Questions and Comments Received From Webinar Attendees Directed to Specific Speakers: Harvey Clewell

Q: If it is required to show that toxicity differs above the kinetic maximum dose (KMD) vs. below the KMD (*i.e.*, toxicity is not relevant at lower doses), would increased blood levels and changes in compound distribution qualify as a sufficient factor for the lack of relevance of toxicity at high doses? Would this require a verification of different distribution into affected organs vs. blood levels?

A: Saturation of pharmacokinetic processes like metabolism and binding does not, by itself, indicate that effects seen at higher doses are irrelevant to lower doses. There also needs to be some rationale for deeming higher dose studies unnecessary. For saturation of absorption, the rationale is that the interest is only in systemic effects, not portal-of-entry effects. For saturation of metabolism, the rationale might be that the concern is for toxicity of a metabolite rather than the parent compound, and dosing above saturation would not increase metabolite exposure. For changes in distribution, the rationale might be that induction of binding of the chemical in a tissue is associated with activation of a receptor (e.g., dioxin). Each of these rationales would require evidence.