Farrer David G

From: Holly Dixon
Sent: Friday, April 12, 2024 10:34 AM
To: Joseph Haney
Subject: RE: Exposure Duration Adjustments

Kip,

Thank you for reaching out and sending me this information on the exposure duration adjustment. We are going to reach out to our Oregon Air Toxics Science Advisory Committee today to provide them with the information you included in your email as well as additional information we received from ToxStrategies.

Thanks again,

Holly

Holly Dixon, PhD (she/her)
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From: Joseph Haney <Joseph.Haney@tceq.texas.gov>
Sent: Tuesday, April 9, 2024 6:53 AM
To: Holly Dixon <Holly.M.Dixon@oha.oregon.gov>
Subject: Exposure Duration Adjustments

Dr. Dixon:

Camarie Perry with ToxStrategies called me the other day to briefly talk about exposure duration adjustments. Below is a quick summary of some of my perspectives on the subject that I conveyed to her, which she said you may have some interest in as well. Maybe it could further conversations between y'all, and I'm also available for general conversation on the subject.

Reasoned scientific judgment is critical when justifying duration adjustments in deriving toxicity factors, and consideration of TK/TD half-life relative to the duration between exposures is important. For example, if a chemical directly causes CNS effects and even though workers are exposed 8 h/day each day of the work week, both the chemical and all effects entirely clear overnight, each daily exposure is essentially operating as an independent acute exposure experiment as there is no accumulation of dose or effect. By contrast, if a chemical or its toxic metabolite accumulates in a target organ with each daily exposure or causes some effect that does not entirely reverse overnight but rather accumulates with each daily exposure to ultimately produce an observable adverse effect, each daily exposure is not operating as an independent acute experiment and effects would be expected to increase day to day with increased exposure duration. For such chemicals, if the total exposure duration appreciably exceeds that of interest for derivation of a toxicity factor (e.g., 90 hours vs. 24 hours), then it may not be necessary to use an 8- or 6-hour/24-hour duration

adjustment to derive a 24-hour value since it was not the single day exposure that produced the effect, it was the accumulation of dose and/or effect that ultimately produce the adverse effect observed at the end of the exposure regimen.

This latter scenario is one that applies to the 24-h Mn ReV Camarie referred to in our discussion. For example, that DSD states [*emphasis added*], "This minimal LOAEL will be applied to exposure durations up to 24 h of exposure since study data demonstrated that the *accumulation of Mn in the lung predominated over the 90-h total, 3-week exposure period*. That is, *after 15 exposure days, lung Mn was statistically significantly increased over controls*, demonstrating that *toxicokinetic clearance did not occur after each daily 6-h exposure* but rather that *Mn accumulation in the lung occurred from day to day*, and in fact appears to have reached steady state (see Table 2 of Dorman et al. 2005), supporting use of results from this 90-h total exposure for derivation of a 24-h value."… "For the 24-h ReV, the LOAEL/POD of 1.5 mg Mn/m^3 was used as the 24-h POD_{ADJ} since the total exposure duration was considerably longer (i.e., 90 h) and *lung tissue data from the study indicates that the accumulation of Mn in the lung predominated over the 3-week exposure period*. Thus, the POD_{ADJ} for derivation of the 24-h ReV is 1.5 mg Mn/m^3."

Looking back, I note that use of both soluble Mn and minimally adverse effects are conservative choices as a basis of acute toxicity factors.
I hope this helps further any continuing conversations about this important subject. Have a great day.

Sincerely,

Joseph "Kip" Haney, MS
TCEQ
Toxicology Division