Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

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Microplastics - Inhalation route - Background

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1. In 2019, as part of horizon scanning, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) identified the potential risks from microplastics as a topic it should consider to inform UK Food Standards Agency (FSA) discussions on this area (TOX/2019/08). Since then, several discussion papers have been presented to the COT and in 2021, the COT

published an overarching statement on the potential risks from exposure to microplastics (COT Statement 2021/02), which contained their working definition of microplastics as synthetic particles or heavily modified natural particles with a high polymer content that are submicron-mm in size (0.1 to 5,000 µm or micrometres). Plastics that are below this size range are classed as nanoplastics (i.e. 1 nm to 0.1 µm) (COT, 2021). The Statement also includes available information on such particles.

2. The Statement provided a high-level overview of the current state of knowledge, data gaps and research requirements with regards to the topic. This was followed by a sub-statement considering oral exposure to microplastics in more detail.

3. The COT previously noted that there is little data on the effects of microplastics on mammals (including humans) whether taken in orally or via inhalation. The majority of microplastics (>90%) are excreted from the body but small amounts may remain in the gut (gastrointestinal tract (GIT)) or move from the GIT into organs or tissues due to endocytosis by M cells or paracellular persorption. No epidemiological or controlled dose studies that evaluated the effects of orally ingested microplastics in humans were identified and there is a similar lack of information on inhaled microplastics.

4. Although exposure to airborne microplastics can arise from a wide range of environmental sources (see paragraphs 65-73) there is still limited information regarding the concentrations of airborne microplastics.

5. In 2022, England’s Chief Medical Officer Professor Chris Whitty published a report on indoor and outdoor air pollution which included comments on microplastics. In the report it is noted that microplastics are in the air unintentionally by stating:

“The airborne transport and inhalation of microplastics is an example showing how unintended air quality consequences might possibly arise far downstream from the public use of an originally safe synthetic product. Too great a focus on only meeting existing air quality standards and regulations, without considering how atmospheric composition may change with society and technology more broadly, may lead to problems that could have been intercepted earlier with greater non-targeted surveillance and horizon-scanning. A clear evidence gap exists between the extensive regulatory efforts placed on monitoring existing regulated air pollutants and research studies of emerging atmospheric composition, the latter being rarely systematic or long-term in nature” (CMO, 2022).

6. The fate and dispersion of microplastics in outdoor environments is dependent on several factors (see paragraph 68).

7. Atmospheric deposition of microplastic particles (MPPs) onto food prior to consumption must also be considered as a potential source of exposure. For example, Catarino et al., (2018) compared the potential exposure of humans to household dust fibres during a meal with the amounts of MPPs present in edible mussels from Scottish waters, showing that exposure was considerably higher from the household source. However, this is out of the scope of the present statement. Further information is available in COT Statement 2021/02 the Overarching Statement.

8. An American study (Cox et al., 2019) estimated daily consumption and inhalation to be 142 MPPs and 170 MPPs in adult males, respectively. For adult females, the estimated values are 126 MPPs and 132 MPPs, respectively. Based on these values, an estimated exposure of ~120,00 and ~98,000 MPPs annually was calculated in male and female adults, respectively

9. The deposition of inhaled microplastics within the lung is dependent on the particle’s physicochemical properties, as well as the subject’s physiology and lung anatomy shown from paragraph 39.

10. Inhalation of microplastics could result in toxicity due either to the particles (i.e. physical effect) or their leachates (i.e. chemical effect). The mechanisms of inhaled particle injury are covered in paragraph 74. With regard to the available inhalation studies in laboratory animals, Environment and Climate Change Canada and Health Canada (ECCC and HC) in their review of the scientific literature noted that no dose-response relationship had been observed in mortality, survival time, behaviour, clinical observations, or tumour incidence from inhalation exposures (ECCC and HC 2020).

11. The COT previously reviewed risk assessments of MPPs carried out by various groups such as the European Tyre and Road Wear Platform; Tyre Industry Project (Jekel, 2019), Joint Research Centre (Grigoratos & Martini, 2014), Defra (AQEG, 2019), Health and Safety Executive (RUBIAC, 2007; HSE, 2011), Committee on Medical Effects of Air Pollutants (COMEAP, 2015; 2020), WHO (WHO, 2013), National Institute for Public Health and the Environment (Verschoor et al., 2016), and ECHA (ECHA, 2017).

12. The COT concluded that the literature data on exposure to particles from tyre wear would need separate consideration from microplastic exposure since the particles are chemically quite different in their polymeric nature. The COT considered that inhalation was likely to be the most significant route of exposure to TRWPs (tyre and road wear particles). Detailed risk assessments of such materials were considered outside of the scope of the current exercise, however some information has been included to provide context.

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Microplastics - Inhalation route - Scope and purpose

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13. As there is evidence for the presence of plastic particles in both indoor and outdoor air, inhalation is a possible route of exposure (Gasperi et al., 2018; Domenech & Marcos, 2021).

14. The purpose of this sub-statement is to provide supplementary material to the overarching statement (COT Statement 2021/02) and to consider

in detail the potential toxicological risks of exposure from microplastics *via* the inhalation route. It is based on the currently available literature and data from internal tools at the FSA (these include: a literature search application and signal prioritising dashboards).

Microplastics

15. Currently there is no internationally agreed definition of a microplastic, however, publications by Verschoor (2015) and Hartmann et al., (2015) have proposed criteria that could be included in the definition of microplastics. In Europe, the European Chemicals Agency (ECHA) has proposed a regulatory definition for a microplastic under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (ECHA, 2019). In the US, the California Water Boards also recently published a proposed definition of microplastics in drinking water in March 2020.

16. Verschoor (2015) included 5 major properties that could be considered including chemical composition, physical state, particle size, solubility in water and degradability. Similarly, Hartmann et al., (2015) proposed seven criteria; chemical composition, solid state, solubility, size, shape and structure, colour and origin (i.e. primary or secondary particles; also known as pristine and aged), as discussed in the following paragraphs.

17. In Europe, the definition of a microplastic (which includes nano size) proposed by ECHA is a “material consisting of solid polymer-containing particles, to which additives or other substance(s) may have been added, and where ≥ 1% w/w have (i) all dimensions 1 nm ≤ x ≤ 5 mm or (ii) for fibres, a length of 3 nm ≤ x ≤ 15 mm and length to diameter ratio of >3. Polymers that occur in nature that have not been chemically modified (other than by hydrolysis) are excluded, as are polymers that are (bio)degradable.” (ECHA, 2019).

18. The current definition of microplastics (which excludes nano size) in drinking water adopted by the California Water Boards is: “Microplastics in drinking water are defined as solid polymeric materials to which chemical additives or other substances may have been added, which are particles which have at least two dimensions that are greater than 1 and less than 5,000 µm. Polymers that are derived in nature that have not been chemically modified (other than by hydrolysis) are excluded.” (California Water Boards, 2020).

19. As noted above, the definitions of microplastics are broad. Therefore, for the purposes of this document, the COT has adopted a working definition that

microplastics are defined as synthetic particles or heavily modified natural particles with a high polymer content that are submicron in size (0.1µm to 5 mm). Plastics that are below this size range are classed as nanoplastics (i.e. 1 nm to 0.1 µm) (COT, 2021; Bermúdez and Swarzenski, 2021; Frias and Nash, 2019). However, consensus on the size range is challenging.

20. The Committee also noted that microplastic particles that are present in the environment are not stable in size, meaning that as the duration of the degradation and agglomeration processes lengthen, the particle size continues to change due to fragmentation and erosion/weathering.

Nanoplastics

21. Nanoplastics have been defined as a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale (1 nm to 0.1 µm) (EFSA, 2016, European Commission, 2011). Nanoparticle is a general term based on the physical properties for a variety of chemical compositions. There is currently no further proposed definition.

22. A number of authoritative bodies have assessed the risks of nanomaterials and provided guidance on their assessment, which could also apply to nanoplastics. For example, the European Food Safety Authority (EFSA) Scientific Committee published an opinion on the potential risks arising from nanoscience and nanotechnologies on food and feed safety in 2009 (EFSA, 2009). This opinion did not provide any definitions; however, it was stated that the term nanoscale refers to a dimension of the order of 100 nm and below. Engineered nanomaterial was described as any material that is deliberately created such that it is composed of discrete functional and structural parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less.

23. The EFSA Scientific Committee recommended that the addition of other metrics (e.g. specific surface area which is independent of the agglomeration status of particles) should be included into the current definition of nanoscale materials (EFSA, 2009).

24. In 2011, EFSA published a guidance document on how EFSA’s Panels should assess potential risks related to certain food-related uses of nanotechnology. New guidance on assessing the safety for humans and animals of nanoscience and nanotechnology applications in the food and feed chain was published in 2018 (EFSA, 2018).

25. The EFSA 2018 guidance is applicable to:

- A material that meets the criteria for an engineered nanomaterial, as outlined in Novel Food Regulation (EU) No 2015/2283 and Regulation (EU) No 1169/2011 (i.e. have particle sizes in the defined nanoscale; 1-100 nm).
- A material that contains particles having a size above 100 nm which could retain properties that are characteristic of the nanoscale (not further elaborated).
- A material that is not engineered as nanomaterial but contains a fraction of particles (<50% in the number-size distribution. Elsewhere (EFSA Tech Req, 2021), less than 10% particles (number-based) with at least one dimension smaller than 250 nm no nano RA required) with one or more external dimensions in the size range 1-100 nm or less.
- A nanomaterial having the same elemental composition but that occurs in different morphological shapes, sizes, crystalline forms and/or surface properties.
- A nanoscale entity that is made of natural materials.

26. In July 2020, EFSA held a public consultation on its draft “Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles”. The draft guidance outlines appraisal criteria grouped in three sections, to confirm whether or not the conventional risk assessment should be complemented with nano-specific considerations.

27. The first group of criteria addresses solubility and dissolution rate as key physicochemical properties to assess whether consumers will be exposed to particles. The second group establishes the information requirements for assessing whether the conventional material consists of small particles or contains a fraction thereof, and its characterisation. The third group describes the information to be presented for existing safety studies to demonstrate that the fraction of small particles, including those at the nanoscale, has been properly evaluated. Post-finalisation, this guidance was to completement the EFSA 2018 guidance (as described above) (EFSA, 2020).

28. The definitions of nanomaterials above (paragraphs 25-28) are based on EFSA Guidance, but their guidance for the risk assessment of nanomaterials could also apply to nanoplastics.

Types of microplastics

29. Microplastics can be divided into two major types. Firstly, those that are deliberately manufactured to be in the size range of 0.1 to 5,000 µm which are known as primary microplastics (generally spherical) and are intentionally used in personal care products (for example, microbeads) or for various industrial applications. Secondary microplastics can be formed in the environment due to fragmentation of larger pieces of plastic caused by a culmination of physical, biological and photochemical degradation. Secondary microplastics have been termed microplastic particles (MPPs). MPPs can be further degraded to form nanoplastics, as defined above.

30. Besides the types of microplastics mentioned above, there is some debate within the scientific field as to whether rubber tyre particles should be considered microplastics. Tyres were initially made of natural rubber from the Brazilian rubber tree (Hevea brasiliensis). Currently, tyres are produced from a mixture of natural and synthetic materials. Synthetic rubbers are made from petroleum products and are functionalised with the addition of sulfur (1-4%), zinc oxide (1%), carbon black/silica (22-40%) and oil (Kole et al., 2017).

31. Car tyres release wear particles through mechanical abrasion, resulting from contact between the road surface and the tyre. The amount and particle size are dependent on several factors such as climate (temperature), composition and structure of the tyre, tyre age, road surface, driving speed, vehicle characteristics and style, and nature of the contact. As such, tyre wear particles could be described as another environmental source of microplastics, depending on the presence of synthetic materials in their composition (Baensch-Baltruschat et al., 2020; Kole et al., 2017).

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Microplastics - Inhalation route - Analytical detection methodologies

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32. From the literature, the detection methods described for microplastics include one or more of the following steps: sample collection and removal of biogenic matter, detection and quantification/enumeration and, the characterisation of the plastic (i.e. its chemical composition or polymer type) (Nguyen et al., 2019; Kwon, et al., 2020). It is important to note that during all these steps, precautions to avoid contamination from particles in the air, or with fibres from clothing, equipment or the reagents used, should be optimised (see Figure 1).

33. As seen in Figure 1, the majority of biological samples have been taken from aquatic species. The pre-separation method is dissection which recovers MPPs >500 µm, followed by separation methods including density separation, digestion using enzymes and various chemical compounds and filtration techniques. The analytical method is split between three categories: visual microscopic analysis, vibration spectroscopy (e.g. Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy) and mass spectroscopy, the last of which is also suitable for the characterisation, quantification and identification of nanoplastics.

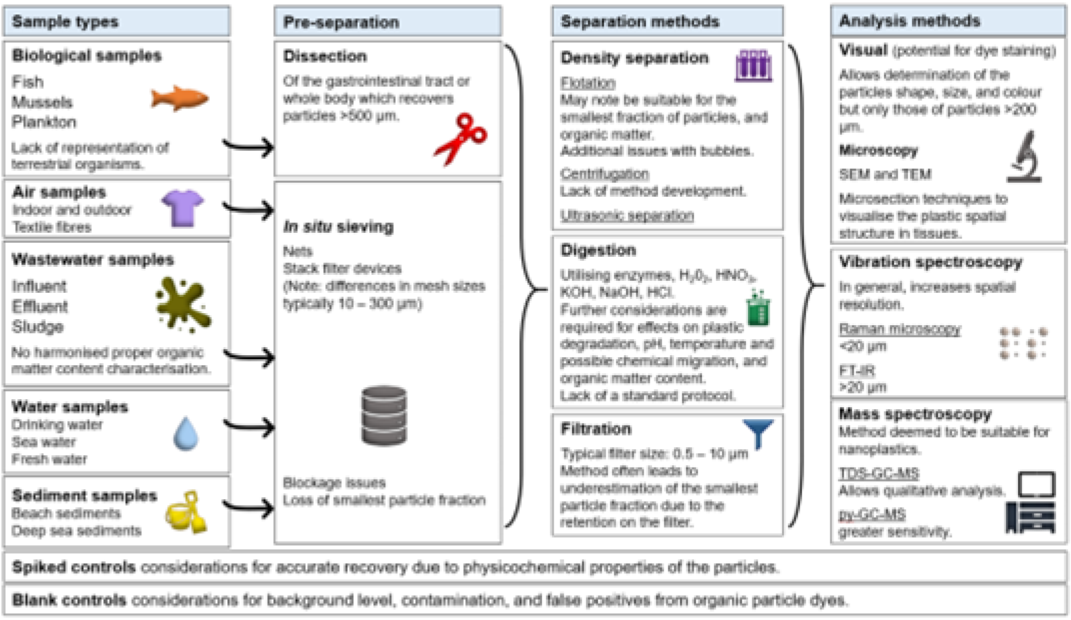
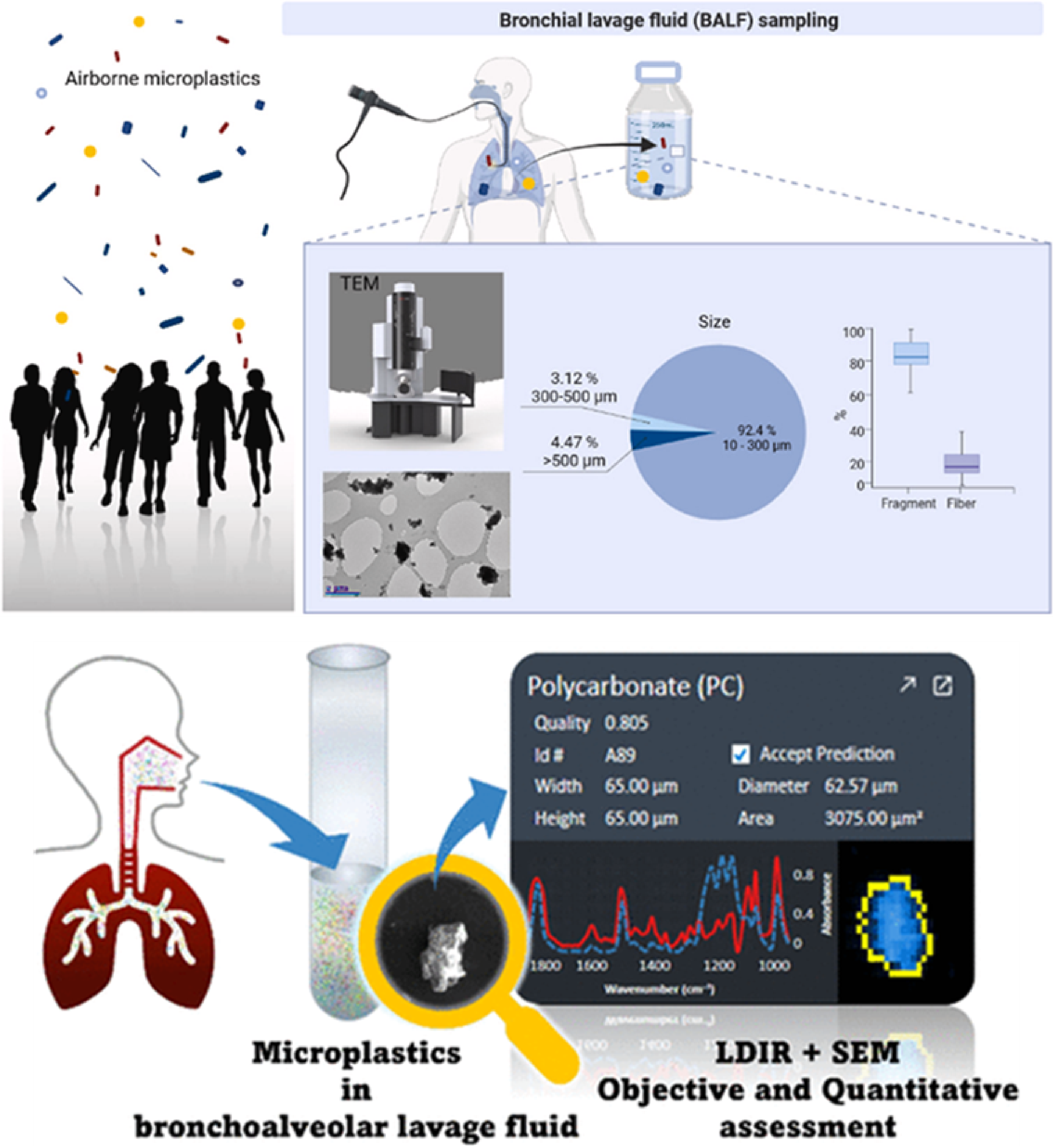


Diagram 1 provides an overview of the methods used in the separation and analysis of micro and Nano plastics in complex environmental samples. This includes biological samples, air samples, wastewater samples, water samples and sediment samples. The diagram is made up of black text and multicoloured images. The image is made up of 4 columns with directional flow lines and arrows. Underneath the columns are rectangle boxes with explanatory text of the Spike controls and Blank control's.

Figure 1. Provides an overview of the methodologies utilised in the separation and analysis of microplastics and nanoplastics in complex environmental samples including: biological samples (fish, mussels and plankton), air samples (indoor and outdoor, synthetic textile fibres), wastewater samples (influent, effluent and sludge), water samples (drinking water, sea water and fresh water) and sediment samples (adapted from Nguyen et al., 2019). Abbreviations: H2O2 = hydrogen peroxide; HNO3 = nitric acid; KOH = potassium hydroxide; HCl = hydrochloric acid; SEM = Scanning electron microscope; TEM = Transmission electron microscopy; FT-IR = Fourier-transform infrared; TDS-GC-MS = Thermodesorption gas chromatography-mass spectrometry; py-GC-MS = Pyrolysis gas chromatography-mass spectrometry (Image taken from COT Microplastics Overarching Statement 2021).



Diagrams taken from two studies observing microplastics in Bronchial Lavage Fluid samples. This image is made up of 2 pictures surrounded by a black outline. At the top on the left is a graphic of people in black silhouette with coloured shapes above them with a line of text which reads "Airborne microplastics". To the right of this is a a heading in black text "Bronchial lavage fluid (BALF) sampling". Under the text is a line drawing of a person and their airways and lungs shaded blue, with a curved black arrow pointing from their lung to a bottle shaded in blue. Underneath this is a grey dotted line forming a triangle above a rectangular box. The box has 2 images, a pie chart and a graph in it. The box is shaded in a pale blue. At the bottom of the rectangle on the left is a line drawing of a persons head, airways and lungs. The Lungs are coloured in red with white lines connecting the 2 parts. From the airways point a blue arrow to a flask. next to he flask is a magnifying glass depicted in yellow and black above a white particle. From the magnifier a blue curved arrow points upwards to a black box with lines of text in grey and small multicoloured images of a heart rate. At the bottom of the whole image are line of bold black text: "Microplastics in bronchoalveolar lavage fluid" and "LDR + SEM Objective and Quantitative assessment".

Figure 2. Diagrams taken from two studies observing microplastics in Bronchial Lavage Fluid samples (Qui et al, 2023; Uoginte et al. 2023).

34. Studies have now reported on human samples obtained during bronchoscopy procedures, whereby bronchoalveolar lavage fluid (BALF) was obtained. A measured fluid, such as saline solution was passed into the lung and then aspirated. These samples were then analysed using optical and TEM-EDX microscopy or SEM microscopy as shown in Figure 2 (Qiu et al, 2023; Uoginte et al. 2023). Other studies have detected microplastics in human lung samples using µFT-IR (Jenner et al. 2021).

35. Currently there are only limited analytical methods available to detect and quantify the presence microplastics in various matrices. These include FT-IR, Nile Red staining techniques, Micro-Raman spectroscopy, quantitative 1H nuclear magnetic resonance spectroscopy (qNMR) (Peez et al., 2019) and mass-spectroscopy; however, each of these methods has its own associated limitations (Nguyen et al., 2019).

36. Additionally, there are neither standardised testing protocols for different matrices (i.e. air, soil, food and water), nor standard refence materials for the analysis, characterization and quantification of micro and nanoplastics. No single technique is suitable for all plastic types or for all particle sizes or shapes. Therefore, the use of either a suite of methods or generation of new techniques will be necessary.

37. Comparison and replication of studies can be difficult due to differences in sampling, extraction, purification and analytical methods for enumerating and characterising microplastics. These methods are not yet standardized and have not been subject to interlaboratory validation. Contamination with airborne microplastics or cross contamination of samples can also occur, so suitable

control samples may be difficult to obtain.

38. Most studies have performed tests on pristine particles; however, this may not be representative of what is present in the environment (i.e. the particles have not been subject to environmental degradation and other changes). Therefore, it is important to consider the variability among samples when comparing studies of the same polymer type.

Physicochemical properties

39. There are four morphological and chemical characteristics of microplastics, i.e. physicochemical properties, which influence their potential hazards. These are:

i). Physical (e.g. bulk, fibres in the lung or those which could lead to gut blockage, as observed in aquatic and avian species);
ii). Chemical composition (unbound monomers, additives, sorbed chemicals from the environment e.g. persistent organic pollutants and metals);
iii). Metabolism or degradation to form monomers or other derivatives, some of which could be chemically reactive (e.g. isocyanates from polyurethane) and;
iv). The presence of biofilms (attachment and colonisation of microorganisms on the plastics).

40. Due to the small size of some nano-/microplastics (NMPs) (0.1 µm to 5 mm), uptake across the gastrointestinal tract (GIT) and uptake into internal tissues is possible and thus they may have both local and systemic effects. Particles <50 µm in size can be absorbed from the gut via intracellular gaps and by phagocytic and endocytic pathways but only those of <1-2 µm in size are able to cross the cell membranes of internal organs.

Physical properties

41. NMPs can differ in their physicochemical properties (shape, size, density, surface charge, etc). The consideration of physical properties during hazard and/or risk assessment of plastic particles is important because the interactions of NMPs with biological systems can vary with differences in their size and shape (Nel et al., 2009), even when they have the same chemical composition.

42. The physical properties and morphologies of tyre materials can also vary under different sampling conditions. Those collected from road runoff and shredded tyres have elongated shapes, whilst samples generated from road

simulator systems in laboratories range between jagged, droplets, granules, warped, porous, irregular, and near spherical in shape (Wagner et al., 2018). A review by Kole et al., (2017) revealed that the size distribution range of tyre wear and tear particles, could be from 6-350,000 nm. This wide size distribution range was attributed to several factors including the use of difference size metrics (e.g. particle mass versus particle numbers), analytical difficulties in separating tyre from road particles, and the large variation in experimental conditions and analytical equipment.

Chemical Properties

43. A particle's chemical properties such as charge or zeta potential (when particles are immersed in a conducting liquid such as water) are dependent on its chemical composition.

44. A particle's properties can also be influenced and changed by its surface chemistry. Each particle could have its own unique corona consisting of proteins adsorbed from plasma and/or intracellular fluid, adsorbed chemicals from the environment or microbiological organisms (see Figure 3).

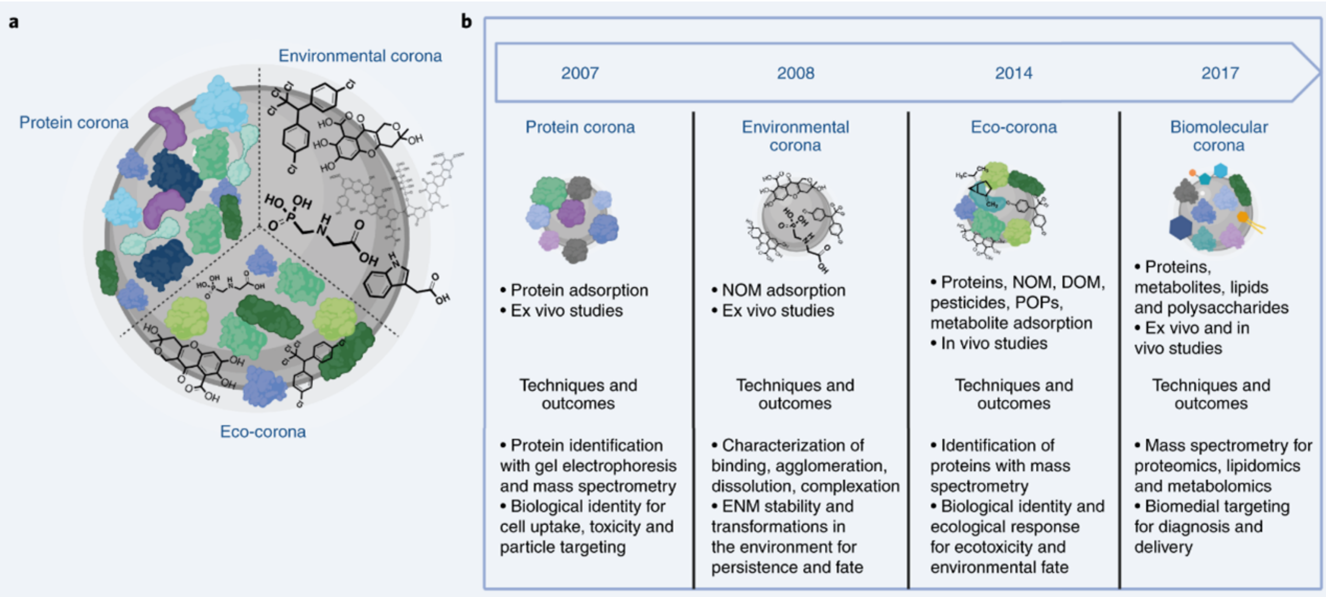


Figure 3 shows the different corona development across the decade from 2007-2017. The figure is a grey box with 2 sections. On the left hand side there is a large multicoloured image of a corona divided in to 3 parts: Protein corona, Eco-corona and Environmental corona. To the right is a timeline arrow of years 2007, 2008, 2014, and 2017. Underneath each year is a heading in blue text with a multicoloured corona and bullet points of black text underneath each year.

Figure 3. (a) Comparison of the protein, environmental, and eco-coronas. Formed within organisms at locations of high protein content, the term protein corona has been used to describe the binding of proteins to ENM (engineered nanomaterials) surfaces, but also incorporates lipids, metabolites (typically <1000 Da which are either reactants, intermediaries or products of enzymatic processes), and other biomolecules. To date, the term environmental corona has described a corona formed in aquatic environments with high concentrations of NOM, including humic substances. By contrast, the eco-corona incorporates features of both the protein and environmental coronas, where the balance of proteins and other molecules varies. (b) The evolution of the protein corona concept, adapted from Hadjidemetriou and Kostarelos. Studies of protein adsorption to surfaces and particles dates back to at least the 1960s. The term protein corona was first coined in 2007. Protein corona studies developed with mass spectroscopy-based proteomics to aid identification of the proteins bound at the surface of ENMs and explore the role of surface curvature in altering protein structure and function relative to macroscale surfaces. Protein corona studies evolved in parallel with those on the environmental corona, but the characterization techniques and goals for each area remained separate, with environmental corona focusing mainly on the dispersion stabilization provided by NOM (natural organic material). The environmental dimensions of the protein corona began to appear later, as the concept of the eco-corona and its role in (nano)ecotoxicity emerged. Both the eco-corona and biomolecular corona embrace the diversity of molecules in solution with the goal of understanding and controlling downstream biological responses to nano-enabled technologies. (Image obtained from Wheeler et al. 2021).

45. The physicochemical properties of micro and nanoplastics can change over their life cycle and can also affect each other. For example, physical degradation resulting in the formation of nano-sized plastic particles and/or plastic particles with different shapes can generate a higher number of particles and thus gives rise to a larger total surface area and higher particle number which in turn affects the concentration. The weathering process can change the surface chemistry and size of microplastics, and chemical migration from the MPPs into the surrounding medium results in altered stability which in turn changes the physical degradation processes (Wheeler et al. 2021).

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

Microplastics - Inhalation route - Toxicity

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46. The COT have previously reviewed the human data on the toxicity of microplastics via inhalation (TOX/2019/62). The available toxicity data in humans was based on studies of occupational exposure. As the COT have previously discussed occupational exposure in the TOX/2019/62 statement, it will not be included in this statement.

47. In their discussion of TOX/2019/62 the COT considered that the assessment of microplastics exposure via inhalation could be easier in comparison to the assessment of oral exposure given the availability of occupational data from the synthetic textile industry, however, the context should be considered. The Committee further noted that microplastic concentrations present in food and water were thought to be lower in comparison to airborne exposure.

48. According to Panko et al., (2019), particulate matter (PM) from tyre abrasion may represent between 0.8 and 8.5 % mass fraction of PM10 and 1 to

10% of PM2.5 in the air. However, it is unknown what percentage of the PM2.5 burden consists of microplastics (Zhang et al., 2020).

49. The toxicological properties of microplastics may differ to that of PM2.5 (or other pollutants) due to the additives present and their particular characteristics such as morphology and chemical composition (Zhang et al., 2020).

50. In 2020, the Committee on the Medical Effects of Air Pollutants (COMEAP) considered that the evidence on non-exhaust particles (road surface wear, re-suspended road dust, brake and tyre wear) from road transport and associated health effects should be re-evaluated. COMEAP concluded that, as a whole, the body of published work is small and did not provide a compelling narrative of adverse health effects of exposure to non-exhaust particles. However, as there was strong evidence that exposure to particulate pollutants in ambient air is harmful to health, some health risk associated with exposure to non-exhaust particles was likely.

51. COMEAP concluded that the available evidence is not very informative about which components or sources of particulate air pollution are particularly harmful to health and that evidence relating to non-exhaust emissions from traffic, is limited (COMEAP, 2020; 2022).

Inhalation studies (2020-March 2023)

In vitro

52. When the Overarching Statement by the COT was published, it included studies up to 2020 and therefore this statement concentrates on those studies published from 2020 to the March 2023.

53. Dong et al., (2020) assessed the pulmonary toxicity of polystyrene microplastics *in vitro* using BEAS-2B lung cells to determine the cytotoxic and inflammatory effects. The polystyrene MPs decreased alpha-1 antitrypsin levels and transepithelial electrical resistance by depleted zonula occludens proteins: these are a type of scaffolding protein. The study results indicated that low levels (10 µg/cm^2) of polystyrene MPs cause disruption to the protective pulmonary barrier and high levels (1000 µg/cm^2) may have an adverse effect on human lung health. This is based on testing in a single cell line which is not representative of *in vivo* exposure. However there are now 3D models available which can provide a more suitable model for examining the effects of airborne microplastics (Winkler

et al. 2022).

In vivo

54. There is limited research on *in vivo* exposure to airborne microplastics. Lim et al., 2021 used a modified version of the OECD guideline (TG 412) 28-day inhalation toxicity study using a whole-body system. Sprague-Dawley rats were exposed to three different concentrations (0.75, 1.50 and 3.00 x 10^5 particles/cm^3) of 0.1 µm polystyrene NMPs for 6 h each day, 5 days/week for 2 weeks. There was a lack of dose response and no definitive link between concentration at 14 days exposure, and observed alterations to the physiological, serum biochemical and haematological parameters or markers of respiratory function. However, there was a concentration-dependent increase in the expression of TGF-β and TNF-α inflammatory proteins. These authors suggest that sustained exposure to higher concentrations of NMPs may result in alterations at the molecular level, thus a risk to health from inhalation of polystyrene micro/nanoplastics. However, caution must be used when weighting this study as the morphology of the airways in the rat differs markedly from that in humans. In addition, exposure was whole body, rather than inhalation only and therefore may not give a realistic representation of exposure in the human lungs. In addition, it is important to distinguish between normal acute particle clearance mechanisms and more persistent, potentially pathophysiological, responses.

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Microplastics - Inhalation route - Toxicokinetics

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55. As discussed in COT Statement Number 2021/02 , the toxicity of microplastics is dependent on a number of factors including size, morphology, chemical composition, additive leaching and surface functionalization.

56. Surface functional groups may affect the adsorption of organic contaminants and heavy metals leading to differences in their mobility and toxicity (Kim et al., 2017; Sun et al., 2020; Yao et al., 2022). However, the MP vector effect is usually framed as ‘complex’, ‘under debate’ or ‘controversial’ (Koelmans et al., 2022b).

57. Deposition of respirable fibres occurs in the lung as a function of the aerodynamic diameter of the particle, whereas non-respirable fibres are often inhaled through the nasal passage but are then caught in mucus and swallowed thus creating a secondary exposure via the gastrointestinal tract. There are four main mechanisms of deposition in the lung: impaction, sedimentation, diffusion, and interception (Darquenne, 2006).

58. Inertial impaction occurs for particles with a diameter > 5 µm or for those with excessive momentum. As a particle travels through the airways, it remains on the same trajectory. If the air flow changes direction, the particle will remain on its existing pathway, deviating from the changed airflow and impacting on to the surface of the airways. Inertial impaction occurs in the upper respiratory tract and the conducting zone only.

59. For particles with a diameter between 0.5 to 5 µm, the main deposition mechanism is sedimentation. This occurs mainly in the bronchi and bronchioles; when air resistance and gravity overcome the buoyancy of the particle causing it to settle on the surface of the lung.

60. Airborne particles are in constant random Brownian motion, due to collisions with gas molecules. This results in random, omnidirectional particle movement, known as diffusion. This occurs only with smaller particles, typically < 0.5 µm. Occasionally particles will collide with the cell surface, causing them to

settle there. Diffusion occurs mainly in the small airways and alveoli, although the particles can also deposit in the upper airways by this mechanism particularly when their diameter is < 0.01 µm (Tsuda et al., 2013).

61. Interception occurs when fibres with a large ratio between their length and diameter travel so close to the surface of the lung that they make contact. Deposition by interception increases with the length of the fibre. The area of deposition in the lung is dependent on the aspect ratio of the fibre but can also arise due to changes in airflow.

62. The deposition of inhaled microplastics in the lung is dependent on the particle's physicochemical properties, as well as the subject's physiology and lung anatomy. Deposition in the upper airways occurs by impaction, while in the small airways it occurs by sedimentation. Fibres have higher potential than spherical particles for penetration due to their high aspect ratio (Donaldson & Tran, 2002). Clearance relies on mechanical processes (e.g. mucociliary clearance where the mucous progresses towards the pharynx caused by the beating of cilia), alveolar macrophage phagocytosis and migration, and by lymphatic transport, which can result in secondary deposition in the GIT.

63. Clearance mechanisms for inhaled MPs > 5 µm, are likely to occur via the mucociliary escalator. Sneezing clears larger particles trapped in the nose/upper respiratory tract. Mucociliary transport clears particles from bronchioles/lower respiratory tract, with swallowing and GIT exposure. Coughing plays a role in both of these mechanisms.

64. Some particles bypass the mucociliary clearance and travel deeper into the lung where phagocytosis occurs. Macrophages may break down particles < 20 µm by either dissolution or degradation but this is dependent on the particle composition. If a particle is > 20 µm in length, macrophages will not be able to fully engulf the particle, resulting in frustrated phagocytosis (Donaldson et al., 2010). This state causes an increased recruitment of macrophages, which can result in the phenomenon known as an "oxidative burst" occurring where inflammatory mediators and oxidants are released in high concentration, potentially leading towards the onset of lung inflammation and fibrosis (Donaldson et al., 2010; Gasperi et al., 2018). Inflammation can induce cell proliferation and secondary genotoxicity due to the continuous formation of reactive oxygen species (ROS), resulting in oxidative stress, but this depends on a number of factors.

65. It is believed that once particles reach the pleura then they may reach the pleural space, however it is currently unknown how this particle migration

occurs. Once particles reach the pleura, they may then travel to the lymphatic system which also helps clear phagocytic cells (Donaldson, et al., 2010; Enyoh et al., 2019). Possible translocation across alveolar walls into blood vessels with secondary translocation into tissues and organs may then occur (Fournier et al., 2020; Wright and Kelly, 2017).

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

Microplastics - Inhalation route - Exposure

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66. Microplastics are present in the indoor and outdoor environment. Sources of MPs include textiles, furniture, toys, electric cables and cleaning agents, construction material and litter (e.g. discarded packaging and containers).

67. The data available on outdoor exposure is limited. However, studies have shown than when comparing inhalation and ingestion routes indoors, microplastic exposure via ingestion is minimal in comparison to that by inhalation.

Outdoor exposure from air

68. Microplastics found outdoors are more likely to fracture due to weathering in comparison to the microplastics present indoors. However, data on the levels and types of microplastics in the air compared to other media are limited (Ageel et al., 2021).

69. Environmental exposure to airborne microplastics occurs from a wide range of sources with synthetic textiles and the erosion of synthetic rubber tyres being the most frequently reported in the literature. Resuspended city dust which contains a fraction of settled synthetic fibres/rubber tyre wear is a secondary source of airborne microplastics. Wind transfer is estimated to be responsible for 7% of the ocean's contamination (Boucher & Friot, 2017).

70. The fate and dispersion of microplastics in outdoor environments are dependent on several factors. These include the vertical concentration gradient where there are higher concentrations near the ground due to deposition and settling, wind speed and direction, land topography, precipitation, and temperature. Concentrations of airborne microplastics in outdoor air are expected to be low, due to dilution. O'Brien et al. (2023) noted in their review that the concentration of microplastics in outdoor ambient air ranges between <1 and >1000 MPPs/$m^{3,}$ while the outdoor deposition concentrations ranged between 0.5 and 1357 MPPs/m^2/day.

71. There is limited information regarding the concentrations of airborne microplastics, however, the Dris et al. (2016, 2017) studies carried out in Greater Paris found average outdoor deposition rates of 53 and 110 particles/m^2/day. Data for Central London on outdoor deposition rates of microplastics have also been reported, and these range from 575-1,008 total MPPs/m^2/day; 510-925 fibres/m^2/day (Wright et al., 2020). These numbers are affected by climate conditions and seasonality and are also affected by the sampling and analytical methodologies used.

72. An American study (Cox et al., 2019) has proposed an estimated daily consumption and inhalation of 142 MPPs and 170 MPPs in adult males, respectively. For adult females, the estimated values are 126 MPPs and 132 MPPs, respectively for the same exposure routes. Based on these values, a total annual estimated exposure of ~120,00 and ~98,000 MPPs was calculated for male and female adults, respectively. These exposure estimates were based on reported microplastic concentrations in salt, alcohol (beer), seafood (fish, shellfish and crustaceans), added sugars (sugar and honey), water (bottled and tap), and in air.

Note that the estimated annual exposure values did not take into account atmospheric deposition of microplastics during food preparation and consumption. The authors are of the view that “these estimates are subject to large amounts of variation; however, given methodological and data limitations, these values are likely underestimates.”

73. As noted previously, inhalation of microplastics can result in toxicity due either to the physical effects of the particles or the chemical effects of their leachates. Amato-Lourenço et al. (2020) concluded that the response in humans depends on differences in individual metabolism and susceptibility. It is not yet known how the toxicity of synthetic fibres compares with that of organic/natural fibres (Donaldson & Tran, 2002). However, it is known that fibres from synthetic textiles are quite flexible (Bunsell (ed), 2018) and hence do not possess the characteristic rigid, long, thin morphology of asbestos fibres, which is responsible for their toxicity and carcinogenicity.

74. In general, the mechanisms of inhaled particle injury include dust overload where high surface area particles induce high chemotactic gradients that prevent macrophage migration, oxidative stress (production of reactive oxygen species, which induces cell injury and release of inflammatory mediators), cytotoxicity (where free intracellular particles damage cellular structures), and translocation (injury of secondary sites and vascular occlusion by particles or increased coagulability). Depending on the nature of the particle and the extent of exposure, such mechanisms might lead to adverse endpoints such as fibrosis, which can develop as a result of chronic cytotoxicity and inflammation.

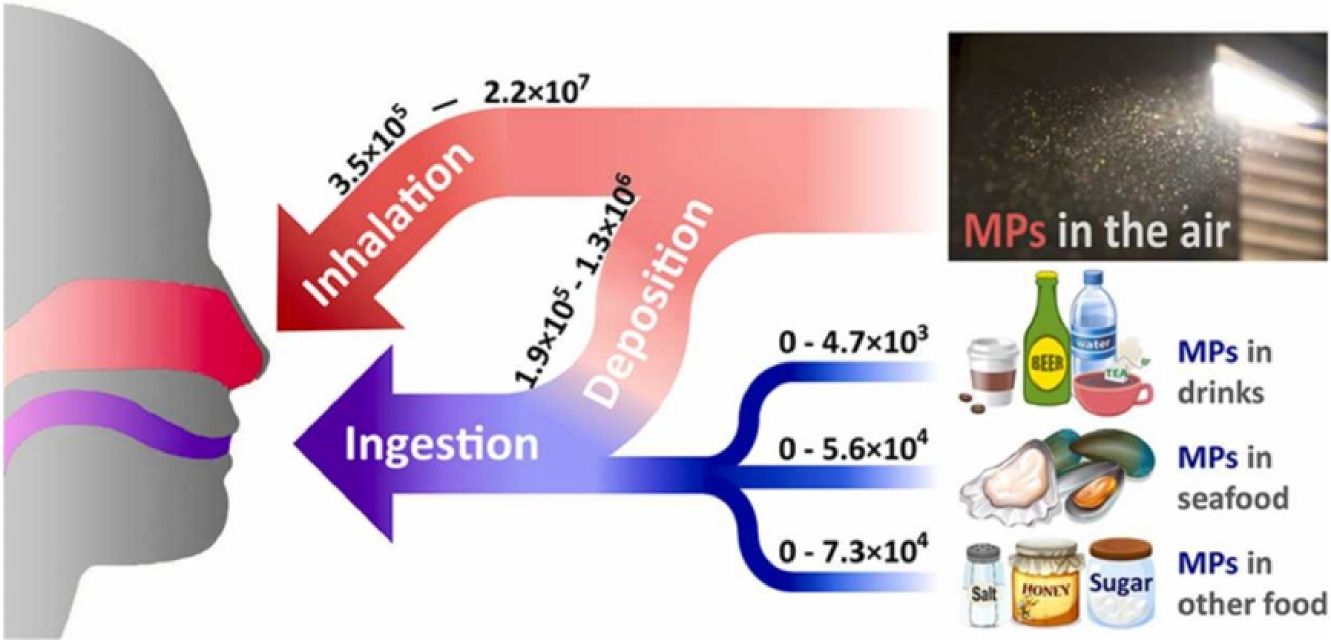
Indoor exposure

75. The indoor behaviour of airborne microplastics is dependent on factors including room partition, ventilation and airflow.

76. Dris et al., (2017) investigated indoor (two apartments and one office) air samples in the city centre of Paris. Indoor concentrations of microplastics ranged between 1.0 and 60 fibres/m^3. The fibres that were measured indoors consisted of 67% of natural materials, primarily made of cellulosic materials and the remaining 33% contained petrochemicals, predominantly polypropylene.

77. Zhang et al., (2020) collated data from 46 studies and calculated the annual intake of indoor and outdoor microplastics using an inhalation rate of 14.3 m^3 per day as 1.9×10^3-1.0×10^5 and 10^1-3.0×10^7 particles respectively, with approximate means of 3×10^4 for indoor exposure and 4×10^3 for outdoor

exposure, confirming that there is increased exposure to microplastics in the indoor environment. Whereas Fang et al., (2022), calculated the annual atmospheric deposition of MPPs as 3.5×10^5 – 2.2×10^7 items (Figure 4).



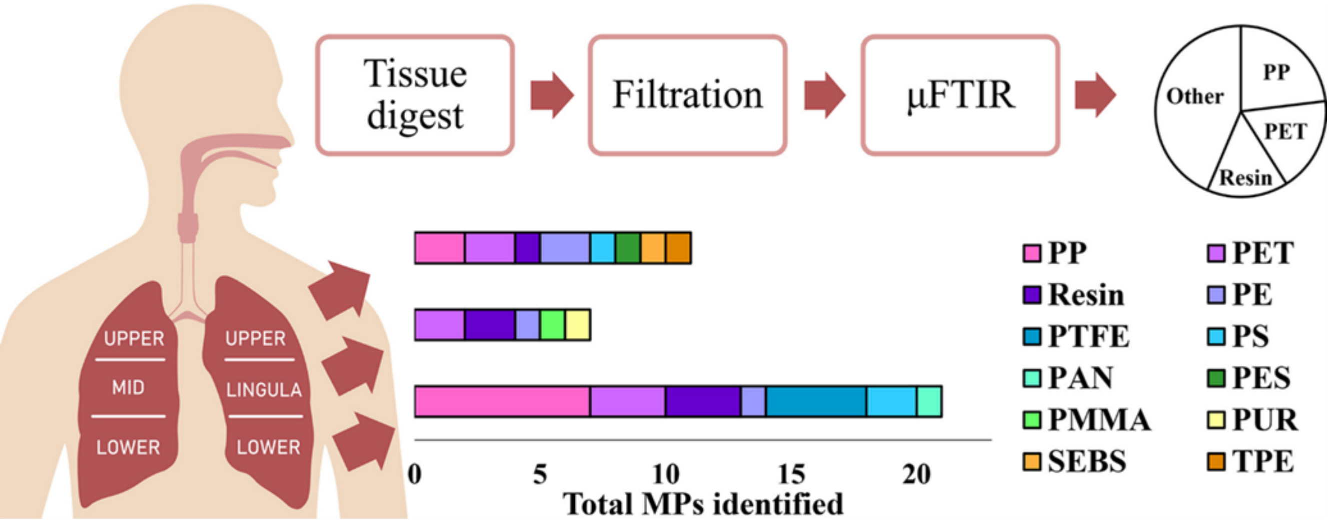
The diagram shows the estimated amount of microplastics inhaled from the air ranging from 3.5 x 10^5 to 2.2 x 10^7 particles. It shows that ingestion of microplastics is minimal in comparison to the inhalation route.

Figure 4. Diagram of microplastics (MPs) via the inhalation and ingestion routes of exposure showing that ingestion of microplastics (items/year) is minimal in comparison to the inhalation route, whereas microplastics that have deposited on food and then ingested was of a similar magnitude to the microplastics via the inhalation route (Taken from Fang et al., 2022).

78. A recent study conducted in Hull, UK sampled 20 households each month for a 6 month period for atmospheric fallout, detecting an average of 1414 MPPs/m^2 per day with particles in the size range of 2-250 µm contributing 90% of the particles found. Polyethylene terephthalate (PET), polyamide (PA) and polypropylene (PP) were the most abundant materials in the samples collected (Jenner et al., 2021).

79. Microplastics have been identified in all areas of the lung from tissue samples obtained following surgical resection for cancer or lung reduction surgery. Data was not normally distributed ($p = 0.013$) and a Kruskal-Wallis test showed that the number of MMPs in the lower region was significantly higher than

the middle/lingular (p = 0.038) and the upper region (p = 0.026). Within the upper region (n = 6, total mass = 33.66 g), 11 MMPs were identified; PE (polyethylene) (18%), PP (18%), PES (polyester) (9%), PS (polystyrene) (9%), resin (9%), SEBS (styrene-ethylene-butylene co-polymer) (9%), TPE (thermoplastic elastomer) (9%). Within the middle/lingular region (n = 3, total tissue mass = 12.19 g), 7 MMPs were identified; PET (29%), resin (29%), PE (14%), PMMA (polymethylmethacrylate) (14%), PUR (polyurethane) (14%). Within the lower region (n = 4, total tissue mass = 9.56 g), 21 MMPs were identified; PP (33%), PTFE (polytetrafluoroethylene) (19%), PET (14%), Resin (14%), PS (10%), PAN (polyacrylonitrile) (5%), PE (5%) (Jenner et al. 2022) (see Figure 5).



The diagram shows the range of different polymers discovered in the lungs and the area of the lung. Polypropylene (PP) is found in the highest amount in the lower and upper lung.

Figure 5. Diagram showing the difference polymer types discovered in the lung and the area of the lung Particle number (total MPs detected with no account taken for MPs found in controls) and polymer type of MPs identified within human lung tissue samples, assigned to their lung region (Figure image taken from Jenner et al., 2022).

80. The concentration of microplastics in indoor air is dependent on what occurs in the environment, for example, whether it is a home or occupational setting (discussed below in paragraphs 87-88).

Occupational exposure

81. Occupational exposure was not included in this statement as it was previously discussed in TOX/2019/62.

Microplastics - Inhalation route - Potential new approaches

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82. To date there are no standardised characterisation, collection, and analytical methods for airborne microplastics or comprehensive risk assessment of NMPs. However, studies are beginning (Koelmans 2022a) to suggest ways in which this could be done.

83. It has also been suggested that an adverse outcome pathway (AOP) framework including the mechanisms of adverse effects, and new approach methodologies (NAMs) can be used in improving the decision-making process with regard to microplastic hazard assessment. The use of read-across, microphysicochemical systems (such as organs on a chip), fluid dynamics, computational models and “omics” can not only reduce the number of animals used and the traditional testing methodologies, but might also provide a more robust scientific basis for decision-making (Halappanavar and Mallach 2021). However, to date, these methods have had only limited success in relation to ambient air pollutants.

Microplastics - Inhalation route - COT evaluation

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84. NMPs are widespread, they are either intentionally added to products or occur as a result of plastics being fragmented down into smaller sizes by natural processes such as wear, weathering and corrosion. There is no internationally agreed definition of what a microplastic is, however, the most widely used size range is from 0.1-5,000 µm. Plastic particles that are smaller than the lower range are considered nanoplastics (i.e. 1 nm – 0.1 µm).

85. Microplastics can have a wide range of physicochemical properties, depending on the primary purpose of the plastic; however, these properties may not be the same in secondary microplastics, where fragmentation has occurred as a result of natural processes (and as such the MPPs are not considered pristine).

86. Analytical methodology is currently limited to Fourier-transform infrared spectroscopy (FT-IR), Nile Red, quantitative nuclear magnetic resonance(

qNMR), Micro-Raman spectroscopy and mass-spectroscopy.

87. There are no standardised testing methods for different matrices such as air, soil, food and water; the available methods have their own associated limitations, and suitable reference materials are not currently available. Furthermore, no single technique is suitable for all plastic types and/or for all particle sizes or shapes. Using a suite of methods or generation of new techniques may be necessary to fully assess microplastics.

88. In terms of the toxicity of NMPs, there are no studies suitable for identification of No Observed Adverse Effect Level (NOAEL) for any polymer type (with the possible exception of PET powder at 2,500 mg/kg bw/day in rats for oral exposure as reported by Merski et al., 2008, however, this study has several limitations and was conducted using the oral exposure route). Available data from the European Chemical Agency Registration, Evaluation, Authorisation and Restriction of Chemicals (ECHA REACH) database relates only to the starting materials i.e. the monomers. Furthermore, variability in exposure routes must also be considered.

89. Comparing studies using different methodology and analytical techniques can be challenging as there is currently no standardization for characterizing and testing microplastics.

90. Contamination with airborne microplastics or cross-contamination of samples may also affect the interpretation of studies, so suitable control samples may be difficult to obtain.

91. Most toxicity studies have been performed with pristine particles, mostly polystyrene; however, these may not be representative of what is present in the environment as the particles have not undergone degradative processes or contain any additional pollutants that attach to the microplastic. There are no specific reference materials that can be used and batch to batch variation can also occur.

92. Currently a full risk assessment on the potential toxic effect(s) of NMPs could not be carried out due to several data gaps including:

- The unavailability of harmonised methodologies to characterise, quantify and identify NMPs.
- The lack of toxicokinetic and toxicity data in general. There are no studies suitable for the identification of NOAELs for the different polymer types except possibly for PET powder by the oral route at 2,500 mg/kg bw/day in

rats, (see paragraph 88), which had a number of limitations (e.g. particle size and count were not determined/reported).

- The paucity of currently available data for microplastics and airborne exposure.
- The difficulty of performing an accurate exposure assessment.

93. For the reasons above, a case-by-case approach to risk assessments may need to be considered. This aligns with the conclusions reached by other authoritative bodies (WHO, 2022; Environment and Climate Change and Health Canada(ECC and HC), 2020; EU Science Advice for Policy by European Academies (SAPEA), 2019; EU Group of Chief Scientific Advisors; Scientific Advice Mechanism (SAM), 2019, as described in the COT overarching statement on the potential risks from exposure to microplastics; COT Statement 2021/02, paragraphs 101-129).

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

Microplastics - Inhalation route - Research priorities for risk assessment

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Data gaps

94. For the inhalation route the significant data gaps include the lack of:

- Harmonised analytical methods for detection of different NMPs during sample collection.
- Methods of detection of NMPs in tissues and their systemic effects.
- Understanding the contribution and effects of different exposure scenarios (*e.g.* indoor and outdoor environments).
- Understanding how different pre-existing lung and other disease states may be involved in any effects from microplastic exposure.
- How available occupational data and on other particle types should be extrapolated to the general population.
- Data on inhalation exposure to NMPs that are resuspended in an indoor environment.

Priorities for risk assessment

95. The COT recommends the following research priorities ranked in order of importance for addressing the data gaps in the potential toxicity of NMPs in humans and suggest a call should be put out to researchers (Table 1). Information in these areas will assist in the future risk assessment of these particles by inhalation and other routes of exposure.

Table 1. Table of future priorities for risk assessment divided into opportunities for improved study design and reporting, as well as research needs.

Ranking Order	Field	Opportunities for improved study design and reporting	Research needs

1	Physicochemical properties /Analytical methodologies	No information.	Development of reference standards and an appropriate fit for purpose quantification and detection methodologies for NMPs in different matrices. Standardisation of the NMPs used and reported.
2	Biological effects	Studies to explore the effect (s) of the same type of NMP on different tissues and of different types of NMP on the same target tissue. Consistency in the use and reporting of the standards used, the source of the NMPs, clear characterisation of the NMPs used and standardised reporting of dosimetry.	Investigations of the extent to which NMPs with a range of sizes and compositions are assimilated into human tissues and development of techniques capable of identifying the presence of microplastics in the human body (e.g. in biopsies, samples from tissue banks, if possible, histopathology sections; residual controls at point of sampling). Exploration of steady states.

3	Physicochemical properties	Standards in measuring and reporting size of particulates. Consistency in the use and reporting of the standards used, the source of the NMPs and clear characterisation of the NMPs used.	From studies of particles at the nanoscale, it has been reported that nanoplastics can deposit lower down in the lung and have been shown to translocate across the pulmonary cellular barrier to secondary organs. Further research needed to confirm. More studies needed looking into the potential effects of nanoplastics are needed to understand size related effects.

			Studies on the absorption, distribution, digestion and removal (excretion) of different particle types and sizes.
4	Adsorption, Distribution, Metabolism and Excretion Toxicokinetics.	Studies on the persistence and potential accumulation of NMPs in the human body and on the extent to which NMPs are digestible.	Steady states studies. Provide and maintain a data base of information assessing biodistribution of NMPs. Evaluation of current dosimetry models for use with NMPs.
5	Migration and degradation.	Assessment of the degradation of novel/emerging plastic-based materials on the market such as biobased plastics (e.g. bamboo ware, polylactic acid, chitin) and other advanced polymer matrix composite materials during their use and end of life for their contribution to NMPs.	It is unclear whether, and by how much, they already contribute to the burden of NMPs or similar particles. Research is needed to explore this and apply to future novel materials.

			Microplastic concentrations in the environment are expected to increase in the future. In addition, increased and widespread use of single-use plastic personal protective equipment due to the COVID-19 pandemic may also be a significant contributing source of plastic pollution.
6	Migration/degradation and analytical methodology/detection.	Regular assessment of NMPs in water, air and relevant food stuff as well as establish a monitoring programme.	The quantification methods for microplastic particulate matter are currently limited and can only be estimated, thus improved technology is required. Regular assessment of NMPs in water, air and relevant food stuff as well as establish a monitoring programme. This can then be shared between academia, researchers and government bodies both nationally and internationally.

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

Microplastics - Inhalation route -COT conclusions

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96. The COT noted that there are limited data regarding the toxicokinetic fate of inhaled microplastics in mammalian species. The extent to which retention in the lung is of concern is not yet clear. No epidemiological or controlled dose studies that evaluated the effects of inhaled microplastics in humans were identified.

97. As such, the COT concludes that based on the available data, it is not yet possible to perform an assessment for the potential risks from exposure to micro and nanoplastics *via* the inhalation routes; however, the COT concurs with the conclusions reached by other authoritative bodies (EFSA (2016, 2020, 2021), WHO (2019, 2022), ECCC (2020) and HC, SAPEA (2019), SAM (2019), as described in the COT overarching statement on the potential risks from exposure to microplastics : COT Statement 2021/02, paragraphs 101-129).

98. The COT concluded that the literature data on exposure to particles from tyre wear would need separate consideration from microplastic exposure

from food, since the particles are chemically quite different in their polymeric nature. Risk assessment of such material was considered potentially outside the scope of the current exercise.

99. The most significant data gaps are the lack of appropriate and harmonised analytical methods for the detection of micro- and nanoplastics (together with suitable reference standards), as well as information on their toxicokinetic and toxicity profiles in/relevant for humans.

100. The COT highlighted that additional information will be needed from all exposure sources, which include indoor and outdoor air, dust and soil before a risk assessment can be completed. The presence of MPs in food and water needs to be put into perspective with other sources of MPs such as atmospheric fallout.

101. Current studies typically focus on only one type of particle/tissue interaction, as such, further research is necessary to explore the effects of the range of particle types in different tissues *in vitro* and/or *in vivo*. This range of particle types should also take account of emerging/novel plastic-based materials such as bioplastics. The future priorities for risk assessment are shown in Table 1.

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January 2024

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

Microplastics - Inhalation route - Abbreviations

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1 α-antitrypsin	Alpha-1 antitrypsin
ABS	Acrylonitrile butadiene styrene
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
COMEAP	Committee on Medical Effects of Air Pollution
CONTAM	Contaminants in the Food Chain
Defra	Department for Environment, Food and Rural Affairs
EC	European Commission
ECC	Environment and Climate Change
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
FT-IR	Fourier-transform infrared spectroscopy

FSA	Food Standards Agency
GIT	Gastrointestinal tract
HC	Health Canada
ILSI	International Life Sciences Institute
MILC	Mothers’ information on lactation and collection
MOE	Margin of exposure
MPPs	Microplastic particles
NEE	Non-exhaust emission
NMPs	Nano- and microplastics
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PAHs	Polyaromatic hydrocarbons

PCBs	Polychlorinated biphenyls
PE	Polyethylene
PET	Polyethylene terephthalate
PM10	Particulate matter (10 μm)
PP	Polypropylene
py-GC-MS	Pyrolysis coupled with gas chromatography and mass spectroscopy
qNMR	Quantitative Nuclear Magnetic Resonance
RAC	Committee for Risk Assessment
REACH	Registration Evaluation Authorisation and Restriction of Chemicals
ROS	Reactive oxygen species
RUBIAC	Rubber Industry Advisory Committee
SAM	EU Group of Chief Scientific Advisors; Scientific Advice Mechanism
SAPEA	EU Science Advice for Policy by European Academies
SEAC	Committee for Socio-economic Analysis

TDS-GC-MS	Thermodesorption gas chromatography with mass spectrometric detection
TWPs	Tyre wear particles
TRWPs	Tyre and road wear particles
UK	United Kingdom
UKWIR	United Kingdom Water Industry Research
US	United States
VOCs	Volatile organic compounds
WHO	World Health Organisation
Zonula Occludens	Scaffolding proteins

Microplastics - Inhalation route - References

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