Disposition of Peer Review Comments for Toxicological Profile for Uranium

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Peer reviewers for the second draft of the Toxicological Profile for Uranium were:

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ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below

Review comments provided by Reviewer #1

COMMENT: The Reviewer disagreed with the primary reporting and reliance on NOAELs and/or LOAELs as points of departure for MRLs and suggested using modern statistical technologies, such as the BMDL/BMCL approach. If the data do not allow modeling, then call should be made to raise the scientific community's standards for data generation and production. The Reviewer additionally noted that accumulation of substandard data are poor reason to resort to a substandard statistic such as the NOAEL/LOAEL.

RESPONSE: *It is the Agency's practice to identify the point of departure for an MRL using benchmark dose modeling; however, in the absence of adequate data or when the data do not fit available models, a NOAEL/LOAEL approach is used. Although there are a number of limitations to using a NOAEL/LOAEL approach, the need to have MRL values outweighs the limitations to using this approach. A benchmark dose approach was used to derive the chronic-duration inhalation MRL for insoluble uranium compounds and the acute-duration oral MRL. For each of the other MRLs for uranium, an attempt was made to fit the data to a benchmark dose model. However, limited reporting of the incidence data for several inhalation MRL critical studies precluded using a BMD approach for the other inhalation MRLs. For the intermediate-duration oral MRL, the incidence data for renal effects did not fit any of the available dichotomous benchmark dose models. For MRLs with inadequate data for benchmark dose modeling, a data need for additional studies providing concentration/dose-response data were identified in Section 3.12.2.*

COMMENT: The Reviewer noted that there was a serious statistical error in the BMD analysis for the acute-duration oral MRL because Table A-3 lists multiple p-values that are greater than 1.

RESPONSE: *The column in Table A-3 labeled χ^2 Goodness-of-fit p-value was mislabeled; the column lists the χ^2 values. The table was revised to correct the label and an additional column listing the p-values was added. These revisions to the table did not result in any changes to the MRL values.*

COMMENT: The Reviewer expressed concern that the PBPK model (Valdés 2009) equations are displayed with specific numerical parameters but without any indication of the variation/error/uncertainty in these numerical values. The Reviewer requested that additionally information be added regarding the point estimates.

RESPONSE: *In general, the purpose of Section 3.4.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models) is to identify available pharmacokinetics models that may be useful for dosimetry calculations to support public health assessments, provide brief descriptions of the structures of the models, and identify novel or important features of each model that may particularly useful in public health assessments. Evaluations of model equations, parameter values and performance are not objectives of the profile. Section 3.4.5 is not intended to provide the reader with all information needed to implement models or to evaluate their validity for any specific application. Pertinent literature on these topics is cited, if available.*

The Valdés (2009) lung model was included in the profile because it is a new model that provides some conceptual representations of absorption of uranium from the lung that are different from existing models (e.g., macrophage compartment). The model is implemented with a relatively simple set of linear differential equations, which may also make it attractive implementation. Although, Valdés (2009) cites literature on observations used to estate parameters in the model, the methods for fitting parameters to the data are not reported. Valdés (2009) reported a comparison of prediction urinary uranium to an observation of urinary uranium from a single case of uranium exposure. The case was not described and

confidence in the observations is not discussed. More detailed information on statistical methods used to develop the model and analyses of uncertainty in the model equations, parameter values and predictions may be available directly from the Marcelo Valdés.

COMMENT: Regarding a population mean of 0.8 pCi/L reported on page 194, the Reviewer noted that it is not likely what is intended.

RESPONSE: *The term population mean was changed to population-weighted average.*

All other comments provided by Reviewer #1 were addressed as suggested.

Review comments provided by Reviewer #2:

COMMENT: The Reviewer noted that there is a significant need for studies on the toxic effects of uranium in children, particularly since uranium targets bone and marrow spaces.

RESPONSE: *The following data need was added to Section 3.12.2:*
Because children undergo periods of rapid bone growth and remodeling and uranium is stored in bone, there is a need to examine the potential toxicity of uranium to bone. However, few studies have examined this endpoint and additional studies are needed.

COMMENT: The Reviewer noted that uranium can also be found in wells drilled for drinking water and requested that this information be added to Section 1.2

RESPONSE: *The following statement was added to this section under Sources:*
Uranium can be found in drinking water from wells drilled in uranium-rich rock formations.

COMMENT: Regarding the discussion of cancer in the beginning of Section 2.2, the Reviewer expressed concern that the potential effect of length of time of exposure on the carcinogenic effects in bone and bone marrow is not discussed.

RESPONSE: *The section in question was deleted to better reflect the purpose of the section.*

COMMENT: The Reviewer noted that the issue of whether uranyl ions have the ability to cross the placental barrier and enter into the fetus was not addressed directly in Section 2.2.

RESPONSE: *A statement was added that there is suggestive evidence for transplacental and/or lactational transfer of uranium.*

COMMENT: The Reviewer commented that very little is mentioned about uranyl acetate in Section 3.4.

RESPONSE: *No data on uranyl acetate were identified which would be relevant to this section.*

COMMENT: The Reviewer noted that 17% of the US population suffers from various forms of chronic

renal disease and that impaired renal function is generally not detectable before there is a 75-80% loss of renal function.

RESPONSE: *A statement was added to Section 3.10 that individuals with renal disease may be unusually susceptible to uranium toxicity.*

COMMENT: Regarding Chapter 6, the Reviewer questioned whether there were available data on the content of uranium in the water of private wells drilled in areas of higher underground quantities of uranium.

RESPONSE: *Data on uranium levels in water from private wells with higher underground uranium levels are discussed in Section 6.4.2.*

All comments provided by Reviewer #2 were addressed as suggested.

Review comments provided by Reviewer #3

COMMENT: The Reviewer noted that the format of the toxicological profile, in particular the categorization of effects by route of exposure, encourages repeated presentation of effects using the same or similar references. The Reviewer suggested another approach in which a discussion of the routes of exposure, toxicokinetics, and distribution in the body is followed by discussion of the effects related to the affected organ systems.

RESPONSE: *ATSDR will consider this comment in future revisions to the format of toxicological profiles.*

COMMENT: The Reviewer noted that the Cookfair publication on lung cancer incidence in uranium process workers was not discussed in the text of Chapter 3 but was used to establish a CEL for lung cancer in humans in the LSE table. The Reviewer questioned the quality of the Cookfair data.

RESPONSE: *The Cookfair study was eliminated from the LSE table; as discussed in Canu 2008, there are limited data to establish a relationship between cancer mortality and internal radiation dose from uranium among nuclear workers; thus individual studies were not discussed.*

COMMENT: The Reviewer noted that the apparent difference in the renal toxicity of insoluble uranium dioxide and soluble uranyl fluoride is not discussed in the renal effects section after intermediate duration exposure.

RESPONSE: *The relative renal toxicity of soluble and insoluble uranium compounds are discussed in numerous sections of Chapters 2 and 3.*

COMMENT: Regarding page 14, line 25 and page 47, line 2, the Reviewer noted that emphysema is not a feature of inhaled metals and metal compounds and that coal dust exposure is associated with emphysema.

RESPONSE: *In the referenced sentences, emphysema was deleted as a possible uranium-related effect on the respiratory tract.*

COMMENT: Regarding the discussion of the Stearns et al. (2005) genotoxicity study, the Reviewer questioned how the concentration and time dependence differentiate the chemical and radiological mechanisms.

RESPONSE: *The sentence was revised to avoid misinterpretation that the concentration and time-dependence of the DNA adduct formation was used to determine that the adduct formation was due to a chemical mechanism rather than radiological.*

All other comments provided by Reviewer #3 were addressed as suggested.