Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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

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 FSA discussions on this (TOX/2019/08). Since then, several discussion papers have been presented to the COT (see Annex B) 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.

Scope and purpose

2. There is evidence for the presence of plastic particles in some foodstuffs (Touissant *et al*., 2019; Bai *et al*., 2022) and awareness of the extent and range of foodstuffs affected is increasing with developments in analytical detection methodologies and growing consumer interest.

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 ingested *via* the oral route (*i.e.* resulting from the presence of microplastics in food, drinking water and bottled drinks). It is based on current available literature and data from internal tools at the UK Food Standards Agency (FSA) (these internal tools include: a literature search application and signal prioritising dashboards).

Toxicokinetics

4. Oral ingestion involves a number of processes that influence the interactions and biological effects of particles. For example, the pH levels of the saliva/digestive fluids may change their surface charge and zeta potential, formation of protein coronas and therefore, their interaction with cells/organs and any subsequent observed health effect.

5. The size of particles is one of the key determining factors of uptake in the gastrointestinal tract (GIT). Particles within the nanoscale (1 to 100 nm) can distribute to all organs and can be translocated across the blood-brain and placental barriers. The extent of such absorption is poorly described. It is generally accepted that large particles > 150 µm will not be absorbed and thus there is no systemic exposure to such particles.

6. Two uptake pathways of microplastics (0.1 > 10 µm) from the GIT lumen have been described in the literature.

7. Firstly, particles can be taken up by endocytosis[1] by the microfold (M) cells of the Peyer's patches, where the M cells take up and transport particles from the intestinal lumen to the mucosal lymphoid tissues. It should be noted that the Peyer's patches are located in the ileum of the small intestine, which represents a small fraction of the total GIT surface area.

8. Secondly, uptake may be *via* paracellular persorption[2], where particles (such as microplastics) may be mechanically kneaded through loose junctions in the single-cell epithelial layer into the tissue below. Dendritic cells can phagocytose[3] such particles, subsequently transporting them to underlying lymphatic vessels and veins. Distribution to secondary tissues including the liver, muscle and brain may then occur (Wright & Kelly, 2017).

9. The uptake pathway is dependent on the property of both the cell type and the target particle, including its surface chemistry and size. Surface charge, and hydrophobicity also influence the adsorption of proteins to the particle surface.

10. The COT has previously reviewed relevant animal toxicokinetic studies on exposure from microplastics *via* the oral route (these are tabulated in Annex A). At the time of review, only one study was found to describe the potential fate of microplastic particles in human GIT (Schwabl *et al*., 2018;

[1] Endocytosis is a cellular process by which cells take in substances from outside of the cell by engulfing them in a membrane vesicle.
[2] Paracellular transport refers to the transfer of substance across an epithelium by passing through the intercellular space between the cells (often referred to as tight junctions).
[3] Phagocytosis is a cellular process by which a cell uses its plasma membrane to engulf a particle, giving rise to an internal compartment called a phagosome.

2019). Available data for maternal transfer of nano- and microplastics (NMPs) to embryo/fetus are also limited (Ragusa *et al*.,2021)

11. Based on the available information, the COT concluded that there are only limited data regarding the toxicokinetic fate of orally ingested microplastics in mammalian species, and that microplastic particles can either translocate from the GIT into organs or tissues (*via* endocytosis by M cells and paracellular persorption), and/or be excreted. Whilst retention in the GIT is also a possibility, there is little evidence for this in mammalian species. It is estimated that over 90% of the particles are ultimately excreted (~>90%). There is lack of information on possible metabolism. Furthermore, no epidemiological or controlled dose studies in which the effects of orally ingested microplastics in humans have been evaluated were identified.

Toxicity

12. At the time of review, the COT observed that whilst there is a large quantity of literature regarding the presence and toxicity of micro- and nanoplastics in the marine environment, there is limited data that are of direct relevance to humans. The background papers (which includes summaries of literature) previously reviewed by the COT are presented in Annex B.

13. Due to the current uncertainties and lack of data, the potential toxic effects of microplastics are often hypothesised rather than observed. These hypotheses are hazard based and are driven by the physicochemical properties of micro- and nanoplastics. The proposed effects are:

i). Physical (*e.g*. bulk, 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).

Physical hazard

14. A common hypothesis is the local irritation of the intestinal tissues caused by physical mechanical disruption of the intestinal epithelium cells (IECs) membrane layer by retained plastic particles in the lumen. However, intestinal crypts undergo constant cycles of IEC replenishment and renewal, and under normal homeostatic conditions it is estimated that an entire crypt is replaced every 4-5 days (van der Flier & Clevers, 2009).

15. However, shedding of IECs from the epithelial monolayer may cause transient gaps or micro-erosions in the epithelial barrier, resulting in either: increased intestinal permeability or malabsorption to micro- and nanoplastics but also to other chemicals and solutes that may be present in the intestinal tract. There is limited knowledge on the rate and effect of this process on the absorption of either the particles or other components present in the gut, and the resulting toxicity of micro- and nanoplastics is not known.

16. In certain disease states (*e.g.* individuals with gastrointestinal issues such as inflammatory bowel disease) the integrity of the intestinal barrier may be weaker and thereby affect the crossing of particles (including plastic particles), their systemic bioavailability and subsequent toxicity. The COT note that the behaviour of micro- and nanoplastics in normal gut conditions and in certain disease states warrants further investigation.

Chemical hazard

17. The majority of toxicological studies of micro- and nanoplastics have investigated the toxicity of additives used in plastics such as phthalates, unbound monomers such as styrene or sorbed chemicals from the environment such as persistent organic pollutants and metals.

18. Based on the available information, chemical leachates and adsorbed substances from microplastics are not expected to increase adverse health effects in humans as their contribution to the overall exposure from other sources of the same chemical is very small, as evidenced by the EFSA, 2016 review and the WHO, 2019 margin of exposure calculations.

Metabolism or degradation products

19. Particles >150 µm usually do not translocate across the gut epithelium, whilst smaller particles especially those within the nanoscale (1 nm to 0.1 µm) have the potential for uptake by organs (see *paragraph 5*). Microplastics may be taken up into cells but there is a lack of information on their possible metabolism in humans, therefore this hazard is yet to be fully characterised.

20. However, it remains unknown whether large plastic particles (*e.g.* 5 µm) breakdown into smaller sizes in the GIT. If they do, it is not clear if these smaller plastic particles release a higher level of leachates/sorbed chemicals or produce new degradation products from the polymer itself.

Microbiological hazard

21. The UK FSA is currently performing a critical literature review on the microbiological colonisation of nano- and microplastics (NMPs) and their significance to the food chain (FS307021), which was contracted to the Centre for Environment Fisheries & Aquaculture Science. Preliminary outputs from this review were first presented by Bakir *et al*., (2021) in a poster format during the European Food Safety Authority's (EFSA) Scientific Colloquium 25;

"A coordinated approach to assess the human health risks of micro- and nanoplastics in food", 6-7 May 2021.

22. The four research areas as part of this work package (WP) include: NMPs in the environment (WP1); pathways of colonised NMPs into food chains (WP2); interactions between NMPs and microorganisms (WP3); and NMP-specific microbial risks to consumers (WP4).

23. The evidence gaps and recommendations for further work in WP4 are summarised here. It was found that data on the presence of viruses on NMPs is currently lacking, and in general very little attention is focused on the potential role of plastic associated microorganisms. Available studies reporting the presence of pathogens on NMPs in environmental settings were found to be anecdotal and lack robust controls (*e.g.* comparison to other substrates). Additionally, published studies on the possible presence of antimicrobial resistant organisms in NMPs were found to be of low quality (*e.g.* lack of appropriate controls), which made data comparison challenging when attempting to ascertain the overall relevance of this hazard to the risk. No human specific study on dysbiosis was found, although studies in other, model organisms were available (*e.g.* mice and zebrafish).

24. Overall, for WP4, the authors considered that there is little data regarding the impacts of NMPs on pathogens and human health outcomes. Furthermore, there is a clear lack of available epidemiological data.

25. An authoritative full synthesis report and special report document will be published later in 2021 to provide a collated and impartial summary of the scientific evidence on the impacts of microplastics and microbiological risk to human health, utilizing the most relevant and contemporary scientific data available.

COT evaluation

26. The COT noted the following concerns regarding the toxicological studies available:

- Reliability (*e.g.,* small number of animals per dose group).

- Low quality of the toxicological data (*e.g.,* unclear methodologies, lack of control groups).

- Lack of standardisation and/or harmonisation of study methods for investigating potential toxicological risk(s) from exposure to microplastics *via* the oral route. This includes lack of consistency on the dose metrics used, their assessment and reporting, which leads to issues relating to study comparability and reliability.

- Most studies have performed tests on pristine particles, which can have batch variability (*e.g.,* different specification profiles). Therefore, there is a lack of a consistent source of test material that can be used in wet lab experiments.

- Pristine particles may not be representative of what is present in the environment as particles have not been subject to environmental degradation processes and thus what may become present as contaminants in foodstuffs.

- There are neither standardised testing protocols for different matrices for foodstuffs, nor standard reference materials for analysis, characterization and quantification of micro and nanoplastics. No single technique is suitable for all plastic types and for all particle sizes or shapes. Therefore, the utilization of either a suite of methods or generation of new techniques will be necessary to undertake reliable analysis.

27. At the time of review, a full risk assessment on the potential toxic effect(s) of micro and/or nanoplastics could not be carried out due to several data gaps including:

- The unavailability of harmonised methodologies to characterise, quantify and identify NMPs (van Mourik *et al*., 2021) .

- The lack of toxicokinetic and toxicity data in general. There is no identified no-observed-adverse-effect level (NOAEL) for the different polymer types, with the possible exception of PET powder where a NOAEL of 2,500 mg/kg bw/day in rats was reported (Merski *et al*., 2008). However, this study had a number of limitations, for example, particle size and count were not determined/reported.

- The paucity of currently available data for microplastics in different food types and matrices.

- The difficulty of performing an accurate exposure assessment.

28. 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 (ECCC and HC, 2020; SAPEA, 2019; SAM, 2019, as described in the COT overarching statement on the potential risks from exposure to microplastics; COT Statement 2021/02, please refer to paragraphs 101-129).

Research priorities for risk assessment

Data gaps

29. The most significant data gaps hindering a robust risk assessment for exposure *via* the oral route include the lack of:

- Appropriate and harmonised analytical methods for the quantification of different NMPs in various food matrices.

- Understanding of human exposure and contributions from different food types and sources and of non-food sources such as atmospheric deposition.

- Human-relevant information on the absorption, distribution, metabolism and excretion (*i.e.* the toxicokinetic profile) and on the toxicity profiles of NMPs.

30. The COT recommends the following research priorities for addressing the data gaps in the potential toxicity of micro- and nanoplastics in humans. Information in these areas will assist in the future risk assessment of these particles by oral and other routes of exposure.

- Development of reference standards and materials for use in wet lab/experimental settings. As well as the development of appropriate and fit-for-purpose quantification and detection methodologies for micro and nanoplastics in different matrices.

- Comprehensive assessment of MPs and associated contaminant concentrations in different food types (*e.g.* seafood, edible meat tissue and offal, vegetables, fruit, drinks) and matrices (*i.e.,* food and water) and the impact of the effect of cooking on the desorption and subsequent bioavailability of contaminants/leachates.

- 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 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, and if possible, histopathology sections).

31. Microplastic contamination of food is expected to increase in the future. In addition, an increase 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). Hence, there will be a need to regularly assess the levels of microplastics in relevant food stuffs, water and the air, such as by establishing a monitoring programme. This would best be achieved by collaboration among academia, researchers, and government bodies at a national and international level.

COT Conclusions

32. The COT noted that there are limited data regarding the toxicokinetic fate of orally ingested microplastics in mammalian species, and that microplastic particles can either translocate from the GIT into organs or tissues (*via* endocytosis by M cells and paracellular persorption), and/or be excreted. The extent to which retention in the mammalian GIT tract is of concern, if at all, is not yet clear. No epidemiological or controlled dose studies in which the effects of orally ingested microplastics in humans have been evaluated were identified.

33. 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 to humans *via* the oral route. It should be noted that the COT's conclusions are consistent with those reached by other authoritative bodies (EFSA, 2016; WHO, 2019; ECCC and HC, 2020; SAPEA, 2019; SAM, 2019, as described in the COT overarching statement on the potential risks from exposure to microplastics; COT Statement 2021/02; please refer to paragraphs 101-129).

34. The COT previously considered the extent to which exposure to tyre wear (a source of synthetic polymeric material) might contribute to the total burden of adverse effects of NMPs in humans (Annex B of TOX/2020/15). The COT concluded, however, 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 to be outside the scope of the current exercise.

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

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

37. Comprehensive assessment of microplastics and contaminant concentrations in different foods and the impact of cooking on the desorption and subsequent bioavailability of contaminants/leachates, need to be further investigated to better understand the implications for human health.

38. 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.

COT
November 2021
Statement Number 2021/05

Abbreviations

COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
ECCC	Environment and Climate Change Canada
EFSA	European Food Safety Authority
FSA	Food Standards Agency
GIT	Gastrointestinal tract
HC	Health Canada
NMPs	Nano- and microplastics
NOAEL	No-observed-adverse-effect level
PET	Polyethylene terephthalate
SAM	EU Group of Chief Scientific Advisors; Scientific Advice Mechanism
SAPEA	EU Science Advice for Policy by European Academies
UK	United Kingdom
WHO	World Health Organisation

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Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Sub-statement on the potential risks from exposure to microplastics: Oral route

The COT has previously reviewed relevant animal toxicokinetic studies as a result of exposure from microplastics *via* the oral route. Table 1 below presents brief summaries of each reviewed article.

Table 1 - Summaries of reviewed *in vivo* animal toxicokinetic studies.

Polymer type and size	**Animal Model**	**Dose**	**Exposure route and duration**	**Results**	**Reference**
Polystyrene (50 nm)	Male Fisher 344 rats	125 mg/kg bw *via* oral gavage	6 hours	High amounts were found in the stomach and intestinal wall, heart, and kidney. Estimated bioavailability was 0.2 to 1.7%.	Walczak *et al*., (2015)
Polystyrene (nominal diameter of 42 nm)	Zebrafish	~1 mg/g of fish	7 days	F1 fish – embryos and larvae of PS-NP exposed F0; PS-NPs were found in the yolk sac, GIT, liver, and pancreas.	Pitt *et al*., (2018)
Polystyrene (spherical; 24 or 250 nm)	English scallops	15 µg/L	6 hours	An uptake of 30% of 24 and 15% of 250 nm PS-NPs from the available NP burden in the medium.	Al-Sid-Cheikh *et al*., (2019)
Polystyrene latex (spheres; 2 µm)	Mice (both sexes)	6.84 x10^8 particles in 0.1 mL distilled water	Oral gavage 5, 30 and 90 minutes	Proportion of uptake was almost entirely villous rather than associated with mesenteric lymphoid tissues. Highest percentage of uptake in the intestine was 0.32% in mice, whilst in rats and guinea pigs this was 0.13% and 0.12%, respectively.	Doyle-McCollough *et al*., (2007)
Polystyrene latex (spheres; 2 µm)	Rats (both sexes)	1.42 to 1.95 x 10^9 particles in 0.25 mL distilled water	Oral gavage 5, 30 and 90 minutes	Proportion of uptake was almost entirely villous rather than associated with mesenteric lymphoid tissues. Highest percentage of uptake in the intestine was 0.32% in mice, whilst in rats and guinea pigs this was 0.13% and 0.12%, respectively.	Doyle-McCollough *et al*., (2007)

Polystyrene latex (spheres; 2 μm)	Guinea pigs (both sexes)	1.42 to 1.95 x 10^9 particles in 0.25 mL distilled water	Tube to the pharynx 5, 30 and 90 minutes	Proportion of uptake was almost entirely villous rather than associated with mesenteric lymphoid tissues. Highest percentage of uptake in the intestine was 0.32% in mice, whilst in rats and guinea pigs this was 0.13% and 0.12%, respectively.	Doyle-McCollough *et al*., (2007)
Polystyrene (5 μm)			Water; *ad libitum* 28 days	Both PS-MP sizes displayed tissue accumulation over time and steady-state was reached in the liver, kidney, and gut within 14 days post exposure. MCT of 5 μm PS-MPs in the liver, kidney and gut were 0.30, 0.95 and 1.39 mg/g, respectively. For the 20 PS-μm MPs, the MCT for the same tissues were 0.76, 0.78, and 0.78 mg/g, respectively.	Deng *et al*., (2017)

Abbreviations: GT; PS-NPs – polystyrene nanoplastics; GIT – gastrointestinal tract; NP – nanoplastic; PS-MP - polystyrene microplastic; MCT – Multi

Annex B

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Sub-statement on the potential risks from exposure to microplastics: Oral route

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 A	First draft overarching statement on the potential risks from exposure to microplastics
Annex B	Paper for information: Background on tyre wear
Annex C	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 A	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 A	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