Questions and Comments Received From Webinar Attendees Directed to Specific Speakers: Chad Blystone

Q: What does the National Toxicology Program (NTP) think about the issues of detection limits and dose-dependent transitions in mode of action?

A: I don't know if I can speak for all of NTP with the variety of folks here. However, I think a conservative approach is frequently taken, in the sense that dose-dependent transitions can exist with exposures, but *a priori* assumptions of when (*e.g.*, dose/age) and where (*e.g.*, tissue) this happens are difficult to make with a high degree of confidence. NTP is sensitive to issues of detection and interpretation, so depending on the specific concern, study designs may use larger numbers of animals to increase detection at all exposures or lower ones. Of course, this is all based on the confidence of the mode-of-action data available from animal studies for a particular agent. Frequently, real-world or even experimental exposure data are limited, and part of a research program will try to improve that area.

Q: Please clarify your bullet about the maximum tolerated dose (MTD) being used to put findings from middle and low doses into context. Does your comment mean that findings at the MTD can be disregarded if not replicated at lower doses? As you indicated at the start of your talk, findings at the MTD may represent toxicity due to overwhelming the biological systems of the test species.

A: The bullet point was not meant to say that responses at the MTD should be disregarded *a priori*, but to highlight that the removal of an MTD dose that had a statistically significant effect can decrease the confidence in the interpretation when the lower exposures had an effect that was not statistically significant. I wasn't trying to make any assumptions about the relation of the biological response to the internal dose. Rather, I was instead highlighting issues of interpreting response data with and without the MTD. "Effects" at lower doses may be related to exposure but can be difficult to interpret with a limited response curve.

Q: Given the advances in technology and ability to detect toxicologically relevant mechanisms of action at a subcellular level, is it fair to say that the concept of the MTD and (outdated) study designs that were originally designed for hazard identification are now wholly irrelevant for assessing points of departure for risk assessment?

A: The challenge is extrapolating dose response from the subcellular level to the systemic circulatory level and then from the systemic circulatory level to external exposure. Dr. Lowit covered this in her talk where she discussed the use of physiologically based pharmacokinetic and toxicokinetic/toxicodynamic modelling and the integration of physiologically based toxicokinetics and toxicokinetics/toxicodynamics with surrogate exposure assessment modeling for pesticides.

Q: I would suggest the workgroup have a more thorough discussion of MTD and its appropriate definition as we move forward. The original definition by the National Cancer Institute and ultimately NTP programs was around the minimally toxic dose as the maximum dose in an up-to-90-day study to make sure the animals would survive to the end of the chronic study (18 or 24 months depending on species). The current thought about the maximum tolerated dose, or how much you can cram into an animal, seems to have no relevance in understanding the human situation. I would encourage the

workgroup to go back to first principles in defining the minimally toxic dose using modern tools including toxicokinetics.

A: There would also need to be consideration of the impact to study design if chronic/carcinogenicity studies are to be waived.