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Three-tiered approach for standard information requirements for polymers requiring registration under REACH

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ABSTRACT

Polymers are a very large class of chemicals comprising often complex molecules with multiple functions used in everyday products. The EU Commission is seeking to develop environmental and human health standard information requirements (SIRs) for man-made polymers requiring registration (PRR) under a revised Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation. Conventional risk assessment approaches currently used for small molecules may not apply to most polymers. Therefore, we propose a conceptual three-tiered regulatory approach for data generation to assess individual and groups of polymers requiring registration (PRR). A key element is the grouping of polymers according to chemistry, physico-chemical properties and hazard similarity. The limited bioavailability of many polymers is a prominent difference to many small molecules and is a key consideration of the proposed approach. Methods assessing potential for systemic bioavailability are integral to Tier 1. Decisions for further studies are based on considerations of properties and effects, combined with systemic bioavailability and use and exposure considerations. For many PRRs, Tier 1 data on hazard, use and exposure will likely be sufficient for achieving the protection goals of REACH. Vertebrate animal studies in Tiers 2 and 3 can be limited to targeted testing. The outlined approach aims to make use of current best scientific evidence and to reduce animal testing whilst providing data for an adequate level of protection.

1. Introduction

Synthetic polymers are large and complex molecules composed of multiple monomer units. Polymers cover a wide spectrum of properties and are essential components of everyday products (Koltzenburg et al., 2018). Polymers are subject to the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation but currently do not require registration; however, this status is being reconsidered in the context of policy changes within the EU (European Commission, 2020). This raises several technical and scientific challenges due to the size, properties and/or form of polymers, such that not all conventional risk assessment (RA) approaches applied to chemicals may be suitable for polymers (which may also require alternative or additional data). One of the reasons for this is that polymers represent a different chemical universe than small molecules, for which existing concepts were usually developed in the past. To explain and to address this, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Polymers Task Force (TF) has published a trilogy of technical reports (TRs) to enable polymer RA (ECETOC, 2019, 2020, 2021a). The first report (TR 133-1 (ECETOC, 2019)) provided a conceptual framework for the RA, with basic guiding principles for consideration when assessing

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
CLP	Classification, Labelling and Packaging
CASG-polymers	Competent Authorities Sub-Group on Polymers
CHESAR	CHEmical Safety Assessment and Reporting tool
CMR	carcinogenic, mutagenic or toxic to reproduction
CSR	chemical safety report
DART	development and reproductive toxicology studies
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EU	European Union
EUSES	European Union System for the Evaluation of Substances
FGEW	functional group equivalent weight
GI	gastrointestinal
IAS	intentionally added substances
ISO	International Organisation for Standardization
IVIVE	*in vitro - in vivo* extrapolation
LD_{50}	lethal dose 50 (dose of a substance that produces death in 50 per cent of a population of experimental animals)
MW	molecular weight
NAMs	new approach methodologies
NAMW	number average molecular weight
NIAS	non-intentionally added substances
OECD	Organisation for Economic Co-operation and Development
PBPK	physiologically based pharmacokinetic modelling
PBTK	physiologically based toxicokinetic
PRR	polymers requiring registration
QSAR	Quantitative Structure Activity Relationship
RA	risk assessment
RCR	risk characterization ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	risk management measure
SIRs	standard information requirements
TF	task force
TOC	total organic carbon
tpa	tonnes per annum
TR	technical report
UVCBs	substance of unknown or variable composition, complex reaction products and biological materials
WAF	water accommodated fraction

potential ecological and human health hazards and risks posed by polymer products to facilitate consistency. The second report (TR 133-2 (ECETOC, 2020)) provided a detailed review of standard analytical tools and test methods and their applicability to polymers and identified research needs where knowledge gaps in testing exist. The third report (TR 133-3 (ECETOC, 2021a)) presented seven case studies to evaluate the usefulness of the conceptual framework for polymer RA in TR 133-1, as well as the applicability of tools, test methods and models for the RA, for different types of polymers and with different intended uses and hazardous properties. These case studies highlighted that there is no single RA approach that can be applied to all polymers (ECETOC, 2021a). However, they also highlighted the need for critical, case-by-case assessment of the suitability and relevance of models, methods and concepts used in polymer RA.

The EU Commission, with the support of its agencies, is currently seeking to develop standard information requirements (SIRs) for those polymers requiring registration ('PRR') in the future (under REACH), taking into consideration various sources of information, e.g., the ECETOC reports (TRs 133-1 to 133-3), as well as the Wood/PFA report (EC et al., 2020). Building on its three TRs, the ECETOC TF has developed a three-tiered approach for standard information requirements for polymers under REACH with the principal mindset that the use of vertebrate animal testing is employed as 'a last resort' while fully maintaining the adequacy of the information for the required regulatory decision making. Science and methods have made great progress during the past 40 years (i.e. since the previous and current information requirement schemes for chemicals were designed), and a series of methods and approaches are now sufficiently mature to be taken up in the REACH SIRs for PRR, in particular for human health. For example, non-animal methods are available and offer opportunities, so-far unused, for reduction of vertebrate animal testing (Burden et al., 2017; Dent et al., 2021) in human health RA. Also, for the assessment of environmental risks, there are methods with so far less exploited opportunities (OECD 2013, 2018a, 2018b, 2021). Also, Quantitative Structure Activity Relationship (QSAR) models support grouping approaches and similarity assessment for a variety of chemistries (Floris and Olla, 2018; Luechtefeld et al., 2018; Mellor et al., 2019; Janer et al., 2021a).

The three-tiered SIR approach put forward here allows that other means have been fully exploited in a testing scheme before entering testing proposals for animal studies, and that the base set of information in Tier 1 is designed without the use of vertebrate studies.

A key element early in the SIR approach involves the grouping of polymers according to chemistry, physico-chemical properties and hazard similarity (Simeone and Costa, 2019; ECETOC, 2021a, 2021b; Janer et al., 2021b). This approach allows for multiple tests on the same endpoint to cover diverse members of a large group of polymers using read-across by interpolation, which is referred to as 'bracket testing'. This allows to only test a small number of representative polymers out of a group and still enable RA for all group members. The more information on the physico-chemical properties, fate and hazard that are available at the grouping stage, the better the group can be defined and the greater the certainty of the assessment. In contrast to the current REACH SIR for non-polymers, this ECETOC proposal for polymers does not use manufactured tonnage volume as a criterion for testing decisions for human health. This is particularly relevant for the protection of human health since a large production volume does not necessarily correlate with high exposure of individual persons, and *vice versa*, low production volumes can still cause high exposure of individuals. A targeted testing approach leading to the full hazard characterization of those polymers that lead to relevant exposures of individuals can be assumed to reduce uncertainty compared to an untargeted, tonnage-based approach. Indeed, currently, for most non-polymers, information 'suitable for full hazard identification', as triggered by REACH Annex IX and X testing, is not available for more than half of the registered substances as their manufactured volume does not meet the tonnage trigger of 100 tonnes per annum (tpa). The ECETOC scheme proposed here includes exposure estimates derived from manufactured volumes, usage and other information to prioritize testing for environmental assessment. Prioritizing testing according to material properties and uses of polymers will result in an approach which is targeted to both human health and the environment. For environmental considerations, the tiered assessment makes use of effects data, combined with bioavailability estimates, and volume, use and exposure considerations to inform the RA and any higher tier testing needs.

This concept paper describes the general principles for a regulatory testing scheme for PRR under REACH and for the Classification, Labelling and Packaging (CLP) Regulation. General scientific and technical aspects of polymer safety are provided to a broad, global audience, and for a large range of applications which underlie a multitude of regulations. The translation and application of scientific principles into regulatory information requirements under the EU REACH framework for PRR polymers are also described. Furthermore, the need to critically

check existing testing guidelines (e.g., OECD, ISO) and models, such as for PBPK, with regard to their applicability for larger molecules like polymers is highlighted. This holds true especially for those test systems which establish exposure via aqueous media.

2. General considerations: polymer grouping concept and information requirements

For the tiered approach, grouping of PRRs should be performed based on the principles of the ECETOC polymer grouping approach, as described in the ECETOC TR 133-3 (ECETOC, 2021a). From a regulatory perspective, the evidence to develop initial PRR groups and – where needed – to support the hazard similarity hypothesis of the grouping rationale, is independent of information required for registration dossiers and RA. Nonetheless, it can be assumed that in many cases, the same types of endpoints and studies will be used to justify grouping and subsequently to fulfil more specific regulatory information requirements for compliance. This notion is also a key element in the impact assessment described in European Commission et al. (2020), where it is implicitly stated that successful polymer grouping approaches are a key aspect in the significant reduction of vertebrate animal testing, and, the overall resources of registering PRRs.

The information requirements as proposed here are applicable to individual polymers or groups of polymers. In the case of groups, for each endpoint an informed decision should be taken on which and how many group members to test for a certain property or endpoint to obtain the information necessary for the RA of the group. QSAR and modelling approaches, depending on the endpoint requested, should be applied whenever possible in combination with the information requirements proposed below. This will follow the principles of 'bracket testing', as recently described by ECETOC (ECETOC, 2021b). The functional group equivalent weight (FGEW) or other properties like molecular weight are used as descriptors in defining the polymers in a group and thus, the group boundaries. It is unnecessary and impossible to test the hazard potential of all members of a group of polymers. Therefore, the polymers representing the boundaries, as well as the middle, of the key descriptor of the entire group are tested. This is called 'bracket testing', which is similar to the concept of category formation and read-across for non-polymer chemicals (ECHA, 2008, 2017a). SIR Tier 1 basic hazard data can be generated from representative subsets of these polymers over a range of values spanning the group boundaries. The hazard can then be interpolated between the representative data points. If necessary, i.e. where safe use cannot be established from Tier 1, or appropriate risk management measures cannot be determined, subsequent SIR Tier 2 (and potentially Tier 3) data are then generated from a subset of the group. This enables an assessment of new polymers by integration into the existing groups and interpolation based on the relevant and defined group properties.

3. Tiered testing scheme for PRR under REACH

An overview of the proposed testing scheme for PRR under REACH is summarized in Fig. 1 and more detailed information on the Tier 1, 2 and 3 PRR Information Requirements is shown in Fig. 2. This tiered testing scheme offers the advantage of targeted testing in that only the relevant information is generated in higher tiers as determined by the data of the lower tier. Compared to a rigidly pre-defined SIR, this will generate all the relevant information which may have been missed by a pre-defined, general trigger, such as production volume. At the same time, the generation of information not relevant to the RA is not required, including animal tests. The proposed 3-tiered testing scheme allows for safety assessments based on non-animal data, if this is sufficient for a reliable

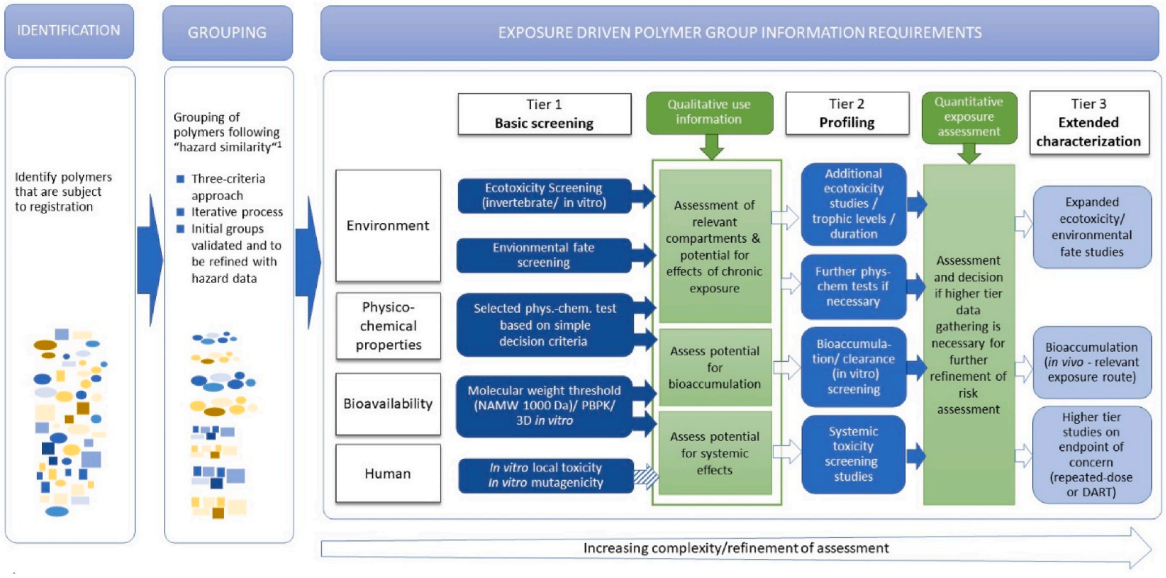

Fig. 1. Overview of the proposed PRR Information Requirements. The testing and assessment approach starts with a basic screening dataset for selected members of a polymer group which will be expanded based on the results of prior testing in combination with use and exposure information. The complexity and depth of the assessment will increase from Tier 1 to 3, while all PRR will undergo Tier 1, but only few will advance to Tier 3. Qualitative use information will typically be sector of use and product categories. Blue boxes: property endpoints, green boxes: decisive boxes based on use and exposure information.

Solid arrows: information is considered in the following assessment.

Hatched arrow: further assessment only in case of positive results from in vitro mutagenicity.

Arrows without fill: Assessments might trigger further studies. Testing may be applied only if physico-chemical properties permit. For certain types of polymers sample preparation, e.g., via extraction, may be needed (see section 3.1 on sample preparation). Abbreviations: NAMW = number-average molecular weight; PBPK = physiologically based pharmacokinetic modelling; DART = development and reproductive toxicology studies. 1For an outlined proposal on grouping of polymers, please refer to ECETOC Task Force Report 133-3 (ECETOC, 2021a).

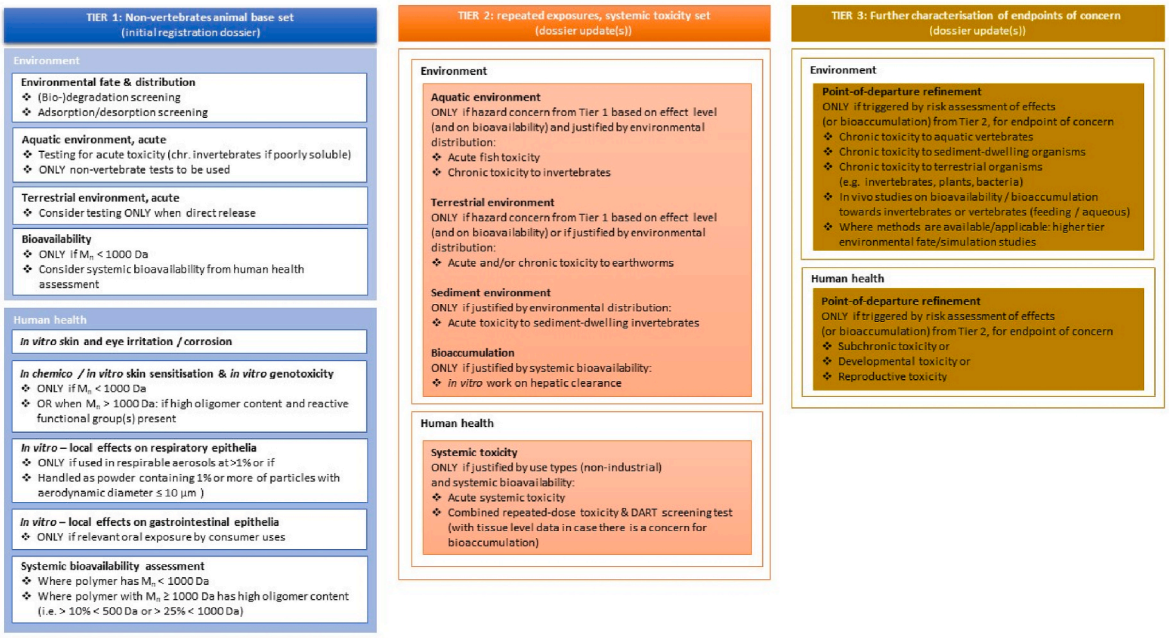

Fig. 2. Detailed Outline of the Tier 1, 2 and 3 PRR Information Requirements.
Footnote to figure Notes for Tier 1: Local effects by relevant exposure route, i.e. skin and eye, and if relevant local effects to lung tissue or gastrointestinal (GI) tissue, are to be addressed by the base set. For PRR with low MW or high oligomer content, *in vitro* skin sensitization and mutagenicity studies are foreseen when reactive functional groups are present. An assessment of systemic bioavailability according to the scheme in Fig. 2 for all identified relevant routes of exposure is included in Tier 1 to enable judgement on whether animal studies should be proposed to characterize systemic effects upon acute and/or repeated exposure. Positive *in vitro* mutagenicity assays in Tier 1 would trigger follow-up at Tier 2. *Notes for Tier 2: Acute systemic toxicity removed as separate endpoint, as it can be addressed by the dose-rangefinder for the repeated dose study*.

assessment. It assesses physico-chemical properties, systemic bioavailability, human health toxicity, environmental fate, and ecotoxicity. Tier 1 of this approach is entirely based on *in silico* and *in vitro* methods (and short-term aquatic toxicity testing using invertebrates and algae) for toxicology and ecotoxicology endpoints. The decisions for further studies and the next tier are based on considerations of a polymer's properties and effects, combined with systemic bioavailability estimates, and use and exposure considerations. The considerations between Tier 1 and 2 are based on qualitative use information combined with test results. The assessment for further refinement and additional testing needs at Tier 3 are based on elements of quantitative risk characterization (risk characterization ratios; RCRs). This results in a flow of experiments guided by defined criteria rather than a predefined unspecific list of tests. Consideration of the physical form of the polymer at ambient temperature and pressure is a pre-requisite starting point in the assessment process (Section 4.1 and Fig. 3). It should be noted that already existing experimental data should be used for the assessment, even if these historical data are not specifically requested at a lower tier (for example, if an *in vivo* acute fish toxicity study already exists, there is no requirement to generate *in vitro* fish toxicity data for Tier 1).

3.1. Sample preparation for testing

Most polymers will contain a variety of lower molecular weight substances: residual monomers, additives that are intentionally added, and NIAS (non-intentionally added substances, including reaction- and degradation products of process chemicals and additives as well as oligomers). These are usually obtained and tested via elution. Elution samples may be obtained via conservative extraction procedures which should nonetheless be realistic and relevant to exposure scenarios of the given PRR. Appropriate elution conditions vary between different polymer types (ECETOC, 2022). Standard conditions representing worst cases of intended and foreseeable use can be identified (as was done for plastics food safety assessment). It may, however, be necessary to use realistic worst-case elution or extraction of the solid polymer to gain further insights in the properties of the polymer product. The proposed regulatory testing scheme does not exclude the use of additional testing for lower molecular weight substances as required by some end use of the polymer, e.g., food contact and medical devices. Furthermore, there will be cases where some or all of the eluting chemicals can be assessed based on information available already. However, for REACH registrations, such assessment is required only in case that the substance extracted, or migrating, is part of the composition which has to be registered according to the REACH substance identity rules. For example, additives and solvents not necessary to stabilize the polymer have to be registered separately and are not part of the regulatory polymer for registration. In cases where additives or solvents do not theoretically belong to the REACH registration scope of the PRR, but practically could influence the results of the tests, it will be particularly valuable to use test materials without such components, if available.

4. Tier 1 information requirements

4.1. Tier 1: physico-chemical assessment

Polymer SIR should start from careful consideration of the various physical forms in which PRR are produced (either as 'polymeric substance' (the chemical (co)polymer and possibly present oligomers) or as a 'polymer product' (a chemical product with a polymeric substance as main component, and NIAS and sometimes IAS (intentionally added substances) as other components, and only in some cases these are the finished articles), as defined by ECETOC TR 133-1 (ECETOC, 2019)). This will be an important factor in how to approach testing and will determine what type of physico-chemical testing will be possible and informative, as well as how to dose and measure polymers in fate and (eco-)toxicity tests. Physical forms of polymers can vary widely from concentrated (viscous) liquids, gels and waxes, to elastomers, glass-like materials and solids (solids as such, in solutions or in suspensions). The

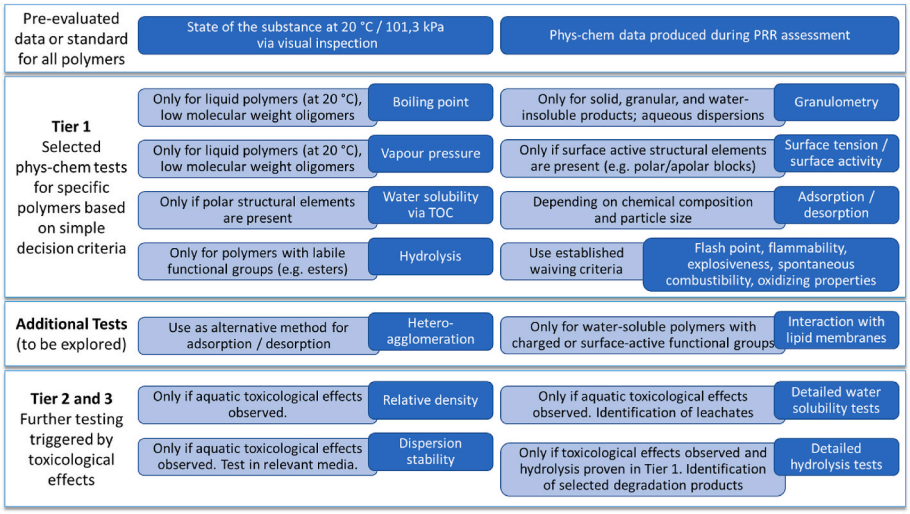

Fig. 3. Overview on physico-chemical data and appropriate trigger and dependencies for all Tiers, combining established and exploratory test methods. Footnote to figure. The light blue boxes lefthand of the physico-chemical properties mention criteria or information to be applied in the decision whether measurements of the respective physico-chemical properties are valuable or not. Exploratory test methods are mentioned to cover recent developments (middle part of figure, "Additional Tests") but are not part of the current proposal towards regulatory SIRs on polymers. Abbreviations: TOC = total organic carbon.

polymer physical properties and state at room temperature will strongly determine which physico-chemical properties are relevant. The availability of measured (or predicted) key physico-chemical properties, such as e.g., water solubility, is usually a pre-requisite to proceed to subsequent steps (Morrow, 1988; Driscoll and Borm, 2020; Stratmann et al., 2021).

After identifying the polymer as a PRR, it then needs to be grouped for structural and/or biological similarity, based on existing information and according to bracketing criteria (ECETOC, 2021b). This initial grouping based on chemistry and existing information may be refined, once more information becomes available. Grouping requires a description of the boundaries of the group, which are not necessarily obvious. Tier 1 testing focusses on physico-chemical properties and interactions that are relevant to bioavailability and hazard assessment. In view of the diversity of polymer chemical structures, and in analogy to the established ECETOC polymer grouping scheme (ECETOC, 2021a), DF4nanogrouping (Arts et al., 2015) and ECETOC NanoApp[2] (Janer et al. 2021a, 2021b), the selected properties enable a targeted testing strategy. Fig. 3 outlines potential physico-chemical data to be tested depending on whether a certain criterion is fulfilled, e.g., granulometry is determined only for solid granular polymers (right-hand side of Fig. 3). Note that many of the criteria are not well defined for polymers, as polymers are naturally a mixture of substances with individual physico-chemical properties. For example, each chain length of a polymer has a different boiling point. The determined value "boiling point" is thus only an average for the distribution of the individual chain lengths. As outlined in ECETOC Technical Report No 133-3 (ECETOC, 2021a), there is a great need for appropriate methods to determine meaningful physico-chemical data of polymers. The state of the substance is a natural first step and provides one of many criteria for decision-making in Tiers 1–3. Although the guidelines for physico-chemical endpoints are well established for small molecules, there is an urgent need to adapt these guidelines for polymers. The close interaction between the (eco)toxicological assays, the chemical structure and the results of the physico-chemical tests (within Tier 1) can trigger further testing requirements with a focus on functional assays. Considering recent literature (Landsiedel et al., 2017; Koltermann-Jülly et al., 2018; Stone et al., 2020; Jeliazkova et al., 2022), developments have been highlighted in the assessment of physico-chemical properties (right-hand side of Fig. 3) to improve the assessment of interactions between the polymer and physiological or environmental compartments (which often are natural polymers themselves, such as humic and fulvic substances). Hetero-agglomeration or interaction with lipid membranes could be relevant to characterize the adsorption of a polymer to physiological or environmental matrices. However, these methods are not yet fully developed. The availability of partitioning protocols and analytical tools for polymers in environmental matrices is limited and discussed in more detail in ECETOC TR 133-2 (ECETOC, 2020).

4.2. *Tier 1: systemic bioavailability*

The assessment of systemic bioavailability is an integral part of Tier 1, as it determines - in particular for human health assessment - whether non-local toxicological endpoints are of concern and need to be evaluated in the subsequent Tiers. The estimated systemic bioavailability – combined with information on the intended uses – will provide a sound basis for decisions on Tier 2 testing. If a PRR is not significantly bioavailable, it will not require higher tier testing for human health (Fig. 1). If the polymer is not bioavailable, it is also not expected to bioaccumulate. In some cases, the extractable and potentially bioavailable fraction of a polymer may consist of structures which have already been characterized for hazards, e.g. additives or structures having been registered as No-Longer-Polymers. In such cases, further characterization of bioavailability may be less relevant. 'Significant systemic bioavailability' is defined as bioavailability which will yield internal doses potentially causing systemic toxicity. There is still a need to develop methods which can identify PRR with low systemic bioavailability with confidence and to review applicability to environmental species. A suggested tiered approach for the assessment of systemic bioavailability for humans is shown in Fig. 4. In many cases, significant systemic bioavailability can be sufficiently assessed based on simple considerations, such as molecule size and molecular weight distribution, including the content of oligomeric constituents with less than 1000 Da molecular weight. Based on approaches used by e.g., EFSA and other agencies, the proposed scheme here focusses on systemic bioavailability of molecules with number average molecular weights below 1000 Da and if containing >10% of oligomers with <500 Da, or >25% of oligomers <1000 Da ((EFSA Panel on Food Contact Materials et al., 2008); PLC criteria as described by the OECD (OECD, 2009)).

[2] https://www.ecetoc.org/tools/nanoapp/.

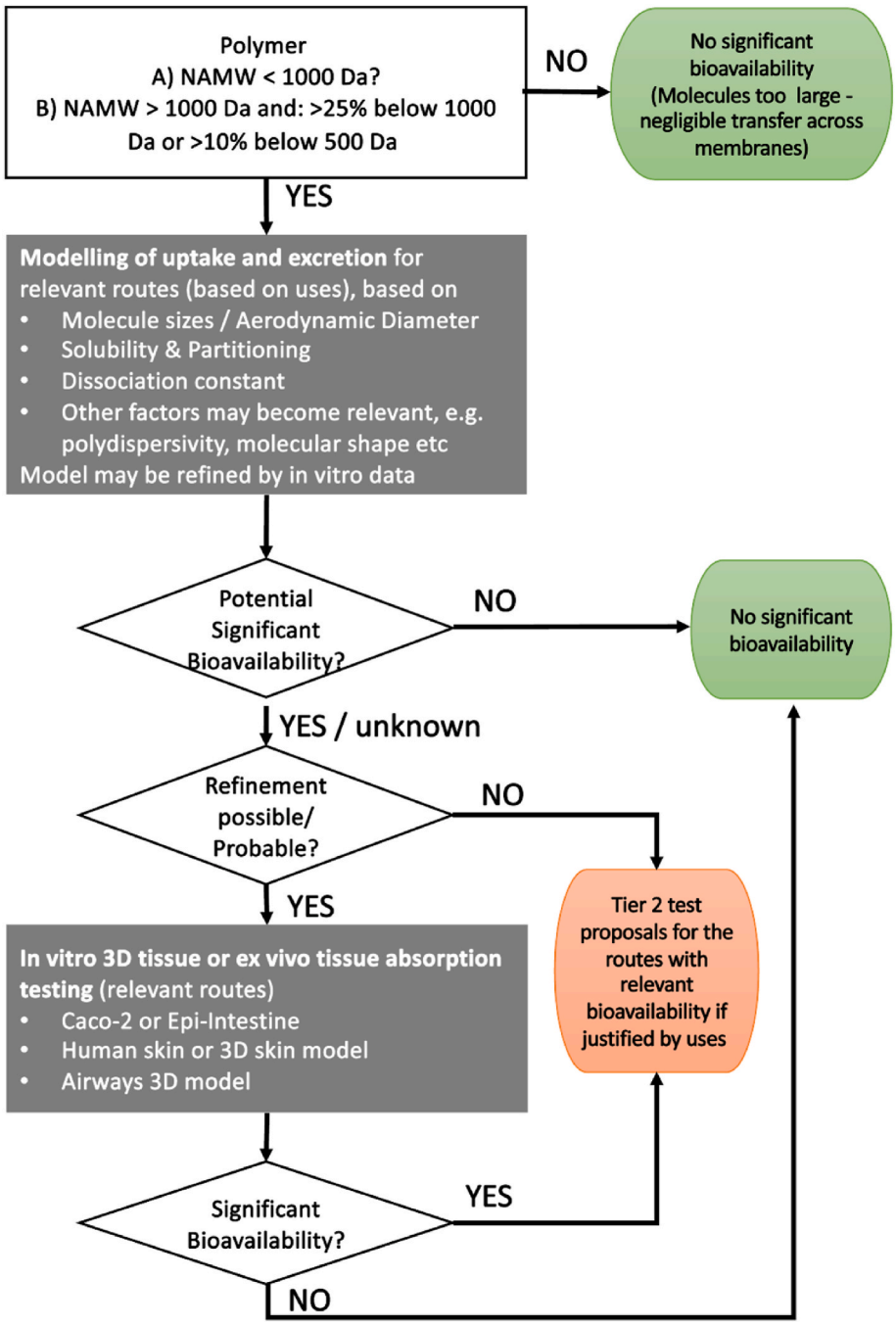

Fig. 4. Tiered Approach for Assessment of Systemic Bioavailability as integral part of Tier 1, with focus on human health *Footnote to figure*. The assessment of systemic bioavailability determines whether non-local toxicological endpoints are of concern and need to be evaluated in the subsequent tiers. Combined with knowledge of the intended uses, estimated systemic bioavailability will provide a sound basis for decisions towards progressing with human health testing at Tier 2. If the polymer is not bioavailable, it is also not expected to bioaccumulate. Negligible transfer across membranes refers to transport processes related to diffusion. Not all physico-chemical properties mentioned may be applicable to all polymers, and other properties may be more appropriate (also see Fig. 3). Abbreviations: NAMW = number average molecular weight.

The first two rectangles of the approach depicted in Fig. 4 focus on transmembrane transport processes related to diffusion. Other transport processes such as endocytosis can be addressed by *in vitro* 3D tissue or ex vivo tissue absorption testing (lowest rectangle). If relevant systemic bioavailability cannot be excluded, uptake, distribution and excretion can be estimated by physiologically based pharmacokinetic (PBPK) models which can be refined by *in vitro* absorption, distribution, metabolism and excretion (ADME) parameters e.g., hepatic clearance in humans, rats or fish (e.g. OECD, 2018a), plasma protein binding and plasma to blood ratio, in combination with *in vitro* membrane penetration models (e.g. OECD, 2004a). If not already included and needed, such endpoints are added to the Tier 1 *in vitro* assessment. The potential for bioavailability will be included in the bioaccumulation assessment. If the polymer is not bioavailable, it is also not expected to bioaccumulate.

It is acknowledged that for some PRR, measurement of bioavailability may be technically challenging so that the need to conduct Tier 2 studies will only depend on worst-case assumptions on bioavailability and use considerations. It is accepted that the approach proposed here will require (i) definitions of triggers (to be applied solely, or, in

combination) towards higher tier studies; (ii) mastering analytical challenges and (iii) a proof-of-concept by case studies. Moreover, it needs to be discussed whether extractability testing of solid or liquid polymers could be used to inform on systemic bioavailability estimates.

4.3. Tier 1: human health

Tier 1 toxicity testing provides information on local toxicity from *in vitro* skin and eye irritation studies (Fig. 1). If warranted, due to polymer properties or intended uses in inhalable aerosols at >1% (CIR 2012), local toxicity to respiratory tissues is to be evaluated at Tier 1 by *in vitro* models. While methods for local effects on the skin and eyes are well-developed, validated and described in OECD test guidelines, *in vitro* models of the respirable tract still need development and validation.

It has to be emphasized that the vast majority of polymers subject to REACH registration and the REACH SIR discussed in this scheme will be industrial substances handled at chemical industry sites and by professional users only and will not be handled directly by consumers. Nevertheless, the scheme is applicable to polymers in products used by consumers as well. The scheme will be instrumental in identifying polymers and uses that require Tier 2 or even Tier 3 data.

For most polymers with low bioavailability, Tier 1 information will be sufficient to determine whether the uses are safe or whether appropriate risk management measures should be implemented, so that the animal testing of Tier 2 can be avoided. For example, Tier 1 assays for skin and eye irritation as well as for skin sensitization would be sufficient for hazard characterization and risk management as long as the tested PRR was in the applicability domain of the methods. Positive *in vitro* mutagenicity alone would not be sufficient for hazard characterization, but would require Tier 2 follow-up, as well as indications of relevant systemic bioavailability. Polymers used in significant concentrations as ingredients of specific consumer products (e.g., food or medication) will require additional separate consideration and are regulated outside of REACH.

In general, skin sensitization requires sufficient dermal bioavailability and mutagenicity requires sufficient oral or dermal bioavailability. Hence, testing should not be required for polymers with no significant bioavailability (see Section 4.2).

Oral uptake of high doses which could result in local effects to gastrointestinal tissues are accidental and rare: health and safety measures are in place to reduce or minimize accidental ingestion in the workplace; consumer uses via oral uptake typically are extremely low, unless a polymer is used e.g., as an excipient, an application which is not addressed by REACH, but by specific legislation.

4.4. Tier 1: environmental fate and ecotoxicology

The Tier 1 environmental fate assessment includes an initial step to assess which of the existing test methods is best applicable for the PRR. Focus at Tier 1 is on the level of ultimate biodegradability (mineralisation) a polymer can achieve. As a minimum requirement, a standard OECD 301 B, F (OECD, 1992a), or OECD 310 (OECD, 2006a) type screening test should be performed, although without the 10-day window requirement as is the practice for substances of unknown or variable composition, complex reaction products and biological materials (UVCBs) and complex mixtures (OECD, 2006b). Still within Tier 1, the registrant has the option to complement the former test with more targeted/realistic screening tests or to substitute if standard OECD 301 or 310 are not applicable. This includes 'enhanced ready testing' (e.g., prolonged test duration or larger vessels (ECHA, 2017b; Nabeoka et al., 2020; Nabeoka et al., 2021)), an inherent biodegradability test as laid down in test guideline OECD 302 (OECD, 1992b) and, where considered informative, the different methodologies of the ISO framework (e.g., ISO 14851 (ISO, 2019a) or ISO 14852 (ISO, 2021), ISO 14853 (ISO, 2016a), ISO 18830 (ISO, 2016b) or ISO 19679 (ISO, 2020a), ISO 22403 (ISO, 2020b), ISO 22404 (ISO, 2019b), ISO 23977-1 (ISO, 2020c) or ISO 23977-2 (ISO, 2020d), ISO 17556 (ISO, 2019c)).

However, most of the existing OECD methods are presently not fully applicable to insoluble and/or particulate substances, especially complex products with multiple constituents. Further alignment on method adaption and/or a revision of existing assessment schemes for biodegradation is warranted.

Testing towards adsorption/desorption behavior is also indicated at this initial tier to inform environmental distribution aligned to the use pattern and routes of environmental emission. Based on use patterns and emission routes, expert qualitative and potentially quantitative environmental distribution assessments can be conducted. The initial bioaccumulation in the environment assessment step is strongly aligned with the 'Human Health' Tier 1 step and, therefore, focusses mainly on bioavailability. As such, basic molecular descriptors are used as input parameters in this step, as indicated in ECETOC TR 133-2 (ECETOC, 2020).

The Tier 1 assessment for ecotoxicity focusses on acute effects to aquatic organisms on all three trophic levels (Fig. 1). This includes aquatic invertebrates (OECD 202 (OECD, 2004b)), aquatic plants (either unicellular algae (OECD 201 (OECD, 2011)) or *Lemna* sp. (OECD 221 (OECD, 2006c)). Tests with *Lemna* are warranted in case shading effects, e.g., from insoluble particles or colored test solutions, are expected. To avoid vertebrate (fish) tests at the Tier 1 level, the Fish Embryo Toxicity Test (OECD 236 (OECD, 2013)) or the new Fish Gill Cell Test (OECD 249 (OECD, 2021)) are foreseen, provided that there is adequate evidence that these alternative methods are sufficiently predictive for the PRR. Special consideration should be given to water soluble or dispersible large polymers, such as large cationic polymers, that have low/no systemic bioavailability but can exert adverse local external effects on aquatic organisms. Where low water solubility is given, chronic testing on Daphnia (OECD 211) can be considered instead of acute tests. It should be noted that the current aquatic test methods neither account for the testing of particulate materials nor for insoluble PRR. Hence, establishing a constant and homogenous exposure of the test organisms could be challenging during sample preparation, depending on the physico-chemical properties of the PRR (ECETOC, 2020). Further alignment is needed on best practices to set up representative and reliable test systems. The difficulties in performing aquatic toxicity testing with low soluble and particulate test material has been extensively discussed in the ECETOC TR 132 (ECETOC, 2018) and the need to differentiate between the intrinsic toxic effects impaired by the test material and those associated with that of direct or indirect physical interaction effects, the sum of intrinsic and physical impairment described as the overall adverse effect. The technical report also outlines the research needs related to the testing of particulate and low soluble test items. In summary, either testing conditions need to be adapted or there may also be no need to test such material for the given compartment or environmental conditions.

Concerning the terrestrial compartment, it should be assessed first whether a direct release to soil is likely based on the known use patterns, e.g., in plant protection or fertilizer applications. If this is the case, an initial acute test on earthworm according to OECD 207 test guideline (OECD, 1984) should be foreseen at Tier 1 level.

4.5. Outcome of tier 1: base set information requirements

Tier 1 will deliver information for development of an assessment document which describes physico-chemical properties, a base set of local toxicity, environmental acute toxicity, and environmental fate combined with qualitative use and exposure information, i.e. information on sectors of use, product categories, relevant exposure frequencies (single and/or repeated exposures) and routes (dermal, oral and/or inhalation), environmental releases, and an assessment of systemic bioavailability and relevant environmental compartments (based on basic physico-chemical information). This will define the need for further testing, justify no further testing to be done as hazards or risks

are unlikely, or suffice in determining appropriate risk management measures. In the context of REACH, this should be documented as a rational for testing proposals or definite assessments without further testing, for review by the regulatory authority.

5. Tier 2 information requirements

5.1. Tier 2: physico-chemical properties

The Tier 2 assessment of physico-chemical properties is triggered by the results of Tier 1 tests (Fig. 2). For example, it can be necessary to investigate biokinetics or degradation mechanisms and to identify the degradation products. Ideally, selective methods for both molecular weight and chemical composition will be applied at this stage rather than sum parameters, as different fractions of the test item might differ in fate and degradation (e.g., by molecular weight or copolymer composition). Additionally, it may be necessary to quantify the polymer in tissue or environmental matrix.

5.2. Tier 2: human health

The objective of Tier 2 for human health (Fig. 1, middle panel) is to enable the assessment of systemic effects, if warranted by the Tier 1 information on relevant external exposures, combined with significant systemic bioavailability. Based on the current state of the science, the preferred study type for Tier 2 is the OECD 422 combined repeated toxicity study with repro-developmental screening (OECD, 2016), due to the longer exposure duration and broader range of information generated as compared to a 28-day study (OECD 407 (OECD, 2008a)). However, there might be reasons to perform a 28-day or developmental toxicity study (OECD 414 (OECD, 2018c), for example, if the complementary data already exist. If the systemic bioavailability assessment indicates a concern for bioaccumulation for any constituents of the PRR, intelligent sampling and analysis may be conducted on samples (biological fluids, tissues) obtained from the OECD 422 study. The dose-range-finder necessary for the OECD 422 (OECD, 2016) study will, in parallel, provide sufficient information on acute lethality which will render dedicated LD_{50} testing unnecessary (Buesen et al., 2016; Gissi et al., 2017). We do assume that advancement in science and legislation within the next decade(s) will allow to replace the OECD 422 and other *in vivo* studies by alternative approaches for most if not all polymers, as for example discussed by Dent et al. (2021). If repeated exposure to respirable aerosols is of concern, based on the results of the respective Tier 1 *in vitro* study, a 90-day inhalation study (OECD 413 (OECD, 2018d)) with recovery period may need to be performed to better characterize effects on respiratory tissues. Any positive results from mutagenicity testing at Tier 1, may warrant a follow-up by *in vivo* studies. Again, organ burden and mutagenicity investigations can be included in the respective *in vivo* repeated-dose toxicity studies.

5.3. Tier 2: environmental distribution and ecotoxicology

Tier 2 testing is informed by the outcome of Tier 1 assessment and additional considerations on bioavailability and routes of exposure. Factors to evaluate the relevance of exposure in the different environmental compartments include environmental distribution and environmental emissions in turn informed by use patterns and tonnage. This will dictate the nature of the ecotoxicity studies (Fig. 1, middle panel), if any, to be performed at this subsequent tier.

For the aquatic compartment, further studies are triggered if a concern (based on effect level above an acceptable threshold) is indicated based on the Tier 1 testing regime and if the aquatic compartment is relevant. Once this prerequisite is fulfilled, the decision for further testing is based, in general, on the most sensitive trophic level from Tier 1 testing. Considerations on bioavailability may be part of the assessment, if relevant to the polymer, or factors determining the relevant compartment (e.g., sorption and water solubility). If the *in vitro* test with fish embryos or fish gill cells indicate a $\geq$10-fold higher sensitivity compared to aquatic plants and invertebrates, an acute fish test (OECD 203 (OECD, 2019)) should be performed. If this is not the case, a chronic test with aquatic invertebrate *Daphnia magna* (OECD 211 (OECD, 2012)) should be performed. *In vivo* confirmatory acute testing in fish is not necessary if the applicability domain has been proven for the *in vitro* acute fish testing of the particular polymer class. This differentiation would allow to minimize the number of fish tests at this level, as testing focusses strongly on the most sensitive organism group only. Regardless of which aquatic toxicity test is performed, the bioavailable fraction of the polymer should be applied via generation of a water accommodated fraction (WAF) in case the polymer cannot be solubilized for testing.

With regards to the terrestrial compartment, the Tier 2 assessment foresees a check as to whether soil is a relevant environmental compartment with significant distribution via indirect exposure. This is an add-on to the check on direct release to soil from Tier 1. If soil is a relevant environmental compartment based on direct release or indirect exposure, an acute earthworm test (OECD 207 (OECD, 1984)) would be required. For those PRRs which yield an effect level from acute testing above an acceptable threshold, taking exposure (distribution & sorption processes) into consideration, a long-term reproduction test with earthworm would be recommended. Depending on their density and/or charge, polymers that reach a water course will likely distribute to the sediment compartment over time, especially if they are poorly soluble, or even particulate, or if they show strong adsorption properties. Therefore, a test with sediment-dwelling organisms is warranted if the environmental distribution and use pattern identifies sediment as a priority compartment for distribution. The need for higher tier testing should include a review of the potential bioavailability in the environmental compartment. It is expected that uptake may be limited by strong sorption and a limited desorption from the environmental matrix.

If any concerns remain regarding the bioaccumulation potential of the polymer (i.e. Tier 1 does not exclude systemic bioavailability of the polymer or a relevant fraction of it), additional insight is proposed in Tier 2 using *in vitro* metabolism (biotransformation) assays such as the OECD 319 A fish liver hepatocyte (OECD, 2018a) or OECD 319 B fish S9 liver fraction study (OECD, 2018b). The test should be conducted with the bioavailable fraction only as any substance needs to enter the hepatic cells first before any biotransformation can take place and only if the concentration decrease in the test systems can be measured with a valid analytical method. The latter could be difficult to establish depending on the complexity of the bioavailable polymer fraction and may be a roadblock in certain cases with potential for further method development. Once such data are available (i.e., the component of focus in the assessment of kinetics is identified), they could be proceeded e.g., by applying *in vitro - in vivo* extrapolation (IVIVE)/physiologically based toxicokinetic (PBTK) modelling to inform the bioaccumulation assessment. The reader is referred to ECETOC TR 133-2 (ECETOC, 2020) for a deeper discussion on bioaccumulation assessment.

Tier 2 does not foresee additional (higher tier) biodegradation or other fate studies which, if required, are carried out under Tier 3.

5.4. Outcome of tier 2

In the context of REACH, the outcome of Tier 2 would be a Chemical Safety Report (CSR) with RA for all identified uses, and, if necessary, testing proposals for targeted Tier 3 studies. Further animal studies in Tier 3 may be necessary if the RA demonstrates undue uncertainty which cannot be resolved by new approach methodologies (NAMs) or proportionate risk management measures. Further discussion will be necessary to agree on which types and degrees of uncertainty are required to trigger Tier 3 studies. As many applications leading to potentially higher exposure of consumers are covered by specific

legislation (e.g., drugs, excipients, food additives), it seems unlikely that Tier 3 studies will become necessary from a scientific perspective for RA of many polymers under REACH registration.

6. Tier 3 information requirements

6.1. Tier 3: physico-chemical properties

Depending on the results of Tier 2 testing, further assessment might be necessary. This will, however, only be necessary for particular cases as most of the properties have been assessed at Tier 2.

6.2. Tier 3: human health

For the assessment of impacts on human health, higher tier studies demanding large numbers of animals will only be triggered where potential risks cannot be assessed by data obtained in Tier 2 with sufficient confidence (Fig. 1, right panel). This might be the case if the RCR is close to 1 based on the DNEL derived from the OECD 422 (OECD, 2016) study, or if Tier 2 studies were inconclusive. If a specific concern or mode of action has been identified in Tier 2, or based on structural or metabolic similarity to other polymers, functional groups or chemicals, it should be assessed if additional *in vitro* studies or targeted *in vivo* studies using fewer animals can be applied to enable an appropriate RA. If this was judged impossible, the study types would, at the current state of regulatory science, typically be the 90-day repeated dose study (OECD, 2018d, e), prenatal development toxicity (OECD 414 (OECD, 2018c)) or the extended one-generation reproductive toxicity study (OECD 443 (OECD, 2018f)), depending on the type of effects observed in the OECD 422 (OECD, 2016) screening study.

6.3. Tier 3: environmental distribution and ecotoxicology

An RA step is introduced between Tier 2 and Tier 3. This risk assessment step concluding the Tier 2 assessment identifies potential testing needs on target environmental compartments or species (Fig. 1, right panel). In case it is not possible to derive an RCR at the end of Tier 2 due to missing exposure models, the Tier 3 environmental information requirements should be established based upon (1) the identified relevant environmental compartment(s) and (2) hazard concerns (based on effects measured in Tier 2 accounting for bioavailability for certain species if relevant) identified in Tier 2. Hence, further studies will only be triggered for PRR where a proper RA based on Tier 2 information indicates such need.

The focus of Tier 3 fate testing is on realistic removal and degradation information in relevant compartments. However, it is doubtful that the currently available exposure models (as e.g., implemented in EUSES/CHESAR) allow the derivation of accurate environmental exposure levels for many types of polymers especially those with a higher MW. This is mainly due to the fact, that necessary physico-chemical input parameters for the tools mentioned above are likely either not available or meaningful for many polymers. Therefore, fate processes and predicted environmental concentrations can generally not yet be established for many types of polymers. In this context, a distinction should be made between the need to adapt model formulation and/or choice of input parameters, as opposed to obtaining better parameter estimates for polymers for use in existing models. For example, a fate simulation study (such as OECD 314 B (OECD, 2008b) and OECD 303 (OECD, 2001) tests) can provide a robust experimental alternative for modelling the behavior, degradation and distribution of a polymer in a wastewater treatment system. For experimental studies in the laboratory or monitoring in the field it is, however, a prerequisite that suitable analytical methods are available. In certain cases, the use of higher-tier environmental fate simulation testing (OECD 307 for soil (OECD, 2002a), OECD 308 in sediment-water systems (OECD, 2002b), OECD 309 for surface water (OECD, 2004c)) may be feasible to establish information on environmental fate, degradation, and distribution of polymers. However, with the currently existing technologies, the ability to follow the environmental metabolism of most polymers will present a huge analytical challenge even if a radiolabeling of the polymer is possible. Information on adsorption to and desorption from e.g., soil and/or activated sludge, as relevant, or potential formation of non-extractable residues should be considered to decide on the need for Tier 3 simulation testing and the relevant environmental compartments to be targeted by such studies. Once again, detailed guidance is required on the implementation and interpretation of such studies as well as a need for considerable advancement in analytical means.

Tier 3 environmental fate simulation studies, including related analytical procedures, are identified as a research need, as are in-depth discussions on the applicability domain and adaptation of such higher-tier environmental studies for polymers. For example, major practical difficulties can be envisaged for most polymers in performing studies that include environmental metabolism, and elucidation of metabolites with a possible concern, which is a specific application of higher-tier fate tests. Much development and dialogue is needed before such studies can be implemented as a standard requirement.

Higher tier fish studies can be part of the Tier 3 evaluation, when identified as relevant and necessary information based on Tier 1 and 2 assessments. Additional hazard characterization may be deemed necessary at this potential step to refine risk characterization and management. This may also include chronic studies towards aquatic vertebrates (fish), sediment-dwelling organisms, and/or terrestrial organisms, depending on the route of exposure, the bioavailability and distribution in the environmental compartment as well as any identified effect at Tier 1 and 2.

Chronic testing for a sediment-dwelling organism may be included such as on Chironomids or *Lumbriculus* oligochaetes (e.g., OECD 218 (OECD, 2004d), OECD 225 (OECD, 2007)). For very poorly soluble and particulate polymer forms, careful consideration should be given to the test concentrations employed in such toxicity tests. These should be conservative, yet realistic worse-case, and should be based on conservative predicted environmental concentrations and will be maintained within limits which do not lead to an alteration of the sediment matrix properties.

Dietary or aqueous uptake studies could also be added here to gain a better understanding of bioavailability and bioaccumulation, when identified as relevant and necessary information based on Tier 1 and 2 assessments. Care should be exercised when interpreting results from bioaccumulation tests performed using small organisms (e.g., *Hyalella azteca* (Kosfeld et al., 2020)), since polymers may adsorb to the surface of the test organism, rather than undergo internal uptake, leading to an overestimation of the bioaccumulation potential. Thus, considerations on bioaccumulation may need to distinguish between external adsorption and internal bioaccumulation (by analogy to external vs systemic bioavailability).

6.4. Outcome of tier 3

The outcome of Tier 3 will be a CSR and an update of the REACH dossier for those endpoints which were tested following approved testing proposals in Tier 2.

7. Discussion

We propose a three-tiered approach to fulfil standard information requirements for polymers for REACH. The key elements of this approach are:

- Generally, polymer identity, form and physico-chemical properties define the nature of the test item, i.e., the polymeric substance, the polymer product, or an extract of the polymer product. Therefore, the polymer form needs careful consideration for testing.

Table 1
Sources of uncertainties in SIR approach and related opportunities for improvement.

Source of Uncertainty	ECETOC Approach	Current REACH testing approach
Methodology – Some of the guideline methods used in regulatory requirements may not be applicable to some polymers or not deliver results meaningful for hazard characterization or exposure assessment	• Some methods will have to undergo validation for polymers • Requirements will have to allow for justified deviations • Systemic bioavailability approach to be further developed	• Some methods will have to undergo validation for polymers • Requirements will have to allow for justified deviations • Hindered uptake and various extract testing approaches to be further developed
Exposure/risk-based triggers	Uncertainty in exposure assessment and use descriptions applied at testing phase needs to be reduced	Uncertainty in exposure assessment and use descriptions applied at risk assessment phase needs to be reduced
Volume-based triggers	This concern is not raised by the ECETOC approach but circumvented by targeted grouping and bracket testing approach.	Uncertainty whether protection goals for individual humans are achieved. Uncertainty how this will allow targeted selection of test materials for PRR groups

- Full use of the grouping approaches by similarity of chemistry, physico-chemical properties, and hazard, avoiding fragmentation along inappropriate thresholds of e.g., MW or tonnage, thus facilitating clear definitions of group boundaries. The grouping approach will allow to only test a small number of representative polymers out of a group and still enable RA for all group members.
- Testing for physico-chemical data is triggered by considerations of structure, known properties and effects, rather than by the tonnage. The main criterion to trigger a physico-chemical measurement for a specific polymer is its relevance for the hazard and exposure assessment.
- An integrated testing strategy: Based on already available data and data obtained in Tier 1, decisions for moving to Tier 2 and further studies are based on considerations of properties and effects, combined with systemic bioavailability estimates and use and exposure considerations.
- No vertebrate animal testing at Tier 1, as this tier addresses bioavailability, local effects to human health and acute effects for relevant indicator species. Any vertebrate animal studies for REACH registration would be routed via test proposals in Tiers 2 and 3 at the earliest if non-animal approaches to characterizing risk have been exhausted in Tier 1.
- QSARs and modelling approaches (where applicable) should be used in combination with data from other sources e.g., testing whenever possible, especially to foster grouping approaches of polymers.
- A targeted testing approach, based on clearly defined triggers, bioavailability, and following scientific and practical considerations, and leading to a balanced and protective approach.

This approach is a conceptual proposal and does not specifically address the availability of validated methods nor the applicability of existing test guidelines for polymer testing. Key considerations and requirements to adapt existing test guidelines to permit the derivation of meaningful endpoints have been discussed in the ECETOC TR 133-2 (ECETOC, 2020), where several areas requiring further research and development have been highlighted.

An informed decision making with this approach should take into account the various sources of uncertainty. Table 1 provides an overview of sources of uncertainties and how these could be addressed. If RAs result in an RCR >1, exposure assessment can refine such RAs. Under REACH, manufacturers communicate intended uses, exposure scenarios and risk management measures (RMM) in a formalized manner down the value chain. Refining RA by exposure data can be preferred over additional hazard data, since, it seems ethically and politically questionable to perform additional vertebrate animal testing (Fentem et al., 2021; Ball et al., 2022) where concerns can be more effectively and more appropriately addressed by improving the communication of use and exposure information. On these grounds, the approach proposed herein pursues the objectives of chemical safety by RA, and risk management by communication of handling and use instructions. Notably, our approach does not aim for full hazard identification of all PRR polymers, but only for some of them, selected by the criteria described. This is because neither a volume-driven testing approach nor a risk-driven testing approach will lead to full hazard characterization of all PRR, while a tonnage-driven scheme is associated with higher uncertainty about risks, particularly to humans (Table 1).

8. Summary and conclusions

In summary, we propose a three-tiered approach to fulfil SIR under the EU REACH framework for PRR. Conventional RA approaches applied to chemicals may not be suitable for polymers and may not offer the most efficient approach using the lowest possible number of animals. A key principle of the approach is initial grouping followed by Tier 1 testing which can be sufficient for a definite assessment of a polymer or will direct targeted testing in higher Tiers. Tier 1 is entirely based on *in silico* and *in vitro* methods, with the exception of non-vertebrate short-term aquatic toxicity testing. Assessing systemic bioavailability is an integral part of Tier 1, as it defines toxicological concerns. The decisions for further studies are based on considerations of properties and effects obtained in Tier 1 (or already known before), combined with systemic bioavailability estimates and use and exposure considerations. It is likely that for most PRR, the Tier 1 data on hazard, use and exposure will be sufficient for the protection purpose of REACH. Any vertebrate animal studies for REACH registration would be routed via test proposals in Tiers 2 and 3. SIR need to be sufficiently simple and clear but at the same time, they should be proportionate regarding the use of vertebrate testing and resources and use scientific consideration in order to allow for effective chemical risk management. The proposed approach aims at an optimum balance of these different aspects. To gain acceptance and formal incorporation into practice, this approach will be presented and discussed with regulators and stakeholders, including animal welfare organizations, and it will be tested in case studies. Based on the outcomes and experiences, the approach will be further refined. We believe that the principle of a tiered approach with no vertebrate animal testing at Tier 1, followed by justified, limited and targeted vertebrate testing in higher tiers while considering bioavailability, environmental distribution, and material properties first, provides a basis for modern and considerate data generation for the next decade to ensure the selection of polymers for safe production, use and recycling, until a transition to fully NAM based RA will be achievable in chemical regulation.

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Declaration of competing interest

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Data availability

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