COT’s discussion

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The COT discussed the paper presented in Annex A (COT, 2023). Members of the Committee considered the emerging market for novel/bioavailable formulations and noted that it is important to remain aware of its current state and possible future developments. In terms of the scientific literature around these formulations, the Committee suggested that any reporting bias present in the literature is likely to skew findings in the positive direction. This is because most studies will have been conducted or commissioned by manufacturers with interests primarily in increased bioavailability of proprietary formulations and negative studies are less likely to be submitted. Although the possibility of such bias should be noted, this is not considered to be a major issue with respect to risk assessment because the bias would be towards a more conservative scenario.

Members emphasised that although certain conclusions may be reached regarding novel formulations in general, it is key to assess specific active compounds and their formulation on a case-by-case basis. For instance, in reviewing the case studies presented in the Discussion Paper, the Committee noted that the ways in which the kinetic parameters of xenobiotics such as curcumin and cannabidiol (CBD) are affected will not be the same as for essential vitamins such as vitamin C. The latter are subject to a number of homeostatic mechanisms. Specifically, at standard doses vitamin C is fully bioavailable, and although changing its formulation may affect its homeostatic regulation, lipophilic molecules have more scope for increased bioavailability *per se*, when formulated in novel ways to increase their solubility and -uptake. However, Members also noted that the potential, dose-dependent, toxicity of vitamin A and vitamin D are topical issues (COT, 2023) and it would be prudent to consider the possible effect of formulation on their absorption. Members also stated that novel formulations of iron and iodine would be important to consider. Further to this, Members explained that feeding state (period since last meal, meal frequency/size, nutritional content etc.) significantly affects the bioavailability of fat-soluble compounds administered via the oral route. Specifically, the presence of dietary fat/lipids favours the absorption of lipophilic molecules. Feeding state, therefore, will fundamentally affect the interpretation and evaluation of bioavailability studies with novel formulations.

Members discussed the challenges in translating findings from conventional toxicology studies to interpreting the impacts of novel formulations. Members raised the question of potential non-linearity in the dose-responses of these formulations and the point at which increases in area under the curve become

toxicologically relevant. Understanding the precise mechanisms driving the alterations in bioavailability, for instance saturation of efflux transporters and/or saturation of metabolic deactivation, are also important for assessing the toxicological implications of novel formulations. Again, this will vary on a case-by-case basis. For instance, whereas increasing the absorbed dose of vitamins and minerals will saturate regulatory mechanisms in the body, the disposition of non-essential supplements is regulated in different ways. In terms of these toxicokinetic considerations, Members argued that interspecies differences in these processes are also important to consider when evaluating the safety of novel formulations.

In reviewing the potential adverse effects of novel lipid-based formulations, as noted above, it is important to distinguish between studies conducted in the fed and fasted state. Because absorption requires carrier lipids and bile acids that are modulated by feeding state, feeding status may have important effects on toxicokinetics. The interaction between lipid-based formulations and the GIT was also raised, and it was argued that some formulations may prevent the absorption of dietary nutrients during equilibration in the gut.

The COT discussed the implications of novel formulations for health-based guidance values (HBGVs) for specific compounds. Where these values already exist, for example for curcumin, they may not be protective for formulations with increased bioavailability. Members argued that the critical factor here was understanding how external dose represents the internal dose for standard and novel formulations, and when/if these differ. Here, Members reiterated the issues of cross species differences and extrapolation of no observed adverse effect levels. In cases where kinetic data are available relating to changes in bioavailability, Members suggested that this may be used to determine an additional uncertainty factor that can be applied to HBGVs for standard formulations of compounds, where they exist. This approach is similar to that already undertaken when exposure is by inhalation. In the absence of specific kinetic data, Members argued that a conservative approach would be to assume 100% bioavailability of the active compound. Members discussed how these kinds of data are often unavailable, and that the pharmaceutical industry is likely to have more expansive datasets that could aid in these kinds of assessments.