# COT’s discussion

## In this guide



The COT discussed the paper presented in Annex A. 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 if a reporting bias is present - for instance where studies are conducted or commissioned by manufacturers - it is likely to skew findings in the positive direction. Although such bias should be noted, this is not considered to be a significant issue with respect to risk assessment because it approximates a worst-case scenario.

Members emphasised that although certain points may be drawn 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 xenobiotics such as curcumin and Cannabidiol (CBD) will differ in their kinetic parameters to essential vitamins such as vitamin C. Specifically, at standard doses vitamin C is fully bioavailable, whereas lipophilic molecules have more scope for increased bioavailability when formulated in novel ways to increase their solubility and uptake. However, Members also noted that the potential toxicity of vitamin A and vitamin D are topical issues, and it may be prudent to be aware of formulations altering their absorption. The formulation of iron and iodine, Members also stated,

would be relevant to consider.

Members discussed the challenges in translating 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, non-essential supplements are 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 Members argued it was 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, Members noted that feeding status may have important effects on toxicokinetics. The interaction between lipid-based formulations and the GI tract 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 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 depart. 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 this may serve as an additional uncertainty factor that can be applied to Health Based Guidance Value HBGVs for standard formulations of compounds, where they exist. This approach is similar to that undertaken for the lung, already. 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.