General Questions and Comments Received From Webinar Attendees

Q: How will the kinetic maximum dose (KMD)/toxicokinetic (TK) approach be integrated into United Nations Globally Harmonized System for Classification and Labelling (GHS) classification?

A: If toxicity isn't observed at the kinetically determined dose, one approach would be to conclude that the no-observed-adverse-effect level (NOAEL) is greater than the KMD. Alternatively, one could try to do benchmark dose modeling using the available knowledge on the few basic models that apply. With that knowledge one might be able to conclude that the benchmark dose level is greater than the KMD. Another consideration is what we name a toxic or adverse effect. As long as adversity is characterized through findings in organ histopathology, body weight loss, or organ weight loss, it will remain difficult to talk about KMD. Although metabolic saturation alone is not considered a good indicator of adversity because it does not tell which organ is affected, there ought to be suitable alternative indicators that could be used in combination and integrated into harmonized test methods that produce data that can be used for classification of hazards.

Q: Is the issue with not seeing toxicity (as discussed in Ms. Gourmelon's talk) really a question of whether or not the test system is working, and thus a quality assurance (QA) issue? Or is the issue with not seeing toxicity at the tested doses a question of whether or not the test chemical is a true negative? If the latter, then statistical power solves this issue. If it's a QA issue, then we can use historical data for the data provider (if it's a standard test model) and better QA surveillance to address that question. It is possible that the issue we are dealing with is a belief that true negatives (lack of toxicity) do not occur at low doses.

A: This was addressed in Ms. Gourmelon's talk by the comment that at least one of the doses must be at or just above the KMD. Just because a dose is below the KMD does not mean that no toxicological effect will be detected. Critically, being below the KMD likely increases the probability that the observed toxicological effect is actually chemical-specific and not just a stereotypical non-chemical-specific effect due to saturation of metabolism and excretion. The issue is the lack of ability to make a decision on the GHS/Classification, Labelling & Packaging classification in the low hazard categories, because of the high doses required to classify a chemical.

Q: While one of the goals of chronic testing is to predict potential toxicity for real-life exposures in humans, there is also a need to be able to identify rare events from a small sample size (extrapolating from about 50 rats per dose group to millions of people). What do you anticipate as potential challenges with the KMD approach in being able to identify these rare events? It is imperative that we do not sacrifice the sensitivity of the assays, as the ultimate goal is to protect the human population.

A: This is really a matter of statistical power rather than KMD, especially when you are getting non-chemical-specific effects due to saturation and other effects. One of the reasons for using the KMD is to try to ensure that the effects in studies are chemical-specific and not just nonspecific effects due to pharmacokinetic overload. The point is that the highest dose is almost never used for the risk assessment for either humans or environment, and hazard(s) of a chemical can be determined using many *in vitro* and short-term studies that are available now, if you have an appropriate mode of action (MOA) or adverse outcome pathway (AOP) for the effect. This is not always true right now but

knowledge of MOAs and AOPs is rapidly expanding. Part of the challenge at the moment is quantitatively relating key events to each other in appropriate key event relationships.

Q: I suggest that the KMD community drop the use of the term "inflection point," as that has a very specific meaning in math: inflection point is the point where there is a change in concavity. The curves we're looking at do not exhibit a change in concavity, so we should stop saying "inflection point." It's become a point of confusion, and there are some opponents of KMD who latch onto the mathematical definition of "inflection point" to say that the approach doesn't work.

A: Agreed, "point of departure from dose-proportionality" is a better term.

Q: Just how frequently will the kinetics **not** be linear?

A: It is not uncommon to see nonlinear absorption in high-dose studies. Absorption slows down for some chemicals but frequently we don't reach complete saturation. Consider, for example, a situation where a fourfold increase in the dose results in a two- to threefold internal dose increase. Clearly treating with a higher dose at this point would be appropriate, as compared to a situation where absorption is completely saturated.

Q: Industrial chemicals are not data-rich when it comes to toxicokinetic data.

A: Methods for developing kinetic predictions are improving all the time, and could also be applicable to support dose selection.

Q: Isn't the saturation of absorption, metabolism, or excretion itself a toxicological endpoint? And wouldn't the dose that causes such saturation be considered as exceeding tolerance? In that respect, KMD could be considered a maximum tolerated dose.

A: Many absorption/distribution/metabolism/excretion (ADME) processes are saturable without any adverse effects. For example, we commonly fail to absorb substances in food. There is no toxicological consequence of such saturation per se, but there could be secondary consequences. Hence, the need for information on mode of action.