



## Plastics Fate and Effects in the Human Body

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**Compilation of existing regulatory documents applicable to  
microplastic particles of various origin**

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## Executive Summary

This report aims to compile relevant regulatory documents to provide an overview on (I) the current practices in European regulatory frameworks for non-natural polymers in general; and (II) review the current state of nano- and microplastic risk assessment according to ongoing research activities.

The formation of microplastic particles from larger polymer items is considered an inherent property of most artificial polymers. Currently, polymers are exempted from registration under REACH. However, the registration of selected polymers is anticipated and concepts such as the Polymers of Low Concern (PLC) and the Polymers Requiring Registration (PRR) concept are under consideration to allow scientifically sound justifications for selecting polymers that will require registration. In that regard, criteria describing the physical and chemical properties relevant for risk assessment have been formulated. However, primary as well as secondary nano- and microplastic particles are currently not considered explicitly in regulatory frameworks.

In addition, risk assessment strategies specifically for nano and microplastic have been proposed by several scientists. These approaches are summarized here and put into the context of WP4 goals and the work conducted in the experimental WPs.

This report shows also the need for progress in our scientific understanding to clarify the connection between physico-chemical properties and potential hazardous effects of polymers, and identify the potential for read-across from pristine materials used in laboratory testing to the weathered or aged material found in the environment that humans are ultimately exposed to. In addition, new EU initiatives fostering the development of restriction and mitigation measures to reduce plastic use and prevent plastic product release into the environment are highlighted, such as the EU Plastics Strategy or the Towards zero pollution action plan, as part of the EU Green Deal (see also D6.3).

This overview on the current regulatory situation provides a starting point and basis for the work planned within WP4, specifically for the development of an integrated risk assessment strategy for human and environmental health within T4.1 and T4.2.

## 1. Description of task

Our current understanding of the risk of nano- and microplastic particles for human health is incomplete and there is a need for a scientific strategy, supported by reliable and validated methodologies, to assess exposure and hazards associated to these materials for humans and their direct environment along their lifecycle. Such a strategy will be developed in PlasticsFatE focusing on consumer (food, drinks), occupational (air) and environmental (agricultural soils) risks in compliance with existing regulations and guidance. This strategy will be based on the results achieved in PlasticsFatE WP1-3 and WP5, in close cooperation with the other CUSP projects, and on research and innovation outside the projects concerning the development of safe and sustainable plastics.

## 2. Description of work & main achievements

### 2.1. Regulatory background

Polymer particles are characterised by their longevity and persistency in the environment. Plastic waste (“plastic debris”) is wide-spread and accumulates in the environment, where it slowly breaks down into micro- and subsequently also nano-plastic particles. Generally, polymers are considered to be of low concern, but it is currently under scientific debate, as well as of public concern whether micro- or even nanoscale polymer particles may pose specific threats to humans and the environment. Polymer particles come with chemicals added to the plastics to improve their performance, functionality and ageing property (e.g., plasticizers, flame retardants or light and heat stabilizers), or adsorbed to MP/NP particles from the environment, including persistent organic pollutants (POP). Due to their hydrophobicity and small size, MP/NP particles may become vectors for these contaminants to enter the human body. At the same time, there is evidence that they may also act as vectors for pathogens. In this chapter, the regulatory background for polymers (and not specifically for nano- or microscaled polymer particles) is summarized.

#### 2.1.1 Polymer of low concern concept

Based on several polymer expert meetings held by the OECD, first a polymer definition was agreed on, followed by the development of the polymer of low concern concept [1].

The PLC (Polymer of low concern) concept defined criteria that if met, imply that a polymer has a low potential to exert hazardous effects. These criteria are:

- (1) Concerning monomers (Mn): the range of 1,000 - 10,000 Mn was agreed as a likely range of the concern value.
- (2) Concerning molecular weight (MW) of low MW compounds giving rise to concern: the agreement was MW below 1,000.
- (3) Concerning percentage of low MW compounds of concern: no agreement
- (4) Concerning functional groups: only one value, applicable to epoxy and anhydride groups was mentioned (it was 1 reactive group in 20 monomer units); no general conclusion was reached.
- (5) Metal content: no value agreed.
- (6) Extractivity in water: 10mg/l was seen as acceptable, provided that test conditions were standardized
- (7) Cationic charge density: the 5,000 equivalent weight value was accepted (as defined by EPA: not more than one cationic charge in 5000 monomer units).

Source: [<https://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm>].

However, these criteria were set based on a limited database (i.e. not enough background data available), and for some of them no agreement was reached. Nevertheless, the PLC concept has been implemented in various jurisdictions around the globe (US-EPA and most other non-EU jurisdictions), but has not been applied in the EU under the REACH legislation [2, see Table 1].

### 2.1.2 Exemption of polymers from REACH

Under REACH, polymers are currently exempted from registration. The guidance document for monomers and polymers [3] states: “Owing to the potentially extensive number of different polymer substances on the market, and since polymer molecules are generally regarded as representing a low concern due to their high molecular weight, this group of substances is exempted from registration and evaluation under REACH. Polymers may however still be subject to authorisation and restriction”. Further, the guidance specifies with regard to monomers: “Nonetheless, manufacturers and importers of polymers may still be required to register the monomers or other substances used as building blocks of the polymer, as these molecules are generally recognised as of higher concern than the polymer molecule itself.” Because the exemption of polymers from registration under REACH was mainly driven by the fact that the high number of different polymer materials will not be manageable for registration, there are now activities to implement a prioritisation concept under REACH legislation in order to request the registration of a range of selected polymers. Here, a practical and cost-effective procedure to select polymers requiring registration shall be established. This includes the elaboration of two registration approaches for future use: (i) Grouping polymers for registration, and (ii) defining a category (or categories) of polymers of low concern. The duty of registration of certain polymers of concern under REACH was also proposed in the EU’s Chemicals Strategy for Sustainability (CSS) [4, 5].

### 2.1.3 Towards the registration of selected polymers under REACH

The Polymers requiring registration (PRR) concept by the European Commission specified criteria in the so called Wood/PFA report [6]. Here, PLC criteria, as well as criteria relating to the bioavailability of polymers are discussed. The following polymer types were identified to be PRRs:

- Cationic polymers
- Anionic polymers
- Amphoteric polymers
- Nonionic polymers with surface-active properties
- Low molecular weight polymers
- Polymers containing low molecular weight oligomers
- Polymers with reactive functional groups
- Some types of degradable polymers

The main assumptions underlying this selection are that transfer across biological membranes does not occur for the high molecular weight polymers, and that surface charges and reactive groups induce toxicity. However, there is so far no clear understanding established regarding which chemical features of a polymer would be predictive of toxicity [see for example 7]. The report also tries to quantify the benefit of polymer registration under REACH and points to the many unknowns and uncertainties in the field: “Data gaps make it difficult to draw direct, statistically robust comparisons between the costs and benefits of registering PRRs. Quantified estimates of health and environmental benefits through registration of PRRs amount to around €30 billion over 40 years (range €14 to €52 billion), while costs are estimated at €2.5 billion (range €0.8 to €5.2 billion), though

several important costs and benefits could not be quantified.” After considering the Wood/PFA report the Commission will draft a proposal to review the REACH regulation to add registration requirements for polymers by the end of 2022.

The criteria have been critically reviewed and suggestions for refinements and specification have been made by scientists [8]. For example, microplastic should be considered for PRR definition, as formation of microplastic is an inherent property of many polymers, and it is highly persistent. Also the larger polymers, which are exempt from REACH due to molecular weight limits, need more specific consideration in their view, as for example an increased uptake of associated chemicals into organisms may occur, but these types of co-exposure to additives, monomer residues or other chemicals is not considered (see also 2.6).

Industry is also actively reviewing the need for polymer regulation under REACH. ECETOC (the European Centre for Ecotoxicology and Toxicology of Chemicals) is an independent, non-profit organisation funded by 35 chemicals companies that works with other leading organisations including ECHA, UNEP, Cefic and a number of European academic and research institutes to address issues regarding chemical safety through workshops, expert meetings and task forces. A task force built by ECETOC provided two reports dealing with the selection of polymers that require registration under REACH. The first report [9] outlines a full risk assessment framework, the *ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers)*, aligned with the internationally agreed paradigm for chemical RA as published by the WHO IPCS (2004, 2010). The second report [10], reviews available analytical tools as well as hazard assessment methods for environmental and human health with regard to their applicability for risk assessment of polymers. Both reports provide common specific recommendations for future directions:

**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 (1) to substantiate the PLC concept and (2) to identify under which conditions the presence of specific structural alerts or physico-chemical properties poses 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.*

Micro- and nanoplastic particles were excluded from the consideration on polymer registration in both reports [9, 10], i.e. size is not decisive for registration, and micro- and nano-plastics are not considered to require a special treatment in terms of registration. But information from the research field of micro- and nano-plastic analytics, fate, and hazard assessments was considered for building the framework.

A summary of intended restriction measures to reduce release of plastic waste and use of primary microplastic in the EU is provided in PlasticsFatE deliverables report D6.3 (e.g. ECHA restriction plan for plastics).

### 2.1.4 Regulation food contact materials

The EFSA Panel on Contaminants in the Food Chain (CONTAM) dealt with the topic of contamination of food intended for human consumption (e.g. sea food) by MNP particles. It points to the fact that there is no regulation in place for microplastic contamination in food, a general lack of knowledge regarding human hazard, test models to assess human hazard, and plastic particle identification and characterisation in food matrices [11].

To date, the focus of activities is on additives added to food contact materials [12-15]. EFSA have provided guidance documents on the use of substances added to food contact material made from plastic. These focus on the migration of such substances from the packaging into the food, in order to prevent human exposure to these substances. In addition, there is guidance on the use of recycled plastics for food packaging. (see also 2.1.9). Among other recommendations, it states that only plastic materials and articles complying with the provisions laid down in Directive 2002/72/EC (positive list of substances contained in plastics) should be used as input for the recycling process. Basically, the plastic recycling process needs to be able to produce a reproducible quality of the recycled plastics, to be controlled by an effective quality assurance system. Therefore, only recycled plastics from a recycling process managed by an effective quality assurance system should be placed on the market [16].

In the scope of the EU's Chemicals Strategy for Sustainability (CSS) following the European Green Deal, the European commission clearly lays down the intention to minimise the presence of substances of concern in products, in particular those with highest potential for circularity, including food packaging. Particular focus is on those chemicals that are carcinogenic, affect the reproductive or the endocrine system, or are persistent and prone to bioaccumulation. Based on this strategy, recently a list of "food contact chemicals of concern" was elaborated and these chemicals were proposed to be phased out [15]. For most of these, there is no strict regulation, with the exception of some specific substances, for example phthalates, for which evident endocrine disruption has been shown in the past [17].

In addition, polymers might be used as food additives, and evaluation of potential hazard is possible by using available methods [18]. However, it was pointed out that uncertainties arise from the unknown degree of impurities stemming from manufacturing (crosslinker, polymerisation initiators, polymerisation solvent). These impurities should be specified for use of the polymer as food additives since these need to be part of the safety assessment.

### 2.1.5 Occupational exposure levels in European countries

Exposure to polymer dusts is not often regulated in the EU but a few maximum exposure levels at workplaces have been set in some European countries:

- For acrylic acid polymer (no CAS identity number) an eight-hour average and a short term limit value of fifty micrograms per cubic metre has been recommended by the German IFA [19].
- For polymer dust (polyamide, polyformaldehyde, polycaprolactam, polyethylene, polymers based on acrylic monomers, polypropylene, polyurethane etc.) (no CAS identity given) an eight-hour average limit value of five milligram per cubic metre has been set in Latvia [19],
- For polymeric diphenylmethane diisocyanate, polymeric MDI, CAS 9016-87-9, an eight-hour average and a short term limit value of fifty micrograms per cubic metre has been recommended by the German IFA [19].
- For PVC, polymers of vinylchloride and vinylidene chloride (no CAS identity number) an eight-hour average limit value of ten milligram per cubic metre has been set in Latvia [19].



### 2.1.6 Microplastics in drinking water

The European Parliament seeks to improve the drinking water quality in Europe, and to reduce the use of (plastic) bottled water. Accordingly, the European drinking water directive was adopted to ensure a better drinking water quality monitoring. “By early 2022, the Commission will draw up and monitor a list of substances or compounds of public or scientific concern to health. These will include pharmaceuticals, endocrine-disrupting compounds, and microplastics. The Commission shall also establish European lists indicating which substances are authorised to come into contact with drinking water.” (<https://www.europarl.europa.eu/news/en/press-room/20201211IPR93619/parliament-adopts-deal-to-improve-quality-of-tap-water-and-reduce-plastic-litter>). So far, the list has not been published for unknown reasons.

### 2.1.7 Restriction of microplastics

A summary of intended restriction measures to reduce the release of plastic waste and use of primary microplastic in the EU is provided in PlasticsFatE deliverables report D6.3 (e.g. ECHA restriction plan for plastics, Reach Annex XV).

### 2.1.8 Quality criteria aiming at transparent description of polymer particle properties

In addition to the PLC and PRR criteria that have been formulated with the focus on selecting polymers that will require registration under REACH, there has been effort to develop quality criteria with a broader background. In addition to the PLC and PRR criteria, these have been selected specifically for microplastic and nanoplastic (MNP) particles [20, 21]. They focus on the hazard assessment for these particles and are hence much more specific, and use existing criteria from engineered nanomaterials research as a basis. The quality criteria set up a list of particle characteristics and properties, as well as of interactions with surrounding media (Figure 1).

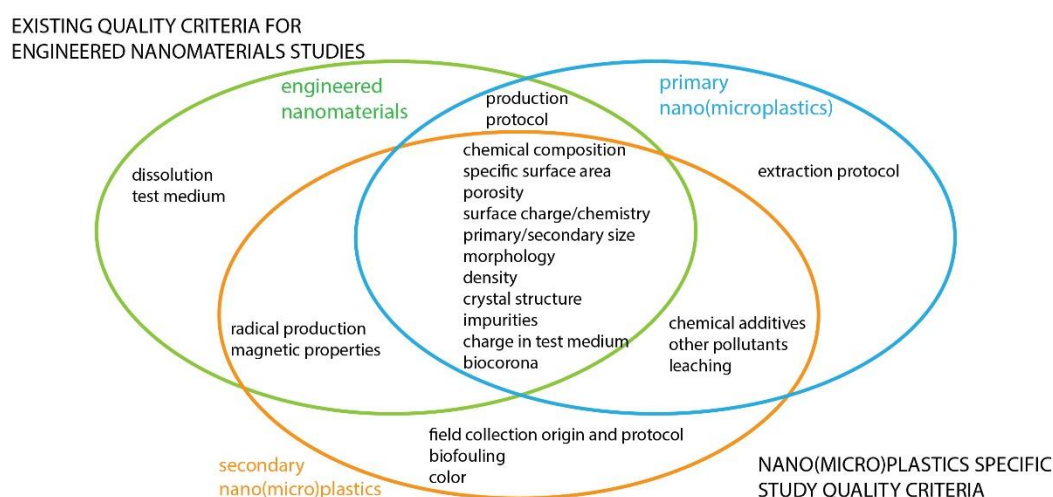


Figure 1. Summary of criteria and parameters relevant for reporting and interpretation of hazard studies related to nano- and microplastic. Modified after [21]. More elaboration on each criterion is provided in the publication.

By describing as much of these parameters as possible alongside to a hazard study shall ensure that results are comprehensible and also easier to compare among studies. This will foster a better harmonisation of studies, identification of hazardous polymers, and use of hazard data for regulatory purposes. As stated accordingly in [20], “In far too many instances, studies suggest and speculate mechanisms that are poorly supported by the design and reporting of data in the study. This represents a problem for decision-makers and needs to be minimized in future research.”

### 2.1.9 Additives, impurities, unreacted monomers and polymer degradation products

In addition, there is rising concern regarding the human and environmental hazard posed by the cocktail of substances that are associated with plastic materials from different sources. Impurities, unreacted polymers and degradation products are chemicals not added intentionally to a polymer. According to the REACH Guidance on Monomers and Polymers “...These stabilisers and impurities are considered to be part of the substance and do not have to be registered separately.” [3]. Due to this, and to non-transparent production and supply chains, the exact composition and concentrations of plastic associated chemicals are mostly unknown. There are several studies on the release as well as on hazardous effects of chemical mixtures from polymers, however these studies focus on environmental organisms [e.g. 22]. There are no data yet available on human cell models or similar, but the effects of single chemicals used as plastics-additives have been shown [23, 24].

On the other hand, additives are added intentionally to polymers to obtain specific properties, and require registration under REACH, and when used in food contact materials (Article 3(7) of Commission Regulation (EU) No 10/2011). Based on the publicly available information in the REACH registrations database, ECHA together with industry build an inventory of the most commonly used additives (i.e. produced in high volumes), including pigments (<https://echa.europa.eu/de/mapping-exercise-plastic-additives-initiative>). This inventory is not yet linked to hazard data, but provides a profound basis to do so. In addition, additives in food contact materials have been explored [12, 13], leading to an inventory of plastic food packaging associated chemicals and linking hazard data to identified chemicals: “Of the 906 chemicals likely associated with plastic packaging, 63 rank highest for human health hazards and 68 for environmental hazards according to the harmonized hazard classifications assigned by the European Chemicals Agency within the Classification, Labelling and Packaging (CLP) regulation implementing the United Nations' Globally Harmonized System (GHS).” [12]. The authors point to the fact that many plastic-associated chemicals remain unidentified, and for many of those identified hazard data is lacking. Within PlasticsFatE, we will investigate this issue for the IATA development (see 2.2.2) as a specific case study.

## 2.2 Scientific progress towards microplastic risk assessment

### 2.2.1 Current status of risk assessment according to the scientific literature

There are a growing number of articles addressing the potential risks of micro- and nanoplastic particles to human health. As well, hazard and fate studies employing human cell cultures or other models for human toxicity are increasingly conducted, however, these are not elaborated in detail here.

A recent review by Rahman et al. (2021) [25] evaluated 129 research articles for their assessment of human health risks. Toxicological analyses are now available for the three major routes of human exposure: Ingestion, inhalation, and dermal contact [see e.g. 25, 26, 27]. The presence of MNP may cause oxidative stress and cytotoxicity, either due to the physical or chemical properties of the foreign matter or the response of the exposed tissue [26]. In chronic cases, inflammatory reactions can lead to cancer, which has been observed in workers in synthetic textile or flock factories [28]. Altered metabolism, neurotoxicity, reproductive toxicity, and disruption of the immune function are also cited as potential health risks [25, 26]. And even if only small fractions of MNP are able to overcome epithelial barriers, the long-term effects of persistent particles and associated chemicals should not be underestimated [29].

Moreover, MNPs may move from the site of entry to distant organs or tissues in the body. As early as 1990, Jani et al. reported polystyrene spheres in the liver and spleen of rats after administration by gavage [30].

However, these assumptions are predominantly based only on observations in animal models or in vitro approaches. It remains unclear to what extent the toxicological effects observed in animal models are transferable to humans [31, p. 109]. In addition, polystyrene in the form of monodisperse spheres is the most commonly used polymer in toxicological studies to date, even though it accounts for less than ten percent of the total amount of plastics produced [32]. Therefore, it is doubtful whether, without extensive standardization, representative reference materials, and inclusion of physicochemical properties as well as associated substances; a realistic assessment of health risks to humans is possible [29, 32, 33]. Toxic effects may also depend on the size and shape of the plastic particles. Kooi and Koelmans therefore suggested to consider continuous scales for probabilistic risk assessment of microplastics [34]. The complex mixtures of different chemicals found in environmental samples of MNPs may ultimately present too high a hurdle to separate the different effects of combinations of chemicals and particles [35].

Recent studies point to the need for adopting tools and models to estimate exposure and fate of microplastics, to ultimately perform risk assessment. For example, modelling human exposure to microplastic and the associated chemicals needs to consider microplastic particle characteristics and leaching rates of chemicals in a combined manner for a holistic risk assessment [e.g. 36]. As well, screening and prioritization tools for hazard data are needed, in order to ensure the use of fit-for-purpose data for risk assessment [35]. In principle, the same is true for the assessment of environmental exposure and hazard data, for example in freshwater [37].

There are divergent views on the integration of plastic associated chemicals into risk assessment. On the one hand it is argued that the risk assessment of plastic associated chemicals is fully covered via REACH and the related guidance for the assessment of mixtures [32, 38]. On the other hand, it is argued that the kinetics of ad- and desorption of plastic associated chemicals needs to be taken into account in order to reliably calculate human exposure levels. In addition, the effect of complex mixtures need consideration, here guidance on mixture assessment is available [39].

Besides primary microplastic falling under restrictions (see D6.3), there is also intentionally produced microplastics powders for industrial use. One example is 3D printing. No bans apply for these primary

microplastic particles, because they are considered as an intermediate stage during the full life cycle of the final product, then fused together during the sintering/melting processes. A careful adoption of regulation for microplastics, not hindering material innovation is claimed by Mitrano & Wohlleben (2020) [2].

Overall, promising steps have been made towards identifying and prioritizing major research needs as well as current limitations in microplastic risk assessment, and the development of the respective tools and models [40, 41]. However, a fully operational human health risk assessment is not available to date [33].

In this regard, data gaps that have been identified and include the characterisation of target populations that may be specifically sensitive or vulnerable to MNP exposure, for example the elderly, infants and young children. These populations can be considered in risk assessments by using assessment factors. Here, no data are available. Further, there needs to be greater consideration of ingestion of microplastics and their associated chemicals via routes not directly associated with purchased food and drink. For example, there is growing evidence of the prevalence of microplastics (particularly fibres) in household dust, and therefore there is opportunity for hand to mouth transfer, as well as from other domestic plastic objects, such as toys, food and drink containers, particularly for very young children (see D2.1 Overview of human exposure sources and levels of MP/NP). Therefore, other exposure locations, particularly in domestic settings, need further identification and characterisation.

The following table (Table 1) summarizes the main gaps and obstacles that need to be overcome by developing a new risk assessment strategy for nano- and microplastic and associated chemicals (as indicated in the PlasticsFatE DOA):

Table 1. Summary of scientific literature on risk of nano- and microplastic and the identified research needs, and if and how they are addressed within PlasticsFatE.

<b>Specific gaps and obstacles in microplastic research related to risk assessment were pointed out to be:</b>	<b>PlasticsFatE is addressing these issues by:</b>	<b>Reference</b>
General need for improved quality of methods (characterisation, exposure, fate, hazard) and international harmonisation of methods	In various tasks in WP1-5, e.i. WP1: establish representative reference, benchmark and test materials, develop advanced methods for basic physicochemical characterization of MP/NP and associated additives/contaminants, protocols for dispersion development and monitoring of particle behaviour in testing media WP2: new and advanced protocols for determination of exposure and fate of MP/NP in food, water, air and in the human body WP3: Adapt, apply and validate current test methods, including in vitro and in vivo methods, for the detection of molecular effects and adverse outcomes, new in vitro models as validated alternatives to reduce animal models	[31] SAPEA 2019, [42], [43]

Risk of microplastic particles against the background of naturally occurring particles	(not addressed in PlasticsFatE)	[41] Koelmans 2022
Use of AOPs to identify microplastic hazard	WP3: identification of novel modes of action and biomarkers WP4.1 and WP4.2: AOP will be integrated into the IATAs WP4.3 for predictive risk assessment in the context of multi-criteria decision analysis	[44] Koelmans 2017
<p>Test materials do not reflect the diversity of industrially produced plastics</p> <ul style="list-style-type: none"> <li>• Reference materials mimicking weathered plastic materials</li> <li>• Labelling for detection in organisms</li> <li>• Only few chronic data available</li> </ul>	<p>Microplastic particle portfolio consists of different polymers with different sizes and shapes made available in WP1 (WP1-3; see also D1.1 Analytical methods)</p> <p>---</p> <p>Use of Europium-doped particles (WP3) Analysis of chronic inflammatory effects of nano and microplastic particles (WP3 and 5)</p>	[32] Brachner 2020
<ul style="list-style-type: none"> <li>• Development of protocols for creating and maintaining dispersions, sample preparation, and analytical methods to minimize test artifacts and strengthen reproducibility and interpretability</li> <li>• Development and use of standard reference materials for method validation and test control</li> <li>• Identification of sentinel test species based on mechanistic understanding</li> <li>• Consensus regarding appropriate effect endpoint(s), ideally based on (environmentally) relevant chronic exposure scenarios (selected from Textbox 1)</li> </ul>	<p>WP1: develop advanced methods for the physicochemical characterization of nano and microplastic particles and associated additives/contaminants, protocol for dispersion development and monitoring of particle behaviour in testing media establish representative reference, benchmark and test materials</p> <p>WP2: generation of scientific data on human exposure to MP/NP in food, water, air and packaging materials across Europe and their presence in the human body, new approaches and strategies for exposure and fate monitoring and bio-monitoring of MP/NP, new models to accurately assess chronic exposure</p>	[40] Gouin 2019
<p>Standard methods: Sampling and analysis of NMP ... require robust, quality-assured methods and suitable reference standards representative of environmentally relevant NMP.</p> <ul style="list-style-type: none"> <li>• Particle characterization: Quality-assured environmental monitoring studies ... prepare reference standards for environmentally relevant testing of toxicity.</li> <li>• Sources of NMP: better define</li> </ul>	<p>WP1: establish representative reference, benchmark and test materials Selection of a variety of test materials based on major usages and sources, aged test materials Inter-laboratory method validation and calibration exercises</p> <p>WP3 and 5: assessment of nanoplastic particle transfer across biological barriers</p>	[33] WHO report

<ul style="list-style-type: none"> <li>Uptake and fate of both inhaled and ingested NMP: Information on the absorption and systemic uptake. More information is required on the absorption, distribution and elimination</li> <li>Toxicology: Quality-assured experiments suitable for risk assessment should be conducted</li> </ul>	in newly developed human 3D cell models to assess cell barrier interaction, uptake, translocation and toxicity of MNP, validated by selected animal models WP3 and 5, in cooperation with data management team: research data management, SOPs and data storage strategies	
Harmonized criteria to assess study quality, fostering also comparability among studies	Refinement of proposed criteria for nanoplastic studies within WP4 [45]	Based on [21]
Appropriate methods for detection and quantification of nano- and microplastic in various complex matrices, specification of exposure levels	Method development in WP1 and 2 (see above)	See D6.3 for details
Quantification of human exposure levels along different exposure pathways  Non-food/drink ingestion (e.g. hand to mouth transfer) for both particles and chemicals, and exposure locations, e.g. synthetic carpet fibres, plastic toys	WP2: generation of scientific data on human exposure to MP/NP across Europe and their presence in food and drinking water, and the human body, new approaches and strategies for exposure and fate monitoring and bio-monitoring of MP/NP, new models to accurately assess chronic exposure (see WP2 and WP5) Assessment of uptake mechanisms at the cellular level / co-culture models in WP3 Transfer of additives via ingested plastics has been demonstrated for marine organisms. This issue is not addressed in PlasticsFatE.	Review on human exposure (D2.1), submitted  [46]
Identification of specifically vulnerable groups of individuals (e.g. elderly persons, early life stage, e.g. babies children)	(not addressed in PlasticsFatE)	See PlasticsFatE D2.1
Estimation of the risk posed by plastic-associated chemicals	Small scale case study in WP3 addressing zinc additives and UV-blockers, integration in IATAs developed in WP4	See references provided in 2.2.2, [43, 47]
Consideration of nanoplastics-specific aspects on human health	Assessment of uptake mechanisms and effects at the cellular level / co-culture models in WP3	[48]
Environmental exposure via freshwater to estimate human exposure	Review on human exposure (D2.1), submitted; estimating uptake via food in T5.3	[33, 37]
General issue within PlasticsFatE and beyond: data and knowledge transfer between WPs, and between projects, specifically important for IATA development	Research data management plan and strategy, PlasticsFatE common Teams folder for data sharing, eNanoMapper: timely upload of SOPs; regular scientific coordination meetings on cross-cutting issues	[43, 49]
Consideration of physicochemical properties	Addressed in WP3, T3.4; Effects of physicochemical	[43, 47]

	properties of plastic particles on their toxicity will be described in D3.4	
Consider continuous scales	Addressed in WP3, T3.4; various sizes and shapes of MP/NP will be tested for their toxicological effects	[34]
Toxicity-relevant fraction of smaller particles <10 µm is not adequately considered in the exposure analysis	Addressed in WP2, Subtask 2.3.1 “Exposure levels in food and drinking water” and Subtask 2.4.2 “Fate of MP/NP in the human body and excretion”	[43]

## 2.2.2 Integrated approaches to testing and assessment (IATAs) in the context of microplastic risk assessment

According to the JRC, Integrated Approaches to Testing and Assessment (IATA) are flexible approaches for chemical safety assessment based on the integration and translation of the data derived from multiple methods and sources ([https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/iata-integrated-approaches-testing-and-assessment\\_en](https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/iata-integrated-approaches-testing-and-assessment_en)). One major goal in PlasticsFatE is to foster the use of *in vitro* data for risk assessment, thereby reducing the need for animal testing. The OECD conducted in total 24 case studies on IATA development since 2015 (<https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>). Basically, an IATA aims at integrating and combining the results from various methodologies and approaches ((Q)SAR, read-across, in chemico / in silico, in vitro, ex vivo, in vivo or omic technologies) to create a holistic understanding of the mechanisms underlying the hazard of a substance, and make this knowledge usable for regulatory decision making. The Adverse Outcome Pathway (AOP) concept can be applied as a framework to develop IATA [44, 50]. Guidance on reporting for IATAs is available by OECD [51].

For engineered nanomaterials, IATAs were developed in order to characterise the hazard of these materials and allow a prediction of toxicity depending on their physical-chemical properties. Much work has been performed in the frame of the EU project Gracious (<https://www.h2020gracious.eu/>) [52, 53]. Most work was dedicated to the development of IATAs related to human hazard, but also environmental hazard was considered [e.g. 54, 55-58]. Even though there are differences between polymer micro and nanoscaled particles and engineered nanomaterials, in terms of risk assessment there are also many parallels, in the sense that a case-by-case assessment of each material is not feasible and that each material comes in a variety of different modifications concerning e.g. size, shape or surface charge. Hence, the IATAs developed in Gracious project for human and environmental hazard will serve as basis for our work within PlasticsFatE.

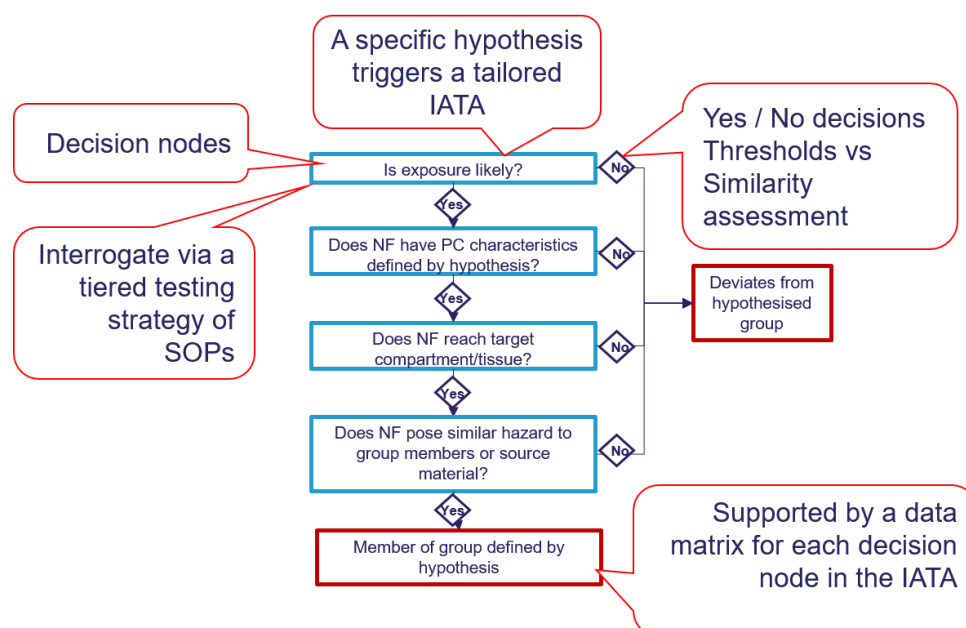


Figure 2. Principle for developing an IATA as outlined in the Gracious project.



A review of the Gracious IATAs (provided by partner Willie Peijnenburg, Uni Leiden) will enable relevant IATAs for nano and microplastic to be selected, gaps analysed hypotheses for hazard of NMP towards humans formulated. In close collaboration with PlasticsFatE WP3, mechanistic information on nano as well as microplastic particle effects will be incorporated into the IATAs. Knowledge of particle physical-chemical characteristics that were identified as crucial for hazardous effects will be considered as well, together with the methods to detect them.

Further, in the scientific literature, some AOPs for nano and microplastic were proposed [59, 60], one of the approaches also considered hazard from mixtures of plastic associated chemicals [61]. The studies demonstrated the main involvement of oxidative stress and its responding pathways, including inflammatory responses in microplastic hazard. However, a high uncertainty due to data scarcity as well as data quality (e.g. are ROS formed due to microplastic particles or due to associated chemicals?) is stated. Here, in the future the quality criteria discussed under 2.1.8 will allow to select reliable mechanistic data.

### 3. Deviations from the Work plan

There have been no deviations from the working plan.

### 4. Performance of the partners

The deliverable was prepared by UFZ with contribution by STAMI, UNILJ, UB and BOKU. It was reviewed by ENAS and Optimat.

### 5. Conclusions

In this deliverable, we compile and review relevant documents on (I) the current state of polymer regulation and (II) the most recent developments in terms of risk assessment specifically focussing on nano- and microplastic. We come to the following conclusions:

- There are intentions to implement restriction measures to reduce release of plastic waste and use of primary microplastic in the EU (PlasticsFatE report D6.3), but micro- and nanoplastic particles are currently not regulated or are under consideration for registration.
- Polymers, which are an inherent component and source of MNPs, are currently exempted from registration under REACH. However, the registration of selected polymers is anticipated and concepts such as the Polymers of Low Concern (PLC) and the Polymers Requiring Registration (PRR) are under consideration to allow scientifically sound justifications for selecting polymers that will require registration.
- Concern is paid at the potential presence of MNP in food intended for human consumption. However, currently, there is no regulation in place for MNPs contamination in food. The focus of activities is rather on additives potentially migrating from food contact materials. There is no strict regulation for most of these additives, except for some specific chemicals with long history of demonstrated health effects, for example phthalates.
- There is also concern regarding the exposure of vulnerable groups to other sources of MNP, such as household dust, via hand-to-mouth, but little data to date

- Promising steps have already been made towards identifying and prioritizing major research needs as well as the limitations in microplastic risk assessment, and the development of the respective tools and models. However, a fully operational human health risk assessment is not available to date.
- PlasticsFatE will develop a new risk assessment strategy that is based on a broader scope, also including rather “exotic” or rarely used polymers as well as associated additives/contaminants, as they may exert hazard towards humans and the environment.
- We will use several available approaches for quality assurance and the selection of fit-for-purpose data that need further refinement. Also, integration of the intrinsic potential of plastic for degradation and fragmentation as well as the toxicity of associated chemicals and mixture toxicity into the micro- and nanoplastic risk assessment schemes is needed. The data generated by the experimental work (in WP1-3 and WP5) of PlasticsFatE will provide a solid scientific basis for the development of the risk assessment strategy.

This overview on the current regulatory situation provides a starting point and basis for the work planned within WP4, specifically for the development of an integrated risk assessment strategy for human and environmental health within T4.1 and T4.2.

## Annex

### Abbreviations & Glossary

CLP	Classification Labelling and Packaging
Degradation	cleavage of the polymer backbone, four mechanisms: photodegradation, thermooxidative degradation, hydrolytic degradation and biodegradation by microorganisms
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
Fragmentation	following -> degradation, formation of small plastic particles from larger plastic items
IATA	<i>Integrated approaches to testing and assessment</i> , flexible approaches for chemical safety assessment based on the integration and translation of the data derived from multiple methods and sources ( <a href="https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/iata-integrated-approaches-testing-and-assessment_en">https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/iata-integrated-approaches-testing-and-assessment_en</a> )
Monomer	(ancient Greek <i>monos</i> 'one', 'single' and <i>meros</i> 'part', 'portion'), a substance which, via the polymerization reaction, is converted into a repeating unit of the polymer sequence. (ECHA definition)
Microplastic	fragments of any type of plastic less than 5 mm in length, according to the U.S. National Oceanic and Atmospheric Administration (NOAA) and the European Chemicals Agency. (Wikipedia, assessed 15 <sup>th</sup> Aug 2022, <a href="https://en.wikipedia.org/wiki/Microplastics">https://en.wikipedia.org/wiki/Microplastics</a> )
Mn	Monomer
MW	molecular weight
Nanoplastic	fragments of any type of plastic less than 1 µm (1000 nm) in length
NIAS	<i>non-intentionally added substances</i> , substances from various sources not added for technical reasons, subdivided into by-products, degradation products and contaminants (ECHA Guidance for monomers and polymers Version 2.0, 2012)
Plastics	Plastics are a wide range of synthetic or semi-synthetic materials that use polymers as a main ingredient. (Wikipedia, assessed 15 <sup>th</sup> Aug 2022, <a href="https://en.wikipedia.org/wiki/Plastic">https://en.wikipedia.org/wiki/Plastic</a> )
Polymer	(from the ancient Greek <i>polý</i> 'much' and <i>méros</i> 'part', "built up from many (equal) parts"), a substance consisting of molecules characterised by the sequence of one or more types of monomer unit. Such molecules must be distributed over a range of molecular weights. Differences in the molecular weight are primarily attributable to differences in the number of monomer units. (ECHA definition)
PLC	Polymer of Low Concern
PoC	Polymer of Concern

Primary microplastic small pieces of plastic that are purposefully manufactured (Wikipedia, assessed 15<sup>th</sup> Aug 2022, <https://en.wikipedia.org/wiki/Microplastics>)

PRR Polymer requiring registration

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

ROS Reactive Oxygen Species

Secondary microplastic: small pieces of plastic derived from the breakdown of larger plastic debris, both at sea and on land. (Wikipedia, assessed 15<sup>th</sup> Aug 2022, <https://en.wikipedia.org/wiki/Microplastics>)

Weathering -> Degradation due to chemical and physical changes caused by environmental stresses such as sunlight, heat, moisture, pollutants, mechanical stresses, and biological growth

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