Questions and Comments Received From Webinar Attendees Directed to Specific Speakers: Anna Lowit or Anne Gourmelon

Q: There is a visceral resistance in some areas to accepting kinetic maximum dose (KMD) approaches, even when the guidance on toxicokinetics in the Organisation for Economic Co-operation and Development's Guidance Document 116 has been fully complied with in other regards and the studies are considered otherwise acceptable. What do you think the reasons may be for this: lack of harmonized approaches, or nervousness that hazard information is not identified in animal studies?

A: There is resistance to accepting any change, not matter how realistic it may be. In my opinion, use of KMD is the way forward and will be accepted by all in the near future. The U.S. Environmental Protection Agency's Office of Pesticide Programs have been pushing this since 2006.

Q: Is KMD applicable to *in vitro* tests?

A: KMD itself applies to a maximum tolerated dose driven by pharmacokinetics, which is not measured by the *in vitro* toxicity test. For the *in vitro* toxicity test itself, statistical techniques like benchmark dose can identify deviation from linear or baseline responses. However, we would need to extrapolate *in vitro* concentrations to systemic concentrations in humans using *in vitro* to *in vivo* extrapolation, taking any *in vitro* saturation into account. Application of KMD also depends on what the *in vitro* test is measuring and whether there are other purely kinetic factors that may saturate before the *in vitro* response is observed *in vivo*.