Clarification of DoD comment #73 regarding the toxicokinetic factor for UF_A and UF_H, if forestomach hyperplasia is chosen as the critical noncancer oral effect for benzo[a]pyrene

During the benzo[a]pyrene (BaP) IASD on Aug 4, EPA asked for clarification on DoD's comment regarding the toxicokinetic factor for UF_A and UF_H, if the forestomach hyperplasia is chosen as the critical noncancer oral effect for BaP. Below is more detailed explanation of DoD's comment and supporting references.

DoD Suggested Action, Revision and References #73:

"EPA does not provide sufficient justification for discounting forestomach hyperplasia as the critical effect, and needs to answer the question: how do the reproductive and fertility effects better characterize noncancer low dose effects? Please revise the critical effect choice and discussion to be consistent with EPA guidelines. Without appropriate justification to exclude forestomach hyperplasia, Beland and Culp (1998) would be the principal study and forestomach hyperplasia from this study would be the critical effect for developing the oral RfD for benzo[a]pyrene. EPA should appropriately qualify its discussion of this endpoint.

If forestomach hyperplasia were chosen as the critical effect, then the toxicokinetic factor for experimental animal to human and within human variability might not be needed as per EPA's Acute Exposure Guideline Level methods. EPA authors need to explore this alternative or more clearly justify the selection of Xu et al. (2010) as the principal study and decreases in ovary weight, estrogen, and primordial follicles, and altered estrus cycling as the critical effects."

Background and reason for comment:

Despite several studies [e.g., De Jong et al. (1999), Kroese et al. (2001), Beland and Culp (1998) and Culp et al. (1998)] reporting dose-dependent and statistically significant increases in the incidence of forestomach hyperplasia, and modeling results identifying this as the most sensitive effect at the lowest dose level, EPA did not select the forestomach effects as the most sensitive measure (p. 208, parag. 1). Instead, EPA selected the Xu et al. (2010) study as the principal study (see also page 245, line 7, and elsewhere). This latter study observed biologically and statistically significant decreases in ovary weight, estrogen, and primordial follicles, and altered estrus cycling in treated animals (see p. 208, parag. 1). The rationale for this selection is the statement found on EPA's draft BaP assessment, pg 209, line 5:

> "Forestomach hyperplasia was not selected as the critical effect, even though it was observed at lower doses compared with other effects, based on the consideration that the reproductive and fertility effects, observed in animals and supported by human data, appear to better characterize noncancer low dose effects of BaP."

Further explanation of DoD Comment #73:

DoD believes that the selection of principal study and critical requires additional justification. Given that EPA has selected forestomach hyperplasia as a critical effect for other chemicals, and in this case, this endpoint is the most sensitive noncancer BaP effect, if EPA feels these that the quantitative analysis of effects observed in the forestomach is not reasonable, this needs to be appropriately and transparently discussed. We acknowledge that selection of rat forestomach hyperplasia as the critical endpoint for evaluating human non-cancer effects of BaP is problematic; it may be argued that rodent forestomach hyperplasia following gavage administration of BaP is not relevant to humans and/or that foresomach hyperplasia is not appropriate as a noncancer endpoint (due to potentially being a cancer precursor effect). Dose and route extrapolation, tissue concordance, tissue specificity, and mode-of-action (MOA) should all be considered when assessing the relevance of rodent forestomach effects on a case-by-case evaluation. This in-depth, BaP-specific, analysis may warrant modifications to the uncertainty factors applicable to the point of departure (POD).

The emphasis on MOA in the evaluation of dose-response assessment, as typified by EPA's methods for Reference Dose (RfD) and Reference Concentration (RfC) (EPA, 2002), further supports the case-by-case consideration of forestomach hyperplasia as a critical effect. For example, NAS (2001) describes methods for the development of Acute Exposure Guideline Levels (AEGLs), which depend on MOA information to determine the appropriate uncertainty factor for experimental animal to human extrapolation. Specifically, from Section 2.5.3.2.2:

> "If evidence is available indicating that the mechanism or mode of action, such as direct-acting irritation or alkylation, is not expected to differ significantly among species, an interspecies UF of 3 is generally used. The rationale for the selection of a UF should include the following. 1. A description of the mechanism of action. 2. A discussion of

why the mechanism of action is unlikely or likely to differ. 3. Is bioavailability, metabolism, detoxification, elimination likely to be an issue?" (NAS, 2001)

In addition, EPA's Office of Pesticide Programs is making judgments on uncertainty factors on the basis of MOA understanding, including the use of irritation data as the critical effect. For example, EPA's decision on the safe concentration of chloropicrin after short-term human exposure included the evaluation that the critical effect, trigeminal nerve stimulation resulting in eye irritation, was without toxicokinetic variability. Thus, the uncertainty factor for within-human toxicokinetic extrapolation was reduced to 1-fold; no toxicokinetic variation was expected for this irritant effect (EPA, 2008).

DoD has identified two potentially helpful references for evaluation of the MOA and the human relevancy of forestomach hyperplasia; Poet et al. 2003 and Proctor et al. 2007. Undoubtedly there are others. Please feel free to request additional clarification if needed. We appreciate the opportunity to provide comment and to clarify our official comments.

References

National Academy of Sciences (NAS). (2001) Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Subcommittee on Acute Exposure Guideline Levels Committee on Toxicology. Board on Environmental Studies and Toxicology. National Research Council. National Academy Press, Washington, DC. Available at: http://www.epa.gov/opptintr/aegl/pubs/sop.pdf

Poet T.S., Soelberg, J.J., Weitz, K.K., Mast, T.J., Miller, R.A., Thrall, B.D., Corley, R.A. (2003) Mode of action and pharmacokinetic studies of 2-butoxyethanol in the mouse with an emphasis on forestomachdosimetry. Toxicological Sciences 71: 176-189.

Proctor, D.M., Gatto, N.M., Hong, S.J., Allamneni, K.P. (2007) Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer assessment. Toxicological Science 98(2):313-326.

U.S. EPA Office of Pesticide Programs Registration Eligibility Decision (RED) for Chloropicrin July 9, 2008. Available at: http://www.epa.gov/oppsrrd1/reregistration/REDs/chloropicrin-red.pdf