of AEs, but only together with CAS or EC numbers and information on molecular weight or degree of ethoxylation.

7.3.1.3 Structural and morphological descriptors

Structural and morphological descriptors of AEs should describe if the carbon chain is linear or branched, and if it is unsaturated or saturated. Depending on the structure, pure AEs are either liquid or solid substances. The AEs whose mean C-chain lengths and mean EO numbers are low are generally liquid (e.g. C10EO4, C10EO6, C12EO2), while the materials become increasingly solid as the C-chain length changes and the degree of ethoxylation increases. For the technical products (which are mostly complex polymer products resembling UVCBs), the physical state can be found in the corresponding section of their material safety data sheets.

The physical state of the (polymeric) AEs (i.e. with average EO ≥ 3) may affect the applicability of some test methods addressing physico-chemical hazards (e.g. explosivity), but it is less likely to affect the applicability of ecological or toxicological test methods, except possibly with regard to the ease of dosing the given AE to the respective test systems (Table CS6.1).

There are no relevant reactive functional groups present on either C12-15EO7 or C16-18EO≥20.

7.3.1.4 Weight-average and number-average molecular weight

The molecular weight is important to inform on the potential of the polymer to pass biological membranes. In a regulatory setting, it is generally accepted that molecules with molecular weights > 1,000 Da have a low likelihood of penetrating through the skin, or through other biological membranes (see e.g. EFSA, 2008a; US EPA, 2013). This has implications for some hazard properties or the ability to bioaccumulate.

AEs cover a moderate molecular weight range. For C12-15EO7, the molecular weight ranges from 494-536 Da (HERA, 2009), whereas the molecular weight of C16-18EO≥20 generally exceeds 1,000 Da and is e.g. 2,356 Da for C18EO50 (Table CS6.1).

For polymeric AEs in general high performance liquid chromatography (HPLC) and GC are suitable analytical techniques. For AEs with very short C-chains and LMW, GPC is an appropriate separation method to determine the molecular weight. However, for larger AEs this experimental method, and similarly other chromatographic methods, become difficult if not impossible to perform because, at the higher molecular weights, the fractional differences between homologues become smaller and smaller. A pragmatic approach is to calculate the molecular weight based on the average structure (average C chain length, average number of EO).

Commercial AEs have a broad EO distribution range, with a polydispersity index of about 1.4.

Table CS6.1: Alcohol ethoxylates – physical state, molecular weight and water solubility

Parameters	Comments related to different types of alcohol ethoxylates			Further notes
Physical state	The following homologues are liquid: C10EO4, C10EO6, C12EO2 On account of the versatility of the underlying alcohols, AEs may have properties resembling UVCBs, e.g. C9-11 < 2.5EO, C9-11 + 7EO, C12-14 + 7EO, C12-18 + 7EO	Data unavailable	The following homologues are solid: C10EO8, C14EO2, C16EO2, C16EO4, C16EO8, C16-18 < 2.5 EO, C16-18 + 9 EO, C16-18 + 50 EO	Dependent on the pure structure, AEs are liquid or solid substances. The physical state of the AEs may affect applicability of test methods for some physico-chemical endpoints, but it is not expected to affect the overall applicability of fate, ecotoxicity or toxicity test methods, except with respect to substance administration to the test system
Molecular weight	Ranging from 156 Da (C8EO1) up to 2,356 Da (C18EO50)	The technical products of AEs have properties resembling UVCBs. The C-chains are usually mixtures of structurally related alkyl chains (e.g. distillation cuts). Likewise, the EO moieties have a broad chain distribution, resulting from a statistical chain propagation	For technical products, the EO suffix refers to the number of EO moles reacted with the starter alcohol, and it indicates the peak maximum of the broad EO chain distribution (Figure CS6.1) Commercial AEs have a broad range EO distribution (polydispersity index approx. 1.4)	Specific solvents (e.g. tetrahydrofuran) are needed to submit water-insoluble polymers to GPC. For polymeric substances with very short chains and LMW, HPLC is an appropriate separation method. Pragmatic approach: Calculate molecular weight based on the idealised structure (average C, average number of EOs)
Solubility in water	Standard methods (OECD TG 105) - When AE solubility > 10 mg/L: Shake flask - When AE solubility < 10 mg/L: Column elution Surfactant-specific methods - Critical micelle concentration: see beside	CMC-based solubilities of technical branched C13 AEs (mg/L): C13EO8 = 57; C13EO12 = 110; C13EO20 = 250; C13EO40 = 1000	CMC-based solubilities of pure AE homologues (mg/L): C10EO8 = 510; C12EO8 = 38.2 C14EO8 = 5.1; C12EO5 = 26.4 C12EO6 = 30.6; C12EO7 = 34.1 C12EO8 = 38.2	Aqueous solutions of nonionic surfactants such as these AEs can have a Lower Critical Solution Temperature (or cloud point). In case their number of EO is rather low, their cloud point could even be well below room temperature. It is not possible to determine CMC values in such milky mixtures

Footnote to Table CS6.1

Abbreviations: AE: Alcohol ethoxylate; CMC: Critical micelle concentration; Da: Dalton; EO: Ethylene oxide; GPC: Gel permeation chromatography; HPLC: High-performance liquid chromatography; LMW: Low molecular weight; UVCB: Substance of unknown or variable composition, complex reaction products and biological materials.

7.3.1.5 Acid dissociation constant

The acid dissociation constant is not a relevant parameter for AEs since they do not tend to dissociate.

7.3.1.6 Solubility in water

The water solubility (and dispersibility) of AEs depends on the length and type (linear, branched) of the C-chain and the degree of ethoxylation. Although water solubility data generally need to be provided in a regulatory setting, water solubility is not a key physico-chemical property (or suitable descriptor) for AEs, as surfactant molecules will form aggregates (micelles) and liquid-crystalline phases above certain concentrations, as long as the temperature is below the so-called cloud point (i.e. the temperature above which the solution turns milky and the alkoxylate comes out of solution).

Instead, the critical micelle concentration (CMC) should be provided (see Section 7.3.1.9 on surface tension for details). Thereby, the solubility of AEs in water can be differentiated in

1. Molecular solubility (below CMC); and
2. Micellar solubility (above CMC).

Generally, the water solubility (molecular solubility) of linear AEs decreases with increasing C-chain length and increases with increasing EO number.

The CMCs of AEs range from about 1 mg/L to 1,000 mg/L (see Table 3.1 in HERA (2009)). For a linear C12-14EO7, a CMC of 15 mg/L has been recorded (HERA, 2009; referring to personal communication from the company Sasol), and for C14EO8 a CMC of 5.1 mg/L (HERA, 2009; citing a link to the Nikkol Chemicals Group that is no longer valid).

Therefore, for long-term ecotoxicity studies complete molecular solubility of these AEs is given down to the lowest concentration that is relevant for classification and labelling (< 1 mg/L; United Nations, 2019; EP and Council, 2008). It is expected that the presence of technical mixtures (complex polymer products with properties resembling those of UVCBs) generally leads to an increase in molecular / water solubility (Table CS6.1; see also Sasol, undated; Stepan, 2008; BASF SE, 2014; Evonik Corporation, 2017).

7.3.1.7 n-Octanol/water partition coefficient

Just as water solubility (Section 7.3.1.6), the n-octanol/water partition coefficient (log K_{ow}) is a physico-chemical parameter that is generally requested in a regulatory setting. Nonetheless, its biological relevance for surfactants should be treated with caution since surfactants tend to concentrate at the interface between water and n-octanol (ECB, 2003; ECHA, 2017d). For this reason, the ECETOC Polymers TF has decided against including any (irrelevant) log K_{ow} values for AEs in this case study. (A liposome-water partitioning coefficient has been proposed as alternative coefficient for describing AE interactions with membranes (Müller et al., 1999a, b). However, the ECETOC Polymers TF is unaware of a formally standardised protocol to measure this parameter.)

If the log K_{ow} needs to be provided for regulatory purposes, Hodges et al. (2019) recommended the slow-stirring method (OECD TG 123) as best suitable experimental method for surfactants in general, including AEs. Hodges et al. further provide examples of log K_{ow} estimations for C8EO4, C12EO4, and C12EO8 that were derived using different QSAR models. In contrast to other types of surfactants, the QSAR results for AEs correlate reasonably well with experimental data from the slow-stirring method and the HPLC method (OECD TG 117) (Hodges et al., 2019). Both experimental and QSAR-based data could therefore be used in a weight of evidence approach to estimate the log K_{ow} of AEs.

7.3.1.8 Adsorption/desorption and organic carbon/water partition coefficient

For sorption of AEs onto activated sludge and river water solids, van Compernolle et al. (2006) have developed two QSARs to predict the adsorption/desorption distribution coefficient (K_d) and the organic carbon/water partition coefficient (K_{oc}), respectively. Both the K_d and the K_{oc} are a function of the C-chain length and the number of EO (HERA, 2009).

For the log K_d, the QSAR developed by van Compernolle et al. (2006) is based upon the formula:

$$\text{Log } K_d = -1.126 + 0.331 \times (\text{chain length}) - 0.00897 \times (\text{ethoxylate number}); \text{ for AEs: } R^2 = 0.64.$$

7.3.1.9 Surface tension

AEs fulfil the general criteria for surfactants implemented in the EU Detergents Regulation (EP and Council, 2004a) in that they reduce the surface tension of water.

According to *Council Regulation No 440/2008 laying down test methods pursuant to the REACH Regulation* (Council, 2008), substances showing a surface tension < 60 mN/m should be regarded as being surface-active materials. By comparison, pure water has a surface tension of 72.0 mN/m at 20 °C. The ECETOC Polymers TF suggests that the threshold of < 60 mN/m is too conservative for the identification of potentially hazardous polymers. For example, non-amphiphilic polymers, such as pure polyethylene oxide, which has a surface tension of 58 mN/m for 5 g/L (Kim, 1997), would also fall under this criterium. However, such substances are not at all surfactant-like, i.e. they cannot adsorb to hydrophobic matter or interact with membranes and hence should not fall under this criterium.

Indeed, in the context of the EU Detergents Regulation, the 'international trade tariff value' of 45 mN/m reduction in surface tension is referred to in order to identify surfactants (European Commission, 2018).

The *Harmonized Tariff Schedule of the United States* defines organic surface-active agents as products "*which when mixed with water at a concentration of 0.5 percent at 20 °C and left to stand for one hour at the same temperature:*

1. *Give a transparent or translucent liquid or stable emulsion without separation of insoluble matter; and*
2. *Reduce the surface tension of water to 4.5 x 10^{-2} N/m (45 dyne/cm) or less"* (US Government, 2021).

The ECETOC Polymers TF maintains the view that the threshold of < 45 mN/m is appropriate to establish if a polymer is surface-active to a relevant degree (ECETOC, 2019).

Of note, work on the case studies has revealed opportunities to revise Section 3.6 (Surface tension) in ECETOC TR No. 133-2 and specifically, to update Table 3 therein (*Analytical methods potentially suitable to determine the surface tension-lowering properties of polymers*) to reflect the state-of-the-art in science and industrial practice as well as commercially available equipment. While an update of ECETOC TR No. 133-2 is being planned, Appendix CS6-A.1 of the present report proactively summarises the new insight. Additionally, in the revision of TR No. 133-2, currently ongoing work by the European Committee of Organic Surfactants and Their Organic Intermediates (CESIO) Working Group 'Test Methods of Surfactants' and the Association of Manufacturers of Process and Performance Chemicals (TEGEWA) Working Group 'Surface Active Substances' (Venzmer, 2020) as well as work by the European Committee for Standardisation / Technical Committee (CEN/TC 276) – Surface Active Agents (Working Group 1 'Analytical Methods' and Working Group 2 'Methods

of Test') to standardise amongst other issues the physical, chemical or other test methods of surface-active agents[9] shall be considered.

Surface tension is an important physical property to consider when selecting a surfactant. Aqueous solutions of nonionic surfactants, such as AEs, exhibit significantly lower surface tensions and consequently better wetting characteristics than water alone. As the surfactant concentration is increased in very dilute solutions, surface tension decreases. This effect continues until a particular concentration is reached above which the surface tension remains nearly constant. This particular concentration is termed the 'critical micelle concentration' (CMC) of the surfactant.

The CMC of a surfactant is *"the value at which the solution property of the molecule shows an abrupt change. At this concentration, surface active ions or molecules in solution associate to form larger units. These associated units are called micelles (self-assembled structures), and the first formed aggregates are generally approximately spherical in shape. Each surfactant molecule has a characteristic CMC value at a given temperature and electrolyte concentration*" (Tadros, 2013).

Examples of surface tension values for commercial AEs can be found in the producers' respective technical information, product guides, etc., e.g.:

- Lutensol® TO types: **approx. 27 mN/m** at 1 g/L in distilled water (BASF SE, 2014)
- Tomadol® ethoxylated alcohols: **27-34 mN/m** at 1 g/L in distilled water (Evonik Corporation, 2017)
- Marlipal® O13 surfactants: **27-29 mN/m** at 1 g/L in demineralised water (Sasol, undated)
- BIO-SOFT®: **29-30 mN/m** at 1 g/L in distilled water (Stepan, 2008)

Hence, at 1 g/L (0.1% by weight), the surface tension of commercial AEs generally ranges between 25 and 35 mN/m and thus is well below the international trade tariff threshold of 45 mN/m to identify substances with surfactant properties.

7.3.1.10 Analytical verification of polymer concentrations in environmental media

Commercial AEs are like UVCBs in that they consist of polymeric substances with several alkyl chain-lengths, which are each ethoxylated covering a broad, statistically distributed ethoxylation range. Analytical verification of the concentration of the respective AE in the test medium is required for proper hazard assessment particularly when addressing ecotoxicological endpoints. Standard cold analytical (mass spectrometry) and radioanalytical approaches could be available for the given AE but could take significant effort to conduct (see Section 3.7 in ECETOC TR No 133-2).

The method described by Dunphy et al. (2001), which uses 2-fluoro-N-methylpyridinium p-toluene sulphonate derivatisation followed by electrospray liquid chromatography/ mass spectrometry detection, is suitable for the detection of all 114 AE homologues in the range C12-18 and EO0-18 at ng/L levels in environmentally relevant aquatic samples. This allows obtaining a much more complete environmental profile of AE homologue distribution than when using cold analytical and radioanalytical approaches (Eadsforth et al., 2006). Eadsforth et al. (2006) provide examples of monitoring data for individual AE homologues in effluents from WWTPs. When taking samples for AE analysis, care should be taken to ensure that microbial degradation of the AEs is prevented during handling and storage. This can be achieved by freezing the samples in dry ice and storing them at -18 °C or by adding formalin as applied by Eadsforth et al. (2006).

[9] https://standards.iteh.ai/catalog/tc/cen/e0d6e5f4-7375-4ec3-9fe3-9016081635d9/cen-tc-276

7.3.2 Step 2.2: Identification of additives

Additives are not relevant for AEs as they do not need, e.g., stabilisers.

7.3.3 Step 2.3: Identification of NIAS and/or residual substances (monomers)

A common NIAS in commercial AEs is unreacted EO (synonym oxirane; CAS No. 75-21-8) from the ethoxylation reaction. The amount of EO present in commercial AEs is < 10 ppm. Similarly, depending on the polymerisation process used, AEs may contain residual (free) alcohol and/or 1.4-dioxane (CAS No. 123-91-1) by-product of ethoxylation.

It is of note that various European and North American regulatory initiatives are currently focused on limiting the presence of 1,4-dioxane in the environment, drinking water and cleaning/cosmetic products. As an example, in the European Union, 1,4-dioxane has been included in the '*registry of substances of very high concern intentions until outcome*'[10]. In the USA, the state of New York has introduced legislation setting the final maximum allowable concentrations of 1,4-dioxane to 1 ppm for household cleansing and personal care products by December 2023. In that same law, a maximum concentration level of 10 ppm was set for cosmetic products by December 2022[11].

7.4 Case Study 6: CF4Polymers (Step 3) Polymer component strategy

This case study focuses on the polymeric substances, i.e. the AEs (as present in the final formulations). Any NIAS present in the polymer products are not considered relevant in this case study.

7.5 Case Study 6: CF4Polymers (Step 4) Grouping approach evaluation

The CF4Polymers (Step 4) grouping approach evaluation (Section 1.3) for AEs takes benefit of the circumstance that AEs are generally data rich since they have been widely used in consumer applications for many decades (and to a lesser extent also in industrial applications). As the consumer applications in cleaning products are critical regarding human exposure and environmental exposure (down-the-drain release), the detergent industry has thoroughly tested AEs to determine their hazard profiles and to conduct a risk assessment. This database has been published e.g. in the *Human and Environmental Risk Assessment (HERA) on ingredients of European household cleaning products - alcohol ethoxylates* (HERA, 2009).

To enable a meaningful grouping, this part of the case study is not restricted to the linear C12-15EO7 and C16-18EO≥20 but considers all linear AEs that are based on primary alcohols and have C-chain lengths of 8-18 and

[10] https://echa.europa.eu/registry-of-svhc-intentions/-/dislist/details/0b0236e1857f0d76
[11] https://www.dec.ny.gov/chemical/121658.html?_cldee=amtsYXBhY3pAZG93LmNvbQ%3d%3d&recipientid=contact-8c830405624be4119940005056813 4c0-dd805547e5934d06b05a0787a2bf5684&esid=ffdffa8d-6f2b-eb11-80d7-0050568106e4

1-50 EO moles in the backbone. Additionally, branched and unsaturated AEs are considered for the human health toxicity endpoints.

7.5.1 Step 4.1: Use expert judgement to identify key parameters / Criterion 1: Chemical nature

The common key feature of the linear AEs considered here is that they all have the same structural key element, i.e. a hydrophobic alkyl moiety linked via an ether linkage to a hydrophilic (poly)oxyethylene moiety. Thereby, all of these AEs are amphiphilic molecules. They have the general structure Cx-yEOn (x-y = 8-18; n = 1-50), and their molecular weight ranges from 200 to 2,500 Da.

Although the AEs considered here have different C-chain lengths and degrees of ethoxylation, they are 'similar' as defined by internationally agreed grouping approaches (OECD, 2014; ECHA, 2008, 2013, 2017c) since they all have in common the same structural key element (see Glossary for definition of similarity). These structural characteristics of AEs can, however, result in varying outcomes for specific hazard endpoints and systemic bioavailability; these are used to stratify the grouping approach of AEs and are described in later steps.

7.5.2 Step 4.2: Use expert judgement to determine polymer similarity / Criterion 2: Physico-chemical and fate properties

Due to the common key feature (Section 7.5.1), that determines the amphiphilic nature of the molecules, AEs also have common physico-chemical properties. The most important common (physico-chemical) property of AEs is that they reduce the surface tension of water to below 45 mN/m (at 5 g/L).

Another relevant property of all AEs considered in this case study, which is indeed related to the common key feature, is their rapid biodegradability (Section 7.7.2.1). (AEs that are not biodegradable are out of scope of this case study.) Biodegradability is an important parameter as it determines whether a substance can potentially elicit long-term effects on the environment, or not. Therefore, it is meaningful to use sameness regarding biodegradability as a further key parameter for grouping in this case study. All AEs follow the similar pattern of biodegradation resulting in similar breakdown products that are the same as common endogenous (non-hazardous) substances (Section 7.7.2.1).

Summary of Step 4.2: The AEs included in this case study are defined as being linear, as having the general chemical structure Cx-yEOn (x-y = 8-18; n = 1-50), as reducing the surface tension of water, and as being readily biodegradable. The additional consideration of ready biodegradability as key property for grouping safeguards a clear category definition. It ensures that chemical structures, which may fall under the solely chemical-category-based description Cx-yEOn (x-y = 8-18; n = 1-50), but that are not readily biodegradable (and thus may exhibit different ecotoxicity profiles), are not covered in the grouping approach evaluation.

7.5.3 Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data

Note: As compared to the structure of the CF4Polymers presented in ECETOC (2019), Step 4.4 (identify available ecotoxicity and toxicity data) is presented before Step 4.3 (define hypothesis for grouping and read-across and determine relevant approach) in this case study since the ecotoxicity and toxicity databases are referred to in Step 4.3 (Section 7.5.4).

7.5.3.1 Ecotoxicological data

Background for grouping by aquatic hazard similarity

Aquatic toxicity of the AEs is driven by their non-polar narcotic mode-of-action (Boeije et al., 2006) resulting in a strong, structure-dependent increase in aquatic toxicity potential with increasing overall hydrophobicity of the AEs (Figure CS6.2). Based on the comprehensive acute aquatic toxicity dataset available, QSARs have been established (in the context of the grouping exercise described here), which allow predicting the acute aquatic toxicity potential of untested category members, by interpolation. Also, chronic aquatic toxicity data are available, allowing to establish chronic aquatic toxicity QSARs, although with a somewhat higher degree of uncertainty.

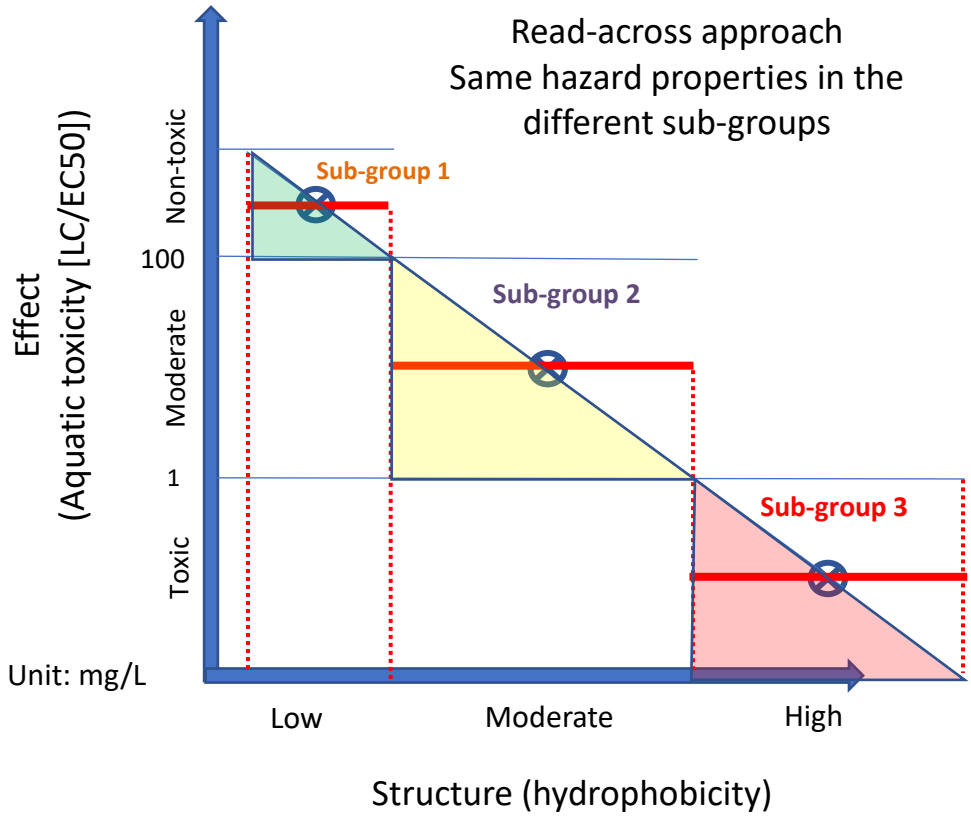


Figure CS6.2: General schematic illustrating the hypothesis for an association between alcohol ethoxylate ecotoxicity and (structural) hydrophobicity of the molecules

Footnote to Figure CS6.2: Abbreviations: EC_{50}: Concentration required to achieve 50% effect change from the control; LC_{50}: Concentration required to achieve 50% change in lethality from the control.

Other ecological endpoints, e.g. biodegradation and bioaccumulation, are mainly determined by the metabolic pathways of the AEs. As the AEs in this category have the same common key feature (Section 7.5.1; CF4Polymers Step 4.1), they are easily biodegraded (by microorganisms) and/or metabolised and excreted (by higher organisms). Therefore, regardless of their structure, all AEs included in this case study are readily biodegradable and have a low tendency to bioaccumulate.

Ecotoxicological hazard data matrix for AEs

Figure CS6.3 presents the ecotoxicological hazard data matrix for AEs (see Section 7.8.1 for details on the preparation of a hazard data matrix for AEs and Section 7.8.2 for details on the ecotoxicological database for

AEs). The data matrix includes all commercially available AEs considered in the European Committee of Organic Surfactants and Their Organic Intermediates (CESIO) *Recommendations for the harmonised classification and labelling of surfactants* (CESIO, 2017). While the AEs included in CESIO (2017) cover linear and branched AEs as well as saturated and unsaturated AEs, this is not considered to affect the present grouping that focuses on linear AEs: As the mode-of-action for AEs is non-polar narcosis, the main driver for toxicity is the hydrophilic/lipophilic balance of the molecules (Ríos et al., 2017), and this is almost not influenced by branching or double-bonds.

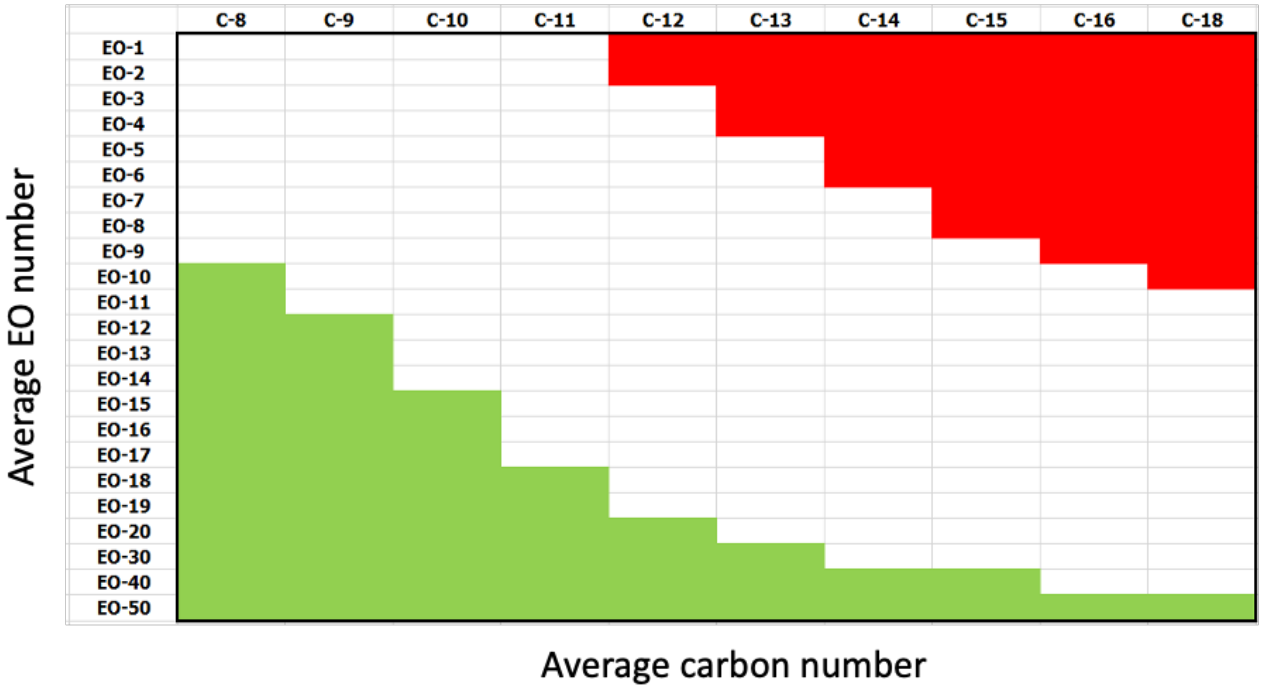


Figure CS6.3: Ecotoxicological hazard matrix (acute aquatic toxicity in fish / algae / *Daphnia*) for alcohol ethoxylates

Footnote to Figure CS6.3: Note: See text for preparation of the hazard data matrix that includes both experimental data and QSAR predictions (adapted from CESIO, 2017).

Colour legend:

Green no hazard in algae, *Daphnia* and/or fish (LC_{50} > 100 mg/L) = no EU CLP hazard classification.

White: moderate hazard in fish, algae and/or *Daphnia* (LC_{50} = 1-100 mg/L) = EU CLP hazard classifications: H401 (toxic to aquatic life), H402 (harmful to aquatic life), H412 (harmful to aquatic life with long-lasting effects).

Red: significant hazard in algae, *Daphnia* and/or fish (LC_{50} < 1 mg/L) = EU CLP hazard classifications: H400 (very toxic to aquatic life), H410 (very toxic to aquatic life with long-lasting effects), H411 (toxic to aquatic life with long-lasting effects).

Abbreviations: CLP: Classification, Labelling and Packaging Regulation (EP and Council, 2008); LC_{50}: Concentration required to achieve 50% change in lethality from the control; QSAR: Quantitative structure-activity relationship.

On the hazard data matrix, the x-axis represents the range of C-chain lengths (C8-C18) and the y-axis the numbers of EO (EO1-EO50). To prepare the database, first, all available experimental data (derived from studies using algae, *Daphnia* and/or fish) were inserted into the matrix. Then, these hazard data were sorted by the respective hazard classifications implemented in the EU CLP Regulation (EP and Council, 2008), distinguishing between (1) no hazard; (2) moderate hazard; (3) significant hazard; see Footnote to Figure CS6.3 for details on the hazard classifications. The experimental data are generally available on products which span multiple fields of the matrix with their constituent distribution. For example, field C13-EO3 represents one

homologue molecule which will in practice be present as part of a molecular weight distribution together with C12-EO3, C13-EO2, C13-EO4, C14-EO1, etc.

Based on the 'semiquantitative' assignment of the AEs to different ecotoxicity profiles, in the second step of the preparation of the data matrix presented in Figure CS6.3, the following QSAR was developed using 48-hour EC_{50} values from acute aquatic toxicity studies using *Daphnia* as most sensitive species (the available QSARs for fish and algae are almost identical as the mode-of-action for AEs is non-polar narcosis):

$$\log(EC_{50}) \text{ in mmol/L} = 0.95 - (0.34 \times C) + (0.11 \times EO)$$

The further consideration of the QSAR data in the hazard data matrix then allowed the quantitative assignment of structures (i.e. distinct borders) to the corresponding ecotoxicity profile that covers a continuum of properties.

The comprehensive hazard data matrix (Figure CS6.3) shows that acute aquatic toxicity in fish / algae / *Daphnia* depends both on the length of the C-chain and on the degree of ethoxylation (see also Section 7.8.2.2 for the presentation and discussion of available ecotoxicity studies addressing AEs). Different hazard levels (i.e. hazard classifications) can be demonstrated for different AE subgroups when applying the limit values for acute aquatic toxicity implemented in the CLP Regulation (EP and Council, 2008) or the GHS (United Nations, 2019), i.e. no acute hazard if EC_{50}/LC_{50} > 100 mg/L; moderate acute hazard if EC_{50}/LC_{50} > 1 to ≤ 100 mg/L; and significant acute hazard if EC_{50}/LC_{50} ≤ 1 mg/L.

7.5.3.2 Toxicological data

Background for grouping by toxicological similarity

The comprehensive database on acute and long-term systemic toxicity as well as local endpoints (Yam et al., 1984; Talmage, 1994; Danish EPA, 2001; HERA, 2009; Section 7.8.3) facilitates the hazard and risk assessment, as well as grouping, of AEs. The major hazard potential presented by AEs is due to local action / skin and eye irritation mainly observed at high concentrations, but not at the typical use conditions. Depending on structure, the undiluted AEs could be 'not classified' or CLP Category 1 or 2 (irreversible or reversible effects on the eye, respectively). By contrast, under typical use conditions of diluted detergent solutions containing 0.1% AEs, AEs are practically non-irritating to skin and not irritating to eyes (Section 7.8.3). AEs are also either CLP Category 4 acute oral toxicity (LD_{50} > 300 to ≤ 2,000 mg/kg bw) or not classified; these are either metabolised to physiologically occurring metabolites (fatty acids), or to compounds of low toxicity.

Toxicological hazard data matrices for AEs

In consideration of the toxicological profile of AEs (see above), two human health hazard matrices were prepared to address (1) acute oral toxicity and (2) eye irritation. As has been described above for the ecotoxicological data matrix, also the human health data matrices include all commercially available AEs considered in the CESIO (2017) *Recommendations for the harmonised classification and labelling of surfactants*. While the AEs included in CESIO (2017) cover linear, quasi-linear, and branched AEs as well as saturated and unsaturated AEs, this is not considered to affect the present grouping which focuses on linear AEs.

Figure CS6.4 Panels A and B present the human health hazard data for eye irritation and acute oral toxicity potential of AEs (with both data sets combined into one matrix). All AEs that elicit severe eye damage (H318 as per EU CLP Regulation) are included in the blue outline (i.e. all AEs that lie outside the blue outline exhibited either no eye irritation or reversible eye irritation (H319)). With respect to acute oral toxicity, all AEs that are classified as Category 4 acute oral toxicity (300-2,000 mg/kg bw) lie inside the purple box, whereas all AEs that

lie outside the purple box have no classification for acute oral toxicity. Acute oral toxicity Categories 1-3 have not been assigned to AEs: In the rat, the oral LD_{50} values range from between 544 mg/kg bw in females for C14-15EO11 to more than 16,000 mg/kg bw in both sexes for C18EO10 (Section 7.8.3.6 and Appendix CS6-A.2).

The data matrix shows that eye irritation is dependent on C-chain length and degree of ethoxylation. The eye irritation of AEs increases with increasing C-chain or EO-chain length up until the mid-ranges of chain lengths. The most hazardous properties of AEs are observable between EO5 and EO15 chain lengths. Above these mid-ranges, hazard properties decrease again. Currently, no definitive correlation to physico-chemical or surfactant properties could be connected to this behaviour.

Linear and branched AEs behave similarly for eye irritation (Figure CS6.4). AEs with very short or very long EO chain length show lower eye irritation than the mid-range EO numbers (Figure CS6.4, Panel A). Further, the linear and branched AEs are generally either CLP Category 4 acute oral toxicity (LD_{50} > 300 to ≤ 2,000 mg/kg bw) or not classified (Section 7.8.3.6 and Appendix CS6-A.2). A trend in acute oral toxicity is observable (between EO5 and EO15 chain length for CLP Category 4) that is dependent on C-chain length and degree of ethoxylation, which is widely concordant with the trend observed for eye irritation.

7.5.4 Step 4.3: Define hypothesis for grouping and read-across and determine relevant approach

The guiding hypothesis for CF4Polymers (Step 4) grouping approach evaluation of the AEs considered here is that the magnitude of ecotoxicity (relevant hazard property: acute aquatic toxicity) and toxicity (relevant hazard properties: acute oral toxicity and eye irritation) changes in a predictable manner as their C-chain length (C8 – C18) and degree of ethoxylation changes (EO 1-50) (Figures CS6.2 - CS6.4).

Following this hypothesis, a hazard-similarity-based approach is suggested as the relevant approach to subgroup AEs if they exhibit the same hazard classification (for acute aquatic toxicity, eye irritation, or acute oral toxicity) in line with the GHS (United Nations, 2019) and/or the EU CLP Regulation (EP and Council, 2008). Thereby, read-across can be performed for those AEs that are subgrouped together to fill data gaps for target substances using data available for the source substances of that subgroup.

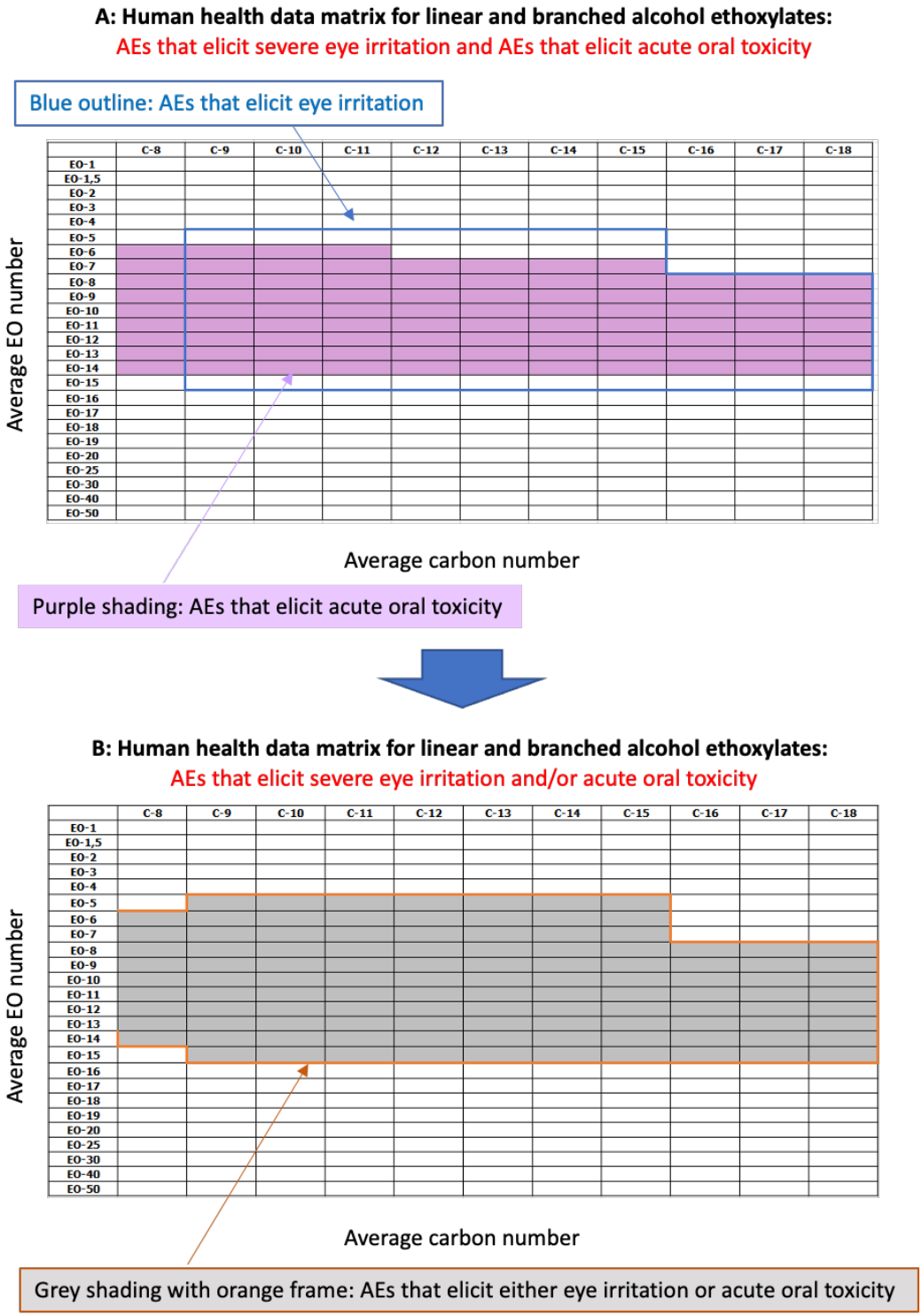


Figure CS6.4: Human health data matrix for linear and branched alcohol ethoxylates (AEs)

Footnote to Figure CS6.4: Panel A: AEs that elicit severe eye damage (H318) (outside blue box = no eye irritation or reversible eye irritation (H319)) and AEs that elicit Category 4 acute oral toxicity (outside purple box = no classification for acute oral toxicity and NOT Category 1-3). Panel B: AEs that elicit severe eye damage (H318) and/or Category 4 acute oral toxicity.

Footnote continued on next page

Footnote to Figure CS6.4, continued:

The human health data matrix is mainly based on experimental data, with limited data intrapolation via read-across. This matrix does not distinguish between data for linear and/or branched AEs; however, they behave similarly for eye irritation, and both are generally of low / negligible acute oral toxicity (with some cases of EU CLP Category 4 acute oral toxicity (LD_{50} > 300 to ≤ 2,000 mg/kg bw)).

Abbreviations: bw: Body weight; CLP: Classification, Labelling and Packaging Regulation (EP and Council, 2008); EO: Ethylene oxide; LD_{50}: Dose required to achieve 50% change in lethality from the control.

7.5.5 Step 4.5: Use expert judgement to justify grouping and to fill data gaps by read-across

Based on (1) structural similarity; (2) trend behaviour of physico-chemical properties; and (3) similar mechanisms for (3a) biodegradation and acute ecotoxicity, as well as (3b) metabolism in mammals and systemic toxicity / local effects, all AEs considered in this case study (C8-18; EO 1-50) are considered a single overarching group since they are all amphiphilic molecules. Their hydrophobic part strongly interacts with biological membranes, leading to a non-polar narcosis mode-of-action in aquatic organisms (Boeije et al., 2006).

With respect to the environmental fate of AEs, and particularly biodegradability and bioaccumulation, the underlying hypothesis is that the AE structure is generally accessible for rapid metabolism. The high metabolic clearance rate results in a coherent high susceptibility for biodegradation and a low potential for bioaccumulation.

The magnitude of acute aquatic toxicity is dependent on the hydrophobicity of the AE, i.e. it increases with increasing chain-length of the alkyl moiety and with increasing numbers of EO in the hydrophilic moiety (Figure CS6.2). Trends in acute aquatic toxicity due to membrane interaction of the AEs could be established and were considered in defining subgroups for the different hazard classifications for acute aquatic toxicity.

With respect to human health effects, AEs generally present a low systemic toxicity potential. Over the entire group of AEs, the toxicological database does not indicate relevant differences in systemic acute or repeated-dose toxicity (Section 7.8.3.6; Appendices CS6-A.2 and CS6-A.3). Therefore, the range of AEs considered herein show no differences in systemic toxicity that would have to be reflected in the (sub-)grouping. The major toxicological effects elicited by AEs are due to local action caused by membrane interaction. Trends in eye irritation potential of the AEs could be established. Further, the comprehensive database enabled the determination that those AEs that have the most pronounced irritation potential (i.e. Category 1 – irreversible damage) are located in the mid-range C-chain length and mid-range number of EO moieties (Figure CS6.3).

Therefore, a category approach based on relevant (structure-dependent) hazard endpoints is suggested as relevant approach for the grouping of the AEs included in this case study (Cx-yEOn (x-y = 8-18; n = 1-50). The overall group is defined by the same environmental fate (i.e. ready biodegradability) and the same systemic behaviour / metabolism while its subgroups are defined by differences in the respective ecotoxicological and toxicological endpoints (established by differences in GHS / EU CLP hazard classifications).

While the present case study only considers ‘theoretical’ AEs, within a practicable grouping approach these considerations can form the foundation to justify read-across to fill data gaps for category members (target substances) based upon the data available from source substances of the same subgroups.

7.6 Case Study 6: CF4Polymers (Step 5) Determination of exposure scenarios

Linear AEs are produced in high volumes, and they are used in a very broad range of applications (Section 7.1.2). Relevant life cycle stages and uses may include manufacturing and formulation steps, industrial and professional uses, and wide dispersive use by consumers (leading to down-the-drain release). Thereby, a long list of human and environmental exposure scenarios may need to be considered during the risk assessment of any given AE.

This case study focuses on the following exposure scenarios:

Consumer use of C12-15EO7 in laundry detergents: Focus is on the final formulation where AEs are present either as powder, in a (concentrated) solution or dispersion, or as a gel/liquid. Generally, laundry detergents are diluted with water before or during use; further, the AE polymers have medium to high solubility in water (Section 7.3.1.6). Therefore, possible environmental compartments include freshwater and seawater. Upon disposal via down-the-drain release, C12-15EO7 used in laundry detergents are found predominantly in the wastewater, so that it reaches WWTPs. After sewage treatment, C12-15EO7 may reach the freshwater compartment in low concentrations, and possibly the terrestrial compartment upon sludge application onto land, and/or the marine compartment (Section 7.7.1 and 7.7.2.1). With respect to human exposure assessment, the general population, including sensitive subpopulations such as children and elderly, are relevant target populations for C12-15EO7. Exposure to humans is most likely via the dermal route of exposure (Section 7.7.4). By comparison, consumer exposure via inhalation is unlikely since household cleaning sprays are typically pump sprays that are formulated to not result in respirable aerosols, particularly for irritating formulations.

Accordingly, relevant exposure categories include (ECHA, 2015):

- Chemical Product Category PC35 - *Washing and cleaning products*
- Environmental Release Category ERC2 - *Formulation into mixture*
- Environmental Release Category ERC8a/b - *Wide-spread use of non-reactive / reactive processing aid (no inclusion into or onto article, indoor)*

Industrial use of C16-18EO≥20 for (1) the manufacturing of water-based dispersions; and (2) for conditioning of textile, leather, and paper: The intended use is entirely industrial and serves to facilitate proper reaction conditions (micelle formation; Section 7.1.2) during the manufacturing of the water-based dispersions and/or textile, leather and paper. Separation of the AEs after polymerisation is technically not feasible. The remaining AE is regarded as an impurity and does not represent a consumer use. Workers are the relevant population, and if exposure occurs, it will be via the dermal route of exposure. If C16-18EO≥20 reaches the environment, water and soil are relevant compartments.

Accordingly, relevant exposure categories include (ECHA, 2015):

- Different Process Categories, depending on the type of manufacturing:
    - PROC1 - *Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions*
    - PROC2 - *Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions*
    - PROC4 - *Chemical production where opportunity for exposure arises*
    - PROC7 - *Industrial spraying*

  - PROC10 - *Roller application or brushing*
  - PROC13 - *Treatment of articles by dipping and pouring*
  - PROC14 - *Tabletting, compression, extrusion, pelletisation, granulatio*n
  - PROC17 - *Lubrication at high energy conditions in metal working operations*
- Environmental Release Category ERC4 - *use of non-reactive processing aid at industrial site (no inclusion into or onto article*

As is further discussed in Section 5.1 of ECETOC TR No. 133-2 (ECETOC, 2020), industry has developed SpERCs for specific classes of substances. These SpERCs can be used in the context of the EU REACH Regulation (EP and Council, 2006) to refine the highly conservative default release scenarios provided in the ECHA (2015) guidance. SpERCs that may be useful to determine exposure scenarios for AEs include:

- SpERCs from the International Association for Soaps, Detergents and Maintenance Products (AISE, 2019) that define environmental release estimates for detergents and cleaning products related to their intended uses; https://www.aise.eu/our-activities/regulatory-context/reach/environmental-exposure-assessment.aspx;
- SpERCs from Cosmetics Europe; https://cosmeticseurope.eu/cosmetics-industry/cosmetics-industry-and-reach/;
- SpERCs from the European Crop Protection Association that can be used to assess emissions of co-formulants used in crop protection products (Dobe et al., 2020).

Since SpERCs are not substance-specific, they should be applicable for the evaluation of polymers including AEs. These SPERCs should be applied when performing a quantitative exposure/risk assessment (see Section 7.7.4 below (human exposure assessment) as well as Section 5.1 in ECETOC TR No. 133-2 for further details on opportunities to use process categories, SpERCs, etc. for polymer exposure assessment and limitations thereof).

7.7 Case Study 6: CF4Polymers (Step 6) Exposure characterisation

7.7.1 Release of alcohol ethoxylates and distribution in the environment

As described in HERA (2009), AEs used in household applications are intended to be released down-the-drain as aqueous solutions or dispersions so that they generally reach WWTPs. Due to the widespread use of cleaning products, down-the-drain release can be considered as almost continuous. Therefore, a steady-state situation will be established between release processes and removal, which will occur predominantly via biodegradation. In WWTPs, some of the AEs will be adsorbed to solids, and the bioavailable fraction may then undergo anaerobic biodegradation in a digester before the resulting sludge is released to agricultural land, for use as fertiliser (HERA, 2009). Dissolved AEs remaining in aqueous solution are subject to aerobic biodegradation processes in the WWTPs. Thereby, a substantial amount of AE is removed (> 99%; HERA, 2009) before the effluent is released to surface water. In surface water, sediment, and soil, further aerobic and anaerobic biodegradation will occur (HERA, 2009; Section 7.7.2.1). Plants or animals living in the surface water or soil may take up AEs in dissolved or sorbed form (HERA, 2009). AEs have also been measured in the marine environment, e.g., originating from river discharges (HERA, 2009), and possibly from offshore petroleum applications (EOSCA, 2000). In seawater and sediments, AEs are expected to undergo further biodegradation if the environmental conditions allow (Jackson et al., 2016). Exposure assessment should consider all these

basic adsorption and degradation processes as well as bioconcentration potential (HERA, 2009; Section 7.7.2.2).

The behaviour of AEs in WWTPs can generally be predicted quite accurately and without major challenges using exposure models such as SimpleTreat (EUSES; Franco et al., 2013; ECHA, 2019a; https://echa.europa.eu/support/dossier-submission-tools/euses). Monitoring data have typically been generated, and environmental models developed and validated, for AEs up to C18 and EO20. Only for AEs with very high EO numbers (> 20) the exposure modelling may be less reliable, as it may be restricted by analytical methodology and model applicability domains. Modelled and measured concentrations in sewage sludge have also been used as part of terrestrial exposure assessments (HERA, 2009).

AEs can be transferred from the aqueous phase to suspended solids, activated sludge, or soil solids by adsorption, and from the aqueous or solid phases to the atmosphere by volatilisation (HERA, 2009). Nonetheless, the fraction of AEs that is volatised will be very low. In the HERA report, it is noted that measured vapour pressure data are unavailable for AEs. Nonetheless, the corresponding data available for fatty alcohols indicate that the vapour pressure of AEs should be well below 0.1 hPa and that it should further decrease with increasing C-chain length (HERA, 2009).

Adsorption to soil, sediment, and activated sludge depends upon the properties of the given AE homologue and those of the material to which the AE is adsorbed (HERA, 2009). Partitioning of AEs between environmental compartments can generally be predicted quite well using the different partition coefficients (HERA, 2009): AEs are a type of surfactant for which the log K_{ow} can be determined experimentally and also predicted using QSARs (Section 7.3.1.7). Van Compernolle et al. (2006) have developed two sorption QSARs for AEs, one predicting log K_{oc} and the other predicting log K_d, which are both a function of carbon number and EO number (further discussed in HERA, 2009; see also Section 7.3.1.8). Interestingly, robust QSARs to predict sorption behaviour (K_{oc} and K_d) as well as ecotoxicity for any homologue mixture, have also been developed based on the log K_{ow} (Boeije et al., 2006). Such sorption coefficients can be used in an aquatic risk assessment to assess the bioavailability of individual homologues.

7.7.2 Environmental fate assessment

Since this case study does not intend to perform a risk characterisation for any specific AE (Section 7.1.1), the below subsections on (bio)degradation and bioaccumulation assessment present and discuss studies investigating AEs also beyond C12-15EO7 and C16-18EO≥20 that were selected for this case study. This broadens the evaluation of (1) the overall suitability of the CF4Polymers (ECETOC TR No. 133-1) for the risk assessment of AEs; and (2) the applicability of relevant tools, methods and models (ECETOC TR No. 133-2) specifically for AEs.

7.7.2.1 (Bio)degradation assessment

Three different AE (microbial) biodegradation mechanisms have been observed (Holt et al., 1992), i.e.

1. Intramolecular scission leading to an alcohol and a polyethylene glycol. This is considered the predominant aerobic biodegradation pathway.
2. Alkyl chain shortening via omega and beta oxidation.
3. EO chain shortening via omega glycol oxidation and removal of C2 units.

In higher organisms, beta oxidation is a mitochondrial process that includes hydrolysis of the ether linkage and subsequent oxidation of the resulting alcohol to fatty acids which finally are degraded to C2-fragments,

shorter alkyl chains, and ultimately to carbon dioxide and water. For the (poly)oxyethylene moiety, uncharged and carboxylated (mainly dicarboxylated) fragments have been the most prominent metabolites identified obtained via the microbial biodegradation of EO moieties by the oxidative dicarbonic acid cycle or the glycerate pathway or both (Steber and Wierich, 1985).

Variations in the length of the alkyl chain (C8-20) or the number of EO units (3-11) have little effect on biodegradation, but some retardment of biodegradation was seen for AEs with ≥ 20 EO (see Holt et al. (1992) and references cited therein).

Aerobic biodegradation

Generally, all AEs that were produced from straight chain primary or secondary alcohols undergo rapid and ultimate aerobic biodegradation in standard laboratory screening tests (OECD TG 301 series) and field conditions, including seawater (Talmage, 1994; Danish EPA 2001; HERA, 2009; Jackson et al., 2016). As AEs have medium to high water solubility, they can be tested without great difficulty in screening and simulation biodegradation tests. However, many commercial AEs are like UVCBs, and this needs to be considered in interpreting the test results.

Screening tests utilising soil as the test matrix

Generally, AEs with high C-chain length and/or high EO numbers can have high K_{oc} values (HERA, 2009).

The ECETOC Polymers TF was unable to find any data for AEs assessed in *standard* biodegradation screening tests utilising soil as the test matrix. Good biodegradation of AEs in soil is expected as long as the AE is not tightly bound to the matrix and remains bioavailable. Indeed, Ang and Abdul (1992), using a non-standardised testing approach, observed good degradation of an AE in soil microcosms.

Screening tests utilising marine water/sediment as the test matrix

The OECD TG 306 (biodegradability in seawater) is applicable for the assessment of AEs provided they are sufficiently soluble in seawater, which is generally the case. Nonetheless, marine biodegradation data on AEs are scarce. Based on mean half-lives, marine biodegradability ranges from alcohol sulphate > linear alkylbenzene sulfonate > AE > alcohol ethoxy sulphate while exhibiting a large overlap between half-life data (Jackson et al., 2016). An ERASM project was initiated in 2020 that investigates the marine persistence of (polymeric) surfactants, including some representative AEs with > 3 EO (Diederik Schowanek, Procter & Gamble, BE; personal communication).

Simulation biodegradation tests

Overall AE removal from WWTPs generally exceeds > 99% (HERA, 2009). Prats et al. (2006) performed OECD TG 303A aerobic sewage treatment simulation tests (activated sludge units) to evaluate the effect of temperature (9, 15 and 25 °C) on the biodegradation of linear alkylbenzene sulfonate and AEs. The removal of both surfactants always exceeded 90%, regardless of the applied temperature (Prats et al., 2006).

If necessary, ^{14}C-radiolabelling can be used to test AEs at lower, environmentally relevant concentrations. Federle and Itrich (2006) successfully ran OECD TG 314 simulation tests to assess the biodegradability of ^{14}C-labelled polymeric AEs (label on the first carbon of the fatty alcohol) discharged in wastewater. Also, Menzies et al. (2017) tested AEs with 3 and 9 EO groups (radiolabel on the terminal EO unit) in an OECD TG 314. However, difficulties in radiolabelling (e.g. selection of radiolabelling precursor) and in evaluating the findings for different components of the polymer product need to be considered when using ^{14}C-labelled AEs. Further, slightly different biodegradation behaviours of certain chain lengths need to be considered. The position of the radiolabel should be carefully considered to correctly interpret the outcome of biodegradation, persistence or metabolism studies.

Anaerobic biodegradation

Linear AEs are anaerobically biodegradable (Danish EPA, 2001; Merrettig-Bruns and Jelen, 2009). Anaerobic biodegradation tests have been performed using both anaerobically digested sludge and anaerobic sediment as inocula (HERA, 2009). Huber et al. (2000) studied the anaerobic biodegradation mechanisms of linear AEs. During the degradation of linear C12(EO)~9, a technical dodecanol ethoxylate with an average of 9 EO units, and linear C12EO8, a stepwise shortening of the ethoxy chain was observed, until the lipophilic moiety was reached (Huber et al., 2000). This contrasts with the aerobic degradation pathway, where central scission prevails (see above).

Abiotic degradation

Abiotic degradation processes such as photodegradation and hydrolysis are not practically relevant for the environmental fate of AEs, as these are readily biodegradable and do not include easily hydrolysable groups / bonds (HERA, 2009). Therefore, photodegradation and hydrolysis tests would not normally be performed for AEs.

Similarly, as AEs have low volatility and are readily biodegradable, photolysis in air and/or atmospheric photooxidation are considered of low relevance (HERA, 2009). A QSAR-derived half-life value can be calculated if needed, e.g. via EPI-Suite's AOPWIN model (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface).

Conceptual Framework for Biodegradation Assessment (Section 4.1.5 in ECETOC TR No. 133-2; ECETOC (2020))

A comparison of the Conceptual Framework for Biodegradation Assessment laid out in ECETOC TR No. 133-2 with the biodegradation information for AEs described above generally confirms that the framework is useful and that it yields the relevant information to evaluate the biodegradability and potential persistence of AEs. Notably, however, when applying the framework in practice, the extent of information that is 'sufficient' to draw a conclusion on biodegradability (the terminology used in ECETOC TR No. 133-2) will need to be determined on a case-by-case basis. The sufficiency of information will be different when performing either a general screening for biodegradability or stringent regulatory assessments to identify / rule out persistence. Further, for high production volume chemicals with wide-dispersive use and hence comprehensive hazard assessment (such as AEs), degradation kinetics need to be obtained that cannot be sufficiently derived from screening level studies. Therefore, the establishment of the 'sufficiency of information' to conclude on biodegradability also needs to consider intended uses and exposure potential.

7.7.2.2 Bioaccumulation assessment

This section follows the structure of the Conceptual Framework for Polymer Bioaccumulation Assessment described in Section 4.2.3 of the ECETOC TR No. 133-2.

Tier 0: Identification of relevant polymer fraction and pre-selection of relevant environmental compartment(s) and species

Following Annex IX, Section 9.3.2 (Column 2), of the EU REACH Regulation (EP and Council, 2006), bioaccumulation testing in aquatic species (preferably fish) needs to be considered for a substance if its log K_{ow} > 3 and exposure to the aquatic environment is likely. Further as per ECHA (2017e), bioaccumulation screening to rule out its 'B' status is necessary, if:

- Log K_{ow} > 4.5 for aquatic organisms
- Log K_{ow} > 2 and n-octanol-air partition coefficient (log K_{oa}) > 5 for air-breathing organisms
- There is potential for non-lipophilic bioaccumulation.

Per Table 3.6 in HERA (2009) and Hodges et al. (2019), the AE considered in this case study, C12-15EO7, is likely to have log K_{ow} > 3. Therefore, bioaccumulation is a relevant parameter for its fate assessment. Likely environmental compartments include surface water and sediment, soil, as well as marine water and sediment (Section 7.6).

By contrast, C16-18EO≥20 is more hydrophilic and so likely to have a log K_{ow} < 3 so that bioaccumulation is not relevant.

Tier 1: Non-experimental screening for bioaccumulation potential

Assessment of K_{ow}, and/or n-octanol/air partition coefficient, if applicable for the given type of polymer

Both experimental and QSAR-based data can be used in a weight of evidence approach to estimate the log K_{ow} of AEs (Section 7.3.1.7).

For the Tier I B assessment, *in silico* prediction models may also be employed provided that discrete chemical structures can be entered. Potentially useful models may include:

- BCFBAF™ QSAR, which is part of the EPI Suite™ Estimation Program Interface and is (freely) available from the US EPA website (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface)
- OASIS-CATALOGIC, a proprietary QSAR model, within which is embedded in the 'BCF BaseLine model' (http://oasis-lmc.org/products/software/catalogic.aspx)

Tier 2: *In vitro* biotransformation assessment

In vitro biotransformation tests with fish cells or homogenates have been conducted for some polymeric AEs, suggesting a general potential for biotransformation. Trout microsomes were more efficient than carp microsomes in transforming C13EO8 and C16EO8, whereas for C12-linear alkylbenzene sulfonate, a higher metabolic rate was observed in carp microsomes than in trout microsomes (Perdu-Durand et al., 2004).

Tier 3: *In vivo* bioaccumulation testing

Generally, the bioaccumulation of AEs in aquatic organisms has only been investigated in fish, i.e. by measuring bioconcentration factors (BCFs) (Danish EPA, 2001; ECCC and HC, 2019). Despite the relatively high log K_{ow}, potential for bioaccumulation is not reflected in high BCFs. Generally, the parent AE (e.g. C13EO8) was rapidly transformed into metabolites, which were then eliminated from the body at slower rates; the highest BCF obtained in fathead minnow was 387.5 L/kg for C16EO8 at steady state (Tolls, 1998; Tolls et al., 2000). Clearly, this BCF is well below the BCF threshold of 2,000 L/kg implemented in Annex XIII, Section 1.2, of the EU REACH Regulation (EP and Council, 2006) to identify substances fulfilling the bioaccumulation criterion. Similarly, the recent comprehensive review by ECCC and HC (2019) concluded that AE surfactants are eliminated from biological organisms through biotransformation and that they are not considered to have significant bioaccumulation potential.

Tolls (1998) further showed that, for AEs with EO = 8, bioaccumulation potential increased with increasing C-chain length (BCF (L/kg): C12EO8: 12.7; C13EO8: 29.5-55.0; C14EO8: 56.7-135.2; C16EO8: 387.5) as one would expect. AEs with lower EO numbers exhibited moderate bioaccumulation potential (BCF (L/kg): C13EO4: 232.5; C14EO4: 237.0), whereas C14-AEs with higher EO numbers did not bioaccumulate in fish (BCF (L/kg): C14EO11: < 5; C14EO14: 15.8) (Tolls, 1998).

Bragin et al. (2020) studied the bioaccumulation potential of AEs derived from branched C11-rich oxo-alcohol (EO = 3) in rainbow trout (in a study similar to OECD TG 305). The growth-corrected whole-body half-life was determined to be 0.36 days, with a corresponding lipid-corrected biomagnification factor of 0.012 (Bragin et

al., 2020). These findings are consistent with other studies (e.g., by Tolls, 1998; Tolls et al., 2000) demonstrating that alcohols and their ethoxylates exhibit a high rate of metabolism. Further, the findings by Bragin et al. indicate that, similar to their parent compounds, AEs derived from branched oxo-alcohols exhibit a low potential to bioaccumulate in aquatic organisms.

Conceptual Framework for Bioaccumulation Assessment (Section 4.2.3 in ECETOC TR No. 133-2)

A comparison of the Conceptual Framework for Bioaccumulation Assessment laid out in ECETOC TR No. 133-2 with the bioaccumulation information for AEs described above generally confirms that the framework is useful and that it yields the relevant information to evaluate the bioaccumulation of AEs.

7.7.3 Environmental exposure assessment

Following the EU REACH Regulation (EP and Council, 2006; ECHA, 2016), the environmental exposure assessment serves to establish PECs in relevant environmental compartments for the subsequent risk characterisation. Since this case study does not aim at performing a risk characterisation for any specific AE (Section 7.1.1), the below subsections discuss issues of relevance for the environmental exposure assessment of AEs in general, i.e. beyond C12-15EO7 and C16-18EO≥20. This broadens the evaluation of (1) the overall suitability of the CF4Polymers (ECETOC TR No. 133-1) for the risk assessment of AEs and of (2) the applicability of relevant methods and models (ECETOC TR No. 133-2) specifically for AEs.

7.7.3.1 Exposure in wastewater treatment plants

Eadsforth et al. (2006) presented AE concentrations in effluent obtained from 12 representative WWTPs from 5 European countries. The total concentrations of AEs in effluent ranged from 1.1 to 16.8 µg/L, with an average of 4.9 µg/L and a 90th percentile of 6.73 µg/L (Eadsforth et al., 2006; further discussed in HERA, 2009).

In the HERA (2009) report, effluent concentrations are calculated as the 90th percentile of the measured AE effluent concentrations in order to derive realistic worst-case values for risk assessment. Thereby, a matrix for the concentrations of AEs with C = 12-18 in WWTPs was calculated from the matrix of the 90th percentiles of the corresponding local concentrations in effluent and was further extended using conservative assumptions to also include C-chain lengths from 8 to 11 and EO numbers up to 22 (HERA, 2009; citing unpublished study reports by Shell Research Ltd. from 2002 and 2003).

7.7.3.2 Exposure in freshwater and freshwater sediment

According to HERA (2009), the PECs for AEs in freshwater and sediment can either be modelled or they can be measured during environmental monitoring.

EUSES (https://echa.europa.eu/support/dossier-submission-tools/euses) can be used to model the PECs of AEs in freshwater and sediment. For this purpose, regional background concentrations need to be added to the local concentrations to derive the total exposure (further discussed in ECB (2003) and HERA (2009)).

Interfaces that are based on EUSES are easyTRA (https://www.easytra.com) and CHESAR (https://chesar.echa.europa.eu/support/manuals-tutorials).

If PECs in freshwater and sediment are measured during environmental monitoring, the 90th percentile of a representative range of analytical data should be used (ECB, 2003). Given the resource intensity to run EUSES calculations on a very large number of homologues, environmental monitoring, though costly, can be advantageous for risk assessment.

Local concentrations of AEs in freshwater can be derived from the concentrations in effluent (Section 7.7.3.1) divided by a factor of 10 to take into account dilution in a receiving water body, with further subdivision into dissolved and adsorbed concentrations (ECB, 2003).

Local concentrations in sediment can be calculated from the local concentrations in freshwater for each AE homologue using the equilibrium partitioning method described in ECB (2003) and the K_{oc} for the respective homologue. Total local sediment concentrations of AEs were calculated to be 1.01 mg/kg wet sediment (HERA, 2009).

7.7.3.3 Exposure in marine surface water and marine sediment

Exposure in the marine compartment was not considered in the HERA (2009) report but can be estimated following the ECB (2003) technical guidance document (TGD) principles by dividing the aquatic PECs by a factor of 10. Estimates could also be made based on data in Chemical Safety Reports from the registration of the corresponding NLP AEs, and/or calculated with EUSES (Section 7.7.3.2).

7.7.3.4 Exposure in soil

The methodology described in the ECB (2003) TGD can be followed in determining the local concentration of AEs in soil that results from a single annual application of 5,000 kg/ha dry weight sludge to agricultural soil. This initial concentration in soil can then be refined by considering AE biodegradation within soil for a 30-day period, and by adding background concentrations of AE which may have been deposited by wet and dry deposition from local, regional, and continental sources (ECB, 2003). However, since the background concentration of AEs is likely very low, due to the low volatility of most AE homologues, it is generally considered negligible. The average half-life of AEs in soil is typically assumed to be 5 days (HERA, 2009). The AE homologue distribution in sewage sludge, as estimated via EUSES calculations, can be used to estimate the concentrations of the individual AE homologues in soil, averaged over the first 30 days after sludge application onto the land, although this may lead to overestimations since removal in the anaerobic digester is not considered.

7.7.3.5 Overall conclusion on environmental exposure assessment

Taken together, the linear AE surfactants have been found to pose no major challenges when assessing their environmental fate and predicting exposure to individual AE homologues (at least up to EO = 20) applying environmental models that are routinely used for the risk assessment of non-polymeric substances (e.g. EUSES). However, the exposure assessment of AEs is rendered complex since they resemble UVCBs (on account of variations in alkyl chain length), as well as their polymeric nature (distribution of EO numbers). Therefore, improved analytical methods may be required for environmental exposure monitoring, to be able to deal with the spectrum of individual homologues. Also, for interpretation of the exposure assessment and risk assessment, it should be decided which homologues can be considered as most representative.

7.7.4 Human exposure assessment

Human exposure assessment serves to establish the external exposure to relevant populations. Since this case study does not intend to perform a risk characterisation for any specific AE, this section presents and discusses overarching issues of relevance for the human exposure assessment of AEs, and of polymers in general.

The major route by which humans may be exposed to AEs is the dermal route. Further, oral ingestion may occur accidentally e.g. by children or via residuals from dishwashing detergents on cleaned dishes. Similarly, accidental contact with the eye is possible (HERA, 2009). By comparison, consumer exposure via inhalation is unlikely since household cleaning sprays are typically pump sprays that are formulated to not result in respirable aerosols, particularly for irritating formulations.

Generally, human exposure assessment for polymers can be expected to be similar to that for non-polymeric substances. This is reflected in the design of Step 6 of the CF4Polymers (ECETOC, 2019; see Appendix 1 of the present report). This is illustrated taking the example of the Tier 1 human exposure assessment tools, which are typically used for exposure assessment under the EU REACH Regulation (EP and Council, 2006; ECHA, 2016). Such tools include the ECETOC Targeted Risk Assessment Tool (https://www.ecetoc.org/tools/targeted-risk-assessment-tra/) and CHESAR (https://chesar.echa.europa.eu/support/manuals-tutorials) for workers and consumers, as well as ConsExpo (https://www.rivm.nl/en/consexpo) for consumers.

These tools are deliberately generic tools meant to be applicable to essentially any type of substance. They are largely based on the characteristics of product usages (Consumer Product Categories) and occupational tasks (Process Categories) (ECHA, 2015), regardless of the nature of the substance. Therefore, they require practically no substance-specific information for conducting the exposure assessment. Molecular weight and (in some cases) vapour pressure are normally the only substance-specific parameters needed to run the tools' algorithms.

In this regard, it is important to note that the aforementioned exposure assessment tools provide conservative overestimations of external dose. The default assumption in the REACH assessment is to consider 100% absorption of the estimated external dose through all relevant exposure routes. This is a conservative assumption for all substances, but in the case of polymers represents a particularly large overestimation, especially for polymers with high molecular weight > 1,000 Da.

7.8 Case Study 6: CF4Polymers (Step 7) Hazard assessment

7.8.1 Preparation of hazard data matrix for polymer products that include large numbers of homologues

The methodology for AE hazard and risk assessment is laid out in HERA (2009) referring to work by Belanger et al. (2006), and it is specific for AEs and/or other polymer products that may include large numbers of homologues. AE hazard assessment involves the compilation of a hazard data matrix (or 'effect matrix') for each relevant endpoint on which the x-axis reflects the increasing number of C-chain length and the y-axis the increasing number of EOs (see Figures CS6.3 and CS6.4). Each cell of the matrix presents the appropriate ecotoxicity or toxicity entry for the respective AE homologue. Entries can be based on experimental data and/or QSAR predictions obtained for AE mixtures of known homologue distribution. During risk assessment, this hazard data matrix is then matched with the matrix containing e.g. the PEC for each AE homologue.

7.8.2 Conceptual framework for polymer ecotoxicity assessment

Generally, ecotoxicity assessments serve to establish the test material concentration that is required to achieve a certain effect change relative to the control (e.g. EC_{20}, EC_{50}), and the findings are used to estimate

e.g. PNECs for the subsequent risk characterisation. Since this case study does not aim at performing a risk characterisation for any specific AE, this section discusses issues of relevance for the ecotoxicity assessment of AEs in general, i.e. beyond C12-15EO7 and C16-18EO≥20. This broadens the evaluation of (1) the overall suitability of the CF4Polymers (ECETOC TR No. 133-1) for the risk assessment of AEs and (2) the applicability of relevant methods and models (ECETOC TR No. 133-2) specifically for AEs.

To facilitate this evaluation, the subsections below have been structured following the tiers of the Conceptual Framework for Polymer Ecotoxicity Assessment described in Section 6.4 of the ECETOC TR No. 133-2.

Consideration of mixture toxicity for the ecotoxicological assessment of AEs

Depending on their manufacturing processes, AEs are like UVCBs, consisting of homologues with a generally broad overlap of constituents in the range of C8-C18 and EO1-EO20. The vast majority of aquatic toxicity studies performed on AEs utilised commercial mixtures, but these do not resemble the exact distribution of AE homologues in environmental effluents. Therefore, it is necessary to relate the commercial AE mixtures with the spectrum of AEs in the effluent. For this purpose, Boeije et al. (2006) developed a QSAR technique for complex substances which interprets mixture toxicity based upon the individual AE components, rather than on the average structure of the AE.

Integrating fate and chronic aquatic toxicity data available for AEs (C = 12-18; EO = 0-18) with this new approach to the interpretation of mixture toxicity, Belanger et al. (2006) developed species sensitivity distributions for a total of 17 species. The QSARs allowed the appropriate interpretation of multicomponent mixtures of AE homologues and their species-sensitivity distributions (Boeije et al., 2006; Belanger et al., 2006).

QSAR predictions to streamline ecotoxicity testing needs for AEs

An exceptional amount of aquatic toxicity test data covering a broad range of test species is available for AEs (Belanger et al., 2006). Since the ecotoxicity of AEs is driven in a predictable way by a continuum of homologous structures, QSARs are well suited to predict the aquatic toxicity of AEs (HERA, 2009). Making use of the comprehensive chronic aquatic toxicity database, Boeije et al. (2006) developed chronic aquatic toxicity QSAR equations for algae, invertebrates (*Daphnia magna*), and fathead minnows (*Pimephales promelas*), as well as for complex stream mesocosms. These QSARs describe a relationship between the NOEC for the respective species and the log K_{ow} of the pure substance or mixture average; see also HERA (2009) for further discussion of the QSARs developed by Boeije et al. (2006).

The ECETOC Polymers TF recommends such QSAR modelling as a suitable approach to streamline ecotoxicity testing needs for AEs (or other polymers whose effects are driven in a predictable way by a continuum of homologous structures).

7.8.2.1 Tier 0: Identification of ecotoxicity testing needs and of relevant environmental compartment(s)

AEs are readily biodegradable (Section 7.7.2.1). Nonetheless, due to the large number of applications and continued emission via wide dispersive uses, they can be encountered in the environment. This will be mainly in the water phase, but they can also partition from the water into sediment. In addition, AEs can be present in soil via disposal of wastewater sludge on (agricultural) land or via specific applications (Section 7.7.1). Further, most AEs can be assumed to become systemically bioavailable since they are generally water soluble and have LMW (often below or around 1,000 Da); see Section 7.8.3.3 for systemic bioavailability to humans. Against this background, toxicity to aquatic organisms is usually a relevant endpoint for AEs and possibly also toxicity to sediment and soil organisms.

Analytical exposure verification during testing may vary from the measurement of few selected representative isomers or homologues, up to the quantification of (almost) all individual homologues (HERA, 2009). If exposure is not verified analytically, it is assumed that the nominal (total applied) concentration corresponds to the effective concentration reaching the test system

7.8.2.2 Tier 1: Screening for acute ecotoxicological effects

Ecotoxicological assessments using aquatic organisms

HERA (2009) summarises the relevant experimentally derived acute aquatic toxicity data for AEs available at the time, with Figure CS6.3 being further based on additional experimental data that may have been generated since for regulatory purposes. Consistently, the available data indicate that acute aquatic toxicity increases with increasing C-chain length and decreases with increasing EO number, as long as the AE remains soluble in water. (On a side note, acute aquatic toxicity data available for branched AEs show that these are not more toxic than the corresponding linear AEs with the same C-chain length (HERA, 2009).) Based on the available data, differences in sensitivity between algae, invertebrates and fish are likely small. Effects seen in aquatic organisms are likely caused by a non-polar narcosis mode-of-action by interaction of the hydrophobic part of the AE with biological membranes (Boeije et al., 2006).

The ECETOC Polymers TF is unaware of data from the fish embryo toxicity test (or other non-animal test methods) for AEs (see ECETOC TR No. 133-2 for opportunities and limitations of non-animal acute aquatic toxicity test methods for polymers).

Ecotoxicological assessments using sediment-dwelling organisms

If sediment data are unavailable, the ECB (2003) TGD allows use of the equilibrium partitioning method to derive the sediment PNEC from the respective aquatic PNEC. Also, ecotoxicological effects in sediment-dwelling organisms may be predicted by QSAR modelling. Indeed, the chronic aquatic toxicity data that were reviewed by Belanger et al. (2006) and used in HERA (2009) to develop a probabilistic QSAR for aquatic species support the ECB (2003) TGD view that the equilibrium partitioning method is appropriate to predict the PNEC for sediment-dwelling organisms.

Since *Daphnia* have further been observed to be amongst the most sensitive invertebrates to AEs, HERA (2009) recommends deriving a sediment PNEC by combining the equilibrium partitioning approach with predictions from the *Daphni*a QSAR developed by Boeije et al. (2006) (Section 7.8.2).

Ecotoxicological assessments using terrestrial organisms

Although some acute and chronic terrestrial toxicity data (obtained in e.g. *Eisenia foetida* and *Avena sativa*) are available for commercial AE mixtures and for some pure AE homologues, this information does not cover the full range of C-chain lengths or EO numbers for AEs (HERA, 2009). In addition, the precise AE homologue distribution is not available for many of the commercial AE mixtures for which experimental terrestrial toxicity data are available (Section 7.8.2). Therefore, the equilibrium partitioning method described in the ECB (2003) TGD has been used to determine the soil PNEC for AE homologues (HERA, 2009). A comparison of the equilibrium partitioning results with available experimental acute and chronic terrestrial toxicity data supported this approach (HERA, 2009).

For testing in agricultural soils, a treatment that includes dosing of polymers in a (digested) wastewater sludge matrix can realistically mimic the route of exposure and actual bioavailability of the polymers.

7.8.2.3 Tier 2: Higher-tier follow-up of ecotoxicological screening

Generally, experimental higher-tier follow-up of ecotoxicological screening should rarely be necessary for the evaluation of AEs since QSARs are well suited to predict the chronic aquatic toxicity of AEs (Section 7.8.2).

The low acute/chronic ratio, as well as the fact that survival is an equally sensitive endpoint as reproduction in daphnids indicate that AEs have a non-polar narcotic mode of action, and that the hydrophobicity of the molecule is the driver of its toxicity (Boeije et al., 2006).

7.8.2.4 Conclusions on ecotoxicity assessment of alcohol ethoxylates and applicability of conceptual framework for ecotoxicity assessment

The comprehensive ecotoxicological database available for AEs confirms that the standard ecotoxicity test methods are generally suitable for the assessment of AEs. Ecotoxicity testing of the polymeric AEs as considered in this case study does not seem to pose major problems in terms of solubility, dosing or stability. While the performance of a full analytical exposure verification on AEs (all homologues) may be laborious and expensive, exposure verification in (eco)toxicity testing is generally recommendable. For technical mixtures, the typical considerations that also apply to UVCB testing will be relevant.

Similarly, the Conceptual Framework for Ecotoxicity Assessment of Polymers described in ECETOC TR No. 133-2 seems generally applicable for AEs. – For this type of polymer, the available QSARs (that could be developed on account of the known correlation between specific physico-chemical properties and effect levels) may considerably limit the need for animal testing.

Improvements to current analytical methods for exposure verification of AEs, and other polymers, are recommendable. Similarly, while predictive toxicity models for non-ionic AEs are available (Bejarano and Wheeler, 2021), more efforts are required to facilitate their acceptance and use.

7.8.3 Human health hazard assessment

Generally, human health hazard assessment serves to establish, e.g. NOAELs that are then used as points of departure in the subsequent risk characterisation e.g. to estimate derived no effect levels. Since this case study does not aim at performing a risk assessment for any specific AE, this section presents and discusses data and issues of relevance for the human health hazard assessment of AEs in general, i.e. beyond C12-15EO7 and C16-18EO≥20. This broadens the evaluation of (1) the overall suitability of the CF4Polymers (ECETOC TR No. 133-1) for the risk assessment of AEs and of (2) the applicability of relevant methods and models (ECETOC TR No. 133-2) for AEs. To facilitate this evaluation, the subsections below follow the structure of Section 7 of the ECETOC TR No. 133-2 on human health hazard assessment.

7.8.3.1 Purpose of the assessment (including intended form and function of the polymer)

While this case study only generally refers to human health hazard assessment of AEs, the intended form and function of C12-15EO7 would be as gel/liquid or powder in laundry detergents. Therefore, the hazard assessment would serve to protect consumers, including sensitive populations such as children. The intended form and function of C16-18EO≥20 would be as solubiliser for water-based dispersions (wetting agents) to be used for industrial processes. Therefore, the hazard assessment would serve to protect workers.

7.8.3.2 Potential for exposure to LMW compounds

See Section 7.3.3 for consideration of LMW compounds (NIAS and/or residual monomers). Since this case study only considers the polymeric substances (i.e. the AEs themselves) with molecular weight distribution, their LMW oxyethylene constituents could be contributing to AE function in the detergent use and would have been captured in test outcomes.

7.8.3.3 Bioavailability

As many AEs have molecular weights < 1,000 Da, these have the potential to become systemically bioavailable including AEs for cleaning applications (Talmage, 1994; see also Section 3.7.1.1 of ECETOC (2019) TR No. 133-1). Therefore, toxicokinetics have to be considered for these AEs. Notably, however, due to their low log K_{ow}, many AEs will also be freely eliminated.

Bioavailability of AEs upon ingestion: Systemic bioavailability of AEs upon ingestion / oral exposure has been studied in rats and in human volunteers (Drotman, 1980; EFSA, 2008b). In rats, more than 75% overall gastrointestinal absorption and rapid excretion predominantly in the urine were reported across different AEs with EO chain length of up to 10 (ECB, 2003; HERA, 2009; Danish EPA, 2001). In the HERA (2009) report, the 75% gastrointestinal absorption value was considered for human exposure and risk assessment of AEs.

Metabolism of AEs: During metabolism of AEs, the alcohols can be hydrolysed from the (poly)oxyethylene moiety to some extent and oxidised to carboxylic acids (Elder, 1985; HERA, 2009). The carboxylic acids (alkyl chain) can be broken down by stepwise removal of one or several C2 units through the beta oxidation process (HERA, 2009; Figure CS6.5; see also Section 7.7.2.1). With increasing alcohol chain lengths, higher percentages of CO_2 were reported in exhaled air, and lower percentages of AE metabolites in urine (HERA, 2009). The released (poly)oxyethylene moiety is generally not extensively metabolised (EFSA, 2006; HERA, 2009). With increasing EO chain length, higher excretion of AE in faeces, and thus lower systemic bioavailability, was reported (HERA, 2009) (see Appendix CS6-A.4 including its Figure CS6-A.4 for further details on ADME of AEs).

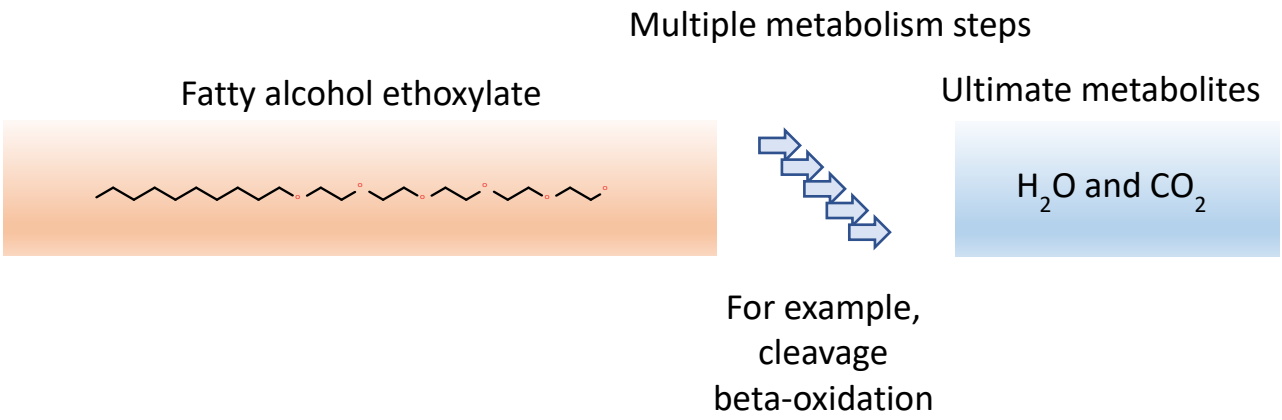


Figure CS6.5: Simplified overview of alcohol ethoxylate metabolism pathways in mammals (here: fatty alcohol ethoxylate)

Bioavailability of AEs upon dermal exposure: With respect to systemic uptake and hence bioavailability of AEs upon dermal exposure as major route of exposure, AEs have been observed to penetrate rat skin fairly well (HERA, 2009). Nonetheless, various dermal acute, subacute and subchronic toxicity studies using rabbits, rats and guinea pigs have overwhelmingly demonstrated the absence of systemic effects following exposures to

AEs (Danish EPA, 2001; EFSA, 2008b; HERA, 2009; Talmage, 1994; Section 7.8.3.6, Appendix CS6-A.2 and Appendix CS6-A.3). By contrast, dermal penetration studies in humans showed that AEs have only limited potential to penetrate the human skin (HERA, 2009).

7.8.3.4 Reactivity and surface activity

AEs do not possess reactive functional groups or critical chemical elements (i.e., heavy metals or fluorine). That they are not reactive, is also seen by their lack of skin sensitising or genotoxic potential as evidenced in the extensive toxicological datasets (Section 7.8.3.6, Appendices CS6-A.5 and CS6-A.6).

However, AEs – being surfactants with separate hydrophobic and hydrophilic structural motifs – exhibit a surface-activity related mode-of-action. Indeed, this surface-active property constitutes the basis for the two intended AE uses considered in this case study (i.e. use in consumer laundry detergents and as wetting agents in different industrial processes) as well as for the many further types of application of AEs. At the same time, the surface-active property manifests itself in the irritating properties observed for AEs (Section 7.8.3.6). Specifically, the eye irritating properties of AEs have been well-studied and are understood to be contributed by the chain lengths of the hydrophobic and hydrophilic moieties. Therefore, eye irritation constitutes the key distinguishing mammalian toxicity endpoint for the (Step 4) grouping approach evaluation (Section 7.5).

7.8.3.5 Exposure route considerations

The major route of human exposure for AEs is direct and indirect skin contact from its use in e.g. laundry detergents, cleaning products or from their industrial use as wetting agents. Further, consumers may be exposed to AEs in laundry detergents by incidental oral ingestion (Section 7.7.4).

7.8.3.6 Endpoint-specific testing

Overview: Systemic toxicity, genotoxicity, and skin sensitisation

AEs generally represent low human health hazard potential. Substantial amounts of *in vitro* and *in vivo* toxicological data are available indicating that the major hazards represented by AEs are due to local action (Talmage, 1994; Danish EPA, 2001; EFSA, 2008b; HERA, 2009). The major mode-of-action behind such local action of AEs is assumed to be the interaction of the surfactant with the cell membrane layers leading to a disruption of the intact cellular structure and cytotoxicity.

In laboratory animals, AEs generally have either EU CLP Category 4 acute oral toxicity (LD_{50} > 300 to ≤ 2,000 mg/kg bw) or are not classified (Talmage, 1994; Danish EPA, 2001; HERA, 2009; Appendix CS6-A.2). For example, in the rat, the oral LD_{50} values range from between 544 mg/kg bw in females (for C14-15EO11) to more than 16,000 mg/kg bw in both sexes (for C18EO10). Also, the majority of available repeated-dose toxicity studies revealed NOAELs above 100 mg/kg bw/day with the lowest NOAEL established to be 50 mg/kg bw/day (Talmage, 1994; Danish EPA, 2001; HERA, 2009; Appendix CS6-A.3). The observed systemic effects are mainly restricted to reduced body weight gain and/or altered organ weights without corresponding histopathological findings with the exception of some cases of liver hypertrophy which were assessed as indicating adaptive responses to metabolism (HERA, 2009). Additionally, there is practically no difference in the NOAEL from oral 90-day toxicity studies versus oral 2-year bioassays (HERA, 2009). There is no evidence for AEs being genotoxic, mutagenic or carcinogenic (Yam et al., 1984; Talmage, 1994; HERA, 2009; Appendices CS6-A.6 and CS6-A.3). Further, no adverse reproductive or developmental effects have been observed (Appendix CS6-A.7), and AEs are not contact sensitisers (Appendix CS6-A.5).

Skin and eye irritation

Skin irritation: High concentrations of AEs with varying C-chain lengths and EO numbers were found to be slightly to severely irritating to the rabbit and rat skin. Depending on structure, the undiluted AEs could be 'not classified' or CLP Category 1 or 2 (irreversible or reversible effects on the eye, respectively). However, under normal use conditions of diluted detergent solutions containing 0.1% AEs, AEs were practically non-irritating to skin both in clinical studies and in animal studies. Notably, the repeated-dose dermal toxicity dataset demonstrates a local irritation threshold value of 5 mg/kg bw/day from a well-conducted subchronic dermal toxicity study that can be used for the local worker and general population risk assessment (Talmage, 1994; Appendix CS6-A.3).

Eye irritation (see also Figure CS6.4): At higher concentrations, AEs may elicit mild to severe eye irritation in rabbits. Generally, AE concentrations of 0.1% were observed to be non-irritating, whereas concentrations of 1 to 10% elicited slight to moderate eye irritation in rabbits. Rinsing the rabbits' eyes directly after product application reduced the severity of effects (HERA, 2009). Concordantly, human experience suggests that accidental eye contact with undiluted detergent product may cause transient mild to moderate irritation and that reversibility is enhanced by immediate rinsing with plenty of water (HERA, 2009).

Conclusions with respect to local irritation: AEs are irritating or corrosive to skin and eyes, respectively, when applied undiluted or in high concentrations. By comparison, under normal use conditions, AEs are virtually non-irritating (Talmage, 1994; HERA, 2009). Hence, the irritation potential of aqueous solutions containing AEs is concentration dependent. The eye irritation potential of AEs presents their most relevant hazard also since some AEs may elicit stronger eye damaging effects when tested undiluted. This predominant hazard characteristic of AEs (i.e. their irritating potential) is also often observed in gavage studies leading to gastrointestinal irritation whereas application via diet does not show these effects (HERA, 2009).

7.8.3.7 Conclusions on human health hazard assessment of alcohol ethoxylates

The comprehensive toxicological database available for AEs confirms that the standard toxicity test methods are generally suitable for the hazard assessment of AEs. Further, also *in vitro* test systems, e.g. for eye irritation testing, have been shown to be able to indicate the hazard appropriately. Toxicity testing of the polymeric AEs considered in this case study does not seem to pose major problems in terms of solubility, dosing or stability. For technical mixtures, the typical considerations that also apply for UVCB testing will be relevant.

Similarly, the structural outline to human health hazard assessment described in Section 7 of ECETOC TR No. 133-2 seems generally applicable for AEs.

7.9 Case Study 6: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for any specific AE. Instead, it has served to evaluate if the CF4Polymers is generally applicable to this type of polymers and if the collated information provides further insight on the applicability of tools, test methods and models for the physico-chemical characterisation and toxicity / ecotoxicity testing of AEs. Generally, the case study has confirmed both the usefulness of the CF4Polymers (ECETOC TR No. 133-1) and also the validity of the information on the applicability of tools, methods and models (ECETOC TR No. 133-2) for the assessment of AEs. Indeed, since these are data rich polymers whose physico-chemical, ecological and toxicological properties are correlated with the chemical structure (C-chain length, number of EO), it has been possible to develop QSARs e.g. for the ecotoxicological assessment of AEs. Also, the amended grouping scheme presented in Section 1.3. of this report has proven useful for the grouping of AEs.

8. CASE STUDY 7: SELECTED PROFESSIONAL AND CONSUMER USES OF POLYURETHANE AND POLYUREA

8.1 Introduction

8.1.1 Scope and outline of Case Study 7

While the other case studies included in this report address different (chemical) types of polymers, this final case study has been designed to show how different intended uses of the same types of polymers should be considered for exposure assessment. The focus is on selected professional uses and consumer uses of polyurethane and polyurea, and, specifically, from amongst the broad spectrum of uses (Section 8.1.2):

- The use of polyurethane / polyurea as shell materials for the microencapsulation of
    - Horticultural / agricultural products for professional use (Zhang et al., 2020); and
    - Fragrances for laundry detergents and fabric softeners for consumer use (Ma et al., 2019; Zhao et al., 2019); and on
- The use of polyurethane / polyurea in professional paint / coating applications.

Encapsulation is a technology that traps active and volatile substances within carrier material to form a solid particle (Trojanowska et al., 2017). Capsules can take many forms and include matrix and core-shell types. Encapsulation aims to protect the core material from the surrounding environment, and it offers opportunities for new applications and release characteristics (Amber, 1994; Arshady, 1999; van Soest, 2007; Dubey et al., 2009; Poshadri and Kuna, 2010). Microencapsulation is defined as *"a process in which tiny particles or droplets are surrounded by a coating or embedded in a homogeneous or heterogeneous matrix, to give small capsules with many useful properties. Microencapsulation can provide a physical barrier between the core compound and the other components of the product. It is a technique by which liquid droplets, solid particles or gas compounds are entrapped into thin films of a food grade microencapsulating agent*" (Poshadri and Kuna, 2010).

Polyurethane and polyurea in microencapsulated horticultural / agricultural products (i.e. fertilisers and active substances for crop protection products) are intentionally released into the environment. For microencapsulated fragrances, release into the environment occurs down-the-drain during use of the detergent. Similarly, release of professional paint applications into the environment is not intentional but may occur in small quantities via abrasion.

In line with its scope to present different intended uses for polyurethane and polyurea, this case study has a focus on CF4Polymers (Step 5) determination of exposure scenarios and (Step 6) exposure characterisation. The case study has a focus on environmental exposure assessment and the subsequent conclusions for (Step 7) environmental hazard assessment and (Step 8) risk characterisation. While human health hazard assessment is not the focus of this case study, some information on human exposure scenarios is presented for comprehensiveness.

As a starting point, the case study presents a theoretical (Step 1) problem formulation followed by a fit-for-purpose (Step 2) polymer identification that considers the key physico-chemical properties of (theoretical) polyurethane and polyurea. Focus is on the polymeric substance (Step 3; polymer component strategy), and

indeed polyurethane / polyurea used for microencapsulation generally do not contain IAS or NIAS (whereas the polyurethane / polyurea produced during professional paint applications commonly include additives).

CF4Polymers (Step 4) grouping approach evaluation is not considered in this case study since its focus is on selected end uses of polyurethane / polyurea rather than on a range of different polyurethane / polyurea, that each would need to be characterised to support grouping.

8.1.2 Production and use of polyurethane and polyurea

Polyurethane and polyurea are very versatile materials and widely used in a variety of applications (Table CS7.1).

Polyurethane polymers are produced by reaction between (poly)isocyanates and polyol (i.e. an organic compound containing multiple hydroxyl groups). Polyurethanes can be tailored to be either rigid or flexible. Primarily, polyurethanes are used as foams that are moulded in applications (e.g. for furniture, bedding, and building insulation). Further major applications of polyurethanes are in coatings and adhesives (e.g. for building and construction) and for various materials that are used in the automotive industry (Engels et al., 2013; Austin and Hicks, 2016; Fridrihsone et al., 2020; see also https://www.polyurethanes.org/en/). An estimated 20 million tonnes of polyurethane were produced in 2015 worldwide (Austin and Hicks, 2016).

Polyurea polymers are produced by reaction between polyisocyanates and polyamine. Polyureas are primarily used in numerous types of coatings, e.g. for pipe and tank protections, the insulation of steel and concrete on bridges and in tunnels, in the maritime industry, for roof insulation, sewage and water supply systems, and in the automotive industry (https://www.polychem-systems.com.pl/en/akademia/properties-and-application-of-the-polyureas/). The global market volume of polyurea was calculated as 121,000 tonnes in 2018 and is estimated to exceed 164,000 tonnes by 2025; https://www.grandviewresearch.com/press-release/global-polyurea-market.

By comparison, horticultural, agricultural and fragrance applications make up only a small proportion of the total production of polyurethane and polyurea.

In horticultural / agricultural applications, polyurethanes are mainly produced from vegetable oil-based polyols, and polyureas are mainly petroleum-based. Polyurethanes are mostly used as coatings on / capsulations for slow- and controlled-release fertilisers (and possibly also for encapsulated crop protection products). Flexible polyurethane foams are used in greenhouses as substrate for hydroponic production (which however does not relate to (micro)encapsulation and hence is not included in this case study). Polyurea are mostly used as encapsulation material for crop protection products.

In fragrance applications, e.g. in textiles, fabric softeners, and laundry detergents, both polyurea and polyurethane can be used for microencapsulation. The microcapsules are either already present on the textiles or deposited onto the fabrics during washing, and the microencapsulation facilitates the controlled release of fragrance. Specifically, the microcapsules break on handling when physical forces rupture the thin shell membrane thereby releasing the fragrance. This occurs over extended periods of time since fabrics can retain fragrances for up to 25 wash cycles. Hence, all of the fragrance is eventually released into the environment during use of the fabric and/or additional wash cycles, following the life cycle of a down-the-drain substance (https://www.fibre2fashion.com/industry-article/6962/microencapsulation-of-fragrances-in-textiles; see also Carvalho et al., 2016).

Table CS7.1: Polyurethane and polyurea areas of application and estimated (global) annual production volume

Type of polymer	Area of application [1-5]	Actual use	Physical form of the polymer	Desired characteristics	Annual production volume (tonnes); global unless noted
Polyurethane	Building and construction	Insulation panel, filling	Rigid foams	Good insulator, strength	2 million [3,4]
	Automotive industry	Coating	Film	Durability, weather resistance	1-2 million (all types of coating)
		Cushions	Flexible foams	Durability, light weight	1.3 million [3,4]
	Furniture and bedding	In-fill material, mattresses	Flexible foams	Durability	5.2 million [3,4]
	Other areas of application	Adhesives/sealants	Two-part polyurethanes	Water and chemical resistance	1.2 million [3,4]
		Engineering materials	Thermoplastic polyurethanes, elastomers	Abrasion and chemical resistance	1.2 million [3,4]
	Agricultural / horticultural	Encapsulation of plant nutrients such as fertilizer	Thin film	Reduce run-off, reduce human exposure, slow/controlled release	10,000 – 50,000 [6]
	Fragrance / consumer products	Encapsulation of active ingredients	Thin film	Slow / controlled release	EU: Minor fraction of total use of polyurethane [6]
	Professional paint	Professional paint	Film	Durability, weathering, chemical resistance	Not available
Polyurea	Infrastructure	Waterproofing coating	Film	Waterproofing, corrosion protection	
	Oil and gas	Protection coating, containment	Film	Corrosion and wear protection	
	Other	Grease			
	Agricultural / horticultural	Microencapsulation of crop protection active ingredients	Thin film	Reduce run-off, reduce non-target injury, slow/controlled release	< 1,000 [6]

Footnote to Table CS7.1:

[1] https://www.polyurethanes.org/en/

[2] Amec Foster Wheeler & Infrastructure UK Ltd. (2017)

[3] Akindoyo et al. (2016)

[4] https://www.plasticsinsight.com/resin-intelligence/resin-prices/polyurethane/

[5] Szycher (2012)

[6] Estimate by ECETOC Polymers TF based upon literature data (data not shown).

Polyurethane and polyurea use for professional paint / coating applications differs from the use in microencapsulations. These paints / coatings are typically sold as two-component packs, one containing the polyol or polyamine and the other the polyisocyanates. The two components are mixed immediately prior to application, in some cases with the further addition of a catalyst. Hence, the polyurethane/polyurea is formed *in situ*. Since application is targeted to the substrate in either industrial or professional settings, there is no intentional release to the environment. Polyurethane / polyurea coatings are designed to provide a long-term, hard wearing, weatherproof, and chemical resistant barrier for the substrate. Therefore, chemical breakdown over the lifecycle of the product is not intended. Nonetheless, there may be physical damage through abrasion that may lead to small loses of the cured coating to the environment.

The use of polyurea / polyurethane for microencapsulation of horticultural / agricultural products and fragrances in detergents as well as for professional paint applications provides significant sustainability and safety benefits.

In horticultural / agricultural uses, the encapsulate shell offers a barrier function, physically separating the payload contents from the external environment. In slow/controlled release products, the encapsulate shell is optimised to allow release of the payload in the right location and at the right time, in order to provide function only where and when it is needed (Vinceković et al., 2019). This supports targeted dosing and improves residual control, thereby also reducing risk for overuse of, e.g. pesticides (Trenkel, 2010; Vinceković et al., 2019). In some pesticidal products, encapsulation reduces damage on non-targets. Encapsulation is also utilised to improve handling and to reduce loss of payload prior to use. Furthermore, in case the payload contents (e.g. pyrethroid insecticides) are toxic to human, encapsulation reduces the risk of human exposure.

In fragrance microencapsulation, the polymers are used to encapsulate a blend of fragrance oils. They protect oils that might otherwise be unstable in the harsh conditions of detergents and similar products (e.g. high concentration of surfactant, aggressive pH). The microencapsulation provides a further benefit by releasing the fragrance over extended periods of time when the fabric is worn. This supports a reduced concentration of fragrance required in the given article as well as reduced needs for re-washing thereby aiming at reducing energy and water consumption (Park and Arshady, 2003; van Soest, 2007; Martins et al., 2014; Bruyninckx and Dusselier, 2019).

The use of polyurethane and polyurea in paint formulation again provides a barrier, in this case a barrier to protect the substrate. Building materials such as wood, steel and plaster can be significantly affected by exposure to local environmental conditions, and the use of paint can prolong the lifetime of the material and subsequently the structure itself. This may result in a reduced need to repeatedly replace the respective articles that may range from domestic windowsills and washing machines to massive infrastructure such as bridges and tunnels. Thus, polyurea and polyurethane paints have considerable potential to reduce the environmental impact for a broad spectrum of articles (Wei et al., 2018).

8.2 Case Study 7: CF4Polymers (Step 1) Problem formulation

This case study refers to the environmental exposure assessment of polyurethane / polyurea that are used for:

1. Horticultural / agricultural applications:
    a. **PU-1** is the selected polyurethane; it is used for the coating / encapsulation of slow/controlled-release fertilisers.
    b. **PUR-1** is the selected polyurea; it is used for the microencapsulation of pesticidal active substances.
2. Fragrance applications:
    a. **PUR-2** is the selected polyurea; it is used for the microencapsulation of a fragrance oil for laundry detergent.
3. Professional paint applications:
    a. Within this case study, no specific polyurethane / polyurea were defined for professional paint applications. Instead, the ECETOC Polymers TF refers to further relevant information for this type of application in the sections below. The intended use is as a protective coating for the superstructure of ships. The polyurethane/polyurea is formed *in situ* during mixing immediately prior to application. The case example assumes that more than one product is applied, e.g., a base coat with good adhesion properties to attach to the substrate and then a topcoat to give the final finish.

The protection goals relate to individual workers and professionals as well as the environment for the horticultural / agricultural and professional paint applications and to individual workers and consumers as well as the environment for the fragrance applications.

Of note, this case study, while applying the CF4Polymers to (theoretical) polyurethane and polyurea in different intended uses, is at the intersection to article-specific legislation. For the horticultural / agricultural and fragrance applications, hazard and risk assessment for the substances included in the microencapsulation (fertilisers, pesticidal active substances, fragrances) will have been conducted following the respective applicable legislation. As regards the professional paint application, it is noteworthy that the polyurethane / polyurea itself is only formed by curing during/after the coating application and is an article (film). Thereby, the polyurethane / polyurea that is formed during professional paint application is generally out of scope of chemical legislation. Nonetheless, chemical risk assessment may be relevant for end-of-life assessments. In this case study, however, waste stages are not considered.

8.3 Case Study 7: CF4Polymers (Step 2) Polymer identification

8.3.1 Step 2.1: Identification of the polymeric substance

8.3.1.1 General description of the selected polyurethane / polyurea

PU-1 and PUR-1 used in horticultural / agricultural applications

PU-1 is the reaction product of castor oil and polymethylene polyphenylene isocyanate (CAS No. 67700-69-0). When used in slow/controlled-release fertilisers, which are produced in form of prills or granules, the

thickness of the PU-1 coating typically ranges from tens to hundreds of µm. The coating covers particles with diameters ranging from 1 mm to 2-3 cm. PU-1 is an integral part of the product. The concentrations of the shell wall polymer in the final horticultural product (e.g. fertilisers, plant protection product) vary typically from 3-15% by weight.

PUR-1 is the reaction product of ethylenediamine and polymethylene polyphenylene isocyanate (CAS No. 31671-95-1). When used in microencapsulated crop protection products, PUR-1 forms the shell of the microcapsules which comprise the active ingredients in the core and have a diameter typically < 100 µm. The thickness of the PUR-1 coating (capsule shell) typically ranges from tens to hundreds of nanometres. The form of the end use product is mostly aqueous suspension but can be dry powder in some cases. PUR-1 is an integral part of the product. The concentrations of the shell wall polymer in the final (total formulated) agricultural product vary typically from 1-10 % by weight.

Both PU-1 and PUR-1 are cross-linked and solid; they are not water soluble.

PUR-2 used in fragrance applications

PUR-2 is a polyurea used in fragrance microencapsulation. It is synthesised by cross-linking isocyanate and polyamine to form a core-shell particle morphology. In the microcapsules, the thickness of the PUR-2 polymer shell can vary depending on the production process, but it is roughly a few hundred nanometres. The microcapsules, filled with perfume oil, can have diameters ranging from several hundred nanometres to approx. 1,000 µm (Carvalho et al., 2016). They are distributed on the surface of the fabric and burst due to physical forces during the wearing (https://www.fibre2fashion.com/industry-article/6962/microencapsulation-of-fragrances-in-textiles).

Professional paint applications

Within this case study, no specific polyurethane / polyurea were defined for professional paint applications.

8.3.1.2 Background

Structural and morphological descriptors

Polyurethane and polyurea are typically generated directly via reactions between polyisocyanates and polyol (polyurethane) or polyamine (polyurea) (Section 8.1.2). Their composition and structure in the final use product is variable and depends on the production conditions and processes. The best way to describe the structural composition of polyurethane and polyurea is by referring to the monomers, e.g. ‘reaction product of toluene diisocyanate and linseed oil’. However, the monomer and the process of polymerisation for commercial products are often proprietary information.

Physico-chemical properties

Polyurethane / polyurea capsules and coatings are designed to protect substrates and thus to be hardwearing and long-lasting along with other protective properties such as weather resistance, chemical resistance, and UV stability. Therefore, many physico-chemical properties of polyurethane and polyurea are universal across different applications. Polyurethane and polyurea are solid, and most polyurethane and polyurea used for microencapsulation have a cross-linked structure in their ‘as-produced’ form. Thereby, they are also insoluble in water or organic solvents.

Molecular weight is hard to determine for polyurethane and polyurea. Due to their highly crosslinked form, most polyurethanes and polyureas can be considered to have extremely high molecular weight, which is (to some extent) limited by the dimensions of the final particle – and in turn dependent on the production process

and final requirements for the polymer. Structural and morphological characterisation of these materials can be carried out through solid-state infrared and nuclear magnetic resonance spectroscopy and optical and electron microscopy; see also Section 3.1 in ECETOC TR No. 133-2 for general discussion of difficulties in determining the molecular weight of polymers.

The urethane or urea bonds of polyurethane / polyurea are generally considered resistant to thermal or hydrolytic degradation. By comparison, physical degradation (photo-induced or mechanical breakdown) or chemical degradation ((photo-)oxidation), and to a lesser extent biodegradation (enzymatic breakdown), can occur to polyurethane and polyurea under favourable conditions (e.g. extreme pH conditions, extreme temperature). Furthermore, (bio)degradable components (e.g. biodegradable monomers, additives that aid in breakdown) can be built into the molecular structure of polyurethane and polyurea to facilitate their breakdown / disintegration. For example, the castor oil part of PU-1 has been reported to potentially undergo biodegradation (Cangemi et al., 2008; Harrell's, 2020). Polyurethanes and polyureas used in agriculture are so designed that the integrity and performance of the material can be maintained throughout the longevity of the product, which can range from several weeks to a couple of years.

Due to the cross-linking nature, polyurethane and polyurea used in professional paint are insoluble in water or organic solvents. Again, the urethane or urea bonds are generally considered resistant to thermal or hydrolytic degradation. The technical properties of the polyurethane / polyurea dry film vary according to the choice of starting materials and additives. Physico-chemical data are not typically generated on the dried film coating. Prior to mixing, the physico-chemical properties will be defined by those of the starting materials.

8.3.2 Step 2.2: Identification of additives

PU-1, PUR-1 and PUR-2 do not contain additives. Indeed, additives (e.g., catalysts) are not commonly used for the production of polyurethane and polyurea for microencapsulations.

For professional paint applications, additives are commonly used in the coating. The types of LMW additives may include fillers, dyes/pigments, plasticisers, stabilising agents, anti-aging agents, additional cross-linking agents and chain extenders as well as catalysts (for the curing). Each of these additives will have undergone independent hazard and risk assessment according to the required legislation prior to its use in the formulation.

8.3.3 Step 2.3: Identification of NIAS

PU-1, PUR-1 and PUR-2 do not contain NIAS. Indeed, for polyurethane and polyurea used for microencapsulation, the presence of unreacted monomers or small oligomers is very rare.

Polyurethanes, that are produced *in situ* when used for professional paint applications, are only expected to include negligible amounts of residual monomers, since the reactions will be near complete.

8.3.4 Conclusion on the polymer identification

Taken together, PU-1, PUR-1 and PUR-2 are assessed as inert. PU-1, PUR-1 and PUR-2 have 'infinite' molecular weight, negligible LMW components, no moderate- or high-concern functional groups (US EPA, 1997), they have negligible charge (from a toxicological perspective), and they further do not possess critical chemical elements (i.e., heavy metals or fluorine). Thereby, they fulfil the criteria to identify 'polymers of low concern'

or 'reduced regulatory requirements polymers' (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021; Section 1.2).

8.4 Case Study 7: CF4Polymers (Step 3) Polymer component strategy

This case study is restricted to the polymeric substance.

8.5 Case Study 7: CF4Polymers (Step 4) Grouping approach evaluation

The CF4Polymers (Step 4) grouping approach evaluation is not considered in this case study that focuses on intended uses and exposure assessment.

8.6 Case Study 7: CF4Polymers (Step 5) Determination of exposure scenarios

8.6.1 Ecological exposure scenarios

Horticultural / agricultural applications

The exposure scenarios for microencapsulated horticultural / agricultural products are likely concordant for the shell and core material. Further, exposure, hazard and risk assessment of the core material (PU-1: fertiliser; PUR-1: active substance), and for the final microencapsulated plant protection products (PUR-1), will have been conducted under the respective applicable legislation (Section 8.2). Therefore, the exposure scenarios for PU-1 and PUR-1 are expected to be well understood.

PU-1 and PUR-1, as highly crosslinked, insoluble solids, are intentionally released into the environment as shells, fragments or particles. Soil and sediment, as well as aquatic compartments, may be relevant environmental compartments for PU-1 and PUR-1 (Section 8.7.1).

Fragrance applications

As has been described above for horticultural / agricultural applications, risk assessment of the core material (fragrance oil) will have been conducted under the respective applicable legislation (Section 8.2). Therefore, the exposure scenarios for PUR-2 are expected to be well understood. PUR-2, as fragrance encapsulation, is released down-the-drain on account of its use in laundry detergents with subsequent sewage treatment according to local standards. Therefore, WWTPs, soil and sediment may be relevant environmental compartments for PUR-2 (Section 8.7.1).

Professional paint applications

Physical abrasion of professional paint applications may result in small losses of the inert film to the environment. Hence, while concentrations are likely to be low, potentially relevant compartments might include the air, soil, and freshwater and marine water (and sediment via the freshwater and marine water).

8.6.2 Human exposure scenarios

While human exposure assessment is not the focus of this case study, some information on human exposure scenarios is provided here for comprehensiveness.

Horticultural / agricultural applications (microencapsulation)

Human exposure to polyurethane / polyurea during manufacturing is expected to be low since both the polymers, and the microencapsulations, are generally produced in closed systems.

The (relatively large) minimum particle size of the as produced PU-1-containing fertiliser encapsulates (and dry paint coatings, see below) in use will always be such that they have minimal biological interaction (e.g. on account of their HMW and large particle size, they are not respirable and do not pass biological membranes).

Also after application of the horticultural / agricultural PUR-1 article, accidental contact with the polymer present in the article may occur, but again the level of exposure is expected to be very low since their contents in the respective article is low. Upon breakdown of the microencapsulation, PU-1 and PUR-1 may also be released (in their original form); however, since the breakdown occurs at a slow pace, the potential release of PU-1 and PUR-1 will also be slow.

Fragrance applications

As regards human exposure to PUR-2 used in fragrance applications, the reaction is expected to be complete so that human exposure to the free polymer is prevented (even some of the final articles containing PUR-2 may be designed to come into direct contact with human skin).

Professional paint applications

For paint applications, the professional user mixes two separate component mixtures together immediately prior to application. At this stage, the exposure is to the individual component's parts and not to the polyurethane / polyurea. After mixing, the coating is applied by brush, roller or spraying onto the substrate. The starting materials are fully reacted once the coating has cured, and the dry film is inert. Risk management measures are in place to avoid potential for dermal / inhalation exposure during application.

Users may have direct contact with the polyurethane / polyurea coating during handling of the coated article. However, the coating material is generally highly abrasion-resistant, which results in no or very low dust off from the article and hence minimal exposure risk to the user.

8.7 Case Study 7: CF4Polymers (Step 6) Exposure characterisation

8.7.1 Release of polyurethane / polyurea

Horticultural / agricultural products

Horticultural products that contain PU-1 (e.g. PU-1 coated fertiliser granules) are typically applied to surfaces with optional incorporation into the soil or the substrate, i.e. to turf, nursery and agricultural land (dry land and paddy field). After the payload is released, the PU-1 coatings may remain on or in the soil or be washed away with surface water. They remain in solid form as thin films or fragments of thin films (after fragmentation by attrition and/or degradation) throughout their lifetime (Harrell's, 2020).

Agricultural products that contain PUR-1 (e.g. PUR-1 microencapsulated pesticide formulations) are used, usually after orders of magnitude folds of dilution, on turf, nursery and agricultural land (dry land and paddy field). PUR-1 makes up 1-10% of the products (Section 8.3.1.1)). The PUR-1 microencapsulated pesticide formulations can be surface applied, sprayed and chemigated. After application, the different constituents of the product may stay on the surface of leafage and soil or migrate into the soil. After the payload is released, the PUR-1 coating may remain on or in the soil (or on leaves) or be washed away with surface water. They remain in solid form throughout their lifetime.

Fragrance encapsulation

PUR-2 is used in a down-the-drain product, i.e. laundry detergent. Only a fraction of the PUR-2 present in the detergent is deposited on fabric, whereas the larger portion is immediately released down-the-drain (Section 8.1.2). For those encapsulations that are deposited on fabric, it is assumed that they also are eventually washed down-the-drain during re-washing of the fabric at which point the shell is likely broken open through friction thereby releasing its fragrance.

Once fragrance encapsulates enter the drain, they will enter WWTPs, where they are either directly released to surface water or adsorbed to sludge particles and removed as solids. Data from unpublished (confidential) company studies suggest > 80% removal of fragrance encapsulates in WWTPs.

Fragrance encapsulates that are released to surface water likely interact with organic matter. Whether they are deposited to sediment or remain buoyant depends on the characteristics of the water body and organic particle concentration. However, this information is generally unavailable as it is difficult, if not impossible, to conduct field studies for the extremely low concentrations of released particles. Those particles that remain buoyant are expected to be transported downstream.

For fragrance encapsulates that are bound to wastewater sludge, the sludge is either incinerated, sent to landfill, or applied to agricultural soil. Currently, data are unavailable to show that these materials can biodegrade in water, soil, or sediment. Depending on the agricultural soil and local conditions, fragrance encapsulates may or may not be subject to erosion processes. They are unlikely to be found in run-off due to the high concentration of organic matter present in the surface layer from the sludge application. In addition, leaching of the fragrance encapsulate particles is unlikely due to their particle morphology and lack of water solubility.

Professional paint products

Polyurethane and polyurea professional paint products are formed *in situ* during application. The reactive components (polyol/polyamine diisocyanate) are supplied in separate containers that are mixed on site and then applied to the substrate with curing taking place on the substrate. There is no intentional release to the environment. Application is usually undertaken in a dedicated facility such as an industrial manufacturing location, construction site, shipyard, etc. Therefore, unintentional or accidental exposure such as spills or overspray can be managed appropriately. The coatings are intended to protect the substrate on large structures. Therefore, they are, by design, hard wearing and resistant to chemical degradation, weathering and abrasion. Physical abrasion may result in small losses of the inert film to the environment, but these will be minimal.

8.7.2 Environmental fate assessment

There are very limited data on the environmental fate of PU-1 and PUR-1 in horticultural / agricultural products (see, e.g., Harrell's, 2020), or of PUR-2 in fragrance applications.

The biodegradation of many types of polyurethanes (by chemical structure rather than by application) has been investigated (Howard, 2002, 2011; Cregut et al., 2013). Generally, polyurethane / polyurea are not considered readily biodegradable. (However, significant amounts of effort are directed at the development of more biodegradable polyurethane / polyurea for use in horticultural / agricultural products – as compared to the traditional polyurethane / polyurea (Petrovic, 2008; Rodríguez-Galán et al., 2011; Noreen et al., 2016).)

Over time, polyurethane / polyurea may partially break up into fragments and release lower molecular weight components: The physical and chemical forms of PU-1, PUR-1 and PUR-2, like any other organic substance, may change over the course of the life cycle due to, for instance, physical and chemical degradation (as well as biodegradation and/or aging pathways). To date, there has been little evidence to demonstrate that polyurethane / polyurea (as present in the horticultural / agricultural and fragrance applications) are subject to mineralisation. However, physical weathering of the particles may lead to disintegration. Just as also stands true for other types of polymers, the (bio)degradation of polyurethane and polyurea is complex, covering physical, chemical, and biological degradation; it can be intended (desirable) or unintended, and this can further depend on the life cycle stage of the polymer. Importantly, assessments surrounding (bio)degradation should consider the duration of (bio)degradation (i.e. half-lives) and the type of evolving breakdown products (ECETOC, 2019, 2020). Based upon the evidence available so far, bioaccumulation of polyurethane / polyurea appears unlikely on account of their 'infinite' molecular weight and inertness.

8.7.3 Environmental exposure assessment

Since little information is available on the environmental fate of polyurethane / polyurea cross-linked materials, exposure characterisation is generally performed through conservative assumptions (Dobe et al., 2017).

Horticultural / agricultural applications

Based on a report by Trenkel (2010), the global use of polymer-coated fertilisers was 247,000 tonnes in 2004/2005. Based upon the annual growth rate provided by Trenkel (2010), it is reasonable to assume that this number will have doubled by now. Considering the small fraction of the polymer-coating on the fertiliser (Section 8.3.1.1), it can be estimated that about 15,000-75,000 tonnes of polymer coating is released into the environment around the world annually. A significant portion (one half to three quarters) of the polymer coating material could be polyurethane, i.e. about 10,000 to 50,000 tonnes (estimations by the ECETOC Polymers TF).

It has been projected that about 22,000 tonnes/year microencapsulated pesticides would be used globally by 2022 (Microencapsulated Pesticides Market Forecast To 2022 by MarketsandMarkets). It is estimated that about one half of the microencapsulated pesticides (i.e. approx. 11,000 tonnes) are produced with polyurea as the coating material – but only a fraction of the products, i.e. 1-10%, are polyurea (Section 8.3.1.1). Therefore, up to about 1,000 tonnes polyurea would be released into the environment globally. The typical use rate of microencapsulated crop protection products is in the range of 0.1 - 10 kg/hectare. Given that the concentration of polyurea in the product is between 1-10 weight%, an estimate of 1 g to 1 kg of polyurea is applied onto a hectare of field.

Generally, polyurethane / polyurea used in horticultural / agricultural products are relatively inert materials at the point of use but are relatively persistent in the environment. Importantly, the polyurethane / polyurea microencapsulations are generally assessed with the horticultural / agricultural products as a whole rather than separately. For this reason, little data is available on the specific exposure of non-target species and operators to polyurethane / polyurea alone. Since the hazard and risk assessment generally focuses on the active ingredient (and, for plant protection products, further on the entire product), the need for any specific exposure, hazard and risk assessments of the polyurethane / polyurea microencapsulations in isolation should be established on a case-by-case basis based on a specific concern separate from that of the product. While release is intentional, such assessments should also consider that the quantity of polyurethane / polyurea in horticultural / agricultural products is much smaller than that in other applications, but which are not directly released into the environment (Section 8.1.2).

Fragrance applications

While the polyurea-based fragrance encapsulates are used in down-the-drain applications, the volume of use is expected to be small (see Table 15 in ECHA, 2019b) and the release of free and non-crosslinked polyurea polymers to the environment is expected to be low. Polyurea-based fragrance encapsulation technologies are comprised of polyurea polymers with infinite molecular weight that form a thin membrane around a fragrance oil core. While the polyurea encapsulate itself can be considered a polymer, the encapsulate is considered to be inert, and not expected to degrade resulting in polyurea fragments of lower molecular weight that would be considered in-scope of traditional concerns associated with non-microplastic polymers[12].

Professional paint applications

The exposure to polyurethane- / polyurea-based professional paints, upon abrasion over their life span, is generally considered to be very low.

Summary of the environmental exposure assessment

While this case study considers (theoretical) polyurethane / polyurea, the exposure assessment conducted for any specific polymer (or non-polymeric substance) serves to identify relevant ecotoxicological and toxicological endpoints (or to establish that there are no such relevant endpoints) taking into account the polymer's (or substance's) key physico-chemical properties.

While polyurethane / polyurea fulfil the criteria for 'polymers of low concern' or 'reduced regulatory requirements polymers' (US EPA, 1997; Canada, 2005, 2021; Australian Government, 2019, 2021), they may still exhibit potential for physical hazard. Lately, this has been reflected in concerns that e.g. microparticles of polyurethane-based plastics may cause adverse effects in ecosystems (see e.g. Danso et al., 2019; Jones et al., 2020; Zimmermann et al., 2020). However, such issues are not further explored here as the scope of this case study is to evaluate the CF4Polymers in the context of standard hazard and exposure characteristics and not to consider unintentional release and/or particle effects by secondary microplastics.

[12] In accordance with the ECHA (2019b) microplastics definition.

8.8 Case Study 7: CF4Polymers (Step 7) Hazard assessment

In line with the focus of this case study, the below considerations on CF4Polymers (Step 7) hazard assessment are restricted to considerations on environmental hazard assessment and hence ecotoxicity testing. (On account of their physico-chemical properties, polyurethane / polyurea coatings are considered to present low human health hazard concern.)

Overall, very few hazard data on polyurethane / polyurea are available in the public domain. Also, polyurethane / polyurea used for professional paint applications are produced *in situ* so that hazard assessment relates to the starting materials.

The vegetable oil-based polyurethanes used in agriculture and horticulture are generally considered inert. Further, ingestion of these solid polymers by soil organisms (or terrestrial and sediment-dwelling animals) has been reported only in cases of artificially high concentrations (Huerta Lwanga et al., 2016; Burns and Boxall, 2018; van Gestel and Selonen, 2018). Therefore, such ingestion of the polyurethane / polyurea coatings at the rates used in agriculture and horticulture is likely to be rare. In case of ingestion, polyurethane / polyurea is considered inert and stable in the gastrointestinal tract. Since it is too large to be absorbed through the intestinal wall, it is not expected to become systemically bioavailable, but is likely to be excreted intact.

Nonetheless, these polymers may exhibit physical hazard potential (Section 8.7.3). Therefore, the need for any hazard assessment should be determined and justified on a case-by-case basis. If at all relevant, such assessments should rather focus on terrestrial organisms, and possibly sediment-dwelling organisms. By comparison, intrinsic hazard potential to aquatic organisms appears unlikely since these polymers are generally solid and not water soluble (for which reason the polyurethane and polyurea are also likely difficult to test in aquatic toxicity studies).

Against this background, it is unsurprising that few published studies address the ecotoxicology of vegetable oil-based polyurethanes (Harrell's, 2020). Literature data is available for generic polyurethane, but the main areas are polyurethane foams and experimental materials rather than commercial material (Skleničková et al., 2020).

No literature was found to address the ecotoxicology of petroleum-based polyurea used in agriculture and horticulture.

8.9 Case Study 7: CF4Polymers (Step 8) Risk characterisation and overall conclusions from the case study

In line with the overall scope of the present ECETOC TR No. 133-3 (Section 1.1), this case study did not aim at performing a risk characterisation for any specific polyurethane or polyurea. Instead, it has served to show how different intended uses of the same types of polymers should be considered for exposure assessment.

Importantly, the exposure, hazard and risk assessment of polyurethane / polyurea used as shell material for microencapsulations of fertilisers, crop protection products, and fragrances are at the intersection to the hazard and risk assessment of the core material, i.e. the fertiliser, active substance, and fragrance oil. Similarly, the example of professional paint applications, where the polymers themselves are only produced in the final article, has shown how the hazard and risk assessment will generally focus on the monomers and/or other

starting substances that are regulated as non-polymeric substances e.g. under the respective applicable chemical legislation.

The above describes the current regulatory situation. Further, potentially hazardous co-formulants (or non-active substances, such as hazardous surface-active polymers / wetting agents) are also taken into account by hazard characterisation and assessment in regulatory schemes. Equally, the CF4Polymers requires the assessor to decide in the (Step 3) polymer component strategy what is relevant for the risk assessment and what not. In this case study, focus has been on the polyurethane and polyurea, despite their low hazard compared to e.g. the active substances and other co-formulants used in plant protection products.

Taken together, this case study showed that the structure of the CF4Polymers is useful to assess the risk of polyurethane and polyurea used for microencapsulation for horticultural / agricultural applications, fragrance applications and professional paint applications.

9. OVERALL DISCUSSION AND RECOMMENDATIONS

The previous sections of this *ECETOC TR No. 133-3 Case studies putting the CF4Polymers into practice* presented seven case studies on (CS1) polycarboxylates, polyacrylates and polymethacrylates; (CS2) cationic polymers – specifically polyquaternium-6 (PQ-6) and PQ-10; (CS3) polyolefins – specifically polypropylene; (CS4) bisphenol-A diglycidylether (BADGE) polymers; (CS5) polyetherols (PEOLs); (CS6) surfactant polymers – specifically alcohol ethoxylates (AEs); and (CS7) selected professional applications of polyurethane and polyurea.

This final section ties the learnings and insights from the seven case studies together and concludes by revisiting the five recommendations from the two previous reports, i.e. ECETOC TR No. 133-1 and 133-2.

As expected, the seven case studies have confirmed that polymers represent a large and broad aspect of the chemical space. This necessitates a careful characterisation of the materials under investigation as well as their complex uses while taking into account that some polymer products can change their form during different life cycle stages. Polymers are usually not present as mono-constituent substances, but as complex polymer products, and some even have properties resembling those of UVCBs. It is recognised that the state-of-knowledge is evolving and that further investigations, building on the ECETOC TR No. 133 series, will be necessary in the future. The seven case studies clearly only cover a small fraction of the seemingly infinite world of polymers. Nonetheless, they cover different polymer chemistries, including polymers that are considered to have some hazardous properties, and others that are not.

It is important to make clear that the case studies were not intended to document a comprehensive risk assessment for any specific polymer. Rather, publicly available data and unpublished TF company data were collated and assigned to the eight steps of the CF4Polymers presented in ECETOC TR No. 133-1 so as to evaluate the scientific usefulness and comprehensiveness of the process through use of examples. The examples covered different types of polymers and/or different types of intended uses. Thereby, the seven case studies have also served to illustrate how the CF4Polymers *can be used* for polymer hazard and risk assessment. Further, the collated data were used to assess the applicability of tools, methods and models for polymer risk assessment presented in ECETOC TR No. 133-2.

Generally, the case studies have confirmed the value of the eight steps of the CF4Polymers for the hazard and risk assessment as applied to a diverse spectrum of polymers. All case study substances were readily processed through the steps of the CF4Polymers. The case studies did not reveal evidence that would suggest that the approach described in the CF4Polymers would be inappropriate, incomplete or misleading.

The case studies have demonstrated that there is no 'one size fits all' polymer hazard and risk assessment process of polymers. This confirms the relevance of having designed the CF4Polymers to be both flexible and non-prescriptive. The order of the eight steps can be changed as required depending on the risk assessment needs and/or on data availability.

In the same way, the case studies have demonstrated that there is no 'one-size-fits-all' approach to determine if any given tool, test method or model is, nor is not, applicable for the assessment of all polymers. Conclusions that that have been derived for the specific polymers considered in this report are not necessarily transferable to all other types of polymers (and possibly not even to other variants of the same types of polymers). However, the findings of this report do highlight the need for critical, case-by-case, assessment of the suitability and relevance of models, methods and concepts by suitably qualified and experienced professionals involved in the assessment of products containing polymers.

Against this background, this section discusses insight following from these case studies related to:

- Section 9.1: Applicability of the CF4Polymers as presented in ECETOC TR No. 133-1 for the evaluation of the polymers considered in the case studies
    - Section 9.1.1: Insight from the case studies: Applicability of the eight steps of the CF4Polymers
    - Section 9.1.2: Insight from the case studies: The polymers considered in the seven case studies
- Section 9.2: Applicability of tools, methods and models for polymer hazard and risk assessment as presented in ECETOC TR No. 133-2
- Section 9.3: A reappraisal of the five recommendations from ECETOC TR No. 133-1 and 133-2 (Section 1.1; Box 2) considering the insight from the seven case studies

9.1 Applicability of the ECETOC TR No. 133-1 CF4Polymers for the evaluation of the polymers considered in the case studies

9.1.1 Insight from the case studies: Applicability of the eight steps of the CF4Polymers

In all seven case studies, *(Step 1) problem formulation* was addressed in a generic manner since the case studies did not aim at performing a concrete hazard or risk assessment. However, this step, i.e. the definition of the purpose of the hazard and risk assessment, is not likely to be fundamentally different between polymeric and non-polymeric substances. Indeed, the outline of this step of the CF4Polymers follows the general approach taken in the internationally agreed paradigm for chemical risk assessment published by the WHO IPCS (2004, 2010). Therefore, a further evaluation of the relevance and coherence of (Step 1) problem formulation within the case studies was not considered to be of paramount importance for the overall evaluation of the CF4Polymers.

(Step 2) polymer identification plays a pivotal role for polymer hazard and risk assessment (both for substance characterisation and to identify and substantiate testing needs), and this has been confirmed in the seven case studies. Further, the case studies have confirmed the view expressed in ECETOC TR No. 133-1 and 133-2 that polymer identification should be fit-for-purpose. The examples have illustrated that the prescribed process for non-polymeric substances does not readily apply to polymers, and instead focus should be on those key properties that are most relevant for the given type of polymer under investigation. The CF4Polymers allows for the necessary flexibility to determine those key parameters that are relevant for the given type of polymers.

Application of *(Step 3) polymer component strategy* is a critical step since polymers can be viewed as complex mixtures and that IAS and NIAS contribute to, and in most cases are responsible for, expressed hazard properties. Application of this step is not expected to pose any difficulties since it is rather an *organisational* step to ensure that the risk assessor clearly establishes beforehand which component of the polymer product is being addressed. Nevertheless, there may exist significant *analytical* challenges e.g. in separating and identifying NIAS, etc. (Section 9.1.2.3: Case Study 3 – polyolefins). Depending on the problem formulation, the component of the polymer product to be included in the assessment may either be the entire polymer product, consisting of the polymeric substance and all potentially present IAS and NIAS including oligomers and residual polymers, or only (combinations of) individual components of the polymer product. While case

studies 1, 2, 6 and 7 focussed on the respective polymeric substances, Case Study 3 (polyolefins) specifically focussed on potentially migrating oligomers as LMW components and also discussed issues of relevance for the hazard and risk assessment of IAS. Further, Case Study 4 (BADGE polymers) considered the entire spectrum of BADGE substances ranging from the BADGE monomer to the BADGE oligomers and BADGE polymers. Similarly, Case Study 5 (PEOLs) considered both the oligomeric polyols and the PEOLs. These case studies showed that, for many IAS (e.g. additives) and NIAS (e.g. impurities including residual monomers and oligomers), as non-polymeric substances, information from prior hazard and risk assessment may be available. In the case studies, opportunities were identified for how to make use of the respective data on these non-polymeric substances for the hazard and risk assessment of (different components of) the particular polymer. Generally, all case studies confirmed the usefulness and relevance of (Step 3) polymer component strategy.

The further elaboration of *(Step 4) grouping approach evaluation* has been a major topic addressed in the present report. In Section 1.3, details to the grouping approach have been described that go beyond the generic outline provided in the ECETOC TR No. 133-1 CF4Polymers (reproduced in the present report in Appendix 1). In this regard, three of the case studies have served to provide further insight into this important step of the CF4Polymers – and of the process of polymer hazard and risk assessment as such. In Case Study 4 (BADGE polymers), the grouping and hazard characterisation was founded on properties of the BADGE monomer. In Case Study 5 (PEOLs), it was focussed on the corresponding oligomeric polyols. Finally, in Case Study 6 (surfactant polymers), it was conducted across a broad range of similar AEs that only differ by mean carbon-chain length and degree of ethoxylation (and hence average molecular weight and molecular weight distribution). These case studies served to enhance the understanding of how different types of polymers may be grouped together to streamline subsequent testing needs.

Just as fit-for-purpose polymer identification needs to be more targeted than substance identification for simpler chemicals, the information to be considered when judging if multiple polymers can be regarded 'the same', or not, needs to go beyond that which is commonly applied to establish 'similarity' for mono-constituent substances. The polymer grouping approach to grouping outlined in Section 1.3 includes three Criteria to describe similarity:

- Criterion 1: Initial grouping according to the chemical nature of the polymers (e.g. PEOLs, AEs) and their common key feature(s). Groups are further subdivided in subsequent iteration steps until a final group is reached.
- Criterion 2: The iteration groups share similar key physico-chemical properties (e.g. molecular weight and polydispersity, fraction of LMW components, degree of cross linking, water solubility, charge density) and associated functionality.
- Criterion 3: The final groups share a similar hazard profile for ecologically and toxicologically relevant hazard properties of the group.

Hence, polymer grouping requires consideration of what can be regarded as sufficiently similar for the purpose of hazard assessment, and/or of which grouping criteria are fit-for-purpose from a safety perspective. Such criteria may vary between different types of polymers.

Consistently, case studies 4, 5 and 6 showed that application of the grouping approach requires sufficient hazard data density for (the) key endpoint(s) and benefits from a continuum of properties both across the given group of polymers as well as towards and across the corresponding non-polymeric substances. Whenever grouping of polymers is performed, it is necessary to have an understanding of key hazards. The number of data points that need to be available for the key hazards will depend on how many endpoints are key endpoints, and how different the polymers are from a chemistry perspective. Therefore, the applicability

of the polymer grouping approach to other types of polymers needs to be explored on a case-by-case basis (for which reason it has been designed to be flexible so that it can be adapted for the particular polymers under investigation, as required).

Finally, in many jurisdictions, the current legal and regulatory schemes rely on CAS numbers to define 'a polymer' in the regulatory sense. Indeed, in many cases, the polymers falling within a given CAS number have comparable ecological and toxicological properties. However, in some cases, the polymers that fall within a particular CAS number can have a different potential for e.g. biodegradation or aquatic toxicity. Hence, from a hazard assessment perspective, it would be extremely helpful to develop more knowledge on grouping, i.e. how far polymers can vary in structure while still having comparable safety properties (see Section 9.2.1 for a further discussion of the limitations of the CAS numbering for polymers).

(Step 5) determination of exposure scenarios and *(Step 6) exposure characterisation* can be very complex for polymers – on account of their diversity and wide range of uses. For example, multiple exposure scenarios can apply to one polymer product, and a variety of ecological receptor(s), different human populations as well as different routes of exposure may have to be considered during polymer risk assessment (ECETOC, 2019). Nonetheless, these steps are not inherently different from the general approach for exposure assessment undertaken for any non-polymeric substance, and this is reflected in the outline of Step 5 and 6 presented in the CF4Polymers. The validity of this approach has been confirmed in Case Study 1 (polycarboxylates, polyacrylates, polymethacrylates), Case Study 2 (cationic polymers), and Case Study 6 (surfactant polymers) that all include details on the exposure assessment of these polymers. Further, Case Study 7 (selected professional and consumer uses of polyurethanes and polyureas) specifically focussed on showing how different intended uses affect exposure assessment. At the same time, methodological challenges can relate to e.g. the applicability of specific exposure models whose underlying database often does not include polymers (Section 9.2).

(Step 7) hazard assessment should be tailored to the information needs for the given type of polymer, and the inherent flexibility of the CF4Polymers allows for such streamlining of testing needs. As applicable, the hazard assessment should address the polymer's potential for intrinsic toxicity and/or physical hazards. Importantly, testing should not be conducted if it does not contribute meaningful data for hazard and risk assessment purposes. For example, if the polymer is unlikely to become systemically bioavailable, the relevance of systemic toxicity tests is questionable. In this regard – and as has been explained above, the fit-for-purpose (Step 2) polymer identification is pivotal to identify potentially relevant ecotoxicological and toxicological endpoints.

(Step 8) risk characterisation (just as *(Step 1) problem formulation)* was addressed in a generic manner since the case studies did not aim at performing a comprehensive hazard or risk assessment. Again, this step is not likely to be fundamentally different between polymeric and non-polymeric substances. Indeed, the outline of this step of the CF4Polymers follows the general approach taken in the internationally agreed paradigm for chemical risk assessment published by the WHO IPCS (2004, 2010). Therefore, a further evaluation of the relevance and coherence of (Step 8) risk characterisation within the case studies was not considered to be of paramount importance for the overall evaluation of the CF4Polymers.

9.1.2 Insight from the case studies: The polymers considered in the seven case studies

The seven case studies have revealed issues to consider when running the selected types of polymers through the eight steps of the CF4Polymers.

9.1.2.1 Case Study 1: Polycarboxylates, polyacrylates, polymethacrylates

This case study focussed on water soluble P-AA/MA and linear P-AA used in laundry detergents (and additionally, for P-AA, used in personal care products), while also referring to insoluble PMMA and moderately soluble EPPAA. P-AA/MA and P-AA are relatively data rich since their use in laundry detergents is a wide dispersive consumer use. The available database covers all relevant ecological and toxicological endpoints, and it confirms that P-AA and P-AA/MA can be submitted to the battery of test methods that is relevant for hazard and risk assessment. Since P-AA and P-AA/MA are water soluble, poor solubility does not pose any problems when submitting them to ecological and/or toxicological test methods. Nonetheless, as complex polymer products, that may include polymeric substances of different molecular weights, solubilities, etc., they do pose the 'usual' challenges during analytical assessment. For example, the molecular weight of polycarboxylates is best expressed as mean value (together with the minimum and maximum values). As regards environmental fate, there is a fairly good correlation between DOC removal and molecular weight of the different P-AA / P-AA/MA. Additionally, most P-AA and P-AA/MA generally possess low ecological hazard and, if they meet respective molecular weight requirements, that they also fulfil the criteria for polymers of low concern.

9.1.2.2 Case Study 2: Cationic polymers

This case study considered PQ-6 and PQ-10 as used in conditioning shampoo, and PQ-6 additionally as used in flocculant for wastewater treatment. Due to their wide dispersive consumer use, PQ-6 and PQ-10 are also fairly data rich. They are further water soluble or otherwise dispersible in water, and they sorb strongly to any negatively charged surfaces present in the aquatic compartments including respiratory surfaces (e.g. gills). Thereby, PQ-6 and PQ-10 depending on the cationic charge may pose a hazard concern towards aquatic species in standardised aquatic toxicity tests. However, cationic polymers have a propensity to sorb to organic matter. Such behaviours likely mitigate the aquatic toxicity potential in the natural aquatic environment. Similarly, sorptive processes to sludge solids in wastewater treatment or dissolved organic matter in the water column are considered the dominant removal process. As regards human health toxicity endpoints, the data available for a broad spectrum of chemically diverse polyquaterniums consistently indicate that their systemic bioavailability is likely low and that they thus do not exhibit systemic toxicity potential. Some polyquaterniums do exhibit potential for mild local irritation, however, mostly at concentrations exceeding realistic human exposures. Case Study 2 showed that, even though high charge density is commonly considered a parameter indicating potential hazard concerns, the ecotoxicological and toxicological profile of the given cationic polymer will need to be established on a case-by-case basis.

9.1.2.3 Case Study 3: Polyolefins

This case study focussed on polypropylene while also considering low-density polyethylene, linear low-density polyethylene and high-density polyethylene. Use as food contact material for fatty food (olive oil bottle) was selected as intended use for this case study, further referring to use in medical devices. This case study was different from the other case studies in that it did not only refer to scientific evidence of relevance to fill in

the eight steps of the CF4Polymers for polyolefins, but also considered the specific and highly demanding end-use legislation that applies to plastic food contact materials and medical devices, respectively. The case study showed that the polymeric substance (polypropylene) itself fulfils the criteria to identify 'polymers of low concern'. Further, all intentionally added substances (IAS) that may be present in the polymer product will have been approved for use and/or are expected to fulfil the safety requirements set out in the food contact material legislation. Therefore, the further exposure and hazard assessment of the polypropylene focussed on the oligomers that might migrate from the polymer matrix. Taken together, the level of oligomers (or other non-intentionally added substances (NIAS), or IAS) that can migrate from the polypropylene matrix is very low, and that the degree of migration is also very low. Such evidence provides the scientific rationale for exposure-based waiving of hazard assessment needs. Further, a number of technical challenges that are specifically related to the hazard assessment of NIAS were highlighted, including difficulties in isolating different NIAS and in synthesising sufficient test material to develop and validate analytical or testing methods for the evaluation of NIAS.

9.1.2.4 Case Study 4: Solid BADGE epoxy resins

This case study considered solid BADGE epoxy resins, BADGE oligomers and as well as the underlying BADGE monomer. Solid BADGE epoxy resins are used exclusively in closed industrial settings, i.e. for the preparation of solvent-based and powder coatings. Focus of Case Study 4 was the application of CF4Polymers (Step 4) grouping approach evaluation. It was hypothesised that the BADGE monomer, as common key constituent, drives the hazard and risk assessment of all members of the group of solid BADGE epoxy resins. The solid BADGE epoxy resins included in this case study contain 0-16% BADGE monomer. Thus, it was further hypothesised that all these BADGE epoxy resins have at most the same, but rather less hazard potential than the BADGE monomer itself. The BADGE monomer has been assigned the CLP hazard classes of skin and eye irritation 2 (at concentrations ≥ 5%), skin sensitisation 1, and aquatic chronic toxicity 2. To address these endpoints, Case Study 4 considered lower-tier toxicity and ecotoxicity data that have been gathered for two types of BADGE epoxy resins. While the findings were inconsistent with respect to the classification for skin irritation and skin sensitisation, they did point to an overall low local toxicity potential of the solid BADGE epoxy resins. Performance of the aquatic toxicity screening studies using daphnids was impaired by the very poor water solubility of the materials. The only suitable vehicle for acute aquatic toxicity testing was Tween 80. Taken together, it was not yet possible to determine if any skin sensitisation that may be elicited by solid BADGE polymers was rather caused by the BADGE monomer or by the free epoxide groups of the BADGE polymer itself. The grouping approach described in Case Study 4, which fits in the first instance for reactive polymers, might also be adapted for various types of polymers. Thereby, the monomers would be grouped according to their use in respective polymerisation chemistries prior to the grouping of the polymers.

9.1.2.5 Case Study 5: PEOLs

This case study addressed PEOLs and the corresponding oligomeric polyols. PEOLs are used exclusively in closed industrial settings where they usually undergo further reactions with methylene diphenyl diisocyanate and toluene diisocyanate to form foams that are used in e.g. mattresses and insulation boards. Focus of Case Study 5 was to apply CF4Polymer (Step 4) grouping approach evaluation to PEOLs. It was hypothesised that data gaps for the group of PEOLs can be filled by read-across from the corresponding oligomeric polyols. The underlying assumption was that the chemistry of the initiator molecule and of the repeating units provide an indication for the physico-chemical and/or ecological / toxicological properties of the polyols. If the initiator molecule exhibits ecotoxicological and/or toxicological properties, these properties will likely diminish with increasing numbers of repeating units. Generally, the oligomeric polyols are devoid of aquatic toxicity

potential. This is regarded an intrinsic property since these oligomers do have the potential to reach aquatic species on account of their high water solubility. Further, the oligomeric polyols have the potential to become systemically bioavailable on account of their low molecular weight. The current database indicates that the human health hazard potential of the PEOLs group is low to absent as regards both acute systemic toxicity and local toxicity. None of the PEOLs included in Case Study 5 show acute dermal toxicity, skin irritation, eye irritation, or skin sensitisation. Preliminary data do indicate that glycerol- and propane-1,2-diol-started PEOLs of a certain molecular weight range (> 500 Da and < 2,000 Da) might elicit slightly more pronounced acute oral and inhalation toxicity. However, these preliminary data deserve further elaboration before reliable conclusions on their hazard properties and consequentially their consideration in the grouping approach can be drawn. Taken together, Case Study 5 provided evidence to support the hypothesis that data gaps for the group of PEOLs can be filled by read-across from the corresponding oligomeric polyols.

9.1.2.6 Case Study 6: Surfactant polymers

This case study focussed on linear AEs that have (1) medium C-chain length and medium degree of ethoxylation (C12-15EO7), or (2) high degree of ethoxylation (C16-18EO≥20). (In AEs, whose alcohols were produced via the synthetic 'oxo-process', a small percentage of the alkyl chains may have an internal methyl branching (so-called 'essentially linear' AEs); nonetheless, for improved readability these polymer products are also referred to as linear AEs in this report.) C12-15EO7 has wide dispersive consumer uses in household and personal care products, including those with down-the-drain release; therefore, the intended use considered here was in household laundry detergents. C16-18EO≥20 is used exclusively in industrial settings, and the selected intended use was for the manufacturing of water-based dispersions and textile, leather, and paper. Both AEs are data rich, and they were taken through all steps of the CF4Polymers. The comprehensive dataset did not indicate any specific difficulties in evaluating the physico-chemical, ecological or toxicological properties of C12-15EO7 or C16-18EO≥20 beyond the specific considerations that are relevant for complex polymer products or for poorly water-soluble test materials (for the hydrophobic AEs). Case Study 6 applied the details of the CF4Polymers (Step 4) grouping approach evaluation to AEs. To facilitate the grouping, this part of the case study considered all biodegradable linear AEs that are based on primary alcohols and have C = 8-18 and EO = 3-50. For some human health endpoints, branched and unsaturated AEs were also considered. Case Study 6 showed that differences in chain lengths between AEs may affect the extent of systemic bioavailability and hence the hazard potential and potency for specific toxicological endpoints (that are common between all group members), but not in inherent differences in the (spectrum of) potentially relevant toxicological endpoints. Trends in acute aquatic toxicity and in eye irritation, likely due to membrane interaction of the AEs, could be established and were considered in defining subgroups for the different hazard classifications for these endpoints. By contrast, the toxicological database did not indicate relevant differences in skin sensitisation, genotoxicity, repeated-dose toxicity or reproductive and developmental toxicity over the entire group of AEs.

9.1.2.7 Case Study 7: Application types

Whereas the other case studies started out from a specific (chemical) type of polymer, Case Study 7 showed how different intended uses of the same types of polymers, i.e. polyureas and polyurethanes, should be considered for exposure assessment. Intended uses included in Case Study 7 were (1) the use of polyureas / polyurethanes as shell materials for the microencapsulation of fertilisers and crop protection products in professionally used horticultural / agricultural products, respectively; (2) the use of polyureas for the microencapsulation of fragrance oils used in laundry detergents and fabric softeners for consumer use; and (3) the use of polyurethane / polyurea in professional paint / coating applications. All polyureas and

polyurethanes considered in Case Study 7 were assessed as inert, and they fulfilled the criteria to identify 'polymers of low concern'. The exposure, hazard and risk assessment of the polymers used for horticultural / agricultural and fragrance microencapsulations are at the intersection to the hazard and risk assessment of the core material, i.e. the fertiliser, active substance, and fragrance oil. Similarly, the example of professional paint applications, where the polymers themselves are only produced in the final article, has shown how the hazard and risk assessment will generally focus on the monomers and/or other starting substances that are regulated as non-polymeric substances e.g. under the respective applicable chemical legislation.

9.2 Applicability of tools, methods and models for polymer hazard and risk assessment as outlined in ECETOC TR No. 133-2

Just as the seven case studies have demonstrated that there is no 'one size fits all' hazard and risk assessment process of polymers, they have shown that the applicability of tools, methods and models to determine the physico-chemical, ecological and toxicological properties of polymers has to be established on a case-by-case basis. Whether a specific tool, method or model is (1) applicable, (2) needs to be adapted to the particular polymer, or (3) is not applicable at all may also differ between different variants of the same type of polymer, for example when some group members are water soluble whereas others are not. Hence, the case studies generally confirm the recommendations and conclusions from the ECETOC TR No. 133-2 while providing further insight for specific issues to consider when assessing specific polymers. In no instance, the evidence from the case studies provided any indication that the contents of the ECETOC TR No. 133-2 would be incorrect or misleading. However, in some instances (e.g. as regards state-of-the-science methodologies to assess polymer surface tension), the case studies revealed opportunities to update the ECETOC TR No. 133-2 and/or add further details to it.

Due to the complexity and versatility of polymers, the naming convention established for mono-constituent substances does not appear useful, on its own, for polymers. A certain CAS number and name can describe a large diversity of different molecules, while the same polymer created by different processes or with differing pH values can have multiple CAS numbers assigned. At the same time, in many cases a certain degree of variation in the structures does not trigger different properties of the polymers with regard to environmental fate, ecotoxicity or toxicity. For many polymers, this is probably due to the high molecular weight, which strongly restricts bioavailability. In the case studies, suggestions have been made for how to complement the CAS numbers and names, e.g. by additionally referring to sector-specific descriptors such as INCI names (Section 2.3.1.1 for polycarboxylates as used in cosmetics) or to pre-defined telling descriptors (Section 6.3.1.2 for PEOLs).

Depending on the type of polymer, the determination of specific physico-chemical properties may be challenging and require adaptation as compared to the measurement of these same properties for mono-constituent substances. Table Disc-1 provides a (non-exhaustive) overview of challenges in applying standard tools and test methods to assess specific physico-chemical properties for the assessment of polymers. Endpoints considered include molecular weight, water solubility, n-octanol / water partition coefficient (log K_{ow}), surface tension, and the analytical verification of polymer concentrations in environmental media (experimental and field), as well as further parameters that were not specifically considered in the ECETOC TR No. 133-2, i.e. charge density, glass transition, density, and vapour pressure.

Further, Table Disc-1 presents a (non-exhaustive) overview of challenges in applying standard tools and test methods for environmental fate, exposure modelling, ecotoxicological and toxicological assessments.

Table Disc-1: Examples for challenges in applying standard test methods to polymers (non-exhaustive)

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
PHYSICO-CHEMICAL PROPERTIES		
Molecular weight and water solubility		
Molecular weight - general	Complexity of polymer products	Polymer products are complex mixtures which contain a multitude of polymeric molecules with different molecular weights as well as LMW constituents including IAS and NIAS such as oligomers and residual monomers. Due to this complexity, analytical methods cannot provide precise information on the whole molecular weight distribution, and sum parameters such as distribution characteristics or secondary properties such as viscosity or melt flow index are typically used to characterise polymers
	Cross-linking (e.g. polyurea, polyurethane)	Molecular weight is not a meaningful concept (comparable to asking what the molecular weight is of a particle of sand); such polymers can be considered as having an 'infinite' molecular weight.
Gel permeation chromatography (OECD TG 118)	Partial solubility or insolubility in water or standard organic solvents	M_n and oligomer content cannot be determined correctly for partially soluble polymers. M_n will be underestimated, and oligomer content overestimated, particularly for cross-linked polymers for which the majority of the polymeric substance is insoluble M_n and oligomer content will strongly depend on choice of solvent, standards and calculation methods → Effect on functional group equivalent weight
	Solid epoxy resins	Can generally well be assessed using a refractive index detector and tetrahydrofuran as solvent; the oligomers are well separated and identified, whereas the higher molecular weight (polymeric) components (> M_n of approx. 1,000 Da) cannot be assigned to discrete peaks, but are rather combined to a very broad band; nonetheless, this does not impair applicability of GPC for epoxy resins, since distinct peak identification is not needed for the higher molecular weight range components
Water solubility (OECD TG 105) Solution / extraction of polymers in water (OECD TG 120)	Reaction in water	Reaction (film formation, hydrolysis), gelation/swelling (superabsorber) will interfere with the determination How to differentiate between physical (e.g. precipitation) and chemical reaction (e.g. cross-linking due the reaction with the solvent)?
	Dispersion / emulsion Liquid polymers: formation of microdroplets	How to differentiate between dilution and dissolution? The use of centrifugation force or filter sizes will influence what is called out as dissolved or not If the polymer itself should be analysed: isolation of the polymer from the dispersion sensible / possible? Stable dispersion – bioavailable?

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Continued Water solubility (OECD TG 105) Solution / extraction of polymers in water (OECD TG 120)	Partial solubility in water	With complex mixtures, it is likely that some constituents may dissolve, but others may not, so that the relevance of water solubility data is questionable; water solubility may depend on chain length (lower M_n will be more easily soluble) TG does not require identification of 'dissolved' molecules, and in many cases, this will not be possible technically, as particularly reaction side products, decomposition products, oligomers etc. are not available as reference standards
	Hydrolytic instability	The TG states: The study does not need to be conducted if the substance is hydrolytically unstable at pH 4, 7 and 9 → see also below: challenges related to OECD TG 111
	Polycarboxylates (P-AA/MA)	Water solubility appears dependent on water hardness and test concentrations
	Cationicity and sorptive properties of polyquaterniums	Water solubility generally difficult to measure, also due to a lack of analytical tools that are suitable for these charged polymers; the exact solubility may also vary between different types of e.g. PQ-6 and PQ-10, respectively On account of their sorptive properties, polyquaterniums may be non-homogeneously distributed in aqueous media
	Polymeric surfactants (e.g. AEs)	Determination of the CMC might be a better approach to determine water solubility for surfactants; thereby, the solubility of AEs in water can be differentiated in (1) molecular solubility (below CMC); and (2) micellar solubility (above CMC); however, in case of polysoaps (i.e. water-soluble polymers carrying few hydrophobic groups) there might be no CMC because of preferential intramolecular aggregation; also, the cloud points have to be considered, which could be low for AEs with low degree of ethoxylation
	Additional pH-dependent effects	Reaction (film formation, hydrolysis) vs. gelation/swelling (superabsorber) vs. solubility
n-Octanol / water partition coefficient (log K_{ow})		
General	Cationic polymers (e.g. PQ-6, PQ-10)	The ECETOC Polymers TF is unaware of suitable methodology to measure log K_{ow} of cationic polymers and maintains the view that this parameter is not relevant to predict their bioaccumulation potential
	Solid polymers (e.g. solid BADGE epoxy resins)	The ECETOC Polymers TF maintains the view that partition coefficients and dissociation constants are generally not relevant physico-chemical properties for solid, insoluble polymers, such as the solid BADGE epoxy resins, since such materials do not dissociate and are not soluble in water
Shake flask method (OECD TG 107)	'Best case' polymers soluble in water and organic solvents	Could the TG be adapted e.g. to perform GPC of both phases after partition and compare the molecular weight distribution in each phase? Could a log K_{ow} be calculated for certain peak slices to account for different homologue distribution? What would be the benefit for the risk assessment? If the measured concentration in the respective phase (and hence also the log K_{ow}) is dependent on the original sample weight, the resulting log K_{ow} is arbitrary → adaption of TG for a specific sample size?

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Continued Shake flask method (OECD TG 107)	Partial solubility of polymers in water and n-octanol	May be dependent on chain length (lower M_n will be more easily soluble, which may lead to over- or underestimation of toxicological effects?) How to distinguish between additives / unreacted monomers and the polymeric substance? Poorly water-soluble polymers: low limit of quantification achievable?
HPLC method (OECD TG 117) Estimation from single solubilities (also mentioned in OECD TG 107)	Aqueous dispersion Dispersion not miscible with either water or n-octanol	Aqueous solvent is not miscible with n-octanol → isolation of polymer sensible / possible? Isolation may alter polymer properties
HPLC method (OECD TG 117)	All	Needs to be evaluated with polymeric reference substances Is the correlation applicable at all for polymers? Many polymer products cannot be assessed chromatographically following the HPLC conditions mandated in OECD TG 117
Surface tension		
General	All polymers with surface active properties	Work on the case studies has revealed opportunities to update Section 3.6 (Surface tension) in ECETOC TR No. 133-2 and specifically, to update Table 3 therein (*Analytical methods potentially suitable to determine the surface tension-lowering properties of polymers*) to reflect the state-of-the-art in science and industrial practice as well as commercially available equipment. While an update of TR No. 133-2 is being planned, Appendix CS6-A.1 of the present report proactively summarises the new insight. Additionally, in the revision of TR No. 133-2, currently ongoing work by the CESIO Working Group 'Test Methods of Surfactants' and the TEGEWA Working Group 'Surface Active Substances' (Venzmer, 2020) as well as work by the CEN/TC 276 – Surface Active Agents (Working Group 1 'Analytical Methods' and Working Group 2 'Methods of Test') to standardise amongst other issues the physical, chemical or other test methods of surface-active agents [a] shall be considered.
Surface tension (OECD TG 115)	Polymeric surfactants Polymer additives in surfactants and washing agent	How to differentiate between surface active additives and the polymeric substance itself if isolation of the polymeric substance is not possible

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Charge density		
General	Cationic polymers (e.g. polyquaterniums)	Methodologies to measure charge density were not explicitly mentioned in the ECETOC TR No. 133-2; there are two indirect methods to measure charge density, i.e. polyelectrolyte/charge titration and measurement of the %TKN; while both methods are valid to measure the charge density of cationic polymers, they both also have limitations e.g. with respect to precision
Vapour pressure		
Vapour pressure - general	Solid vs. non-solid polymers	Vapour pressure was not considered in any detail in ECETOC TR No. 133-2; many polymers are solids, and the vapour pressure will be too low to be relevant for hazard or risk assessment; for non-solid polymers, vapour pressure may need to be considered for exposure modelling
Glass transition temperature		
Glass transition temperature – general	Polycarboxylates, polyolefins	Property has not been considered in any detail in ECETOC TR No. 133-2, but may be relevant for specific types of polymers – however, rather from a technical point of view, while only having an indirect impact on human health hazard assessment (e.g. by resulting in difficulties in applying materials that are solid at room temperature to *in vitro* test systems)
Density		
Density - general	Polycarboxylates, polyolefins	Property has not been considered in any detail in ECETOC TR No. 133-2, but may be relevant for specific types of polymers – however, rather from a technical point of view, while only having an indirect impact on human health hazard assessment (e.g. by resulting in difficulties in applying materials that are solid at room temperature to *in vitro* test systems) Density may need to be considered for exposure modelling (e.g. PMMA)
Analytical verification of polymer concentration in environmental media (experimental or field)		
Mass spectrometry	Polyquaterniums	Mass spectrometry-based methods to verify the concentrations of PQs in (experimental or natural) environmental media at relevant limits of quantification are currently unavailable; therefore, test results are evaluated based upon nominal concentrations; however, since PQs can adsorb to surfaces and precipitate out of solution, the effective exposures may be much lower than the nominal concentrations, thereby potentially leading to erroneous conclusions on the actual concentrations at which effects are absent Substantial pre-work is needed to ensure bioavailability and stability of the test materials within the test systems; variations in test setups (e.g., solution preparation, water quality parameters) may greatly affect the effect concentrations and hence also the test results. The ongoing Cefic LRI project iTAP is exploring appropriate test design procedures and necessary pre-work for aquatic toxicity tests, and it is also engaged in developing cold analytical (mass spectrometry) approaches

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Analytical verification of polymer concentration in environmental media (experimental or field) *(continued)*		
Method described by Dunphy et al. (2001)	Alcohol ethoxylates	This method, which uses 2-fluoro-N-methylpyridinium p-toluene sulphonate derivatisation followed by electrospray liquid chromatography/ mass spectrometry detection, is able to detect all 114 AE homologues in the range C12-18 and EO0-18 at ng/L levels in environmentally relevant aquatic samples; this allows obtaining a much more complete environmental profile of AE homologue distribution than when using cold analytical and radioanalytical approaches (Eadsforth et al., 2006)
ENVIRONMENTAL FATE		
Abiotic degradation		
Hydrolysis as a function of pH (OECD TG 111) (from an analytical perspective)	All; may be dependent on chain length (lower M_n → more easily soluble → underestimation of toxicological effects?) How to distinguish between additives / unreacted monomers and polymeric substance?	How to determine the half-life of polymers? For later testing: test parent compound or degradation products? Cut-off criteria for half-life? How to determine the kinetics? Methods for quantification are needed Typically, when polymer chains hydrolyse, they form shorter chains which lead to an increase of the peak area in GPC chromatography (~ concentration) in the LMW area while the peak area in the higher molecular weight area decreases; thus, the overall peak area would not change although the chains are hydrolysing However, there are also other phenomena which can overlay with each other or even cancel each other out, e.g. (1) insoluble parts of the material become soluble (= overall peak area increases); (2) polymer chains degrade to molecules smaller than the detection limit (= overall peak area decreases); (3) the way of calculating and displaying the results can lead to wrong conclusions (e.g. relative area vs absolute area, normalization of the distribution curves); (4) sample preparation can affect the result (mass balance / recovery)
	All; may be dependent on chain length (lower M_n → more easily soluble → under-estimation of toxicological effects?) How to distinguish between additives / unreacted monomers and polymeric substance?	Detailed structural elucidation will help to understand if only shorter polymeric chains are obtained upon hydrolysis or if neutral losses are also observed during hydrolysis; this will help to postulate a plausible hydrolysis pathway However, as with UVCBs, identification of degradation products could be a never-ending story and require multiple analytical techniques How to decide which degradation products to identify or even quantify?

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Biodegradation		
Biodegradation, general	Use of humic acid	Use of humic acid from different sources may affect the outcome of biodegradation testing
	Conceptual Framework for Biodegradation Assessment laid out in ECETOC TR No. 133-2	A comparison of the Conceptual Framework for Biodegradation Assessment with the biodegradation information for AEs generally confirms that the framework is useful and that it yields the relevant information to evaluate the biodegradability and potential persistence of AEs When applying the framework in practice, the extent of information that is 'sufficient' to draw a conclusion on biodegradability will need to be determined on a case-by-case basis; the sufficiency of information will be different when performing either a general screening for biodegradability or stringent regulatory assessments to identify / rule out persistence; for high production volume chemicals with wide-dispersive use and hence comprehensive hazard assessment (such as AEs), degradation kinetics need to be obtained that cannot be sufficiently derived from screening level studies; therefore, the establishment of the 'sufficiency of information' to conclude on biodegradability also needs to consider intended uses and exposure potential
Biodegradation testing (e.g. OECD TG 301, 302, 307, 308, 309)	Molecular structure	In general, the polymeric substances will take longer to degrade significantly compared to small molecules (e.g. unreacted monomers) Existing testing methods all rely on microbial activity over the test period; longer testing times need adapted methodologies to conserve the microbial activity over the entire test period Other adaptions might be warranted to be able to limit test duration (e.g. inoculum concentration, test substance concentration, etc.)
EXPOSURE MODELLING		
Exposure modelling - general	All polymers	Need to consider on a case-by-case basis if available exposure models are relevant for particular type of polymer (e.g. if they include the same / similar polymers in the underlying database); if not, exposure assessment will rather be qualitative or at best semi-quantitative; especially true for insoluble polymers
	Polycarboxylates, polyacrylates, polymethacrylates	The exposure models EUSES and iSTREEM can be used for the environmental exposure assessment of P-AA/MA and P-AA (highly soluble) and EPPAA (moderately soluble); PMMA (poorly soluble) likely requires a different exposure modelling strategy, e.g. use of SimpleBox4nano or nanoDUFLOW while considering a different set of key physico-chemical parameters (e.g., density, particle size)
	Polyquaterniums	Conventional exposure models generally not applicable for PQs: (1) Usually, effective concentrations must be provided that, however, are generally unavailable for PQs; (2) current evidence indicates that sorptive properties of PQs are relevant for hazard and risk assessment, leading to effects on the outside of the test organisms, such exposure scenarios are usually not covered by the domains of conventional exposure models

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
ECOTOXICOLOGICAL AND TOXICOLOGICAL ENDPOINTS		
General	All polymers	Need to establish if testing is meaningful – and possible – see decision tree from ECETOC TR No. 133-2
Acute and chronic aquatic toxicity		
Testing for aquatic effects - general	Polycationic and amphoteric polymers	May exhibit artificially high toxicity in standard aquatic hazard testing media (e.g. as described in the OECD TGs) that usually have a low total organic content (US EPA, 2013); laboratory water should be standardised at the lowest biologically tolerable hardness and total organic carbon at a reliably measurable level (> 1 to < 2 mg/L) to reduce variability and increase the reliability of the determination of the baseline aquatic toxicity of cationic polymers (Salinas et al., 2020)
Testing on effects in aquatic organisms (e.g. OECD TG 201, 202, 203, 210, 211, etc.)	Virtually no water solubility for certain groups of polymers	Current methods aim to measure the intrinsic toxicity via the water-soluble fraction For polymers, adaptation of methods needs to be discussed to achieve environmentally relevant results; recommendations from OECD (2019) Guidance Document No. 23 on aqueous-phase aquatic toxicity testing of difficult test chemicals may be applicable for poorly water-soluble polymers Use of specific solvents does not reflect realistic exposure conditions, e.g. for aquatic toxicity testing, thereby calling into question the relevance of the test results
Chronic aquatic toxicity studies	Polycarboxylates (P-AA/MA)	Water solubility and precipitation behaviour of P-AA/MA in the presence of ions with 2+ charge (e.g. ubiquitous Ca^{2+} and Mg^{2+}) can greatly affect the outcome of chronic aquatic toxicity studies (with water solubility further appearing dependent on water hardness and test concentrations)
Human health toxicity		
Human health toxicity - general	Workflow outlined in Figure 7 of ECETOC TR No. 133-2	The workflow works well with LMW substances that are of commercial interest such as IAS, where traditional approaches to substance testing can be applied. By contrast, toxicity testing of NIAS (including oligomers) migrating from the food contact material is oftentimes not feasible since it is technically not possible to characterise all NIAS, or to isolate or synthesise the respective test materials in sufficient quantities to enable such testing
In vitro studies or *in chemico* studies (e.g. DPRA)	Water solubility and other key properties of the respective type of polymer	Method applicability depends on key physico-chemical properties polymer, and most importantly on its water solubility (see also Section 7.5 in ECETOC TR No. 133-2); solubility can be facilitated by selection of appropriate solvents / vehicles, but their presence may also alter e.g. the particle size of the test material thereby potentially also enhancing its external / systemic bioavailability and hence toxicity;
In vitro studies	All polymers	Have not (necessarily) been validated for polymers, applicability for particular type of polymers should be established on case-by-case basis

Test method / property / endpoint	Challenging polymer feature / type of polymer	Details
Human health toxicity *(continued)*		
In silico tools	All polymers	Applicability domain often does not include polymers
Grouping in regulatory setting (e.g. under REACH)	All polymers	Polymers are not e.g. registered together with non-polymeric substances; nonetheless, from a scientific perspective, it is expected that – at least for some polymers – read-across from the corresponding lower molecular weight oligomers is possible; therefore, source substances (e.g. the oligomers) and target substances (i.e. the polymers for which data gaps must be filled) may belong to different groups / categories

Footnote to Table Disc-1:

Abbreviations: %TKN: Total Kjeldahl Nitrogen; AE: Alcohol ethoxylate; BADGE: Bisphenol-A diglycidylether; Cefic: European Chemical Industry Council; CEN: European Committee for Standardisation; CESIO: European Committee of Organic Surfactants and Their Organic Intermediates (*Comité Européen des Agents de Surface et de leurs Intermédiaires Organique*); CMC: Critical micelle concentration; Da: Dalton; DPRA: Direct peptide reactivity assay; EPPAA: Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer; EUSES: European Union System for the Evaluation of Substances; GPC: Gel permeation chromatography; HPLC: High performance liquid chromatography; IAS: Intentionally added substances; iSTREEM: In-stream exposure model; iTAP: Improved Aquatic Toxicity and Assessment of Polymers; LMW: Low molecular weight; log K_{ow}: n-Octanol / water partition coefficient; LRI: Long-range Research Initiative; M_n: Number average molecular weight; NIAS: Non-intentionally added substances; OECD: Organisation for Economic Co-operation and Development; P-AA: Poly(acrylic acid) homopolymer; P-AA/MA: Poly(acrylic/maleic acid) copolymer; PMMA: Poly(methyl methacrylate); PQ: Polyquaternium; RAAF: Read-across Assessment Framework; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals; TC: Technical Committee; TEGEWA: Association of Manufacturers of Process and Performance Chemicals (Germany); TF: Task Force TG: Test guideline; TR: Technical Report; UVCB: Substance of unknown or variable composition, complex reaction products and biological materials.

[a] https://standards.iteh.ai/catalog/tc/cen/e0d6e5f4-7375-4ec3-9fe3-9016081635d9/cen-tc-276.

9.3 Conclusions with respect to the five recommendations spelled out in ECETOC TR No. 133-1 and 133-2

In this final section of the ECETOC TR No 133-3, the five recommendations spelled out in ECETOC TR (2019) No. 133-1 and ECETOC TR (2020) No. 133-2 are revisited to discuss how the seven case studies provided further insight to address and/or refine these.

Recommendation 1: *Identify sets of structural and/or morphological descriptors as well as physico-chemical and fate properties that are key parameters for different types of polymer products*.

In further evaluating the evidence collated for the seven case studies, sets of structural and/or morphological descriptors as well as physico-chemical and fate properties have been identified that appear as key parameters for the respective types of polymers. Such key parameters are summarised in Table Disc-2, and this overview confirms the view expressed in ECETOC TR No. 133-1 and 133-2 that polymer identification should be fit-for-purpose and that those properties that are key for the given type of polymer under investigation need to be established on a case-by-case basis. The CF4Polymers allows for the necessary flexibility to determine those key parameters that are relevant for the given type of polymers.

Recommendation 2: *Consider prevailing technical limitations of available tools, test methods and models for polymer risk assessment*.

The seven case studies have served to advance the information presented in ECETOC TR No. 133-2 while at the same time highlighting knowledge gaps that should be addressed to ensure that tools, test methods and models are applied for the assessment of the given polymer in a meaningful manner (Table Disc-1).

In this regard, work on the case studies has revealed opportunities to revise Section 3.6 (Surface tension) in ECETOC TR No. 133-2 and specifically, to update Table 3 therein (*Analytical methods potentially suitable to determine the surface tension-lowering properties of polymers*) to reflect the state-of-the-art in science and industrial practice as well as commercially available equipment. While an update of ECETOC TR No. 133-2 is being planned, Appendix CS6-A.1 of the present report proactively summarises the new insight.

Recommendation 3: *Maintain the CF4Polymers as a 'living', flexible framework, and review and update it in line with emerging knowledge on how it can efficiently and effectively support polymer risk assessment.*

ECETOC TR No. 133-3 complements the two previous reports, ECETOC TR No. 133-1 and 133-2, by providing further evidence to support the general outline of the CF4Polymers and more detailed guidance on how to pass through its eight steps. Importantly, the information evaluated for the seven case studies did not indicate any need to fundamentally change the CF4Polymers. Indeed, it was not necessary to deviate substantially from the eight-step structure for any of the case study polymers considered. This is not necessarily surprising since the CF4Polymers was designed to follow the general outline for hazard and risk assessment implemented e.g. by the WHO IPCS (2004, 2010). The most important addition to this internationally agreed paradigm is (Step 3) Polymer component strategy, an organisational step to ensure transparency on the components of the polymer product considered.

Table Disc-2: Key physico-chemical and fate properties of the case study polymers ('key' with respect to hazard assessment)

Case study	Polymers considered	Key physico-chemical and fate properties ('key' with respect to hazard assessment)	Relevant ecotoxicological and toxicological properties
1	**Polyacrylates:** Polyacrylate homopolymer; polyacrylic / maleic acid copolymer; further: PMMA and EPPAA	(Mean) molecular weight, water solubility, acid dissociation constant Biodegradation generally slow, bioaccumulation unlikely	Low (but mostly not negligible) potential for toxicity to aquatic and sediment-dwelling species; human health-related endpoints: low acute toxicity At most, slight eye irritation (depending on monomers)
2	**Cationic polymers**: Polyquaternium (PQ-6) and PQ-10; other PQs, as relevant	Charge density, (mean) molecular weight, water solubility Biodegradation slow, low potential for bioaccumulation	Some acute and chronic aquatic toxicity potential Low potential for systemic bioavailability; at most, slight skin or eye irritation potential across broad spectrum of PQs
3	**Polyolefins**: Polypropylene; also: Low-, linear-low- and high-density polyethylenes	Molecular weight, proportion of low molecular weight components, absence of charge or reactive functional groups Environmental fate not considered in case study	Ecotoxicological endpoints not considered in case study Polypropylenes as such fulfil criteria for polymer of low concern; relevant for hazard and risk assessment: potentially migrating oligomers
4	**Solid Bisphenol-A diglycidylether (BADGE) epoxy resins**	Fraction of non-polymeric and polymeric low molecular weight constituents present in polymer product, M_n of polymeric substance, amount of reactive functional groups Environmental fate not considered in case study	Dependent on proportion of BADGE monomer in the solid BADGE epoxy resins, some potential for aquatic toxicity, skin irritation / skin sensitisation
5	**Polyetherols (PEOLs)**	Type of initiator molecule, length of propylene oxide / ethylene oxide chain, molecular weight, water solubility Environmental fate not considered in case study	No ecotoxicological potential, generally no to low acute systemic or local toxicity potential
6	**Surfactant polymers:** Alcohol ethoxylates (AEs)	Mean molecular weight and molecular weight range (based upon average numbers of C and ethoxylation, respectively), critical micelle concentration, surface tension All AEs considered in Case Study 6 are biodegradable	Strong, structure-dependent increase in aquatic toxicity potential with increasing overall hydrophobicity of AEs Human health hazard potential due to local action / local irritation, acute oral toxicity (EU CLP Category 4 vs no classification)
7	**Selected intended uses of polyurethanes and polyureas**	Highly cross-linked structure, insoluble solids, absence of charge or reactive functional groups; very high molecular weight; mostly low biodegradation	Fulfil criteria for polymers of low concern; hazard assessment of microencapsulates will focus on the e.g. active substances in the core of the microcapsules

Footnote to Table Disc-2: Abbreviations: EPPAA: Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer; PMMA: Poly(methyl methacrylate).

Nonetheless, due to the broad chemical space covered by polymers, the CF4Polymers has been designed to be both flexible and non-prescriptive. The order of the eight steps can be changed as required depending on the risk assessment needs and/or on data availability.

In the present report, further details have been provided for how to conduct CF4Polymers (Step 4) grouping approach evaluation (Section 1.3). These further details complement the outline for this step presented in ECETOC TR No. 133-1.

Recommendation 4: *Expand the knowledge base to (1) substantiate the polymers of low concern concept and (2) to identify under which conditions the presence of specific structural alerts or physico-chemical properties could be an indicator of environmental or human health hazard concerns*.

The polyolefins (Case Study 3) and polyurethane / polyurea (Case Study 7) typically fulfil the criteria for polymers of low concern. These case studies have shown how specific parameters related to the polymer of low concern concept can be measured. While this concept has been implemented in different non-EU jurisdictions for many years, or even decades, without indications to disprove its validity, the recommended research work shall serve to eventually extend the criteria, if sufficient experimental justification becomes available. Table Disc-2 demonstrates that the key properties identified by the case studies (e.g. molecular weight and relative content of functional groups) often reflect properties that are also used in the polymers of low concern criteria. All seven case studies, also those that did not consider polymers that typically fulfil the criteria for polymers of low concern, have served to advance the evidence collated in ECETOC TR No. 133-1 and 133-2 that is relevant for the advancement of Recommendation 4. Also, they have served to enhance an understanding on the opportunities to group polymers by common physical, chemical and/or biological properties.

Recommendation 5: *Develop environmentally relevant models, methods and/or criteria to assess (bio)degradation to improve the reliability of exposure and fate assessments important to the risk assessment of polymers*.

The seven case studies have provided further details on the applicability of specific types of models and/or criteria to assess (bio)degradation (up until mineralisation) or other key parameters for polymer risk assessment taking into account the type of (bio)degradation, its duration (i.e. half-lives), and whether it is intended during the given life cycle stage of the polymer, or not. Also, they have highlighted limitations of the currently available exposure models and have confirmed the need to develop models that are applicable to different types of polymers (or to expand existing models to enable such assessments).

In summary, the seven case studies presented in this ECETOC TR No. 133-3 complement the ECETOC TR No. 133-1 presenting the CF4Polymers and the ECETOC TR No. 133-2 reviewing the applicability of tools, test methods and models for polymer risk assessment. Clearly, the seven case studies only cover a small fraction of the seemingly infinite world of polymers. Nonetheless, they cover a broad spectrum of polymer chemistries, including polymers that are considered to have some hazardous properties, and those that do not. In the case studies, publicly available data and unpublished TF company data were collated and assigned to the eight steps of the CF4Polymers presented in ECETOC TR No. 133-1 to evaluate the scientific usefulness and comprehensiveness of the process through use of examples. The case studies were not intended to document a comprehensive risk assessment for any specific polymer, and they also did not describe how any specific legal requirements should be met. Instead, the seven case studies, just as the entire ECETOC TR No. 133 series, have described how the process of polymer hazard and risk assessment can be undertaken, regardless of the underlying motivation and/or legal requirements. Further, the case studies have enhanced the understanding on the applicability and/or technical limitations of the corresponding tools, test methods, and models. Overall,

the case studies have demonstrated that there is no 'one size fits all' polymer hazard and risk assessment process of polymers. In the same way, the case studies have demonstrated that there is no 'one-size-fits-all' approach to determine if any given tool, test method or model is, nor is not, applicable for the assessment of all polymers**.** It is recognised that the state-of-knowledge is continually evolving and that further investigations, building on this trilogy of reports, may be necessary in the future. ECETOC has mandated an *ad-hoc* committee to follow up such new insight and proactively update the TR No. 133 series to keep abreast of the state-of-the-art within this domain.

GLOSSARY

Acceptable daily intake: "*An estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight and applies to chemical substances such as food additives, pesticide residues and veterinary drugs"* (https://www.efsa.europa.eu/en/glossary-taxonomy-terms).

Active materials and articles: "*Materials and articles that are intended to extend the shelf-life or to maintain or improve the condition of packaged food; they are designed to deliberately incorporate components that would release or absorb substances into or from the packaged food or the environment surrounding the food*" (Article 3(a) of European Commission (2009)).

Active substance (for pesticides): "*A substance that acts against harmful organisms, such as pests or diseases, which affect plants*" (https://www.efsa.europa.eu/en/glossary-taxonomy-terms).

Alcohol ethoxylate (AE): A polymer with the basic structure Cx-yAEn. The subscript following the 'C' indicates the range of carbon chain units. AEs with alcohol carbon unit ranges between C8 to C18 are most commonly used in household detergent products. AEs contain an ethylene oxide (E) chain attached to the alcohol. The degree of ethylene oxide polymerisation is indicated by a subscript which indicates the average number of ethylene oxide units. In household products, the average ethylene oxide chain length commonly ranges between 3 and 12 units (adapted from HERA (2009)).

Analogue approach (grouping of substances): "*When the focus of the assessment is on filling data gaps for one specific chemical, empirical data from one or more similar chemical(s) ('the analogue(s)') or 'source' chemical can be used to predict the same endpoint for the 'target' chemical, which is considered to be 'similar'. This analogue approach is useful when the target and source chemicals share a known common mode (and/or mechanism) of action, and the adverse effects resulting from this mode (and/or mechanism) of action is evaluated. The analogue approach could also be used in the absence of effects or when no specific mode (and/or mechanism) of action is expected and toxicokinetic behaviour is not expected to differ significantly. In such case, more evidence, or more lines of evidence, should support the assessment*" (OECD, 2014; ECHA, 2013, 2017c).

Article: "*An object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition"* (EP and Council, 2006; Article 3(3)).

Bioaccumulation: "*A process in which the chemical concentration in an organism achieves a level that exceeds that in the respiratory medium (e.g. water for a fish or air for a mammal), the diet, or both"* (OECD TG 305).

Bioavailability: "*The rate and extent to which an agent can be absorbed by an organism and is available for metabolism or interaction with biologically significant receptors. Bioavailability involves both release from a medium (if present) and absorption by an organism*" (WHO IPCS, 2004).

- **External bioavailability**: The condition that some HMW polymers that are too large to cross biological barriers might nevertheless exert local toxicity in tissues (e.g. skin, eyes, respiratory tract). This toxicity may well be due to LMW components (i.e. small oligomers, IAS and NIAS, including unreacted monomers) that migrate under conditions of contact to the transitional fluid (e.g. sweat, tears, saliva), thereby being available to be absorbed and exert their toxic effect. The specific mechanisms by which such effects can occur remain to be determined (ECETOC Polymers TF working definition).
- **Internal (systemic) bioavailability** means that the polymer product is absorbed into the blood stream by an organism thereby becoming systemically available and potentially causing systemic effects (ECETOC Polymers TF working definition).
- **Physical availability** means that one or more individual components of the polymer product are released from the polymer matrix e.g. by migration or leaching (ECETOC Polymers TF working definition).

Bioconcentration factor (BCF): *"At any time during the uptake phase of this accumulation test* [the BCF] *is the concentration of test substance in/on the fish or specified tissues thereof (Cf as mg/kg) divided by the concentration of the chemical in the surrounding medium (Cw as mg/L). BCF is expressed in L/kg. Corrections for growth and/or a standard lipid content are not accounted for"* (OECD TG 305).

Biodegradability: "*The ability of a material to decompose after interactions with biological elements*" (Goswami and O'Haire, 2016).

Biodegradation: "*The process by which organic substances are decomposed by micro-organisms (mainly aerobic bacteria) into simpler substances such as carbon dioxide, water and ammonia*" (OECD Glossary of Statistical Terms; https://stats.oecd.org/glossary/detail.asp?ID=203).

- **Primary biodegradation**: Biotransformation resulting in the loss of a specific property of the original substance (OECD, 2006).
- **Ultimate biodegradation**: Mineralisation by microorganisms to CO_2, water, new microbial cellular constituents (biomass), and other inorganic substances (e.g. NH_3) (OECD, 2006).

Bisphenol-A diglycidylether (BADGE) polymers (BADGE epoxy resins): Epoxy resins in their most simple form are built by mixing the starting components epoxy resin and hardener in a specific mixing (stoichiometric) ratio to produce a thermoset polymer. The most widely commercialised resin of its kind is created by reacting bisphenol A and epichlorohydrin in a 2-step process, which results in its pure form as the basic monomer unit of the epoxy resin BADGE (adapted from https://epoxy-europe.eu/badge-dgeba/).

Bracket testing: During (polymer) grouping, bracket testing can be applied when additional endpoint data are required to characterise hazards and fate of a group of polymeric (or non-polymeric) substances. When bracket testing is applied, few different test materials out of the group are selected for testing and subsequent read-across of the properties across the group members. Therefore, those test materials need to be selected which are at the boundaries and in the middle of the group in terms of chemicals and physico-chemical properties, so that the read-across ideally uses interpolation within known ranges rather than extrapolation of properties (ECETOC Polymers TF working definition).

Category approach (grouping; see also definition for analogue approach): "*Chemicals whose physical-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of chemicals… Within a chemical category, the members are often related by a trend in an effect for a given endpoint, and a trend analysis can be carried out through deriving a model based on the data for the members of the category. The rationale underpinning the analogue and the category approach may be based on the following:*

- *Common functional group(s) (e.g., aldehyde, epoxide, ester, specific metal ion);*
- *A common mode or mechanism of action or adverse outcome pathway;*
- *Common constituents or chemical classes, similar carbon range numbers. This is frequently the case with complex substances often known as… UVCB substances…;*
- *The likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals (e.g., the "metabolic pathway approach" of examining related chemicals such as acid/ester/salt); or*
- *An incremental and constant change across the category (e.g., a chain-length category), often observed in physical chemical properties, e.g., boiling point range*" (OECD, 2014; ECHA, 2013, 2017c).

Cationic polymer: A polymer that has "*one or more monomer units that are covalently bound and bear a net positive charge*" (Government of Canada, 2005).

Common key constituents: Common constituents that are key to the hazard and risk assessment of the member of the type / family of polymers based upon a common hypothesised mode-of-action for the endpoint under consideration.

Common key feature: Common features that are key to the hazard and risk assessment of the member of the group of polymers. These can be structural elements of the polymer (building blocks), substances or structural/physico-chemical elements like shape and size. The common key features are identified based upon common hypothesised related hazard properties or even a mode-of-action for the endpoint under consideration. The definition of common key *constituent* is a specific case and subsumed under the definition of the common key feature.

- Note 1: Key features can also be a fraction of e.g. a UVCB.
- Note 2: Different common key features may be determinants for different endpoints (human health vs environmental, or for different human health endpoints, e.g. local versus systemic, inhalation versus oral, etc.).
- Note 3: The hypothesised mode-of-action may also indicate absence of human health / environmental hazard potential, i.e. if no effects are to be expected for the particular type / family of polymers, the hypothesis assumes 'no mode-of-action' for the endpoint under consideration.
- Note 4: In the context of read-across and fulfilling data requirements for hazard and risk assessment purposes, the frameworks of the OECD (2014) Guidance Document on the Grouping of Chemicals and the ECHA (2017c)

RAAF would define the data rich members of the group as the 'source substance' and the members of the group of polymers for which the data is being used as the 'target substance'.

Component: "*Substance intentionally added to form a mixture*" (ECHA, 2017a).

Constituent: "*Any single species present in a substance that can be characterised by its unique chemical identity*" (ECHA, 2017a).

Copolymer: A polymer composed of at least two repetition units.

Critical micelle concentration (CMC): "*The CMC of a surfactant is the value at which the solution property of the molecule shows an abrupt change. At this concentration, surface active ions or molecules in solution associate to form larger units. These associated units are called micelles (self-assembled structures), and the first formed aggregates are generally approximately spherical in shape. Each surfactant molecule has a characteristic CMC value at a given temperature and electrolyte concentration*" (Tadros, 2013).

Curing: The chemical process of converting a prepolymer or a polymer into a polymer of higher molar mass and then into a network. It is achieved by the induction of chemical reactions which might or might not require mixing with a chemical curing agent (IUPAC, 1997).

Degradation, decomposition, or depolymerisation: *"A type of chemical change in which a polymeric substance breaks down into simpler, smaller weight substances as the result of (for example) oxidation, hydrolysis, heat, sunlight, attack by solvents or microbial action"* (US EPA, 1997).

- **Physical degradation,** induced by e.g. heat, irradiation
- **Chemical degradation**, induced by e.g. the presence of specific acids, bases, or oxidative agents, as applicable
- **Biological degradation** (biodegradation), induced by specific microorganisms (adapted from Doyle et al., 1982).

Environmental fate: The destiny of a substance after release into the environment (adapted from https://www.informea.org/en/terms/environmental-fate).

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"* (WHO IPCS, 2004).

Exposure scenario: "*The set of conditions, including operational conditions and risk management measures, that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. These exposure scenarios may cover one specific process or use or several processes or uses as appropriate*" (EP and Council, 2006).

Extractable: A compound that migrates from the contact surface under more aggressive conditions such as elevated temperature, extended contact time, or aggressive solvent system (https://toxikon.com/testing-service/extractables-leachables-testing/).

Extrapolation: The estimation of a value for a member that is near or at the category boundary using measured values from internal category members (ECHA 2008; OECD 2014).

Functional group equivalent weight (FGEW): The FGEW of resident cationic or reactive functional groups is the weight of the polymer that contains one equivalent weight (one mole) of a particular functional group (Canada, 2005).

Grouping (of chemicals): The general approach for considering more than one chemical at the same time. It can include formation of a chemical category or identification of chemical analogue(s) with the aim of filling data gaps as appropriate (OECD, 2014).

Hazard: "*Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent*" (WHO IPCS, 2004). (Hence, the term hazard is used in its general meaning that is not specific to polymers.)

Hazard characterisation (dose-response assessment): *"The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment"* (WHO IPCS, 2004).

Hazard data matrix (as a part of polymer grouping approach): Technical visualisation (e.g., using a spreadsheet, or graph) of relevant hazard properties and/or relevant physico-chemical parameter(s) of group members along one (or more) dimension(s) (ECETOC Polymers TF working definition).

Hazard identification: *"The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment"* (WHO IPCS, 2004).

Hazard similarity: Basic principle for polymer grouping to describe common groups based on common key feature and relevant hazard properties. The effect level of relevant hazards properties from one end of the group do not necessarily have to be the same to the other. However, the relevant hazard properties need to be the same for the entire group (e.g. acute oral toxicity) and there is a continuum of the effect level for the relevant hazard property within the group. A continuum and predictivity of the relevant hazard property should be present (ECETOC Polymers TF working definition).

Homologue: A compound belonging to a series of compounds differing from each other by a repeating unit, such as methylene group, peptide residue, etc. (adapted from: https://www.chemicool.com/definition/homologue.html).

Homopolymer: A polymer composed of one single type of repetition unit.

Indirect food additives: As per US FDA: "*Food additives that come into contact with food as part of packaging, holding, or processing, but are not intended to be added directly to, become a component, or have a technical effect in or on the food*" (https://www.fda.gov/food/food-ingredients-packaging/food-ingredient-packaging-terms).

Inherent biodegradability tests: "*Aerobic tests that possess a high capacity for degradation to take place, and in which biodegradation rate or extent is measured. The test procedures allow prolonged exposure of the test substance to microorganisms and a low ratio of test substance to biomass, which offers a better chance to obtain a positive result compared to tests for ready biodegradability"* (OECD, 2006).

Intentionally added substance (IAS): A "*substance which is intentionally added to plastics to achieve a physical or chemical effect during processing of the plastic or in the final material or article; it is intended to be present in the final material or article"* (definition for 'additive' in European Commission (2011)).

Interpolation: The estimation of a value for a category member using measured values from other members on both sides of that member within the defined category spectrum (ECHA 2008; OECD 2014).

iTAP: Improved Aquatic Toxicity and Assessment of Polymers (Cefic LRI project).

Leachable (synonym: leachate): A compound that migrates from the contact surface of a medical device under normal or mimicked conditions of exposure (https://toxikon.com/testing-service/extractables-leachables-testing/); synonymous to migrant, the default term used in this report.

Life cycle (of a product): The entire lifespan of a product, i.e. all stages from raw material extraction through materials processing, manufacturing, distribution, use, repair and maintenance, and eventual disposal or recycling (adapted from ICCA (2021)).

(Linear) low-density polyethylene ((L)LD-PE): See definition for polyethylene.

Low molecular weight (LMW) compound: Small oligomers, IAS, and NIAS, including unreacted monomers.

Macromolecule: "*A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetitions of units derived, actually or conceptually, from molecules of low relative molecular mass.*" (IUPAC, 1997)

Margin of exposure: *"A tool used in risk assessment to explore safety concerns arising from the presence of a potentially toxic substance in food or animal feed"* (https://www.efsa.europa.eu/en/glossary-taxonomy-terms).

Medical device: Any apparatus, appliance, software, material, or other article with intended use to support human health and welfare with no or subordinate pharmaceutical function (e.g. diagnosis, prevention, monitoring of diseases) (ISO 10993-1).

Microencapsulation: "*a process in which tiny particles or droplets are surrounded by a coating or embedded in a homogeneous or heterogeneous matrix, to give small capsules with many useful properties. Microencapsulation can provide a physical barrier between the core compound and the other components of the product. It is a technique by which liquid droplets, solid particles or gas compounds are entrapped into thin films of a food grade microencapsulating agent" (Poshadri and Kuna, 2010).*

Migrant: Synonymous to 'leachable' (see definition). Migrant is the default term used in this report.

Mixture: "*A mix or solution of two or more substances. Under the EU chemicals legislation, mixtures are not considered substances*" (https://echa.europa.eu/support/substance-identification/what-is-not-a-substance).

Monomer:

OECD: *"A molecule which is capable of forming covalent bonds with two or more like or unlike molecules under the conditions of the relevant polymer-forming reaction used for the particular process"* (http://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm).

REACH (Article 3(6)): "*A substance which is capable of forming covalent bonds with a sequence of additional like or unlike molecules under the conditions of the relevant polymer-forming reaction used for the particular process*" (EP and Council, 2006).

Monomer, unreacted: Depending on the manufacturing process and intended use of the polymer product, unreacted monomers can either be intentionally added substances or non-intentionally added substances.

No longer polymers (NLPs; often used as synonymous to oligomeric substances): Before the 7th amendment of Directive 67/548/EEC (Council, 1967) was adopted in 1992 (Council, 1992), the EU definition for polymers differed from the OECD definition. Upon implementation of the 7th amendment (Council, 1992), a number of substances which had been considered to be polymers under the European Inventory of Existing Commercial Chemical Substances (EINECS) were no longer considered as such. These substances were called no-longer polymers and mainly included alkoxylated substances; oligomeric reaction products; oligomers from one monomer only; dimers and trimers; polymer-like substances containing ≥ 50 weight% of species with the same molecular weight (ECB, 2007). When the REACH Regulation entered into force, the no-longer polymers had to be registered as phase-in substances in accordance with Article 12 of the REACH Regulation (EP and Council, 2006) (description of NLP adapted from ECETOC (2019)).

Non-intentionally added substance (NIAS): *"An impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product"* (European Commission, 2011).

Non-listed substance (NLS): An IAS which is exempted from the authorisation process, i.e. which is exempted from a positive listing in Annex I to the Plastics Regulation (European Commission, 2011). Solvents are examples for exempted substances (adapted from FCA-Cefic, 2020).

Number average molecular weight (M_n): The arithmetic average (mean) of the molecular weights of all molecules in a polymer: $M_n = \frac{\sum_{i=1}^{n} H_i}{\sum_{i=1}^{n} \frac{H_i}{M_i}}$ (US EPA, 1997).

Oligomer: *"A compound of relatively low molecular weight containing up to five monomer units."* (https://www.collinsdictionary.com/dictionary/english/oligomer); oligomers can be part of the polymeric substance (at the low end of its molecular weight range); in some contexts, they are also referred to as non-intentionally added substances.

Plastic: *"A synthetic material made from a wide range of organic polymers such as polyethylene, polyvinyl chloride, nylon, etc., that can be moulded into shape while soft, and then set into a rigid or slightly elastic form"* (https://en.oxforddictionaries.com/definition/plastic).

Polyacrylate: Linear (or crosslinked) polymer resulting from the polymerisation of acrylate monomers, i.e. esters of acrylic acid. Similar to polycarboxylates, polyacrylates include a carbon-carbon backbone, but they include –COOR ester groups, where R corresponds to the alkyl/aryl/alkylaryl chain of the monomers.

Polycarboxylate: Anionic, linear polymer with a carbon-carbon backbone and multiple carboxylate functional groups (COOH). An example for a polycarboxylate is the poly(acrylic/maleic acid) copolymer (P-AA/MA) as well as the poly(acrylic acid) homopolymer (P-AA).

Polyetherol (PEOL): Polymers which are based on initiator molecules (core molecules, starter molecules) containing multiple hydroxyl or amino functional groups or a combination of the two. During the production of PEOLs, the functional groups of the initiator molecules are alkoxylated with propylene oxide (PO) and/or ethylene oxide (EO).

Polyethylene: Stable polymer produced of ethylene monomers. Polyethylene has the molecular formula $(C_2H_4)_n$ (https://www.plasticseurope.org/en/about-plastics/what-are-plastics/large-family/polyolefins).

- **Low-density polyethylene (LD-PE)**: Highly branched polyethylene with low crystallinity and melting point, and a density of 0.91 to 0.94, prepared at very high pressures (https://www.dictionary.com/browse/low-density-polyethylene).
- **Linear low-density polyethylene (LLD-PE)**: Substantially linear polyethylene, with significant numbers of short branches, commonly made by copolymerisation of ethylene with longer-chain olefins.

- **High-density polyethylene (HD-PE)**: Polyethylene consisting mainly of linear, or unbranched, chains with high crystallinity and melting point, and density of 0.96 or more, produced at low pressure (https://www.dictionary.com/browse/high-density-polyethylene?s=t). Although the density of HD-PE is only marginally higher than that of low-density polyethylene, HD-PE has little branching, giving it stronger intermolecular forces and tensile strength than LD-PE.

Polymer:

IUPAC: "*Substances composed of macromolecules, very large molecules with molecular weights ranging from a few thousand to as high as millions of grams/mole"* (https://iupac.org/polymer-edu/what-are-polymers).

OECD: "*A polymer means a substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or other reactant and consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition a 'monomer unit' means the reacted form of a monomer in a polymer*" (http://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm).

REACH (Article 3(5)): *"A substance consisting of molecules characterised by the sequence of one or more types of monomer units. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. A polymer comprises the following:*

a) a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or another reactant;
b) less than a simple weight majority of molecules of the same molecular weight.

In the context of this definition a 'monomer unit' means the reacted form of a monomer substance in a polymer" (EP and Council, 2006).

Polymer grouping approach: Three-Criteria grouping approach to cover the similarity of polymers considering their chemical/structural properties (Criterion 1), physico-chemical properties (Criterion 2), and hazard properties (Criterion 3) in a balanced way. Nonetheless, all three Criteria are indispensable to describe the hazard similarity of the group. Hazard similarity is taken as the central element and the ultimate goal when defining and justifying the polymer group. The approach focuses on the relevant properties of the three Criteria to describe the members and clearly define borders of the group. Importantly, the approach remains flexible in terms of the relevant parameters as the complexity and versatility of polymer chemistry demands. At the same time, it requests for precision on the definition of the borders. The members of a polymer (sub-)group need to fulfil the respective border specifications and show predictable trends on the relevant properties within their group to demonstrate similarity. Thus, the polymer grouping approach is compliant with the category approach (OECD, 2014; ECHA, 2013, 2017c; see definition) while expanding the focus beyond structural similarity to a broader three-Criteria assessment to allow for the versatility and complexity of polymers (ECETOC Polymers TF working definition).

Polymer matrix: The continuous phase in multi-constituent or multi-phase (composite) systems (adapted from Wang et al., 2011).

Polymer of low concern: Polymers that are "*deemed to have insignificant environmental and human health impacts. Therefore, these polymers should have reduced regulatory requirements*" (OECD, 2009).

Polymer product: A chemical product with a polymeric substance as main component, and NIAS and sometimes IAS as other components. (ECETOC Polymers TF working definition) Polymer products are only in some cases finished articles.

Polymeric substance (polymeric macromolecules): The chemical (co)polymer and possibly present oligomers (both are composed of the same monomeric units) (ECETOC Polymers TF working definition).

Poly(methyl methacrylate) (PMMA): Linear homopolymer resulting from the polymerisation of methacrylate monomers, i.e. esters of methacrylic acid. PMMAs include a carbon-carbon backbone and –COOC functional groups.

Polyol: An organic compound containing multiple hydroxyl groups.

Polyolefins: A family of polyethylene (PE) and polypropylene thermoplastics that are produced mainly from oil and natural gas by a process of polymerisation of ethylene and propylene respectively (https://www.plasticseurope.org/en/about-plastics/what-are-plastics/large-family/polyolefins).

Polypropylene: Thermoplastic polymer produced of propylene monomers.

Polyquaternium: International Nomenclature of Cosmetic Ingredients (INCI) name for polycationic polymers used in the personal care industry that all share the presence of quaternary ammonium functional groups (Cumming, 2008).

Polyquaternium-6: 2-Propen-1-aminium, N,N-dimethyl-N-2-propen-1-yl-, chloride (1:1), homopolymer.

Polyquaternium-10: Cellulose, 2-hydroxyethyl 2-[2-hydroxy-3-(trimethylammonio)propoxy]ethyl 2-hydroxy-3-(trimethylammonio)propyl ether, chloride.

Polyurea: A polymer that is produced by reaction between polyisocyanates and polyamine.

Polyurethane (PU): A polymer that is produced by reaction between polyisocyanates and polyol (i.e. an organic compound containing multiple hydroxyl groups).

Prepolymer: "*A stable usually partially polymerized chemical intermediate that can be fully polymerized at a later time*" (https://www.merriam-webster.com/dictionary/prepolymer).

Reactive functional group: *"An atom or associated group of atoms in a chemical substance that is intended or can be reasonably anticipated to undergo facile chemical reaction"* (US EPA, 1997).

Read-across: A technique for predicting endpoint information for the target substance by using available data from the same endpoint from the source substance(s). The read-across approach encompasses (i) elements addressing the structural similarity; (ii) a read-across hypothesis; (iii) a read-across justification; and (iv) the prediction of the property (properties) of the target substance(s) (ECHA, 2017c).

Ready biodegradability tests: "*Stringent screening tests, conducted under aerobic conditions, in which a high concentration of the test substance (in the range of 2 to 100 mg/L) is used and biodegradation is measured by non-specific parameters like Dissolved Organic Carbon (DOC), Biochemical Oxygen Demand and CO_2 production*" (OECD, 2006).

Relevant hazard property: A property that is key to describe the hazard(s) to the type/family of the polymers. Any given type of polymers may have several relevant hazard properties. The relevant hazard property is identified by consideration of the overall set of hazard properties and endpoints (ECETOC Polymers TF working definition).

Risk assessment: *"A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system"* (WHO IPCS, 2004). The risk assessment process includes the four steps, i.e. (1) hazard identification) and (2) hazard characterisation (together: hazard assessment); (3) exposure assessment; (4) risk characterisation (adapted from WHO IPCS (2004)).

Risk characterisation: *"The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions"* (WHO IPCS, 2004).

Similarity: "*…may be based on the following:*

1. *A common functional group (e.g. aldehyde, epoxide, ester, specific metal ion)*
2. *Common constituents or chemical classes, similar carbon range numbers*
3. *An incremental and constant change across the category (e.g. a chain-length category)*
4. *The likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g. the metabolic pathway approach of examining related chemicals such as acid/ester/salt)"*

   (adapted from ECHA (2008; 2013, 2017c); OECD (2014); see also definition for category approach).

Specific migration limit (SML): "*the maximum permitted amount of a given substance released from a material or article into food or food simulants*" (Article 3(13) of European Commission, 2011).

Source substance (source chemical): Substances for which data on the endpoint in question are available and that belong to the same group (category) as the target substance (see definition) so that the target substances can be compared to these substances (adapted from OECD, 2014).

Surface tension: "*The free surface enthalpy per unit of surface area*" (Council, 2008).

Target substance (target chemical): A substance "*with data gap(s), for which a property or hazard is being estimated from the source chemical(s)"* (OECD, 2014).

Tolerable daily intake: "*A tolerable daily intake is an estimate of the amount of a substance in air, food or drinking water that can be taken in daily over a lifetime without appreciable health risk. Tolerable daily intakes are calculated on the basis of laboratory toxicity data to which uncertainty factors are applied. Tolerable daily intakes are used for substances that do not have a reason to be found in food (as opposed to substances that do, such as additives, pesticide residues or veterinary drugs in foods…)*" (https://ec.europa.eu/health/scientific_committees/opinions_layman/en/phthalates-school-supplies/glossary/tuv/tdi-tolerable-daily-intake.htm).

UVCB (substances of unknown or variable composition, complex reaction products or biological materials): "*A substance that cannot be sufficiently identified by its chemical composition, because (1) the number of constituents is relatively large and/or (2) the composition is, to a significant part, unknown and/or (3) the variability of composition is relatively large or poorly predictable"* (ECHA, 2012b).

Weight-average molecular weight (M_w): $M_w = \frac{\sum_{i=1}^{n} H_i \times M_i}{\sum_{i=1}^{n} M_i}$ where H_i is the level of the detector signal from the baseline for the retention volume V_i, M_i is the molecular weight of the polymer fraction at the retention volume V_i, and n is the number of data points. The breadth of the molecular weight distribution, which is a measure of the dispersity of the system, is given by the ratio M_w /M_n (see definition for number-average molecular weight (M_n)) (OECD TG 118).

ABBREVIATIONS

% surf.: Peak surface percent (chromatography; Tables CS4.1 and CS4.4)

%A-N: Percent amine nitrogen

%TKN: Total Kjeldahl Nitrogen

ADME: Adsorption, distribution, metabolism, elimination

AE: Alcohol ethoxylate

AISE: International Association for Soaps, Detergents and Maintenance Products

ANSI: American National Standards Institute

ASTM: American Society for Testing and Materials

AVA process: Advancement process (polymerisation of BADGE polymers)

BADGE: Bisphenol-A diglycidylether

BCF: Bioconcentration factor

bw: Body weight

CAS: Chemical Abstract Service

Cefic: European Chemical Industry Council

CEN: European Committee for Standardisation (*Comité Européen de Normalisation*)

CEPE: European Council of the Paint, Printing Ink and Artists' Colours Industry

CESIO: European Committee of Organic Surfactants and Their Organic Intermediates (*Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques*)

CF4Polymers: Conceptual Framework for Polymer Risk Assessment

CFR: Code of Federal Regulations (USA)

CHO: Chinese Hamster Ovary (cells)

C_{inf}: Influent concentration (mg/L) (Table CS 1.2 only)

CIR: Cosmetic Ingredients Review

CLP: Classification, labelling and packaging of substances and mixtures

CMC: Critical micelle concentration

Da: Dalton (g/mol)

DADMAC: Diallyl dimethyl-ammonium chloride

DOC: Dissolved organic carbon

DNEL: Derived no effect concentration

DPRA: Direct peptide reactivity assay

EC3: Estimated concentration needed to elicit 3-fold increase in lymph node cell proliferative activity (Table CS4.5)

EC_x: Effective concentration (e.g. EC_{50}: Concentration required to achieve 50% effect change from the control)

ECB: European Chemicals Bureau

ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals

ECHA: European Chemicals Agency

ECPA: European Crop Protection Association

EC_x: Effective concentration (e.g. EC_{50}: Concentration required to achieve 50% effect change from the control)

E-FAST: US EPA Exposure and Fate Assessment Screening Tool

EFSA: European Food Safety Authority

EINECS: European Inventory of Existing Commercial Chemical Substances

EMA: European Medicines Agency

EO: Ethylene oxide

EOSCA: European Oilfield Speciality Chemicals Association

EP: European Parliament

EPA: Environmental Protection Agency

EPPAA: Ethoxylated and propoxylated pentaerythritol and acrylic acid copolymer

Eq.: Equivalent

ERASM: Environment and Health – Risk Assessment and Management (joint research platform of the European detergents and surfactants industries)

ERC: Environmental Release Category (ECHA, 2015)

ErC_{50}: Effective concentration inducing 50% reduction in growth rate (algae) as compared to controls

EU: European Union

EUSES: European Union System for the Evaluation of Substances

f: Female (acronym used in different in tables)

FA: Fatty alcohol (Figure CS6.1)

FACET: Flavours, Additives and food Contact material Exposure Task (EU project)

FCA-Cefic: Food Contact Additives Industry Association organised under the umbrella of Cefic

FCM: Food contact material

FDA: Food and Drugs Administration (USA)

FGEW: Functional group equivalent weight

GHS: Globally harmonised system for classification and labelling of substances

GLP: Good laboratory practice

GPC: Gel permeation chromatography

h: Hour(s) (acronym used in different in tables)

HD-PE: High-density polyethylene

HERA: Human and Environmental Risk Assessment (project; AISE and Cefic)

HH: Human health hazard, exposure and risk assessment (in Table Intro-1 only)

HMW: High molecular weight

HPLC: High performance liquid chromatography

HRIPT: Human repeated insult patch test

IAS: Intentionally added substances

INCI: International Nomenclature of Cosmetic Ingredients

ISO: International Standardisation Organisation

iSTREEM: In-stream exposure model

iTAP: Improved Aquatic Toxicity and Assessment of Polymers (Cefic LRI project)

IUPAC: International Union of Pure and Applied Chemistry

K_a: Acid dissociation constant

K_d: Adsorption/desorption distribution coefficient

kgdw: Kilogram dry weight (sediment and terrestrial toxicity)

kgwwt: Kilogram wet weight

K_{oc}: Organic carbon/water partition coefficient

K_{ow}: n-Octanol/water partition coefficient

LC_{50}: Concentration required to achieve 50% change in lethality from the control

LCD: Liquid-crystal displays

LD_{50}: Dose required to achieve 50% change in lethality from the control

LD-PE: Low-density polyethylene

LLD-PE: Linear low-density polyethylene

LLNA: Local lymph node assay

LMW: Low molecular weight

LO(A)EL / LO(A)EC: Lowest observed (adverse) effect level / concentration

LRI: Long-Range Research Initiative (Cefic)

LT_{50}: Time point at which there is 50% lethality as compared to control

m: Male (acronym used in different tables)

MDI: Methylene diphenyl diisocyanate

MEK: Methyl ethyl ketone (Table CS4.5)

M_n: Number average molecular weight (for which acronym 'NAMW' was used in ECETOC TR. No. 133-1)

MonoID: Unique Monograph Identification Number (INCI)

mPa*s: Millipascal seconds

MTT: A tetrazolium bromide

M_w: Weight average molecular weight (by contrast, acronym 'Mw' used for 'molecular weight' in ECETOC TR. No. 133-1)

n: Number of repeat units (in some tables: number of animals / subjects per test group)

NIAS: Non-intentionally added substances

NLP: No longer polymer

NLS: Non-listed substance

NO(A)EL / NOA(E)C: No observed (adverse) effect level / concentration

NR-LETH: Time interval between initial exposure to the dose and death

NSF: National Sanitation Foundation

OCSPP: Office for Chemical Safety and Pollution Prevention

OECD: Organisation for Economic Co-operation and Development

P-AA: Poly(acrylic acid) homopolymer

P-AA/MA: Poly(acrylic/maleic acid) copolymer

PE: Polyethylene

PEC Predicted environmental concentration

PEOL: Polyetherol

pK_a: Negative base-10 logarithm of the acid dissociation constant K_a

PMMA: Poly(methyl methacrylate)

PNEC: Predicted no effect concentration

PO: Propylene oxide

PQ: Polyquaternium

PROC: Process Category (ECHA, 2015)

PU: Polyurethane

PUR: Polyurea

QSAR: Quantitative structure-activity relationship

RAAF: Read-across Assessment Framework

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

SCAS: Semi-continuous activated sludge (Table CS1.2)

SCCP: Scientific Committee on Consumer Products

SD: Standard deviation (in tables)

SI: Stimulation index (Table CS4.5)

SML: Specific migration limit

SpERC: Specific environmental release category (e.g. AISE, ECPA)

TC: Technical Committee

TDI: Toluene diisocyanate

TEGEWA: Association of Manufacturers of Process and Performance Chemicals (Germany)

TF: Task Force

TG: Test guideline

TGD: Technical Guidance Document

TR: Technical Report

US: United States (of America)

USAPHC: US Army Public Health Command

UV: Ultraviolet

UVCB: Substance of unknown or variable composition, complex reaction products and biological materials

VCRP: Voluntary Cosmetic Reporting Program (US FDA)

WHO IPCS: World Health Organisation - International Programme for Chemical Safety

WWTP: Wastewater treatment plant

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Note: All websites were accessed in September 2021.

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APPENDIX 1: THE EIGHT STEPS OF THE CF4POLYMERS (AS PER ECETOC (2019) TR NO. 133-1)

CF4Polymers (Step 1) Problem formulation

The Step 1 problem formulation includes risk assessment scope definition and protection goal definition.

Identify:

- The life cycle stage(s) and intended uses of the polymer product that shall be covered (e.g. industrial, professional, consumer uses)
- Define the protection goal, i.e. the type of risk assessed and the acceptable level of risk for the environment and/or human health; define target population (e.g. individual, population, subpopulation)
- Determine if only intrinsic or also physical hazards are within scope of the risk assessment
- Parts of the risk assessment that can be set aside because out of scope

CF4Polymers (Step 2) Polymer identification

To ensure a fit-for-purpose identification of the polymer, use expert knowledge to select those key parameters from the list below that are relevant for the polymer at the given life cycle stage(s) (Step 1)

Step 2.1: Identification of the polymeric substance

Standard chemical descriptors

- CAS name and number and/or other relevant names and numbers (e.g. EC number, INCI name)
- Chemical name (and synonyms); monomer units and other reactants (qualitative and quantitative (e.g. monomer ratios))

Commercial identifiers

Trade names, descriptors for market types (e.g. extrusion polymers, casting polymers, sheet polymers)

Structural and morphological descriptors and/or physical, and chemical properties

Depending on the type of polymer under investigation, relevant key parameters may be structural and/or morphological descriptors as well as physico-chemical and screening-level fate properties (no order of properties is inferred):

- Structural descriptors include e.g. chemical formula, degree of substitution, tacticity, molecular weight, molecular weight distribution (polydispersity), M_n, and reactive functional group(s) (see Section 4.3 in ECETOC TR No. 133-1 for further details on reactive functional groups)
- Morphological descriptors include e.g. physical state at ambient temperature and pressure (solid, liquid), shape (e.g. spherical, fibre, tubular), physical form (e.g. amorphous, crystalline)
- Physico-chemical properties include e.g. water solubility, n-octanol/water partition coefficient (log K_{ow}), acid dissociation constant (pK_a), net charge (under conditions that are relevant for ecological and human health hazard assessment), vapour pressure, viscosity / melt-flow index / glass transition temperature, density, degradability

Step 2.2: Identification of additives, if relevant

- CAS name and number
- Relative concentration

Step 2.3: Identification of NIAS, if relevant

- Substance identification, relative concentration, molecular weight

CF4Polymers (Step 3) Polymer component strategy

Based on decisions taken in Step 1 on the risk assessment scope and protection goal, and information acquired in Step 2 on the identity of relevant components, Step 3 serves to decide on those components of the polymer product that shall be addressed in the further steps of the CF4Polymers, i.e.

- the polymer product as such, i.e. including its LMW components (i.e. small oligomers, IAS, and NIAS)
- the polymeric substance
- specific IAS and/or NIAS, separately
- or some or all of the LMW components together (i.e. small oligomers, IAS, and NIAS)

CF4Polymers (Step 4) Grouping approach evaluation

The grouping approach evaluation aims at identifying read-across sources and serves to avoid unnecessary resource allocation to hazard characterisation, especially with regard to animal testing. Step 4 can be skipped if sufficient hazard information is readily available to assess the uses and components in scope for the whole polymer product.

Step 4.1: Use expert judgement to identify key parameters

Collect information on structural and morphological descriptors, physico-chemical properties and screening-level fate data of the polymer product under investigation and of other polymer products with similar structure and/or composition; and/or of the IAS / NIAS and similar substances, if applicable (Step 3 – polymer component strategy).

Depending on the type of polymer that is being evaluated (and of its form in the given life cycle stage), different combinations of the parameters listed in Step 4.2 (and possibly further parameters) might be key in driving hazard potential (see also Steps 2 and 7) and therefore relevant for grouping. Similarly, the set of key parameters may depend upon the (eco)toxicological endpoint(s) for which read-across shall be applied (Steps 4.3 and 4.4).

Step 4.2: Use expert judgement to determine polymer similarity (i.e. potential for grouping)

- Same (or similar) monomer units? Homopolymer or copolymer? Same or similar polymer backbone? Is there cross-linking, and what is the degree of substitution?
- Same form of polymer (e.g. crystalline, amorphous, blended, sheet, pellet)? Same morphology?
- Same chemical elements? Are heavy metals present?
- Same molecular weight range, i.e. < 1,000 Da; 1,000-10,000 Da; > 10,000 Da?
- Similar partitioning in water / solvents? Which environmental compartment is relevant? Which partitioning behaviour is relevant?
- Same or similar composition and proportion of LMW components (< 500 and < 1,000 Da)?
- Same reactive functional groups? Similar charge density, i.e. FGEW above or below 1,000 Da or 5,000 Da, respectively?
- Similar cationic density, i.e. FGEW above or below 5,000 Da?
- Similar water solubility / water insolubility?
- Similar surface tension?
- For insoluble polymers: Same or similar particle shape and size, density, agglomeration, zeta-potential?
- Same or similar screening-level fate properties? Same or similar breakdown products?
- If IAS / NIAS are focus of risk assessment: Identify substances with structural and/or biological similarities.

Step 4.3: Define hypothesis for grouping and read-across and determine relevant approach

- For example, the polymer of interest has the same type of physico-chemical interaction with target structures, adverse effect(s), or the same molecular initiating event / mode-of-action relevant for a given (eco)toxicological endpoint, as structurally similar polymer(s).

- Determine if the analogue or category approach shall be applied for grouping (Glossary).

Step 4.4: Identify available ecotoxicity, fate and toxicity data

- For the (eco)toxicological endpoint(s) that is/are relevant for the hypothesis for grouping: Identify bioavailability and available ecotoxicity, fate and toxicity data for the polymer of interest and the structurally similar polymer(s) (and/or of the IAS / NIAS and similar substances, if applicable, depending on the polymer component strategy), and evaluate relevance and quality of the available data for source polymer.

- Identify data gaps.

Step 4.5: Use expert judgement to justify grouping and to fill data gaps by read-across

For each hypothesised mode-of-action (Step 4.3):

- Refer to the physico-chemical and fate key parameters selected in Step 4.1 to describe the similarities and dissimilarities of the polymers included in the grouping approach evaluation.

- Describe how differences in these key parameters contribute to constant patterns in the changing of the (ecotoxicological and/or toxicological) properties across the group.

- Use this information to justify opportunities to fill data gaps by read-across.

CF4Polymers (Step 5) Determination of exposure scenarios

Step 5 takes into account the life cycle stage(s) of the polymer product identified in Step 1. The results of Step 5 determine which exposures and hazards should be characterised in Steps 6 and 7 to meet the given risk assessment scope defined in Step 1 (problem formulation).

The substances to be addressed in Steps 5.1 and 5.2 will depend on the decisions made in Step 3 (polymer component strategy).

Step 5.1: Ecological exposure scenarios

- Describe form of the polymer product in the relevant life cycle stage(s) (e.g. solid, dissolved, aerosolised).

- Consider structural and/or morphological descriptors as well as physico-chemical and screening-level fate properties relevant to polymer product (e.g. molecular weight, partitioning coefficients, solubility, compound diffusivity) supporting the identification of ecological receptors (e.g. aquatic or sediment organisms).

- Identify source of exposure and ecological receptor(s).

- Describe relevant environmental compartments.

- Identify duration / time frame of exposure.

- Are aggregate exposures relevant?

Step 5.2: Human exposure scenarios

- Describe form of the polymer product in the relevant life cycle stages (e.g. solid, dissolved, aerosolised).

- Consider structural and/or morphological descriptors as well as physico-chemical properties relevant to polymer product supporting the identification of relevant human populations.

- Identify relevant human populations (e.g. workers in production sites, professionals using finished products, consumers), specific population groups (e.g. infants, adults, aged persons) further considering specific preconditions for exposure, if relevant (e.g. pregnancy, life-style habits).

- Relevant routes of exposure include oral, dermal, and/or inhalation routes (see Note 1 below).

- Identify duration / time frame of exposure.

- Are aggregate exposures relevant?

Note 1: The CF4Polymers was not developed with medicinal applications in mind (e.g. intravenous, subcutaneous routes of application, implantation of medical devices). Therefore, it might be applicable for some cases of medicinal applications, whereas it might not be applicable for others.

CF4Polymers (Step 6) Exposure characterisation

Step 6 is performed for the polymer product as such or for those components of the polymer product identified as in scope during Step 1 (problem formulation) and Step 3 (polymer component strategy).

Step 6 may also consider breakdown products of the polymer, if relevant.

It can be necessary to refine Step 6 after an initial passage of Step 7 (hazard assessment).

Based upon the exposure scenarios determined in Step 5:

- Estimate release / emission (via modelling and/or testing, as applicable) to determine physical availability. For LMW components, this includes addressing the potential to migrate from the polymer matrix.

- Assess fate (via modelling and/or testing, as applicable) and exposure pathways.

- Define exposure metrics for environmental, occupational, and consumer exposure, respectively (e.g. daily or lifetime exposure, duration of employment).

- Estimate exposure levels (via modelling and/or testing, as applicable): Establish quantity released into the environment corresponding to relevant life cycle stage taking into account ERCs or SpERCs; or use default value related to process.

- Conclude on exposure assessment (i.e. determination of exposure scenarios and exposure characterisation) and identify prevailing data gaps.

CF4Polymers (Step 7) Hazard assessment

Step 7 is performed for the given life cycle stage of the polymer (Step 1), simulating the relevant ecological receptor(s) and exposed human population (Step 5).

Polymer hazard assessment should be science-driven. The identification of data needs should consider relevant life cycle stages and intended uses of the polymer product, the environmental or human target population to be protected, exposure characterisation, and relevant (eco)toxicological endpoints, taking into account the key parameters and potentially relevant mode-of-actions identified in Steps 2 and 4, respectively.

As determined during Step 3 (polymer component strategy), Step 7 is performed for the polymer product (i.e. including its LMW compounds), for the polymeric substance, and/or for all or selected NIAS or IAS, as relevant. Further, Step 7 may consider the hazard potential of breakdown products of the polymer, if relevant.

Step 6 (exposure characterisation) may have to be revisited and refined using initial results from Step 7, which would then be completed after the reiteration of Step 6.

Step 7.1: Derive ecological hazard descriptors

- Identify structural and/or morphological descriptors as well as physico-chemical properties that are relevant for ecological hazard assessment and that may indicate relevant endpoints and/or potential molecular initiating events / mode-of-actions (e.g. molecular weight distribution, water solubility, surface tension, cationicity, reactive functional groups, heavy metals).

- Identify relevant screening-level fate and partitioning properties (e.g. (bio)degradation, bioaccumulation, adsorption to sludge or soil).

- Identify available *in vitro* and *in vivo* ecotoxicity data and dose-response relationships, including predicted no-effect concentrations, effect concentrations in terms of degree of effect (EC_x), benchmark dose levels; or use suitable *in silico* tools and/or read-across procedures (see Step 4).

- Consolidate all available relevant data within a weight of evidence evaluation.

- If necessary: Define testing needs in accordance with the defined risk assessment scope (Step 1); perform testing and repeat weight of evidence evaluation.

Step 7.2: Derive human health hazard descriptors

- Identify structural and/or morphological descriptors as well as physico-chemical properties that are relevant for human health hazard assessment and that may indicate relevant endpoints and/or potential molecular initiating events / mode-of-actions.

- Assess external and internal (systemic) bioavailability (toxicokinetics).

- Assess reactivity potential (reactive functional groups and/or cationicity) preferably using *in vitro* assays.

- Identify available *in vitro* and *in vivo* toxicity data and dose-response relationships, including no- or lowest-observed adverse effects concentrations / levels, EC_x (or similar), benchmark dose levels.

- Consolidate all available relevant data within a weight of evidence evaluation.

- If necessary: Define testing needs in accordance with the defined risk assessment scope (Step 1); perform testing and repeat weight of evidence evaluation.

CF4Polymers (Step 8) Risk characterisation

- Compare hazard(s) to exposure(s) to generate quantitative estimates of risk for the combinations of components, use scenarios and hazard endpoints which had been defined to be in scope. Conclude on the overall risk from use of the product in scope.

- Qualitatively describe level of confidence, uncertainties and assumptions. Describe conditions under which the risk assessment outcome applies.

- Evaluate risk management measures (which may already be in place) and their impact on the risk characterisation.

- Refine risk characterisation of use scenarios as needed and possible (which may include the need to revisit exposure and hazard assessment).

- Formulate testing proposal to address unanswered concerns if uncertainty remains.

APPENDIX CS1-A: FURTHER INFORMATION TO CASE STUDY 1 POLYCARBOXYLATES, POLYACRYLATES, POLYMETHACRYLATES

Human health toxicity data for acrylates copolymers

To supplement the toxicological database for P-AA and P-AA/MA (Section 2.8.2.1), this appendix summarises data from the CIR Expert Panel report on acrylates copolymers (CIR, 2018). The CIR (2018) report also took account of the safety assessment of carbomers (Elder, 1982), of the original safety assessment of acrylates copolymers (Andersen, 2002); of the safety assessment of PMMA and related ingredients (Becker et al., 2011); and of the safety assessment of crosslinked alkyl acrylates (Fiume et al., 2017).

Skin irritation and skin sensitisation: Different acrylates copolymers were not irritating to rabbit skin, and also did not elicit skin sensitisation in the mouse LLNA or in the Buehler guinea pig maximisation test. In clinical testing, vinyl acetate/butyl maleate/isobornyl acrylate copolymer (as a slurry in ethanol) produced slight erythema in 5 of 25 subjects submitted to 48-hour patch testing. In human repeated insult patch tests, acrylates/hydroxyesters acrylates copolymer (as a product containing < 50% copolymer) was not a sensitiser, and vinyl acetate /butyl maleate/isobornyl acrylate copolymer (in 10% ethanol) was assessed as not likely to be a sensitiser (109 subjects; erythema observed in few subjects at both induction and challenge). Further, vinyl acetate /butyl maleate/isobornyl acrylate copolymer was assessed as not likely to be phototoxic, photoallergenic or photosensitising in humans (CIR, 2018).

Eye irritation: Acrylates copolymers were not irritating to rabbit eyes in one study, but slightly irritating in another. Acrylates/beheneth-25 methacrylate copolymer and acrylates/hydroxyesters acrylates copolymer (as a product containing < 50% copolymer) were slightly irritating to rabbit eyes. Vinyl acetate/butyl maleate/isobornyl acrylate copolymer in ethanol (tested undiluted) was moderately to severely irritating to rabbit eyes (CIR, 2018). CIR (2018) remarked that details were unavailable for several of these studies.

Adsorption, distribution, metabolism, elimination (ADME): In ADME studies assessing radiolabelled acrylates copolymers (either as a fully polymerised copolymer of methyl methacrylate and ethyl acrylate or as a fully polymerised copolymer of methyl acrylate, methyl methacrylate, and methacrylic acid), most of the test material was excreted in the faeces. Very little radioactivity was recovered in the urine or in the carcass (CIR, 2018).

Acute toxicity (oral, dermal, inhalation): In acute oral toxicity studies assessing different linear and cross-linked acrylates copolymers, LD_{50} > 25.2 and > 7.95 g dry copolymer/kg bw were recorded for rats and dogs, respectively. Similarly, acute oral toxicity studies assessing different further acrylates copolymers yielded LD_{50} > 2 g/kg bw in rats. Dermal LD_{50} values of > 2 and > 5 g/kg bw were reported for acrylates copolymers in rats. In rabbits, a dermal LD_{50} of > 2 g/kg bw was reported for vinyl acetate/butyl maleate/isobornyl acrylate copolymer in ethanol. An acute inhalation toxicity study assessing a further acrylates copolymer in rats yielded an LC_{50} of > 3,960 mg/L (CIR, 2018).

Repeated-dose toxicity and developmental and reproductive toxicity: A 35-day repeated dose toxicity test (gavage administration) assessing dry acrylates copolymers yielded no notable findings (NOAEL: 2,000 mg/kg bw/day). Similarly, upon 26-week dietary exposure to acrylates copolymer-coated cellulose pellets, NOAELs > 2,000 and > 250 mg dry copolymer/kg bw/d were determined for rats and dogs, respectively, corresponding

to the highest tested doses. Also, when acrylates copolymers sprayed onto powdered diet were fed to pregnant rats (on gestational days 6-15) and rabbits (on gestational days 6-18), the NOAELs were 2,000 mg/kg bw/day in both rat dams and foetuses and rabbit dams and foetuses (CIR, 2018).

Genotoxicity: An acrylates copolymer (comprised of various monomer combinations) was not genotoxic in the Ames tests (up to 5,000 µg dry copolymer/plate), in mouse lymphoma L5178Y cell mutation assays (up to 6,250 µg dry copolymer/mL), or in a chromosomal aberration assay using human lymphocytes (up to 9,000 µg dry copolymer/mL). Further, the acrylates copolymer was not genotoxic in a micronucleus test using mice up to 2,000 mg dry copolymer/kg bw (CIR, 2018). The CIR (2018) noted that details were not available for many of these studies.

Carcinogenicity: CIR (2018) reported that carcinogenicity data for acrylates copolymers were neither found in the publicly available literature, nor were unpublished studies submitted.

APPENDIX CS2-A: FURTHER INFORMATION TO CASE STUDY 2 CATIONIC POLYMERS

Appendix Table CS2-A.1: Overview of ecotoxicity data available for polyquaternium-1, -6, -10, -11, -15, -28, -32, -33, -42 and -55

INCI name	Trade name	Charge density (Eq./g)	Duration	Endpoint	Test organism	Test result (mg/L or noted)	Reference
PQ-1	Not specified	Not specified	30 minutes	Minimal inhibitory concentration	*Escherichia coli*	0.016	Yan-Li (2012)
					Staphylococcus aureus	0.004	
					Pseudomonas aeruginosa	0.016	
					Candida albicans	0.008	
					Aspergillus niger	0.064	
PQ-6	Not specified	Not specified		DCO	*Pseudomonas species*	38.5%	Mourato and Gehr (1983)
			96 h	LC_{50}	*Carassius auratus*	3.2 – 3.7 [a]	Qiu and Zhang (2007)
			96 h	LC_{50}	*Pimephales promelas*	0.22 – 0.26	US EPA (1992)
			96 h	NOEL		< 0.10 – 0.11	
			96 h	LC_{50}	*Oncorhynchus mykiss*	0.066 – 0.077	
			96 h	NOEL		< 0.059 – 0.043	
			30 d	NOEC	*Salvelinus namaycush*	0.5	Lieber et al. (2005)
			30 d	LOEC		1.0	
			48 h	EC_{50}	*Daphnia magna*	0.075 – 2.1	US EPA (1992)
			48 h	EC_{50}	*Ceriodaphnia dubia*	0.32 – 0.77	De Rosemond and Liber (2004)
			48 h	EC_{50}	*Daphnia magna*	0.075 – 2.1	US EPA (1992)
			7 days	EC_{20}	*Ceriodaphnia dubia*	0.0042 (reproduction)	De Rosemond and Liber (2004)
			7 days	EC_{50}		0.014	
	poly(DADMAC)	4.5×10^{-3}	96 h	EC_{50}	*Gambusia holbrooki*	0.5	Cumming et al. (2008)
PQ-10	UCARE JR125	High (9×10^{-4})	96 h	EC_{50}	*Gambusia holbrooki*	1.2	Cumming et al. (2008)

INCI name	Trade name	Charge density (Eq./g)	Duration	Endpoint	Test organism	Test result (mg/L or noted)	Reference
Cont'd PQ-10	UCARE JR30M	High (1.1×10^{-3})	96 h	EC_{50}	*Gambusia holbrooki*	1.5	Cumming et al. (2008)
	UCARE JR400	High (1×10^{-3})				2.1	
	UCARE LK	Low				100	
	UCARE LR30M	Low				66	
	UCARE LR400	Low				64	
	UCARE JR400	High (1×10^{-3})	72 h	EC_{10} / EC_{50}	*Chlorella sp12*	0.002 / 0.05	Cumming (2008)
	UCARE JR30M	High (1.1×10^{-3})				0.013 / 0.05	
	UCARE JR125	High (9×10^{-4})		EC_{50}	*Chlorella sp12*	0.04	Cumming (2008)
PQ-11	Gafquat 440	7.00×10^{-4}	96 h	EC_{50}	*Gambusia holbrooki*	2	Cumming et al. (2008)
	Gafquat 734	1.00×10^{-3}				1	
PQ-15	Percol (Zetag) 787		48 h	EC_{50}	*Ceriodaphnia dubia*	> 100	Cowgill and Milazzo (1991)
PQ-28	Gafquat HS-100	0.8×10^{-3}	96 h	LC_{50}	*Gambusia holbrooki*	1.9	Cumming et al. (2008)
	Conditoneze NT-20	0.6×10^{-3}	96 h	LC_{50}		1.6	
PQ-32	See PQ-15						
PQ-33	Zetag 64	Not specified	96 h	LC_{50}	*Baicalobia guttata*	> 100	Beim and Beim (1994)
			96 h	LC_{50}	*Daphnia magna*	2.05	
			96 h	LC_{50}	*Eulimnogammarus verrucosus*	1,160	
			96 h	LC_{50}	*Phoxinus phoxinus*	2.82	
PQ-42	Busan 77	7.75×10^{-3} (Cumming, 2008)	120 h	EC_{50}	*Anabaena flos-aquae*	0.11	US EPA (1992)
			120 h	EC_{50}	*Pseudokirchneriella subcapitata*	0.0088	
			120 h	NOEL	*Anabaena flosaquae*	0.05	
			120 h	NOEL	*Pseudokirchneriella subcapitata*	< 0.001	
			120 h	EC_{50}	*Anabaena flos-aquae*	0.11	
			24 h	LOEC	*Acanthamoeba hatchetti*	0.7	Srikanth and Berk (1993)
			24 h	LOEC	*Cochliopodium bilimbosum*	6	
			24 h	NR-LETH	*Vannella sp.*	61	Sutherland and Berk (1996)
			24 h	NR-LETH	*Acanthamoeba hatchetti*	61	
			< 168 h	NR-LETH		62,500	
			120 h	EC_{50}	*Navicula pelliculosa*	0.083	US EPA (1992)
			120 h	NOEL		0.044	

			24 h	NR-LETH	*Colpoda sp.*	61	Sutherland and Berk (1996)
			24 h	NR-LETH	*Tetrahymena sp.*	122	
			48 h	EC_{50}	*Daphnia magna*	0.266	US EPA (1992)
			48 h	LC_{50}	*Ceriodaphnia dubia*	0.218	Giltner and Baumann (1991)
			504 h	LOEC	*Daphnia magna*	0.02	US EPA (1992)
			504 h	NOEC		0.012	
			48 h	NOEL		0.08	
			48 h	LC_{50}	*Dreissena polymorpha*	> 60	Waller et al. (1993)
			48 h	LC_{50}		> 60	
			216 h	LC_{50}		1.2	MacMahon et al. (1993)
			123 h	LC_{50}		4	Martin et al. (1993)
			209 h	LC_{50}	*Corbicula manilensis*	0.6	MacMahon et al. (1993)
			175 h	LC_{50}	*Dreissena polymorpha*	1	Martin et al. (1993)
Cont'd	*Cont'd*	*Cont'd*	556 h	LC_{50}	*Corbicula manilensis*	0.15	MacMahon et al. (1993)
			256 h	LC_{50}		0.3	
PQ-42	Busan 77	7.75×10^{-3} (Cumming, 2008)	101 h	LC_{50}		4.8	
			166 h	LC_{50}	*Dreissena polymorpha*	2	Martin et al. (1993)
			700 h	LC_{50}		0.3	MacMahon et al. (1993)
			50 h	LC_{50}	*Corbicula manilensis*	2.4	
			45 h	LC_{50}		4.8	
			54 h	LC_{50}		1.2	
			499 h	LC_{50}	*Dreissena polymorpha*	0.6	
			107 h	LC_{50}		8	Martin et al. (1993)
			124 h	LC_{50}		4.8	MacMahon et al. (1993)
			174 h	LC_{50}		2.4	
			101 h	NR-LETH	*Corbicula manilensis*	2.4	
			313 h	NR-LETH	*Dreissena polymorpha*	1.2	
			378 h	NR-LETH	*Corbicula manilensis*	0.3	
			144 h	NR-LETH	*Dreissena polymorpha*	8	Martin et al. (1993)
			197 h	NR-LETH		4.8	MacMahon et al. (1993)

			250 h	NR-LETH	*Dreissena polymorpha*	2	Martin et al. (1993)
			283 h	NR-LETH	*Corbicula manilensis*	0.6	MacMahon et al. (1993)
			11 h	NR-LETH		1.2	MacMahon et al. (1993)
			826 h	NR-LETH	*Dreissena polymorpha*	0.3	
			196 h	NR-LETH		4	Martin et al. (1993)
			250 h	NR-LETH		1	
			680 h	NR-LETH		0.6	MacMahon et al. (1993)
			244 h	NR-LETH	*Dreissena polymorpha*	2.4	MacMahon et al. (1993)
			336 h	EC_{50}	*Lemna gibba*	> 0.65	US EPA (1992)
			336 h	NOEL		0.043	
			48 h	LC_{10}	*Rasbora heteromorpha*	0.32	Tooby et al. (1975)
			24 h	LC_{10}		0.47	
			96 h	LC_{50}		0.17	
			24 h	LC_{50}		0.66	
Cont'd	*Cont'd*	*Cont'd*	48 h	LC_{50}		0.39	
PQ-42	Busan 77	7.75×10^{-3} (Cumming, 2008)	96 h	LC_{50}	*Lepomis macrochirus*	0.45	US EPA (1992)
			96 h	LC_{50}		0.206	
			48 h	LC_{50}	*Pimephales promelas*	0.353	Giltner et al. (1991)
			96 h	LC_{50}	*Lepomis macrochirus*	1.21	US EPA (1992)
			48 h	LC_{50}	*Ictalurus punctatus*	3.35	Waller et al. (1993)
			96 h	NOEL	*Lepomis macrochirus*	0.13	US EPA (1992)
			96 h	LC_{50}	*Oncorhynchus mykiss*	0.047	
			96 h	LC_{50}		0.43	
			48 h	LC_{50}		0.044	Waller et al. (1993)
			96 h	NOEL		0.18	US EPA (1992)
			96 h	NOEL		0.037	
			48 h	LC50	*Obliquaria reflexa*	> 60	Waller et al. (1993)
			120 h	EC_{50}	*Skeletonema costatum* (salt water)	0.09	US EPA (1992)
			120 h	NOEL		< 0.024	
			96 h	LC_{50}	*Americamysis bahia* (salt water)	13	

Cont'd PQ-42	*Cont'd* Busan 77	*Cont'd* 7.75×10^{-3} (Cumming, 2008)	96 h	NOEL	*Americamysis bahia* (salt water)	< 7.8	US EPA (1992)
			96 h	LC_{50}	*Cyprinodon variegatus* (salt water)	> 600	
			96 h	NOEL		600	
			48 h	EC_{50}	*Mercenaria mercenaria* (salt water)	0.35	
			48 h	NOEL		0.23	
PQ-55	Styleze W20	0.6×10^{-3}	96 h	LC_{50}	*Gambusia holbrooki*	0.5	Cumming et al. (2008)

Footnote to Appendix Table CS2-A.1:

Note: The accuracy of the data presented in this table may be limited by (1) difficulties in identifying the specific polyquaternium based upon trade name alone; (2) lack of information whether the studied polymer is tertiary or quaternary; (3) differences in reporting methods (Cumming, 2008; Cumming et al., 2008).

Abbreviations: $EC_{20/50}$: Concentration required to achieve 20/50% effect change from the control; h: Hours; LC_{50}: Concentration required to achieve 50% change in lethality from the control; LOEC: Lowest observed effect concentration; NOEC/L: No observed effect concentration/level; NR-LETH: Time interval between initial exposure to the dose and death; PQ: Polyquaternium.

[a] Test result dependent on viscosity level: LC_{50} = 3.7 mg/L (low viscosity level: 0.5 dL/g); 3.6 mg/L (moderate viscosity level: 1.5 dL/g); 3.2 mg/L (high viscosity level: 2.5 dL/g).

Appendix Table CS2-A.2: Human health toxicity data for polyquaternium-7 (adapted from CIR, 1995)

Toxicological endpoint	Route	Species	Doses	Dilution	Results
Acute toxicity	Oral	Not reported	Not reported	8%	LD_{50} > 39.8 g/kg – not toxic
	Dermal			8%	LD_{50} > 21.5 g/kg – not toxic
Sub-chronic toxicity	Dietary	Rats	1,650; 5,000; 16,500; 50,000 ppm		Decreased body weight gains and small decrease in feed intake at 50,000 ppm. Males: Thyroid gland weight decreased at 16,500 ppm (average - 20%) and 50,000 ppm (-26%); heart weight decreased (-13%) at 50,000 ppm; the kidney weight (left) increased (8%) at 1,650 ppm; adrenal gland weight decreased at 5,000, 16,500, and 50,000 ppm (average -11%). Females: liver weight decreased at 16,500 and 50,000 ppm (-11 and -9%, respectively); spleen weight decreased (-13%) at 50,000-ppm. Pathological changes in some animals but without significant dose-response relationship.
	Dermal	New Zealand rabbits	0.25, 0.75, or 2.25 mL/kg / day	8%	Slight erythema but no oedema in animals with abraded skin after day 5. In 4 of 12 animals with abraded skin: slight crust formation. Very slight to slight scabbing and redness in control and treated groups with abraded skin. Of those treatment groups with abraded skin, focal epidermal hyperplasia in 4 animals; focal ulceration in 1; and focal dermal cellular infiltration in 3. Conclusion: Essentially non-irritating to abraded skin and inert on intact epidermis
Skin irritation	Dermal	New Zealand rabbits	0.5 mL of a solution	8%	No evidence of skin irritation
Eye irritation		New Zealand rabbits	0.1 mL of a solution	Not reported	At 15 minutes and 2 hours, slight clear discharge from all treated eyes; three eyes: slight conjunctival injection. By 24 hours, all treated eyes appeared normal, and no further irritation was noted during the 2-week observation period; conclusion: not irritant to eyes
Human repeated insult patch test	Dermal	Humans	0.2 mL	8%	During challenge phase, 5 panellists had sensitisation reactions (4/5: Score 1; 1/5: Score 3; this fifth responder was re-challenged and had reactions with maximum score = 1 on 3 of 4 observation days following reapplication); conclusion: very mild cumulative irritant; non-sensitiser
					Mild skin irritant [a]
Photo-sensitisation	Dermal	Humans	0.3 mL	8%	No signs of treatment-related irritation, sensitisation, or photosensitisation.
Mutagenicity (Ames test)	*S. typhimurium* (TA92, TA98, TA100, TAI537)		0.1 mL /plate		Non-mutagenic (either with or without S9 metabolic activation)

Footnote to Appendix Table CS2-A.2:

[a] Of the 155 panellists who completed induction, two responded with faint erythema that disappeared within 24 h of detection.

CIR (1995): "*The Panel noted that polyquaternium-7 is now used in aerosolized products and noted the absence of inhalation toxicity data. However, in the absence of these data, the Panel determined that polyquaternium-7 can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (around 38 µm) and pump hair sprays (> 80 µm) is large compared to respirable particle size (10 µm).*"

Appendix Table CS2-A.3: Human health toxicity data for polyquaternium-28 and polyquaternium-47 (adapted from Becker et al., 2012)

Toxicological endpoint	Route	Species	Doses	Dilution	Results
Polyquaternium-28					
Acute toxicity	Oral	Rats	Not reported		LD_{50} > 5 g/kg
Eye irritation	Ocular	New Zealand rabbits (n=6)	0.1 mL	20%	Average Draize scores: 13.3, 4.0 and 2.0 at 1 hour; rinsing the eyes at 1 and 2 days had little effect; conclusion: minimal eye irritant
Mutagenicity (Ames test)	*S. typhimurium*		5000 µg/plate		Not mutagenic
Genotoxicity (micronucleus)	Not reported	Mice	Not reported		Did not induce increase in bone marrow polychromatic erythrocytes
Human repeated insult patch test	Dermal	Humans (n=104)	0.2 mL	5%	No signs of irritation or sensitisation
Phototoxicity	Dermal	Humans (n=10)	0.2 mL	2%	No reaction observed at 24 or 48 hours
Photoallergy	Dermal	Humans (n=28)	0.2 mL	5%	Slight skin irritation upon exposure to UVA and UVB irradiation; no signs of photoallergy
Polyquaternium-47					
Acute toxicity	Oral	Rats	5000 mg/kg	< 30%	LD_{50} > 5 g/kg
Eye irritation	Ocular	New Zealand rabbits (n=3)		< 30% in aqueous solution	Conjunctival irritation at 1 hour. All rabbits: Chemosis; 1 rabbit: initial discharge. Initially, all rabbits: conjunctival redness. No signs of corneal or iris irritation; conclusion: slight eye irritant
Mutagenicity (Ames test)	*S. typhimurium* *E. coli*		5000 µg/plate		Not mutagenic
Human repeated insult patch test	Dermal	Humans (n=116)	0.2 mL	20% induction, 5% challenge	During induction, 16 participants: faint erythema; 1 participant: moderate erythema; 13 participants: severe erythema including papules. At challenge, 9 participants: slight erythema: Conclusion: Not skin sensitising
Skin irritation	Dermal	New Zealand rabbits (n=6)	0.1 mL	< 30% in aqueous solution	No oedema for first 48 hours; 1 rabbit: moderate erythema 30 to 60 min after patch removal; all treatment rabbits: at least one erythema at each patch during observation. After 24 hours: 4 rabbits - slight erythema; 1 rabbit - mucoid diarrhoea: Slight skin irritant

Footnote to Table CS2-A.3: LD_{50}: Dose required to achieve 50% change in lethality from the control; n: number of test animals / subjects per test group; UV: ultraviolet.

Appendix Table CS2-A.4: Human health toxicity data for polyquaternium-22 and polyquaternium-39 (adapted from Johnson et al., 2016)

Toxicological endpoint	Route	Species	Doses	Dilution	Study results
Polyquaternium 22					
Acute toxicity	Oral	Rats(n=10)	5 g/kg	Not reported	All animals survived the study: LD_{50} > 5 g/kg
Eye irritation	Ocular	Rabbit (n=6)	0.1 mL	Not reported	Not ocular irritant
In vitro hen's egg test chorioallantoic membrane	[Chorioallantoic membrane]		10% oxidative dye	0.016%	Irritation score of 2.38, 4.51 and 4.60: Slight irritant
Skin irritation	Dermal	Albino rabbits (n=6)	1 mL/rabbit	Not reported	No to slight and none to severe erythema were observed at 24 and 72 hours, respectively. The erythema was more severe at abraded sites than intact sites. There was no evidence of oedema. Primary irritation index score: 1.1
Single occlusive patch test	Dermal	Human (n=30)	10% oxidative dye	0.016%	No evidence of skin irritation
Genotoxicity (Ames test)	Not applicable	*S. typhimurium* *E. coli*	100 to 5000 µg/plate		Non-genotoxic
Polyquaternium 39					
Acute toxicity	Oral	Rats(n=10)	5 g/kg	Not reported	All animals survived the study: LD_{50} > 5 g/kg
Eye irritation	Ocular	Rabbit (n=6)	0.1 mL	Not reported	Not ocular irritant
Skin irritation	Dermal	Albino rabbits (n=6)	1 mL/rabbit	Not reported	No evidence of erythema, oedema or abnormal signs
Human repeated insult patch test	Dermal	Humans (n=153)	0.2ml	Not reported	No adverse skin changes observed during induction; negligible erythema observed on 1 or 2 occasions on single individuals. Conclusion: No skin irritation or skin sensitisation.
Mutagenicity (Ames test)	Not applicable	*S. typhimurium* *E. coli*	100 to 5000 µg/plate		Non-genotoxic

Footnote to Table CS2-A.4: LD_{50}: Dose required to achieve 50% change in lethality from the control; n: number of test animals / subjects per test group.

APPENDIX CS3-A: FURTHER INFORMATION TO CASE STUDY 3 POLYOLEFINS

Appendix CS3-A1: Food contact materials and packaging for cosmetics and pharmaceuticals – EU and US legislation

EU legislation: Food contact materials

Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food (FCM Regulation; EP and Council, 2004b) sets out the general principles of safety and inertness for all FCMs, regardless of their underlying components. As per Article 3(1) of the FCM Regulation, materials should be manufactured in compliance with the provisions of good manufacturing practice and should not transfer constituents to food in quantities which could *"(a) endanger human health; or (b) bring about an unacceptable change in the composition of the food; or (c) bring about a deterioration in the organoleptic characteristics thereof."*

Being a framework regulation, the FCM Regulation only provides general rules, applicable to all types of materials that may be used in FCMs, e.g., paper, board, ceramics, glass, and plastics, as well as coatings, rubbers, adhesive, printing inks, silicones, waxes, etc. In addition to the general FCM Regulation, specific EU measures have been implemented for specific materials (e.g. ceramics, regenerated cellulose, plastics) or substances (e.g. vinyl chloride monomer, nitrosamines, BADGE). As applicable, the specific safety assessment measures are used together with a positive list, and/or provisions to restrict or prohibit the use of certain substances. If specific EU measures are unavailable for any particular material or substance (e.g. specific polymer-based coatings), the implemented national regulations remain applicable; see also: https://ec.europa.eu/food/safety/chemical_safety/food_contact_materials/legislation_en.

Plastic is one of the most common FCMs, and its specific use is regulated by *Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food* (Plastics Regulation; European Commission (2011)). As defined in the Recital 8 of the Plastics Regulation:

> *"Plastics are made of monomers and other starting substances which are chemically reacted to a macromolecular structure, the polymer, which forms the main structural component of the plastics. To the polymer additives are added to achieve defined technological effects. The polymer as such is an inert high molecular weight structure. As substances with a molecular weight above 1 000 Da usually cannot be absorbed in the body the potential health risk from the polymer itself is minimal. Potential health risk may occur from non- or incompletely reacted monomers or other starting substances or from low molecular weight additives which are transferred into food via migration from the plastic food contact material. Therefore, monomers, other starting substances and additives should be risk assessed and authorised before their use in the manufacture of plastic materials and articles*."

The scope of the Plastics Regulation includes (1) materials consisting exclusively of plastics; (2) plastic multi-layer materials held together by adhesives; (3) plastic layers or coatings forming gaskets in caps and closures; and (4) plastic layers in multi-material multi-layer materials. All such plastic materials can further be coated and/or printed. By contrast, ion exchange resins, rubber and silicones are excluded from the scope of the Plastics Regulation. The Plastics Regulation sets out rules to determine the compliance of plastic materials and articles with the safety provisions and specifies certain restrictions of their use.

To support the implementation of the Plastics Regulation, EFSA has published guidance, as for example the EFSA (2008a) *Note for guidance for the preparation of an application for the safety assessment of a substance used in plastic FCMs* and the EFSA (2017) *Administrative Guidance for the preparation of applications for the safety assessment of substances to be used in plastic FCMs*. The application for the safety assessment of a new substance (and hence for its addition to the Positive List) includes a technical dossier with the relevant safety assessment data. Applications are first submitted to the competent authority of a Member State, who then forwards them to EFSA for assessment and adoption of a scientific opinion (via the Panel on Food Contact Materials, Enzymes, Flavourings, and Processing Aids).

Last but least, plastics are also regulated under *Commission Regulation (EC) No 282/2008 on recycled plastic materials and articles intended to come into contact with foods* (European Commission, 2008). Thereby, recycled plastic materials and articles shall only be placed on the market if they contain recycled plastic obtained only from an authorised recycling process. Although recycled plastics are specifically covered by this Regulation 282/2008, only plastics that have been primarily designed and produced in accordance with the Plastics Regulation can be mechanically recovered.

Industry associations have published guidance to support industry in performing the risk assessment of IAS (and specifically NLS that also have not been authorised under another legislation) and NIAS in line with the FCM Regulation (EP and Council, 2004b) and the Plastics Regulation (European Commission, 2011):

- PlasticsEurope (2013, 2014): *Risk assessment of NLS and NIAS under Article 19 of Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food* [i.e. European Commission (2011)]
- International Life Sciences Institute (2015): *Guidance on best practices on the risk assessment of NIAS in food contact materials and articles*
- Food Contact Additives Sector Group under the umbrella of the European Chemical Industry Council (FCA-Cefic, 2020): *The FCA-Cefic Guidelines on risk assessment of NLS and NIAS under the requirements of Article 3 of the Framework Regulation (EC) 1935/2004* [i.e. EP and Council (2004b)]
- PlasticsEurope and FCA-Cefic with support of the European Plastic Converters: *Food contact repeated use applications (Guidance Rev 2) Proposals for exposure assessments for plastic intermediate materials and articles in the frame of Article 19 of Plastic Regulation (EU) No 10/2011* (available from the PlasticsEurope secretariat upon request; info@plasticseurope.org)

Similarly, a task force under the umbrella of Cosmetics Europe, with participation of members from the value chain, has developed a guidance document to facilitate the exchange of information needed for the hazard assessment of cosmetic packaging (Cosmetics Europe, 2019).

Finally, the European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE) has developed two guidelines related to migration studies conducted in the context of human safety assessment of food contact applications, which, however, do not focus on polymers, i.e.

- TSC33 *Guideline on NIAS for coated rigid metal packaging intended for direct food contact* (CEPE, 2019)
- TSC34a *Migration testing guideline for rigid metal packaging coated with organic coatings intended for direct food contact* (CEPE, 2017), which was prepared in response to a Draft Joint Research Centre Science and Policy Report on *Technical guidelines for compliance testing with respect to plastic FCMs* (Joint Research Centre, 2016).

EU legislation: Packaging for cosmetics

Regulation (EC) No 1223/2009 on cosmetic products governs the composition, labelling and packaging of finished cosmetic products (Cosmetic Products Regulation; EP and Council, 2009). Two different terms are used in the Cosmetic Products Regulation for packaging elements, i.e. 'container' for primary packaging and 'packaging' for secondary packaging.

The main aim of the Cosmetic Products Regulation is to assure that cosmetic products are safe for human health when used under normal or reasonably foreseeable conditions of use (Article 3). The requirements for packaging characteristics are laid down in its Annex I. Further, Article 17 states that:

> *"The non-intended presence of a small quantity (traces) of a prohibited substance (prohibited in cosmetic products according to Annex II of the regulation on cosmetic products), stemming from (...) migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3."*

Following the provisions of the Cosmetic Products Regulation, interactions between the packaging/containers and the cosmetic product should be addressed during the safety assessment of the cosmetic product. In the *Commission Implementing Decision 2013/674/EU on Guidelines on Annex I to the Cosmetic Products Regulation* (European Commission, 2013b), similar safety provisions have been established for cosmetic packaging as have been implemented for food packaging in the FCM Regulation (EP and Council, 2004b).

EU legislation: Packaging for pharmaceuticals

The requirements and procedures for the manufacture and marketing authorisation of pharmaceutical substances and products as well as the rules for monitoring authorised products are primarily laid down in *Directive 2001/83/EC on the Community code relating to medicinal products for human use* (EP and Council, 2001) and in *Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency* (EP and Council, 2004c).

In packaging for pharmaceutical substances and products, plastics can be part of the container or the closure. Within the European Medicines Agency (EMA), the Committees for Medicinal Products for Human Use and Veterinary Use, respectively, have developed a *Guideline on plastic immediate packaging materials* (EMA, 2005)

to support industry with their risk assessment obligations. As stated in its general principles, this Guideline should be read in conjunction with the "*provisions of Community legislation on plastic materials and objects in contact with foodstuffs*", i.e. currently the Plastics Regulation (European Commission, 2011).

The EMA (2005) Guideline is addressed at pharmaceutical companies that intend to file a marketing authorisation application for a pharmaceutical substance or product. By contrast, it does not apply to the producers of the materials that are intended to be used as packaging. Also, the EMA (2005) Guideline only covers plastic immediate packaging materials, but no other type of packaging material (e.g. elastomers or natural and synthetic rubber) or the container closure system. This poses regulatory uncertainties for the manufacturers or producers of those materials or packaging, as well as for the pharmaceutical industries using the further materials for the primary or secondary packaging of their products. Therefore, the majority of these manufacturers and producers applies the quality criteria applied for FCMs.

For pharmaceutical immediate packaging made from plastic, 'extractable' and 'leachable' studies are carried out in certain cases. Extractables are ingredients of the packaging that can be extracted under high-stress laboratory conditions (e.g. high temperatures, use of organic solvents as the extraction medium), whereas leachables are ingredients of the packaging materials that, during the lifetime of the product, may migrate into the contents of the packaging

The EMA (2005) Guideline indicates which specific data on the plastic packaging materials should be submitted together with the marketing authorisation application. For the packaging of active (pharmacological) substances, these data requirements depend on the physical state of the active substances (solid versus non-solid). Similarly, the data requirements for plastic materials to package medicinal products depend on their intended route of administration (oral, topical, inhalation, parenteral, ophthalmic) and the physical dosage form (solid versus non-solid). Further, the EMA (2005) Guideline states that, if the material is described in a monograph of the European Pharmacopeia or the Pharmacopeia of a Member State, compliance to that monograph should be demonstrated. If, however, such a monograph is unavailable, the characteristics of the material, as well as the nature and the amount of extractables should be described. The respective extractable studies typically involve exposing a sample of the material to an appropriate solvent system under stress conditions. The resulting information can then be used to support leachable studies where substance migration from the packaging is induced by exposing the packaging to the pharmaceutical product instead of a solvent. In addition, toxicological data should be submitted for the leachables. The requested dataset depends on the exposure level and chemical structure of the leachables. However, the EMA Guidance does not refer to any thresholds, etc., in this regard. Finally, it is stated that if the plastic material or additive is described in the European Pharmacopeia or any Member State Pharmacopoeia, or if it is approved for use in food packaging, toxicological data may not be required (EMA, 2005).

US legislation: Packaging for food, cosmetics, and drugs

US legislation pertaining to food, drugs and cosmetics, as well as their packaging, are included in the US Code of Federal Regulations (CFR), Title 21 (*Food and Drugs*; 21 CFR); for most recent version see: https://www.ecfr.gov/cgi-bin/ECFR?SID=cc7a19ecd123c4c16408cd1a1cc65c5a&mc=true&page=browse. The US Food and Drug Administration (US FDA) is the US authority regulating, amongst other products and articles,

food, drugs, and cosmetics, as well as their packaging. Other than the terminology used in the EU legislation, substances that might migrate from FCMs are called 'indirect' food additives as per 21 CFR Part 174, whereas substances that are intentionally added to food, are called 'direct' food additives (21 CFR Part 172). Indirect food additives mentioned in 21 CFR include adhesives and components of coatings (Part 175), paper and paperboard components (Part 176), polymers (Part 177), and adjuvants and production aids (Part 178). Additional indirect food additives are authorised through the food contact notification programme (US FDA, 2002c). Further, indirect food additives may be authorised through CFR Title 21, Part 170.39 (Threshold of regulation for substances used in food-contact articles), which includes regulatory exemptions for substances whose potential migration is below a predefined threshold; see also: https://www.fda.gov/food/food-ingredients-packaging/food-ingredient-packaging-terms. Finally, 21 CFR, Part 186, provides a list of indirect food additives that have been reviewed by the US FDA and affirmed to be generally recognised as safe "*for the purposes and under the conditions prescribed, providing they comply with the purity specifications listed therein or, in the absence of purity specifications, are of a purity suitable for their intended use*".

Cosmetics marketed in the USA must comply with the labelling requirements for cosmetics implemented in 21 CFR, Parts 700-740, and the general provisions of the Fair Packaging and Labeling Act that is codified in Title 16 of the CFR, Parts 500-503; https://www.ftc.gov/enforcement/rules/rulemaking-regulatory-reform-proceedings/fair-packaging-labeling-act-regulations-0.

The packaging for pharmaceutical substances and products is regulated under 21 CFR, Part 211. Its objective is that "*drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirement*" (21 CFR, Part 211.94). The US FDA has developed a *Guidance for industry - container closure systems for packaging human drugs and biologics* (US FDA, 1999). This Guidance refers to the US Pharmacopeia for specific test methods and acceptance criteria. In the US Pharmacopeia, Chapter 1663 and 1664 include provisions on the assessment of extractables and leachables, respectively, that are associated with pharmaceutical packaging / delivery systems. Thereby, extractables are organic and inorganic chemical entities that can be released from the packaging into an extraction solvent under laboratory conditions, whereas leachables are generally defined as foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into it under normal conditions of storage and use (see also US FDA, 2011).

Appendix CS3-A.2: Medical devices - EU Legislation and ISO 10993 standard series

In 2017, two new EU Regulations on medical devices entered into force, i.e. *Regulation (EU) 2017/745 on medical devices* (Medical Devices Regulation; EP and Council (2017a)) and *Regulation (EU) 2017/746 on in vitro diagnostic medical devices* (EP and Council, 2017b). These Regulations represent a regulatory framework for the placing on the market or putting into service of medical devices for human use, but they do not refer to any specific material (e.g. polymers). The two Regulations replace the former Directives *90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices* (Council, 1990); *93/42/EEC concerning medical devices* (Council, 1993) and *98/79/EC on in vitro diagnostic medical devices* (EP and Council, 1998).

Following the Medical Devices Regulation, devices are assigned to Classes I, IIa, IIb, or III, depending on their intended purpose and inherent risks, which are determined by duration of use and invasiveness and/or activity of the device. Class I devices have the lowest inherent risk (e.g. non-invasive devices with short-term usage) and Class III devices the highest inherent risk (e.g. specific implantable or long-term surgically invasive devices). A comprehensive set of nonclinical studies (or a justification for their absence) is requested for "*devices that are composed of substances… that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body*". Studies are requested addressing (1) ADME; (2) possible interactions of the substances, or of their metabolites, with other devices, medicinal products or other substances; (3) local tolerance; and (4) toxicity, including single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable depending on the level and nature of exposure to the device (Annex I (12.2); EP and Council, 2017a).

Harmonised standards are an important basis to demonstrate conformity with the provisions implemented in the Medical Devices Regulation. As regards practical risk assessment, these are the internationally agreed standards of the ISO 10993 series, which the European Committee for Standardisation (CEN) has adopted as European Standards. These standards describe the general principles for the risk assessment of medical devices (called "*biological evaluation*" in ISO 10993). Several parts of the ISO 10993 standards are relevant for the risk assessment of medical devices that are entirely or partially made of polymers, i.e.:

- Part 1: Guidance on selection of tests
- Part 2: Animal welfare requirements
- Part 3: Tests for carcinogenicity, mutagenicity, reproductive toxicity
- Part 4. Selection of tests for interactions with blood
- Part 5: Tests for *in vitro* cytotoxicity
- Part 9: Framework for identification and quantification of potential degradation products
- Part 10: Tests for irritation and skin sensitisation
- Part 11: Tests for systemic toxicity
- Part 13: Identification and quantification of degradation products from polymeric medical devices
- Part 16: Toxicokinetic study design for degradation products and leachables
- Part 17: Establishment of allowable limits for leachable substances
- Part 18: Chemical characterisation of materials within a risk management process

For a new (polymeric) medical device, the risk assessment relates to its complete chemical composition, i.e. including any 'leachables'. Leachables are compounds that migrate from the contact surface of a medical device under normal conditions of exposure. By contrast, 'extractables' are compounds that migrate from the contact surface under more aggressive conditions such as elevated temperature, extended contact time, or aggressive solvent system (http://toxikon.com/testing-service/extractables-leachables-testing/). Accordingly, leachable compounds are usually a subset of the extractable compounds. Even though the ISO 10993 standards mainly focus on leachables, extractables play an important role from an analytical perspective as a starting point for the risk assessment of the leachables.

With respect to the hazard assessment of leachables, the ISO 10993 series include provisions to limit new testing, e.g. if toxicological data of relevance to the expected exposure (quantity, route and frequency) are available. Therefore, the establishment of the leachable profile of a polymeric medical device has the clear potential for a resource-efficient risk assessment that serves the Three Rs principle to replace, reduce and refine animal testing (Russell and Burch, 1959) as is mandated by *Directive 63/2010/EU on the protection of animals used for scientific purposes* (EP and Council, 2010). However, the identification of leachables can represent a serious analytical challenge that may potentially outmatch efforts for experimental testing. This may be the case when a specific (co)polymer is assessed for the first time and/or when the analytical methods used are so aggressive that it is difficult to distinguish between leachables and extractables.

When the leaching substance represents a toxicological concern, ISO 10993-17 requests that the detected level of the leachable is compared with the respective relevant threshold of toxicological concern (Kroes et al., 2004; EFSA, 2019) as part of a tiered risk assessment.

Finally, proven sameness (or equivalence) of a new medical device to a marketed product in terms of chemistry, manufacture, and use enables a risk assessment with reduced testing requirements, or even without new testing.

APPENDIX CS6-A: FURTHER INFORMATION TO CASE STUDY 6 SURFACTANT POLYMERS

Appendix CS6-A.1 Surface tension

Work on the case studies has revealed opportunities to revise Section 3.6 (Surface tension) in ECETOC TR No. 133-2 and specifically, to update Table 3 therein (*Analytical methods potentially suitable to determine the surface tension-lowering properties of polymers*) to reflect the state-of-the-art in science and industrial practice as well as commercially available equipment. While an update of ECETOC TR No. 133-2 is being planned, this appendix proactively summarises the new insight. Additionally, in the revision of ECETOC TR No. 133-2, currently ongoing work by the European Committee of Organic Surfactants and Their Organic Intermediates (CESIO) Working Group 'Test Methods of Surfactants' and the Association of Manufacturers of Process and Performance Chemicals (TEGEWA) Working Group 'Surface Active Substances' (Venzmer, 2020) as well as work by the European Committee for Standardisation / Technical Committee (CEN/TC 276) – Surface Active Agents (Working Group 1 'Analytical Methods' and Working Group 2 'Methods of Test') to standardise amongst other issues the physical, chemical or other test methods of surface-active agents[13] shall be considered.

Surface tension is defined as the energy required to increase the surface area (energy/area = mJ/m^2 = mN/m); the surface tension of water is 72.1 mN/m. Reduction of surface tension by a surface-active agent (i.e. surfactant) indicates that a molecule is able to interact with/adsorb at interfaces (air/water or hydrophobic matter/water). This is a necessary requirement for the use of a surfactant in its applications. However, this is not sufficient to predict its performance for cleaning/washing/solubilisation. It does not take much to reduce the surface tension of water. For example, polyethylene glycol is purely water-soluble and non-amphiphilic but nonetheless reduces the surface tension of water – depending on concentration and molecular weight – down to even < 50 mN/m (Kim, 1997). Such a polymer, which does not carry any hydrophobic residue, has no tendency to interact with hydrophobic matter or membranes and hence should not be considered surface-active.

In the context of the Customs Tariff Regulation and the EU Detergent Regulation, a threshold of 45 mN/m (5 g/L) is given (European Commission, 2018) to ensure that all products are covered that exhibit a degree of surface activity, which is sufficient to adsorb to hydrophobic matter, to wash, clean or solubilise. Solutions of typical surfactants with alkyl chain as hydrophobic tail have surface tensions of about 28-32 mN/m; using special hydrophobic groups, the surface tensions could be even lower (20 mN/m for silicone surfactants; 15 mN/m for perfluorinated surfactants (Porter, 1991).

[13] https://standards.iteh.ai/catalog/tc/cen/e0d6e5f4-7375-4ec3-9fe3-9016081635d9/cen-tc-276.

While the publication from Ludwig Wilhelmy about the plate method dates back to 1863 (Wilhelmy, 1863), there has been significant progress concerning the equipment. Today, computerised equipment is commercially available for the determination of surface tension, and such equipment is frequently used in both industry and academia. In the last decades, especially the ease of use of the pendant drop method has improved drastically since the drop shape analysis is now easily done in real time with video frequency. Also, the pendant drop method seems to have some advantages over the ring/plate method in case hydrophobic impurities are present. The CESIO Working Group 'Test Methods of Surfactants' has decided to compare the ring/plate method and the pendant drop method especially for surfactant polymers to identify the best suitable methodology and help ensure that polymers are assigned as surface-active on account of their properties, but not on account of the shortcomings of the analytical methodology (personal communication, Joachim Venzmer, Evonik Operations GmbH, DE).

Table CS6-A.1: Comparison of analytical methods potentially suitable to determine the surface tension-lowering properties of polymers

Method	Pro	Contra
Ring/plate method	Well established	Surface age ill-defined; can lead to incorrect results in case small amounts of hydrophobic matter / insolubles are present; especially the auto-dilution mode to determine critical micelle concentrations can lead to incorrect values
Pendant drop method	Well established; for each measurement a fresh drop is generated, and hence surface tension kinetics can be assessed	No auto-dilution; therefore, more labour-intensive
Drop volume method	Especially suitable for dynamic interfacial tension	'Old', commercial equipment hardly available any more
Maximum bubble pressure method	Suitable for fast wetting agents	Too fast for polymers
Capillary rise method	In principle easy	No commercial equipment, results questionable since contact angle within capillary hard to control

Appendix CS6-A.2: Acute systemic toxicity data publicly available for primary linear alcohol ethoxylates

The acute oral toxicity dataset for AEs (covering C = 9-18 and EO = 3-21) is extensive and includes data for rodents, rabbits, guinea pigs and monkeys; further it has been well summarised e.g. by Talmage (1994); Danish EPA (2001); and HERA (2009) (Table CS6-A.2). HERA (2009) has concluded that the available data are mostly of high-quality and enable the conclusion that AEs are of low concern for acute systemic toxicity.

In the rat, the oral LD_{50} values range from between 544 mg/kg bw in females (for C14-15EO11) to more than 16,000 mg/kg bw in both sexes (for C18EO10). Hence, some AEs exhibit CLP Category 4 acute oral toxicity (LD_{50} > 300 to ≤ 2000 mg/kg bw), whereas other AEs are not classified (> 2,000 mg/kg bw). Female rats seem to be more susceptible to acute oral toxicity than males; however, this is found to reflect the animals' body weights rather than a sex-specific phenomenon (HERA, 2009). The major determinant of acute oral toxicity outcome is the degree of ethoxylation; AEs with average EO = 5-14 exhibit higher oral toxicity than those with EO < 4 or > 21 (HERA (2009).

The extensive acute dermal toxicity dataset, which includes data for rabbits, rats, and in few cases guinea pigs, shows that AEs are slightly to practically non-toxic by the dermal route of exposure. Typically, LD_{50} values in rabbits and rats range between 2,000 and 5,000 mg/kg bw. However, most of the reported values are from pre-GLP studies (HERA, 2009). There is no apparent relationship between AE structure and dermal toxicity outcome (HERA, 2009).

The acute inhalation toxicity dataset of AEs is the least robust (compared to the oral and dermal toxicity datasets). Studies have been conducted in rats only and represent non-OECD-TG- and non-Good Laboratory Practice-compliant studies (HERA, 2009). Whereas exposure to saturated AE vapour concentrations does not constitute a hazard, toxicity has seen with some undiluted AEs that were applied in the form of respirable mist or aerosol particulates (HERA, 2009).

Table CS6-A.2: Acute toxicity data publicly available for primary linear alcohol ethoxylates (average EO ≥ 3)

Endpoint, species	Substance	LD_{50} (mg/kg bw; unless noted) / LC_{50} (mg/L) [1]	Reference
Acute oral toxicity			
Rat	C11EO9	1100	HERA (2009)
	C12EO4	m: 8600; f: 9100	Talmage (1994)
	C12EO4	m: 8600; f: 9070	Talmage (1994)
	C12EO7	4150	Talmage (1994)
	C12EO23	m: 8600; f: 9350	Talmage (1994)
	C12EO23	8600	Danish EPA (2001)
	C13EO6	2100	Danish EPA (2001)
	C14EO7	3300	Danish EPA (2001)
	C16EO10	m: 3490; f: 2460	Talmage (1994)
	C16EO20	m: 3510; f: 3950	Talmage (1994)
	C18EO10	m: 2910; f: 2000	Talmage (1994)
	C18EO10	> 16,000	Talmage (1994)
	C18EO10	m: 2910	Talmage (1994) & Danish EPA (2001)
	C18EO20	2070, 2100 [2]	Talmage (1994)
	C18EO20	m: 1920	Talmage (1994) & Danish EPA (2001)
	C18EO20	m: 1920; f: 2330	Talmage (1994)
	C18EO21	> 2000	HERA (2009)
	C7-9EO6	> 2000	HERA (2009)
	C9-11EO5	2900	Talmage (1994)
	C9-11EO6	1400	Danish EPA (2001)
	C9-11EO6	3100, 1378, 1200 [2]	Talmage (1994)
	C9-11EO8	1000, 2700 [2]	Talmage (1994)
	C9-11EO8	1200	HERA (2009)
	C12-13EO6.5	2120, 1439 [2]	Talmage (1994)
	C12-13EO6.5	2100	HERA (2009)
	C12-13EO6.5	m: 2360, ~ 2500, 1738, 2100, 1400 [2]	Talmage (1994)
	C12-13EO6.5	f: > 1250, < 2500, 1637, 1206 [2]	Talmage (1994)
	C12-13EO6.5	m: 2500, F: 1700	HERA (2009)
	C12-14EO3	> 5000	Talmage (1994)
	C12-14EO6.3	m: 2710; f: 1870	Talmage (1994)
	C12-14EO7	m: 2140; f: 1070	Talmage (1994)
	C12-14EO9	m: 2627; f: 1789	Talmage (1994)
	C12-14EO9	2140	Talmage (1994)
	C12-14EO11.6	m: 930; f: 620	Talmage (1994)
	C12-14EO8	2800	Talmage (1994)
	C12-15EO3	2500	Talmage (1994)
	C12-15EO7	1700	HERA (2009)
	C12-15EO7	m: 2000-3145; f: 1321 [2]	Talmage (1994)

Endpoint, species	Substance	LD_{50} (mg/kg bw; unless noted) / LC_{50} (mg/L) [1]	Reference
Acute oral toxicity; continued			
Continued Rat	C12-15EO7	1642	Talmage (1994)
	C12-15EO9	1600, 3200, 5600 [2]	Talmage (1994)
	C12-15EO11	m: > 2000; f: > 1000, < 2000 [2]	HERA (2009)
	C12-15EO12	1800	Talmage (1994)
	C12-16EO3	m: 6500; f: 4920	Talmage (1994)
	C12-16EO5	m: 4290; f: 2530	Talmage (1994)
	C14-15EO7	m: 3300	Talmage (1994)
	C14-15EO7	2380	Talmage (1994)
	C14-15EO11	722, 1772 [2]	Talmage (1994)
	C14-15EO11	m: 1077, 1963; f: 544, 1684 [2]	Talmage (1994)
	C14-15EO11	720	HERA (2009)
	C14-15EO11	1800	HERA (2009)
	C14-15EO13	1000	HERA (2009)
	C14-15EO13	1100	HERA (2009)
Rabbit	C12-14EO7	m: 710; f: 930	Talmage (1994)
Mouse	C12EO9	m: 3300	Talmage (1994)
	C12EO4	m: 4900; f: 7600	Talmage (1994)
	C12EO23	3500	Danish EPA (2001)
Dog	C12-13EO6.5	> 1650	Talmage (1994)
Monkey	C12-13EO6.5	> 1500	Talmage (1994)
	C14-15EO7	> 3300, ≥ 10,000 [2]	Talmage (1994)
Acute dermal toxicity			
Rabbit	C7-9EO6	> 2000	HERA (2009)
	C9-11EO6	< 2000	Danish EPA (2001)
	C9-11EO6	> 2000	HERA (2009)
	C9-11EO6	< 5000	HERA (2009)
	C9-11EO6	> 2000, 5000 [2]	Talmage (1994)
	C12-13EO3	3300	Talmage (1994)
	C12-13EO6.5	2000, > 2000 [2]	Talmage (1994)
	C12-14EO3	> 3000	Talmage (1994)
	C12-14EO3	> 2000	HERA (2009)
	C12-14EO6	> 2000	HERA (2009)
	C12-14EO6.3	m: 2000; f: 2240	Talmage (1994)
	C12-14EO7	m: 930; f: 1780	Talmage (1994)
	C12-14EO9	> 3000	Talmage (1994)
	C12-14EO11.6	m: 1120; f: 1190	Talmage (1994)
	C12-15EO3	3000	Talmage (1994)
	C12-15EO7	2300, 2500-5000 [2]	Talmage (1994)

Endpoint, species	Substance	LD_{50} (mg/kg bw; unless noted) / LC_{50} (mg/L) [1]	Reference
Acute dermal toxicity, continued			
Continued Rabbit	C12-15EO9	2500, 3400 [2]	Talmage (1994)
	C12-15EO12	2500	Talmage (1994)
	C12-16EO3	m: 2380; f: 2140	Talmage (1994)
	C12-16EO5	m: 1780; f: 3250	Talmage (1994)
	C14-15EO7	~ 2000, < 5000	Talmage (1994)
	C14-15EO11	5000	Talmage (1994)
	C14-15EO13	5000	Talmage (1994)
Rat	C9-11EO8	> 4000	Talmage (1994)
	C12-14EO7	m: 11,300; f: 11,300	Talmage (1994)
	C12-15EO7	> 2000	Talmage (1994) & HERA (2009)
	C13EO6	< 2 mL/kg bw	Danish EPA (2001)
	C13-15EO11	> 920	HERA (2009)
	C14-15EO7	> 5000	Talmage (1994)
	C14-15EO11	> 2000	Talmage (1994)
	C15-16EO10	> 800	HERA (2009)
Guinea pig	C12-13EO6.5	> 2000	Talmage (1994)
	C14-15EO7	> 2000	Talmage (1994)
Acute inhalation toxicity			
Rat	C9-11EO5	> 0.22 (4-hour LC_{50})	Talmage (1994) & HERA (2009)
	C12-13EO6.5	1.5-3.0 (4-hour LC_{50})	Talmage (1994)
	C12,14EO7	> 6.6 (4-hour LC_{50})	Talmage (1994)
	C14-15EO7	1.5-3.0 (4-hour LC_{50})	Talmage (1994)
	C10,12,14EO6.3	52 (1-hour LC_{50})	Talmage (1994)

Footnote to Table CS6-A.2: This table only includes data for primary linear alcohol ethoxylates.

Abbreviations: bw: Body weight; f: Female; LC_{50}: lethal concentration required to achieve 50% change (one half) in lethality in a group of test animals; LD_{50}: lethal dose required to achieve 50% change (one half) in lethality a group of test animals; m: Male.

[1] If LD_{50}/LC_{50} results are not provided separately for males (m) and females (f), the findings from both genders were combined to yield a common result.

[2] LD_{50} values reported from multiple studies.

Appendix CS6-A.3: Repeated-dose toxicity and carcinogenicity data publicly available for primary linear alcohol ethoxylates

Just as stands true for acute oral toxicity, there is a comprehensive dataset on repeated-dose oral toxicity, and it has been well summarised (Talmage, 1994; Danish EPA, 2001; EFSA, 2008b; HERA, 2009; Table CS6-A.3). Reliable repeated-dose oral toxicity studies are available for C16-18EO10 (CAS No. 68920-66-1), C9-11EO6 (CAS No. 68439-46-3), C14-15EO7 (CAS No. 68951-67-7), polyethylene glycol 200 and 400 (CAS No. 25322-68-3), C12EO0 (CAS No. 112-53-8) and C16EO0 (CAS No. 36653-82-4). These studies provide a coherent picture on the subchronic and chronic oral toxicity of AEs. Gastrointestinal irritation, particularly of the stomach, was the primary effect after gavage application, but was not seen after dietary application. This is consistent with the irritant properties of (undiluted) AEs and is likely attributable to the bolus application via gavage. The results indicate dietary NOAEL values of ≥ 50 mg/kg bw/day (C14-15EO7), which have been chosen for the risk assessment (HERA, 2009).

The repeated-dose dermal toxicity dataset covers AEs with C-chain lengths = 9-18, and EO = 4-30 (Table CS6-A.3). In 3- to 4-week rabbit studies, no systemic toxicity was reported, whereas in an 18-month mouse study no treatment-related lesions were observed for C12-13EO6.5 applied up to 5% or 270 mg/kg bw/day (Talmage, 1994); however, these studies were not well documented. In other poorly documented subchronic dermal toxicity rabbit studies, no systemic toxicity and mild to moderate irritation at the exposure site were noted (Danish EPA, 2001; Talmage, 1994). In a GLP-compliant OECD TG 411 rat study, C9-11EO6 did not result in any significant compound-related effects (HERA, 2009; Talmage, 1994). In this study, relative kidney weights were increased in both sexes at 25%, and dry and flaky skin was noted at 10% and 25%. Hence, a systemic NOAEL value of 10% (corresponding to 80 mg/kg bw/day) and a local NOAEL value of 1% (corresponding to 5 mg/kg bw/day) were established from this study (HERA, 2009; Talmage, 1994). Although the majority of the available repeated-dose dermal toxicity studies were pre-GLP and poorly documented, the dermal AE dataset overall demonstrated absence of systemic effects and a local skin irritation threshold.

The available 2-year bioassays using rats did not provide any indication for carcinogenic potential of AEs. Further considering the absence of any structural features providing genotoxic potential (Appendix CS6-A.6), AEs have been assessed as not being carcinogenic. Studies investigating the genetic toxicity of AEs *in vitro* (more than 20 studies) and *in vivo* (5 studies) have shown that AEs are not genotoxic (HERA, 2009). Further, the subacute and subchronic toxicity studies showed no substance-related adverse effects indicative for carcinogenicity such as preneoplastic changes. Additionally, AEs are rapidly metabolised to physiological occurring substances, i.e. fatty acids and further shorter alkyl chains (Section 7.8.3.3 and Appendix CS6-A.4). These will chemically behave in the same way as their natural counterparts.

Table CS6-A.3: Repeated-dose toxicity and carcinogenicity data publicly available for primary linear alcohol ethoxylates with average EO ≥ 3

Exposure duration; species; administration; doses	Substance	Result	Reference
Oral administration (diet / gavage)			
4 weeks; rats; diet: 0.0471, 0.2355, 1.1775%	C12EO7	No adverse effects noted	Talmage (1994)
21 days; rats; diet: 0, 0.023, 0.047, 0.094, 0.188, 0.375, 0.75, 1.00, 1.50%	C12-14EO7	NOAEL: 459 mg/kg bw/day	HERA (2009)
	C12-15EO3	NOAEL: 471 mg/kg bw/day	
	C12-15EO7	NOAEL: 502 mg/kg bw/day	
	C12-15EO11	NOAEL: 519 mg/kg bw/day	
	C16-20EO18	NOAEL: 443 mg/kg bw/day	
	C14EO7	No systemic toxicity	
90 days; rats; diet: 0, 125, 250 and 500 mg/kg bw/day	C10EO5	NOAEL: 250 mg/kg bw/day LOAEL: 500 mg/kg bw/day: increased absolute and relative liver weights	HERA (2009)
90 days; rats; diet: 0 and 10000 ppm	C12-14EO3	LOAEL: 1000 ppm or approx. 500 mg/kg bw/day: myocardial degeneration/inflammation	EFSA (2008)
90 days; rats; diet: 0, 0.03, 0.063, 0.125, 0.25, 0.5, 1.0%	C12-15EO7	NOAEL: 0.125% or 102 mg/kg bw/day LOAEL: 0.25%: decreased body weight gains and liver effects	HERA (2009)
	C12-14EO7	NOAEL: 0.125% or 110 mg/kg bw/day LOAEL: 0.25%: decreased body weight gains and liver effects	
91 days; rats; diet: 1%	C13EO6	Increased relative liver weights	Danish EPA (2001)
	C14EO7	Increased relative liver weights	
90 days; rats; diet: 0, 300, 1000, 3000 and 10,000 ppm	C14-15EO7	NOEL: 300 ppm or 15 mg/kg bw/day NOAEL: 1000 ppm or 50 mg/kg bw/day.; effects in females were not of toxicological significance. LOAEL: 3000 ppm: decreased body weight and feed intake in females, increased relative liver weights, haematological effects and plasma urea concentration changes	HERA (2009) & Talmage (1994)
90 days; rats; diet: 0, 0.1, 0.5 and 1.0%	C14-15EO7	NOEL: 1% or 700 mg/kg bw/day	HERA (2009)
90 days; rats; gavage; 0, 20, 100, 500 mg/kg bw/day	C16-18EO10	NOAEL: 100 mg/kg bw/day LOAEL: 500 mg/kg bw/day: delayed growth, Inflammatory changes in forestomach and kidney damage	HERA (2009)

Exposure duration; species; administration; doses	Substance	Result	Reference
Oral administration (diet / gavage); *continued*			
90 days; rats; diet: 20, 100 500 mg/kg bw/day	C16-18EO10	NOAEL: > 500 mg/kg bw/day	HERA (2009)
91 days; rats; gavage; 0, 125, 250, 500 mg/kg bw/day	C16,18EO9	Only mild irritation at exposure site	Talmage (1994)
91 days; rats; gavage; 0, 50, 500 mg/kg bw/day	C16,18EO20	Only mild irritation at exposure site	Talmage (1994)
90 days; rats; diet: 0, 125, 250, 500, 1000, 3000 ppm	C9-11EO6	NOAEL: 3000 ppm or 150 mg/kg bw/day	HERA (2009)
90 days; rats; diet: 0.04, 0.2, 1%	C9-11EO8	NOAEL: 400 mg/kg bw/day;	
90 days; rats; diet: 0, 0.04, 0.2, 1.0%	C9-11EO8	NOEL: 0.2% (80 mg/kg bw/day) LOAEL: 1%: decreased body weight gains and feed consumption	
2-year bioassay; rats; diet: 0, 0.1, 0.5 and 1.0%	C12-13EO6.5	NOAEL (systemic): 0.1% (50 mg/kg bw/day) LOAEL (systemic): 0.5%: decreased body weight gain and relative organ weight increases NOAEL (carcinogenicity): no effects at highest dose	HERA (2009) & Talmage (1994)
	C14-15EO7	NOAEL (systemic): 0.5% (M: 162, F: 190 mg/kg bw/day) LOAEL (systemic): 1%: decreased body weight gain and relative organ weight increases NOAEL (carcinogenicity): no effects at highest dose	HERA (2009)
	C14-15EO7	NOAEL (systemic): 0.1% (50 mg/kg bw/day) LOAEL (systemic): 0.5%: decreased body weight gain and relative organ weight increases	HERA (2009)
		NOAEL (carcinogenicity): no effects at highest dose	

Exposure duration; species; administration; doses	Substance	Result	Reference
Dermal application			
21 days; rabbits	C12EO4	No systemic toxicity	Danish EPA (2001)
4 weeks; rabbits: applied up to 50 mg/day	C13EO6	No systemic toxicity	
13 weeks; rats; 0, 1, 10, 25%; 3x/week	C9-11EO6	NOAEL (local) f: 1% (5 mg/kg bw/day):skin discoloration over treatment area at 10% and 25% (10% and 25%: dry and flaky skin) LOEL (local) m: 1%: skin discoloration over treatment area, including in controls (10% and 25%: dry and flaky skin) NOAEL (systemic): 10% (80 mg/kg bw/day) LOAEL (systemic): 25% (125 mg/kg bw/day): increased relative kidney weights	HERA (2009) & Talmage (1994)
90-day; rabbit: 2.5%, 5x/week for 6 hours	C14-15EO7	LOEL (local): moderate dermal irritation with erythema and oedema NOAEL (systemic): not established	HERA (2009)
Sub-chronic; rabbits	C12EO4	No systemic toxicity	Danish EPA (2001)
13 weeks; rabbits; up to 50 mg/day	C13EO6	No systemic toxicity	
	C14EO7	No systemic toxicity	
91 days; rabbits; 50 mg/kg bw/day	C12,14,16EO12	Only mild to moderate irritation at exposure site	Talmage (1994)
	C12,14,16EO20	Only mild to moderate irritation at exposure site	
Sub-chronic; rabbits; 50 mg/kg bw/day	C16,18EO30	Only mild irritation at exposure site	
18 months; mice; 0,0.2, 1.0, 5.0%; 0.1 mL, 3x/week	C12-13EO6.5	No treatment-related lesions	

Footnote to Table CS6-A.3: Abbreviations: bw: Body weight; f: Female; LOAEL: Lowest observed adverse effect level; m: Male; NOAEL: No observed adverse effect level.

Appendix CS6-A.4: Absorption, distribution, metabolism and elimination data publicly available for primary linear alcohol ethoxylates

Absorption, distribution, metabolism and elimination (ADME) of ^{14}C-labelled AEs has been studied in rats and in human volunteers (Drotman, 1980; EFSA, 2008). In rats, > 75% overall absorption and rapid excretion, predominantly in the urine, were reported across different AEs (Danish EPA, 2001; HERA, 2009). The ADME of C12EO3, C12EO6 and C12EO10 showed almost complete oral absorption in rats, excretion mainly in urine (approx. 80%) with small portions recovered either as respiratory carbon dioxide or in faeces (HERA, 2009). The disposition of AEs was nearly the same in rats and humans (Drotman, 1980). When the ^{14}C-label was in the hydroxyl-carbon atom, the same pattern of disposition was seen regardless of variations in the length of the alcohol or the (poly)oxyethylene backbone. On the other hand, when the ^{14}C-label was in the α position of the alcohol, increasing the chain length from C12 to C15 caused less of the ^{14}C to appear in the urine and faeces, and more (up to approx. 50%) to appear in respiratory CO_2 (Drotman, 1980). In rats, primary branched C12EO6 has been shown to be extensively (94%) absorbed following a 7-day dosing regimen, excreted in approximately equal proportions in urine (59.2 ± 2.5%) and faeces (49.0 ± 2.8 %; via bile and enterohepatic circulation) with less than 1% of the administered dose recovered as respiratory CO_2 (Calvin et al., 1983). In this study, the equivalent of 53-60.4% of each daily dose was detected in 24-hour urine samples and 40.8-56.6% in 24-hour faeces samples. Five days after the last dose, < 0.3 % of branched C12EO6 remained in the body of rats (Calvin et al., 1983). Also, the majority of the administered C12EO6 was metabolised to more polar metabolites, with < 15% of the parent detected in rat urine and < 5% detected in rat faeces overall. In humans, on average 75% of radioactivity from C12EO6 and C13EO6 was excreted via urine in the first 24 hours post-dosing; smaller amounts of radioactivity were found in faeces (5%) and as respiratory CO_2 (4%). During metabolism, the alcohols can be hydrolysed from the (poly)oxyethylene moiety to some extent and oxidised to carboxylic acids (Elder, 1985; HERA, 2009; Figure CS6-A.4). The carboxylic acids were broken down by stepwise removal of one or several C2 units through the beta-oxidation process (HERA, 2009). With increasing alcohol chain lengths, higher percentages of respiratory CO_2 were reported in expired air, and lower percentages of radioactivity in urine (HERA, 2009). C12AE (EO not specified) was shown to be metabolised to polyethylene glycol, carboxylic acids and respiratory CO_2 (Danish EPA, 2001). The polyethylene glycol backbone would not be extensively metabolised (HERA, 2009; EFSA, 2006). With the increase in EO units, higher excretion of AE in faeces was reported (HERA, 2009).

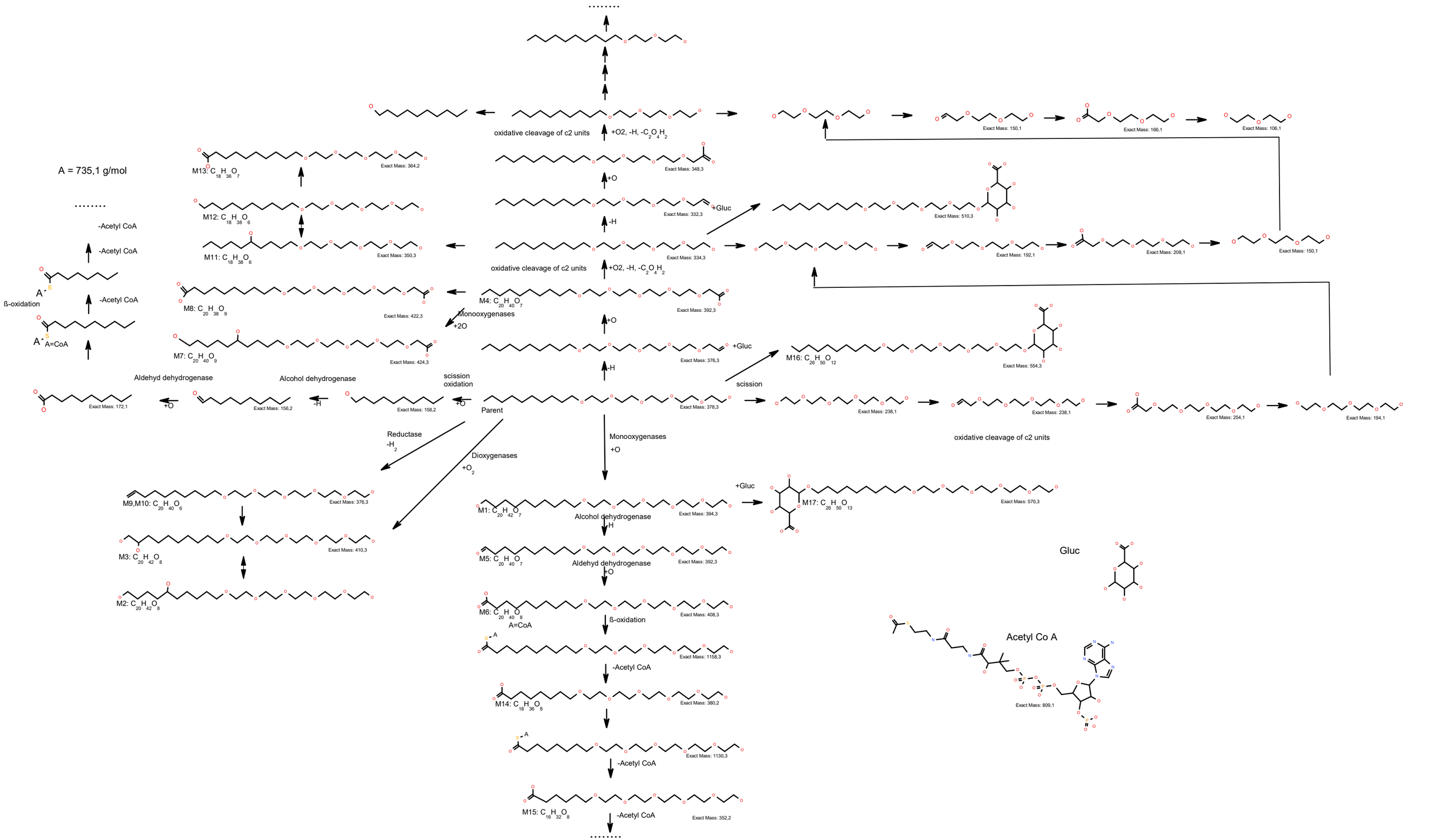

Figure CS6.A-4: Example for an AE metabolism scheme (study underway by Task Force member company to be confirmed in *in vitro* mammalian-cell assays)

Appendix CS6-A.5: Skin sensitisation data publicly available for primary linear alcohol ethoxylates

AEs with C = 7-18 and EO = 3-23 have been tested for skin sensitisation (Talmage, 1994; Danish EPA, 2001; HERA, 2009). GLP and OECD TG-compliant guinea pig studies included assessments of C7-9EO6, C9-11EO6, C11EO9, C12-15EO3, C12-15EO7, C14-15EO7 and C18EO21. An overwhelming (27/28) majority of guinea pig tests (both Magnusson and Kligman and Buehler protocols) and human sensitisation studies, along with one rabbit challenge assay, reported the absence of delayed contact hypersensitivity upon dermal exposure to AEs (Talmage, 1994; Danish EPA, 2001; HERA, 2009; Table CS6-A.5). The only exception were two guinea pig studies that indicated a weak skin sensitisation potential for C7-9EO6 and C12-13EO3. HERA (2009) suggested that the observed minor erythema was indicative of local irritation and not of sensitisation reactions; further, for one of the studies, HERA (2009) noted a lack of experimental follow-up. Furthermore, for C12-13EO3 AE, the very weak response was not reproduced in another sample of the same product that was retested (HERA, 2009). Overall, HERA (2009) concluded that based on a weight of evidence approach and considering study quality criteria, AEs would not be considered to be skin sensitisers.

Table CS6-A.5: Skin sensitisation data publicly available for primary linear alcohol ethoxylates with average EO ≥ 3

Study type, species	Substance	Result	Reference
Guinea pig maximization study	C7-9EO6	Weakly positive	HERA (2009)
Guinea pig study	C9-11EO5	Negative	Talmage (1994)
	C9-11EO6	Negative	Talmage (1994)
Guinea pig Buehler study	C9-11EO6	Negative	HERA (2009) & Danish EPA (2001)
Guinea pig study	C9-11EO8	Negative	Talmage (1994)
Guinea pig Buehler study	C11EO9	Negative	HERA (2009)
Guinea pig study	C12-13EO3	Negative	Talmage (1994)
	C12-13EO3	Weakly positive	Talmage (1994) & HERA (2009)
	C12-13EO6.5	Negative	Talmage (1994)
	C12-13EO7	Negative	Talmage (1994)
	C12-15EO3	Negative	Talmage (1994)
Guinea pig maximization study	C12-15EO3	Negative	HERA (2009)
Guinea pig study	C12-15EO7	Negative	Talmage (1994)
	C12-15EO9	Negative	Talmage (1994)
	C14-15EO7	Negative	Talmage (1994)
	C14-15EO11	Negative	Talmage (1994)
	C14-15EO13	Negative	Talmage (1994)
	C14-15EO18	Negative	Talmage (1994)
Guinea pig maximization study	C12EO9	Negative	Talmage (1994)
	C12-15EO7	Negative	HERA (2009)
	C14-15EO7	Negative	HERA (2009)
	C18EO21	Negative	HERA (2009)
Rabbit challenge study	C12EO7	Negative	Talmage (1994)
Human study	C12EO10	Negative	Talmage (1994)
	C12EO4	Negative	Talmage (1994) & Danish EPA (2001)
Human repeated insult patch test	C12-13EO6.5	Negative	Talmage (1994)
	C12-15EO7	Negative	Talmage (1994)
	C12EO23	Negative	Talmage (1994) & Danish EPA (2001)

Appendix CS6-A.6: *In vitro* and *in vivo* mutagenicity and genotoxicity data publicly available for primary linear alcohol ethoxylates

The substantial genetic toxicity dataset available for a broad range of structurally different AEs indicates no evidence for *in vitro* or *in vivo* genotoxic or mutagenic potential (Yam et al., 1984; Talmage, 1994; Danish EPA, 2001; EFSA, 2008; HERA, 2009; Table CS6-A.6). Mutagenicity and clastogenicity studies performed with AE did also not reveal any mutagenic or clastogenic effect of AE.

Various AEs (ranges: C = 9-18 and EO = 3-20) were clearly negative with and without metabolic activation in bacterial *Salmonella typhimurium* and *Escherichia coli* WP2 *uvrA* tester strains according to or similar to OECD TG 471 (Yam et al., 1984; Talmage, 1994; HERA, 2009); the bacterial assays were described to be reliable, well documented and GLP-compliant (HERA, 2009). Likewise, various *in vitro* mammalian gene mutation and chromosomal aberration assays yielded negative results (Yam et al., 1984; Talmage, 1994; HERA, 2009); some of the studies were conducted following OECD TG 473 and in compliance with GLP (HERA, 2009). Finally, *in vivo* rodent assays to assess cytogenetic damage were also negative for AEs with low average EO = 3-9 (Yam et al., 1984; HERA, 2009); these are known to be bioavailable. HERA (2009) noted that most of these *in vivo* studies were pre-GLP but were well documented and conducted.

In the absence of any structural feature providing genotoxic potential (no alerts for protein or DNA binding), AEs are not considered to be mutagenic or genotoxic. Also, the length of the alkyl chain and the degree of ethoxylation do not affect genotoxicity potential.

Table CS6-A.6: *In vitro* and *in vivo* mutagenicity and genotoxicity data publicly available for primary linear alcohol ethoxylates with average EO ≥ 3

Study type; species	Substance	Results	Reference
Bacterial mutagenesis (Ames test)			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	C9-11EO6	Negative (w & w/o MA)	Yam et al. (1984)
S. typhimurium TA98, TA100, TA1535, TA1537	C13-15EO7	Negative (w & w/o MA)	Yam et al. (1984)
	C13-15EO11	Negative (w & w/o MA)	Yam et al. (1984)
	C13-15EO20	Negative (w & w/o MA)	Yam et al. (1984)
S. typhimurium TA98 and TA100	C16EO15	Negative (w & w/o MA)	Yam et al. (1984)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	C9-11EO8	Negative (w & w/o MA)	Yam et al. (1984)
	C12-13EO3	Negative (w & w/o MA at 2 mg/plate)	Talmage (1994)
	C12-13EO3	Negative (w & w/o MA)	Yam et al. (1984)
	C9-11EO8	Negative (w & w/o MA)	Yam et al. (1984)
	C12-14EO3	Negative (w & w/o MA up to 100 µg/plate)	Talmage (1994)
	C12-14EO9	Negative (w & w/o MA up to 100 µg/plate)	Talmage (1994)
	C12-15EO3	Negative (w & w/o MA up to 2 mg/plate)	Talmage (1994)
	C12-15EO3	Negative (w & w/o MA)	Yam et al. (1984)
E. coli WP2 uvrA	C12-15EO3	Negative (w & w/o MA up to 2 mg/plate)	Talmage (1994)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	C14-15EO7	Negative (w & w/o MA at 1-4 mg/plate)	Talmage (1994)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 *E. coli* WP2 uvrA pKM101	C14-15EO7	Negative (w & w/o MA up to 5,000 µg/plate)	HERA (2009)
E. coli WP2 uvrA	C14-15EO7	Negative (w & w/o MA at 1-4 mg/plate)	Talmage (1994)
S. typhimurium TA102 and TA104	C7-9EO6	Negative	HERA (2009)
	C18EO20	Negative	HERA (2009)
Further *in vitro* mutagenicity / genotoxicity assays			
Sacch. cerevisiae JDI mitotic gene conversions	C12-15EO3	(w & w/o MA)	Talmage (1994)
	C14-15EO7	Negative (w & w/o MA)	Talmage (1994)

Study type; species	Substance	Results	Reference
Further *in vitro* mutagenicity / genotoxicity assays *(continued)*			
Mammalian cell gene mutation; mouse lymphoma	Two AEs	Negative	HERA (2009)
In vitro chromosome aberration; human leukocytes	AE6	Negative	Yam et al. (1984)
In vitro chromosome aberration, rat cells	C12-15EO3	Negative	Talmage (1994)
In vitro chromosome aberration; CHO cells	C14EO12	Negative	HERA (2009)
in vitro cytogenetic assay; Chinese Hamster V79 cells	C12-14EO21	Negative	HERA (2009)
in vitro cytogenetic assay; rat liver cells	C14-15EO7	Negative up to 250 µg/mL	HERA (2009)
Unscheduled DNA synthesis; primary rat hepatocytes	C12-14EO3	Negative up to 100 µg/mL	Talmage (1994)
	C12-14EO9	Negative up to 5 µg/mL	Talmage (1994)
***In vivo* genotoxicity studies**			
In vivo rodent cytogenetic study	AE6	Negative	Yam et al. (1984)
	C12-15EO3	Negative	Yam et al. (1984)
In vivo bone marrow chromosome aberration; Chinese hamster; gavage: 0, 1.7 and 3.4 g/kg	C13-15EO7	Negative	HERA (2009)
In vivo bone marrow chromosome aberration; Chinese hamster; 0, 1.25 and 2.5 g/kg	C12-14EO7	Negative	HERA (2009)
In vivo bone marrow chromosome aberration; rat; 0, 250, 500 and 1000 mg/kg	C14-15EO7	Negative	HERA (2009) & Talmage (1994)
In vivo micronucleus assay; CD-1 mouse; i.p.: 100 mg/kg	C12-15EO3	Negative	HERA (2009) & Talmage (1994)
	C12-14EO9	Negative	HERA (2009) & Talmage (1994)

Footnote to Table CS6-A.6:

Abbreviations: CHO: Chinese Hamster Ovary; *E.*: *Escherichia*; i.p.: Intraperitoneal application; *S.*: *Salmonella* w & w/o MA: with and without metabolic activation; *Sacch*: *Saccharomyces*.

Appendix CS6-A.7: Developmental and reproductive toxicity data publicly available for primary linear alcohol ethoxylates

As regards developmental and reproductive toxicity studies addressing AEs (Table CS6-A.7), a dermal two-generation reproductive toxicity study is available that investigated C9-11EO6 (CAS No. 68439-46-3). Groups of 30 Fischer 344 rats of each sex were dermally exposed to 0, 1, 10 or 25% w/v C9-11EO6 (1 mL/kg bw) three times a week. Treatment began upon weaning and was continued thereafter, except during the mating periods. This treatment equalled exposure levels of about 0, 10, 100 and 250 mg/kg bw/day. No compound-related effects on mating and fertility indices and mean gestational length could be observed in either the first or second generations. Also, no effects on testicular weights, sperm counts and lactate dehydrogenase isoenzyme X activities in parental and first-generation male adults were observed. (In one of two studies, embryo lethality was observed in one generation, which was possibly not-treatment related (Table CS6-A.7)). Macroscopic and microscopic examination of the reproductive organs did not show any significant differences in the test groups compared to the controls. Based upon these observations, the NOAEL for reproductive and developmental toxicity was set at the highest dermally applied dose, i.e. ≥ 250 mg/kg bw/day (Talmage, 1994; HERA, 2009).

The reproductive toxicity and developmental effects of C12EO6 were evaluated in feeding studies with C12EO6 (HERA, 2009; Talmage, 1994). In a pre-GLP developmental toxicity study with 0, 50, 100 or 200 mg/kg bw/day C12AE6, female rabbits exhibited ataxia and a slight decrease in body weight at 100 and 200 mg/kg bw/day. No effects were observed for parameters such as corpora lutea, implantations, number of live foetuses and spontaneous abortions. The maternal toxicity NOAEL for this study was determined to be 50 mg/kg bw/day whereas the NOAEL for developmental toxicity was 200 mg/kg bw/day. In pre-GLP two-generation continuous breeding dietary studies, rats were exposed to the dose levels of 25, 50 or 250 mg/kg bw/day of either C12EO6 or C14-15EO7. No treatment related effects in the fertility, parents or pups on general behaviour, appearance or survival were observed. Reduced body weight gain of parents and pups relative to the control were seen at the highest dose; the NOAEL values for reproduction were set at 0.5% dietary level or 250 mg/kg bw/day for both AEs (HERA, 2009; Talmage, 1994).

The available dataset investigates that AEs do not cause reproductive toxicity when administered orally or dermally with NOAELs for reproductive toxicity being ≥ 250 mg/kg bw/day. The available oral and dermal developmental studies are well conducted and documented (HERA, 2009). In the developmental toxicity studies, reduced pup body weights were observed at higher exposure levels. A developmental toxicity NOAEL of 50 mg/kg bw/day was established following oral exposure and 250 mg/kg bw/day following dermal exposure.

Table CS6-A.7: Developmental and reproductive toxicity data publicly available for primary linear alcohol ethoxylates with average EO ≥ 3

Endpoint / study type; species; administration; doses	Substance	Result	Reference
Oral exposure (dietary administration of gavage)			
Two-generation reproductive toxicity study; rats; dietary administration: 0.05, 0.1, 0.5% on gestational days 6-15	C14-15EO7	NOAEL (reproductive toxicity): > 0.5% or 250 mg/kg bw/day NOAEL (teratogenicity): > 0.5% or 250 mg/kg bw/day NOAEL (developmental toxicity): 0.1% or 50 mg/kg bw/day LOAEL (developmental toxicity): 0.5%: decreased pup body weight NOAEL (maternal toxicity): 0.1% or 50 mg/kg bw/day LOAEL (maternal toxicity): 0.5%: decreased body weight, increased relative liver weights	HERA (2009) & Talmage (1994)
Two-generation reproductive toxicity study; rats; dietary administration: 25, 50, 250 mg/kg bw/day	C12EO6	NOAEL (reproductive toxicity): 250 mg/kg bw/day NOAEL (developmental toxicity): 50 mg/kg bw/day LOAEL (developmental toxicity): 0.5%: embryo lethality [a] and soft tissue anomalies in F_2, decreased pup body weight NOAEL (maternal toxicity): 50 mg/kg bw/day	
Developmental toxicity study; rabbits; gavage; 0, 50, 100, 200 mg/kg bw/day on gestational days 2-16	C12EO6	NOAEL (developmental toxicity): 200 mg/kg bw/day NOAEL (maternal toxicity): 50 mg/kg bw/day	
Dermal exposure			
Two-generation reproductive toxicity study; rats; dermal application; 0, 10, 100, 250 mg/kg bw/day (3x/week)	C9-11EO6	NOAEL (developmental toxicity): 250 mg/kg bw/day NOAEL (reproductive toxicity): 250 mg/kg bw/day NOAEL (maternal systemic toxicity): 250 mg/kg bw/day	Talmage (1994)
Developmental toxicity study; rabbits; dermal application; 310 mg/kg bw/day on gestational days 2-18	C12EO4	No teratogenic or embryotoxic effects observed	
Developmental toxicity study; rats; dermal application; 250 mg/kg bw/day on gestational days 2-15			
Developmental toxicity study; rats; dermal application; 250 mg/kg bw/day from gestational day 15 to weaning			

Footnote to Table CS6-A.7: Abbreviations: bw: Body weight; LOAEL: Lowest observed adverse effect level; NOAEL: No observed adverse effect level.

[a] Possibly not-treatment-related.

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