Executive Summary

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Novel formulations of supplement compounds designed to increase oral bioavailability

Over the past couple of decades there has been an increasing trend within the supplement industry toward the formulation and marketing of bioactive agents (such as vitamins, minerals, and plant metabolites) in novel ways that are designed to increase oral bioavailability, particularly when this is intrinsically low. Amongst these formulations are lipid-based preparations such as liposomes, micelles, and emulsions, as well as non-lipid-based preparations including micronisation and co-formulation with polysaccharides. Although these preparations are often marketed as having improved absorption relative to more traditional formulations, there is a lack of evidence and a large degree of uncertainty as to the impact of these changes. This is complicated by the heterogeneity of novel formulation types and the lack of data characterising their physical-chemical properties. This uncertainty on the effects of supplement formulation on bioavailability means that their possible toxicological effects are similarly uncertain and of potential concern, particularly with respect to under-characterised active agents and/or vulnerable populations. Given this situation, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) have discussed the possible increase in oral bioavailability of supplement compounds formulated in novel ways and the possible toxicological risks associated with the consumption of these. The Discussion Paper sets out the physical-chemical characterisation of several lipid-based and non-lipid-based formulations designed to increase oral bioavailability, the possible physiological mechanisms through which they act, and several case studies reviewing their effects drawn from the literature (curcuminoids, vitamin C, and cannabidiol (CBD)). The uncertainties surrounding novel bioavailable formulations are also discussed. The Discussion Paper can be found in Annex A and this Special Topics Report provides an overview of the paper's contents and the COT's discussions thereon (COT, 2023).

Based on their review of the discussion paper, which is presented below, the COT have made five key recommendations for the ongoing assessment of novel

formulations that are of potentially increased oral bioavailability:

1. Novel formulations and their associated active agents should be assessed for their toxicokinetics on a case-by-case basis.

2. The model systems used to assess alterations in toxicokinetics should consider species differences with respect to metabolism.

3. The effect of the feeding state (fed vs. fasted) is a key determinant of bioavailability and must be critically considered when comparing across different formulations.

4. The suitability of acceptable daily intakes (ADIs) and other health-based guidance values (HBGVs) for an unformulated supplement for characterising the risks from that supplement formulated to increase its bioavailability should always be considered.

5. There are a number of approaches that can be used to consider how HBGVs relate to differences in bioavailability, and these should be assessed and utilised on a case-by-case basis.