Meeting

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

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

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 Food Standards Agency (FSA) discussions on this (TOX/2019/08). Since then, several discussion papers have been presented to the COT (see Annex A1) and in 2021, the COT published an overarching statement on the potential risks from exposure to microplastics (COT Statement 2021/02). This document provided a high-level overview of the current state of knowledge, data gaps and research requirements with regards to this topic.

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

3. 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 (*i.e.* resulting from the presence of microplastics in the air (indoor and outdoor)). It is based on current available literature and data from internal tools at the UK FSA (these internal tools include: a literature search application and signal prioritising dashboards).

Questions for the Committee

4. The Committee are asked to consider the following questions

- Do the Committee have any comments on the content or structure of this sub-statement?
- Does the Committee have any further comments?

Secretariat

May 2022

Annex A to TOX/2022/28

Background

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 (see Annex A1) and in 2021, the COT published an overarching statement on the potential risks from exposure to microplastics (COT Statement 2021/02). This document provided a high-level overview of the current state of knowledge, data gaps and research requirements with regards to this topic. This was followed by a sub-statement considering oral exposure to microplastics in more detail.

Scope and purpose

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

3. 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).

Toxicity

4. The COT have previously reviewed the human data on the toxicity of microplastics via the inhalation route (TOX/2019/62). The available toxicity data in humans was based on occupational exposure studies. In 1975, Pimental et al., found that seven patients who had been exposed to synthetic fibres presented with different manifestations of bronchopulmonary diseases. This was attributed in part to the dose and concentration of exposure and the length of service in the industry.

5. In Hillerdal et al., (1988), three female workers in the synthetic textiles industry reported fibrotic areas of the lung with multiple foreign bodies believed to be inhaled fibres which caused inflammation. However, the size of the fibres was unreported.

6. Pauly et al., (1998) reported inhaled cellulosic and plastic fibres found in human lung tissue with samples taken from different pulmonary sites, indicating the inhaled fibres were distributed throughout the lung. The study concluded that there was a correlation between the inhalation of these fibres with lung cancer.

7. The COT in their discussion of TOX/2019/62 highlighted that assessment of microplastics exposure via inhalation may be easier in comparison to oral exposure given the available occupational data from the synthetic textile industry, however the context should be considered. The Committee considered that microplastic concentrations present in food and water were thought to be lower in comparison to airborne exposure. It was also proposed that an initial risk assessment could be based on microplastic exposure from tyre abrasion.

8. 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 consist of microplastics (Zhang et al., 2020).

9. The toxicological mechanisms of microplastics may differ to that of PM2.5 (or other pollutants) due to the additives and special characteristics they contain (Zhang et al., 2020).

10. In 2015, the Committee on the Medical Effects of Air Pollutants (COMEAP) assessed the components of particulate matter (PM) and considered whether primary particles (e.g. manufactured as a plastic particle for an intended used) were more detrimental to health than secondary particles (formed by the break down of primary particles by physical force or chemical reaction) (COMEAP, 2015), acknowledging that non-exhaust sources (including those from brakes and

tyres) have a high oxidative potential that could exert a health effect.

11. COMEAP concluded that there was evidence to suggest that both primary and secondary (particularly sulphate) particulate matter are detrimental to health.

Inhalation studies (since 2020-present)

In vitro

12. 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 1 α-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 of polystyrene MPs cause disruption to the protective pulmonary barrier and high levels may influence an adverse effect on human lung health.

In vivo

13. 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 105 particles/cm 3) of polystyrene NMPs. There was no definitive link between concentration at 14 days exposure, and observed alterations to the physiological, serum biochemical and hematological parameters or markers of respiratory function. However, there was a concentration-dependent response associated with increased expression of TGF-β and TNF-α inflammatory proteins. These results 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.

Risk assessment tools

14. 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.

15. It has also been suggested that adverse outcome pathway (AOP) framework observing the mechanisms of adverse effects, and new approach methodologies (NAMs) can be used in improving the decision making process regarding microplastic hazard testing as the use of read-across, computational models and “omics” cannot only reduce the number of animals used and the traditional testing methodologies, but also provide a more robust decision-making process (Halappanavar and Mallach 2021).

Toxicokinetics

16. 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 density and surface functionalization.

17. Surface functional groups may affect the adsorption of organic contaminants and heavy metals leading to different 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).

18. Deposition occurs in the lung as a function of its aerodynamic diameter of the particle. There are four main mechanisms of deposition: impaction, sedimentation, diffusion and interception (Darquenne, 2006).

19. Inertial impaction occurs for particles with a diameter > 5 µm or for those with excessive momentum. As a particle travels through the airways, they remain on the same trajectory. If the air flow changes direction, the particle will remain on their 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.

20. 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.

21. Diffusion occurs by chance when particles with diameters < 0.5 µm collide with gas molecules causing them to settle on the surface of the lung via Brownian motion. Diffusion occurs mainly in the small airways and alveoli, although they can deposit in the upper airways by this mechanism if their diameter is < 0.01 µm (Tsuda et al., 2013).

22. Interception occurs when fibres with a large ratio between the 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 length of the fibre, but can also arise due to changes in airflow.

23. Clearance mechanisms for inhaled MPs > 1 µm, is likely to occur via the mucociliary escalator, where the particles are either expelled from the body via sneezing or coughing, or they are swallowed and taken into the gastrointestinal tract.

24. Some particles bypass the mucociliary clearance and travel deeper into the lung where phagocytosis occurs. Macrophage phagocytosis can break down particles < 20 µm by either dissolution or degradation but this is dependent on the particle biopersistence, notably its length. 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, releasing cytokines and oxidants resulting in lung inflammation and fibrosis (Donaldson et al., 2010; Gasperi et al., 2018). Inflammation induces cell proliferation and secondary genotoxicity due to the continuous formation of reactive oxygen species (ROS), resulting in oxidative stress.

25. Microplastics contain ROS as a by-product of processing and polymerization. The amount of ROS present may also be increased following weathering of the MPs by ultraviolet (UV) radiation or the presence of reactive metals (Rahman et al., 2021).

26. It has been suggested that a fraction of deposited particles 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 (Donaldson, et al., 2010; Enyoh et al., 2019). Translocation to secondary tissues and organs may then occur (Fournier et al., 2020; Wright and Kelly, 2017).

Exposure

27. Microplastics are present in the indoor and outdoor environment. The MPs can result from textiles, furniture, toys, electric cables and cleaning agents, construction material and litter.

Indoor exposure

28. 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/m3.

29. 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 m3 per day as 1.9 x 103-1.0 x 105 and 0-3.0 x 107 respectively, confirming that there is increased exposure to microplastics in the indoor environment. Whereas Fang et al., (2022), calculated the atmospheric deposition of MPs as 3.5 x 105 – 2.2 x 107 (Figure 1).

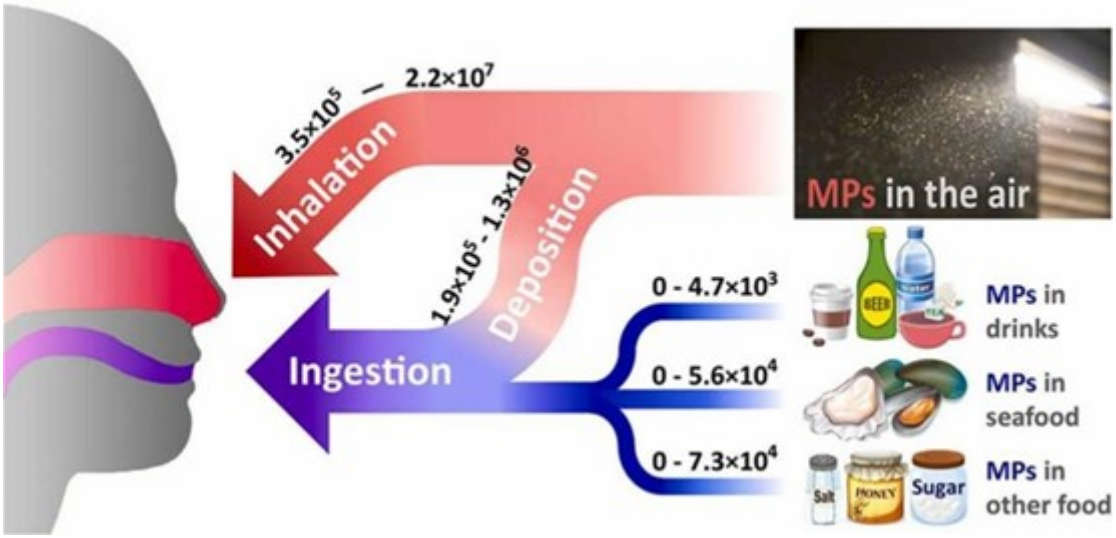

Figure 1. Diagram of MPs via the inhalation and ingestion routes of exposure (Taken from Fang et al., 2022).

30. A recent study in Hull, UK sampled 20 households each month for a 6 month period giving an average of 1414 microplastics/m2 per day with particles in the range of 2-250 µm contributing to 90% of the particles. Polyethylene terephthalate (PET), polyamide(PA) and polypropylene(PP) were the most abundant in the samples collected (Jenner et al., 2021).

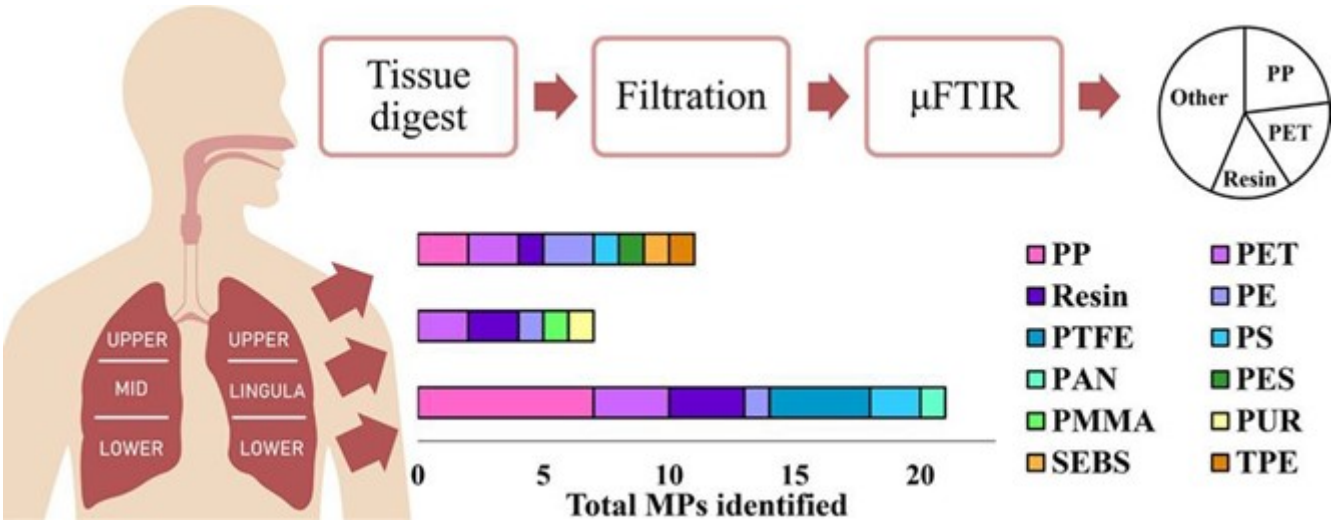

Figure 2. Diagram showing the difference polymer types discovered in the lung and the area of the lung (Taken from Jenner et al., 2021).

31. The concentration of indoor air is dependent on what the environment is used for (e.g. home or occupational setting) and is discussed below in para. 34-35).

Outdoor exposure

32. Microplastics found outdoors are more likely to fracture due to the weathering (*i.e.* UV sunlight, temperature fluctuation and wind) 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).

33. Dris et al., (2017) investigated outdoor air samples (from one of the indoor sites mentioned in para 20 above) in the city centre of Paris. The concentration found in the outdoor sample was 0.3 to 1.5 fibres/m3.

Occupational exposure

34. Certain occupations for example synthetic and flock industries can result in higher exposure of microplastics increasing the risk of developing occupational diseases. Burkhart et al., (1999) reported that in the flocking area of a manufacturing plant, where the particles are applied to a product, the highest concentration of airborne particles reached 7 mg/m3.

35. Characterisation of MPs from nail salons found the predominant sizes to be <50 µm and the estimated average annual indoor exposure of MPs was 67,567 ± 81,782 MPs/year. The polymers were predominantly acrylic (27%), rubber (21%) and polyurethane (13%), however the characteristics and polymer composition

differed between nail salons. Factors that influenced the concentrations of MPs included the type of nail treatment being conducted, the use of air conditioning units and number of people present (Chen et al., 2022). Therefore MPs are more likely to affect human health from occupational exposure compared to indoor exposure at home (Prata, 2018).

COT evaluation

36. 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).

37. 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). Additionally, analytical methodology is limited to Fourier- transform infrared spectroscopy(FT-IR), Nile Red, quantitative nuclear magnetic resonance(qNMR), Micro-Raman spectroscopy and mass- spectroscopy. 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 for all particle sizes or shapes. Using a suite of methods or generation of new techniques may be necessary to fully assess microplastics.

38. In terms of the toxicity of NMPs, there is no identified No Observed Adverse Effect Level (NOAEL) for each polymer type (with the possible exception of PET powder at 2,500 mg/kg bw/day in rats as reported by Merski et al., 2008, however, this study has several limitations and is via the oral route). Available data on the European Chemical Agency registration, evaluation, authorisation and restriction of chemicals (ECHA REACH) database relates to the starting materials *i.e*. the monomers. Furthermore, variability in exposure routes must also be considered.

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

40. Contamination with airborne microplastics or cross-contamination of samples also pose a concern when interpreting studies, so suitable control samples may be difficult to obtain.

41. The COT also considered whether particles arising from tyre wear were considered to be microplastics (Annex B1). It was concluded that human exposure can occur from airborne particulate matter derived from tyre wear material. However, challenges arise in evaluating the risk of this particulate matter due to other variables such as aging and weathering of tyres, temperature effects, the types of road surfaces they are used on and driving style. These variables result in the generation of a variety of chemicals which have significantly different biological and toxicological potencies and effects.

42. Most toxicity studies have been performed with pristine particles; however, these may not be representative of what is present in the environment as the particles have not undergone degradative processes in the environment, 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.

43. 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 is no identified NOAEL for the different polymer types except possibly for PET powder at 2,500 mg/kg bw/day in rats, (see paragraph 38), whichhad 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 and;
- The difficulty of performing an accurate exposure assessment.

44. 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 (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).

Research priorities for risk assessment Data gaps

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

- Harmonised analytical methods for detection of different NMPs during sample collection;
- Understanding the contribution and effects of different exposure scenarios (*e.g.* indoor and outdoor environments);
- Understanding how different lung disease states may be involved in the observed effects from microplastic exposure and;
- How available occupational data should be extrapolated to the general population.
- No data on inhalation exposure to MPs that are resuspended in an indoor environment.

Research priorities

46. The COT recommends the following research priorities for addressing the data gaps in the potential toxicity of NMPs in humans. Information in these areas will assist in the future risk assessment of these particles by inhalation and other routes of exposure.

- Development of reference standards and materials for use in wet lab/experimental settings. Also, development of appropriate fit-for- purpose quantification and detection methodologies for micro and nanoplastics in different matrices.
- From studies of particles at the nanoscale, it is known that nanoplastics can deposit lower down in the lung and have been shown to translocate across the pulmonary cellular barrier to secondary organs (Fournier et al., 2020). Therefore, more studies looking into the potential effects of nanoplastics are needed to comprehend size related effects.
- Comprehensive assessment of MPs and associated contaminant concentrations and matrices (such as air, soil, food and water) and the impact of the effect of cooking on the desorption and subsequent bioavailability of contaminants/leachates in relevant matrices.
- Assessment of the degradation of novel/emerging plastic-based materials on the market such as biobased plastics (for example bamboo ware, polyactic acid, chitin) and other advanced polymer matrix composite materials during their use and end-of-life for their possible contribution to NMPs. It is unclear whether, and by how much, they already contribute to the burden of NMPs or

similar particles.

- Studies (*in silico*, *in vitro* and/or *in vivo*) to explore the effect(s) of the same type of NMP on different tissues (e.g. heart, brain, liver, stomach, intestines), and of different types of NMP (e.g. polymer type, size, shape) on the same target tissue.
- Studies on the persistence and potential accumulation of NMPs in the human body, and on the extent to which NMPs are digestible.
- Investigation of the extent to which NMPs with a range of sizes and compositions are assimilated into human tissues and the 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).
- 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 (e.g. face masks and gloves) due to the COVID-19 pandemic may also be a significant contributing source of plastic pollution (Silva et al., 2021; Ma et al., 2021). However, the quantification methods for microplastic particulate matter is currently limited and can only be estimated, thus improved technology is required. Therefore, there will be a need to regularly assess the levels of NMPs in relevant food stuffs, water and the air, such as by establishing a monitoring programme. This data would best be shared by collaboration among academia, researchers and government bodies at a national and international level.

COT conclusions

47. 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.

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

49. 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 were chemically quite different in their polymeric nature. Risk assessment of such material was considered potentially outside the scope of the current exercise.

50. 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.

51. 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.

52. 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*. These range of particle types should also take account of emerging/novel plastic-based materials such as bioplastics.

Secretariat

May 2022

Abbreviations

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

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Annex B to TOX/2022/28

Discussion papers presented to the COT on the potential risks from exposure to microplastics

TOX/2019/62 (22/10/2019) Paper 1: Scoping paper on the potential risks from exposure to microplastics.

TOX/2020/15 (11/03/2020) Paper 2: Potential risks from exposure to microplastics: First draft overarching statement (Cover page).

Annex A1 First draft overarching statement on the potential risks from exposure to microplastics.

Annex B1 Paper for information: Background on tyre wear

Annex C1 Paper for information: Update on literature.

TOX/2020/40 (15/09/2020) Follow-up to Paper 2: Overarching statement on the potential risks from exposure to microplastics (Cover page).

Annex A2 Second draft overarching statement on the potential risks from exposure to microplastics.

TOX/2020/58 (01/12/2020) Follow-up to September 2020 meeting: Overarching statement on the potential risks from exposure to microplastics: Third draft (Cover page).

Annex A3 Third draft overarching statement on the potential risks to microplastics.

COT Statement Number 2021/02 Follow-up to December 2020 meeting: Overarching statement on the potential risks from exposure to microplastics.

COT Statement Number 2021/05 Sub-statement on the potential risk(s) from exposure to microplastics: Oral route.