UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
LAND AND EMERGENCY
MANAGEMENT

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SOLID WASTE AND
EMERGENCY RESPONSE

DEC 21 2016

MEMORANDUM

SUBJECT: Considering a Noncancer Oral Reference Dose for Uranium for Superfund Human Health Risk Assessments

FROM: Dana Stalcup, Director
Assessment and Remediation Division
Office of Superfund Remediation and Technology Innovation

TO: Superfund National Policy Managers, Regions 1 - 10

PURPOSE

The overall mission of the Superfund program is to protect human health and the environment consistent with the Comprehensive Environmental Response, Compensation and Liability Act, as amended, (CERCLA) and as implemented by the National Oil and Hazardous Substances Pollution Contingency Plan (NCP). This memorandum provides information and recommendations about an oral reference dose (RfD) for non-radiological toxicity of soluble uranium that Regions should consider during various stages of response selection and implementation at CERCLA sites, including the remedial investigation and feasibility study process (e.g., assessing baseline health risks, evaluating risks of remedial alternatives) and five-year reviews.

This memorandum does not alter or provide guidance about EPA's practices or toxicity values for characterizing cancer risk posed by radionuclides, including uranium.

BACKGROUND

As stated on page 2 of OSWER Directive 9285.7-53 *Human Health Toxicity Values in Superfund Risk Assessments*, December 5, 2003 (the 2003 hierarchy guidance), "Superfund risk assessments are performed for a number of reasons, including to evaluate whether action is warranted under

CERCLA, to establish protective cleanup levels, and to determine the residual risk posed by response actions. Generally, toxicity assessment is an integral part of risk assessment." The 2003 hierarchy guidance discusses an updated hierarchy of sources for human health toxicity values to consider when carrying out risk assessments at Superfund sites. It also states that "[t]his revised hierarchy recognizes that EPA should use the best science available on which to base risk assessments." Furthermore, the 2003 hierarchy guidance states that "EPA and state personnel may use and accept other technically sound approaches," and acknowledges "that there may be other sources of toxicological information," referring specifically to OSWER Directive 9285.7-16 *Use of IRIS Values in Superfund Risk Assessment*, December 21, 1993, which offers similar guidance.[1]

In December 1989, the U.S. Environmental Protection Agency (EPA) published toxicity information for soluble salts of uranium in its Integrated Risk Information System (IRIS). For example, a noncancer oral reference dose (RfD) of 0.003 milligrams of uranium per kilogram body weight per day (mg U/kg-day) for chronic exposure was published, which is based, in part, upon dose-response data from a study reported in 1949 [Maynard and Hodge, 1949]. In 2002, the EPA National Center for Environmental Assessment (NCEA), which manages IRIS, conducted a literature review for uranium that identified new relevant studies and acknowledged that new studies by Gilman and colleagues published in 1998 could yield a change in the uranium RfD.[2] The RfD for soluble salts of uranium has not been updated in IRIS, however, to reflect the data Gilman and colleagues obtained.

On the other hand, the EPA Office of Ground Water and Drinking Water (OGWDW) relied upon the Gilman studies to promulgate a revised Maximum Contaminant Level for uranium in 2000 for its safe drinking water program (EPA 2000).

The Agency for Toxic Substances and Disease Registry (ATSDR) also relied upon the Gilman studies to derive a Minimal Risk Level (MRL) for uranium in 2013 (i.e., 0.0002 mg U/kg-day for intermediate-duration oral exposure (15-364 days) to soluble compounds of uranium), as part of "a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic

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[1] See the 2003 hierarchy guidance, page 2, quoting OSWER Directive 9285.7-16: "...IRIS is not the only source of toxicology information, and in some cases more recent, credible and relevant data may come to the Agency's attention. In particular, toxicological information other than that in IRIS may be brought to the Agency by outside parties. Such information should be considered along with the data in IRIS in selecting toxicological values; ultimately, the Agency should evaluate risk based upon its best scientific judgement and consider all credible and relevant information available to it."

[2] Specifically: "The literature published since the oral RfD for soluble uranium salts was derived (1989) contains study data that could potentially produce a change in the RfD (Gilman et al. 1998a; Gilman et al. 1998b; Gilman et al. 1998c)." *IRIS Chemical Assessment Summary for Uranium, Soluble Salts* (January 2016)

and epidemiologic information".[3] As discussed in the 2003 hierarchy guidance, ATSDR MRLs may be a suitable Tier 3 source of toxicity values. ATSDR's toxicological profiles, which underlie its MRLs, "are peer reviewed, are available to the public, and are transparent about the methods and processes used to develop the values" (quoting the 2003 hierarchy guidance).

The 2003 hierarchy guidance also recommends consultation with the Superfund Health Risk Technical Support Center (STSC) in circumstances where a contaminant with a Tier 3 source for its toxicity value(s) "appears to be a risk driver for the site." In this case, the STSC, which EPA's NCEA in Cincinnati operates, reviewed the ATSDR derivation and concluded, as a general matter, that it is reliable and was derived based on similar methods and procedures as those used by the IRIS and Provisional Peer-Reviewed Toxicity Value (PPRTV) Programs (see attached report).

EVALUATION

EPA's toxicological assessment procedures generally entail an evaluation of candidate studies and alternative sources of dose-response data. In this case, the STSC "considers the Gilman et al. (1998) study reliable for hazard identification and dose-response assessment based on current standard U.S. EPA methodology and practice" (see attached report). Table 1 in the attached STSC report facilitates a comparative evaluation of the Gilman study, which underlies both the ATSDR and EPA-OGWDW values, and the Maynard and Hodge study, which underlies the IRIS RfD. This comparative evaluation demonstrates that the Gilman study tested a larger number of animals per dose group, used a larger number of dose groups, was of longer duration, and evaluated more endpoints than did the Maynard and Hodge study. On this basis, the Gilman study is also scientifically superior to the Maynard and Hodge study for characterizing the hazards and dose-response relationship for soluble uranium.

EPA's toxicological assessment procedures also generally entail an evaluation of candidate values for toxicity values, such as the RfD. Table 1 in the attached report from STSC provides such a comparison, considering the IRIS RfD, the ATSDR intermediate MRL, and the EPA-OGWDW chronic reference value. This comparative evaluation also demonstrates that the Gilman study

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[3] *Toxicological Profile for Uranium* (February 2013); currently available on-line at: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=440&tid=77 ATSDR's toxicological profiles are developed under CERCLA. Citing ATSDR, "Each profile:

(A) Examines, summarizes, and interprets available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) Determines whether adequate information on the health effects of each substance is available or being developed to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identifies toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are federal, state, and local health professionals; interested private sector organizations and groups; and members of the public."

encompassed lower administered doses than did the Maynard and Hodge study. All else being equal, a lower value for the Lowest Observed Adverse Effects Level (LOAEL) provides a more appropriate basis for deriving a noncancer reference value.

IMPLEMENTATION

As discussed in the 2003 hierarchy guidance, ATSDR MRLs may be a suitable Tier 3 source of toxicity values. In light of STSC's opinion that the Gilman et al. (1998) study is reliable for hazard identification and dose-response assessment and ATSDR's intermediate MRL was derived based on similar methods and procedures as those used by the IRIS and PPRTV Programs (see attached report), OSRTI recommends the use of the ATSDR intermediate MRL for soluble uranium for purposes of assessing subchronic exposures. For this purpose, there is not a subchronic reference value from a Tier 1 or Tier 2 source (i.e. no corresponding value in IRIS nor a corresponding PPRTV).

As noted, the 2003 hierarchy guidance, encourages the use of the best science available when preparing human health risk assessments for the Superfund program. With the foregoing in mind, and in light of chemical-specific information and considering the scientific judgments of EPA staff toxicologists and science advisors, we believe the ATSDR MRL generally reflects a better scientific basis for assessing the chronic health risks of soluble uranium than the RfD currently available in IRIS in part because it provides more recent, credible and relevant information. In addition, STSC officially opined that the ATSDR MRL for soluble uranium was derived based on similar methods and procedures as those used by the IRIS and PPRTV Programs and that the Gilman et al. (1998) study is reliable for hazard identification and dose-response assessment based on current standard EPA methodology and practice (see attached report). The intermediate MRL for soluble uranium (0.0002 mg U/kg-day) is significantly lower than the chronic RfD (0.003 mg U/kg-day) currently available in IRIS, consistent with the lower LOAEL identified in the Gilman studies. The ATSDR toxicological assessment indicated that, owing to regeneration of the renal tubule epithelium at low doses, continued exposure beyond an intermediate duration is not likely to induce more severe effects. ATSDR concluded, therefore, that the intermediate MRL (intended for exposures of 15-364 days) may be adequately protective for chronic exposures (defined as ≥365 days). OSRTI, therefore, recommends the use of the ATSDR intermediate MRL for soluble uranium without further adjustment, in lieu of the RfD currently published in IRIS, for assessment of chronic exposures also.

Consistent with existing EPA guidance on risk characterization, OSRTI recommends that Regions consider, on a case-by-case basis, the need to qualitatively characterize and address additional uncertainty inherent in using an intermediate duration reference value to assess chronic exposures to soluble uranium.

The recommendations in this memorandum will be re-evaluated if and when IRIS is updated to provide a new noncancer reference dose for soluble uranium.

ADDITIONAL INFORMATION

Please contact Michael Scozzafava (Chief, Science Policy Branch, Office of Superfund Remediation and Technology Innovation) at (703) 603-8833 if you have questions or require further information.

CITATIONS AND REFERENCES

Gilman, A. P., M. A. Moss, D. C. Villeneuve, V. E. Secours, A. P. Yagminas, B. L. Tracy, J. M. Quinn, G. Long and V. E. Valli (1998c). "Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit." Toxicol Sci **41**(1): 138-151. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9520348

Gilman, A. P., D. C. Villeneuve, V. E. Secours, A. P. Yagminas, B. L. Tracy, J. M. Quinn, V. E. Valli and M. A. Moss (1998b). "Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit." Toxicol Sci **41**(1): 129-137. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9520347

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Maynard, E.A. and H.C. Hodge. 1949. Studies of the toxicity of various uranium compounds when fed to experimental animals. In: The Pharmacology and Toxicology of Uranium Compounds. Nations Nuclear Energy Service. Division VI, Vol. I, C. Voegtlin, and H.C. Hodge, Eds. McGraw Hill, New York, NY. p. 309-376.

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U.S. Environmental Protection Agency. 2000. National Primary Drinking Water Regulations; Radionuclides; Final Rule. *Federal Register 65(236):* 76708- 76753.

U.S. Environmental Protection Agency. 1993. *Use of IRIS Values in Superfund Risk Assessment*; OSWER Directive 9285.7-16. Memorandum from William H. Farland. Office of Health and Environmental Assessment, Office of Solid Waste and Emergency Response, Washington, DC. December 21.

Attachment

cc: Mathy Stanislaus, OLEM, AA
Barry Breen, OLEM, DAA
James Woolford, OLEM/OSRTI, Director
Reggie Cheatham, OLEM/OEM, Director
Barnes Johnson, OLEM/ORCR, Director
David Lloyd, OLEM/OBLR, Director
Charlotte Bertrand, OLEM/FFRRO, Director
Carolyn Hoskinson, OLEM/OUST, Director
Cyndy Mackey, OECA/OSRE, Director
Karin Leff, OECA/FFEO, Acting Director
John Michaud, OGC/SWERLO
OSRTI Managers
Regional Superfund Branch Chiefs, Regions 1 – 10
Jill Lowe, Superfund Lead Region Coordinator, Region 3

Attachment

STSC Consultation Memo

Superfund Technical Support Center

National Center for Environmental Assessment
U.S. Environmental Protection Agency
26 West Martin Luther King Drive, MS-AG41
Cincinnati, Ohio 45268

Phillip Kaiser/Hotline Director, Teresa Shannon/Administrator
Hotline 513-569-7300, E-Mail: Superfund_STSC@epa.gov

August 11, 2016

Marc Stifelman
EPA Region 10

ASSISTANCE REQUESTED: (Update) Evaluation of recent ATSDR sub-chronic oral MRL in place of outdated IRIS RfD for R-X Uranium.

ENCLOSED INFORMATION: Attachment 1:
Uranium Response_Marc_Stifelman_Final.pdf

If you have any questions regarding this transmission, please contact the STSC at (513) 569-7300.

Attachments (1)

cc: STSC files

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Regarding your request concerning soluble compounds of uranium, the available oral toxicity values can be found in Table 1 below. Currently there is a chronic RfD derived by the U.S. EPA's IRIS Program in 1989, an intermediate MRL derived by the ATSDR in 2013, and a chronic RfD derived by the U.S. EPA's Office of Ground Water and Drinking Water (OGWDW) from 2000. IRIS derived their chronic RfD using the 30-day toxicity study in rabbits conducted by Maynard and Hodge (1949) whereas ATSDR and OGWDW used the 91-day toxicity study in rats conducted by Gilman et al. (1998) as the principal study to derive their respective values.

The rabbit portion of the Maynard and Hodge (1949) study is limited in that only 6 rabbits (unknown sex/strain) were treated per dose group for 30 days and the only endpoints evaluated were mortality, gross pathology, clinical signs of toxicity, body weights, and kidney histopathology and the study did not present raw data for these evaluations. Compared to the Maynard and Hodge (1949) study, Gilman et al. (1998) is more recent (1998 versus 1949), tested a larger number of animals per dose group (15 rats/sex versus 6 rabbits/unknown sex), used a larger number of dose groups (6 versus 4), was of longer duration (91 days versus 30 days), and evaluated more endpoints: mortality, clinical signs of toxicity, food and water consumption, hematological and clinical chemistry parameters, organ weights, and complete histopathological exams. The Gilman et al. (1998) study tested a comprehensive list of endpoints, although the publication focused mostly on the reporting of kidney and liver effects. Overall, in response to your request, the STSC considers the Gilman et al. (1998) study reliable for hazard identification and dose-response assessment based on current standard U.S. EPA methodology and practice.

The STSC reviewed the ATSDR assessment for uranium with specific focus on the derivation of the intermediate-duration oral MRL. The STSC concludes that the intermediate-duration oral MRL for soluble compounds of uranium was derived using similar general assessment methods and procedures as those used by the IRIS and PPRTV Programs. However, there are quantitative differences between ATSDR methodologies and practice and EPA methodologies and practice which could result in the development of a quantitatively different reference value even when using the same study/endpoint. The ATSDR intermediate MRL value was peer-reviewed, published recently, and appears to be scientifically credible.

The U.S. EPA's Office of Ground Water and Drinking Water (OGWDW) derived a chronic RfD using the Gilman et al. (1998) study; the basis for this value is described in the *Radionuclides Notice of Data Availability Technical Support Document* (U.S. EPA, 2000). It is noted that OGWDW's chronic RfD was first discussed and finalized at an EPA-led workshop in 1998, and subsequently listed in the U.S. EPA's *2012 Edition of the Drinking Water Standards and Health Advisories* (U.S. EPA, 2012).

The STSC has no plans to develop a PPRTV assessment for uranium at this time because a chronic RfD for this chemical is currently available on the IRIS database. For questions regarding the existing IRIS chronic RfD for uranium, the IRIS Hotline can be reached by phone at (202) 566-1749 or by email at hotline.iris@epa.gov.

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ATSDR. (2013). Toxicological profile for uranium. In Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US).

Gilman AP et al. (1998). Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicological Sciences, 41:117–128.

Maynard EA, Hodge HC. (1949). Study of toxicity of various uranium compounds when fed to experimental animals. In: Voegtlin C, Hodge HC, eds. Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Div. VI, Vol. 1. New York: McGraw Hill, pp. 309-376.

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Table 1. Comparison of Toxicity Values for Soluble Uranium Compounds

Source	EPA-IRIS	ATSDR	EPA-OGWDW
Toxicity Value (Year Published)	Chronic RfD (1989)	Intermediate MRL (2013)	Chronic RfD (2000)
Critical Study	Maynard and Hodge 1949	Gilman et al. 1998a	Gilman et al. 1998a
Animal Species/Strain/Sex	6 rabbits/group (unknown sex/strain)	Sprague-Dawley rats; 15/sex/group	Sprague-Dawley rats; 15/sex/group
Study Duration	30 days	91 days	91 days
Compound Administered	Uranyl nitrate	Uranyl nitrate	Uranyl nitrate
Administered Dose	0, 0.02, 0.1 and 0.5% in the diet	0, 0.96, 4.8, 24, 120, and 600 mg/L in drinking water	0, 0.96, 4.8, 24, 120, and 600 mg/L in drinking water
Dose of uranium	0, 2.8, 14, and 71 mg U/kg-day	0, 0.06, 0.31, 1.52, 7.54, and 36.73 mg U/kg-day (males); 0, 0.09, 0.42, 2.01, 9.98, and 53.56 mg U/kg-day (females)	0, 0.06, 0.31, 1.52, 7.54, and 36.73 mg U/kg-day (males); 0, 0.09, 0.42, 2.01, 9.98, and 53.56 mg U/kg-day (females)
Endpoints evaluated in key study	Mortality, clinical signs of toxicity, body weights, kidney histopathology	Mortality, clinical signs of toxicity, food and water consumption, hematological and clinical chemistry parameters, organ weights, complete histopathological exams	Mortality, clinical signs of toxicity, food and water consumption, hematological and clinical chemistry parameters, organ weights, complete histopathological exams
LOAEL	0.02% in the diet (2.8 mg U/kg-day)	0.96 mg/L in drinking water (0.06 mg U/kg-day)	0.96 mg/L in drinking water (0.06 mg U/kg-day)
Effects identified at the LOAEL	Transient reduction in body weight (not specified); moderate nephrotoxicity (histopathological effects on the tubular epithelium)	Renal histopathology (cytoplasmic vacuolization, tubular dilation, and lymphoid cuffing in males, capsular sclerosis, tubular anisokarytosis, and interstitial reticulin in females, and nuclear vesiculation in both sexes)	Renal histopathology (cytoplasmic vacuolization, tubular dilation, and lymphoid cuffing in males, capsular sclerosis, tubular anisokarytosis, and interstitial reticulin in females, and nuclear vesiculation in both sexes)
Effects at doses higher than the LOAEL	Mortality (two highest doses)	Additional changes in kidney histopathology; lesions of the liver, thyroid, and/or spleen	Additional changes in kidney histopathology; lesions of the liver, thyroid, and/or spleen
NOAEL	Not determined	Not determined	Not determined
Approach used	NOAEL/LOAEL	NOAEL/LOAEL[a]	NOAEL/LOAEL[a]
Composite UF	1000[b]	300[c]	100[d]
Toxicity Value	0.003 mg U/kg-day	0.0002 mg U/kg-day[c]	0.0006 mg U/kg-day

[a] Benchmark dose (BMD) models did not provide an adequate fit to the incidence data for kidney lesions.

[b] The composite UF of 1000 is based on 10 for UF_H, 10 for UF_A, and 10 for UF_L. The composite UF does not include 10 for UFs because the acute/subchronic toxicity study is considered adequately sensitive for chronic nephrotoxicity.

[c] The composite UF of 300 is based on 3 for UF_L (use of a minimal LOAEL, since histopathological changes at 0.06 mg U/kg-day were considered minimally adverse), 10 for UF_H, and 10 for UF_A. The ATSDR assessment indicated that chronic data are not sufficient to derive a chronic MRL, but that, owing to regeneration of the renal tubule epithelium at low doses, continued exposure is not likely to induce more severe effects. ATSDR concluded that the intermediate MRL (intended for exposures of 15-364 days) may be adequately protective for chronic exposures (defined as ≥365 days) (Note: ATSDR does not extrapolate across exposure durations).

[d] The composite UF of 100 is based on 3 for UF_L, 10 for UF_H, and 3 for UF_A. It was noted that EPA followed the recommended methodology of the National Academy of Sciences in estimating the uncertainty factor (no further rationale was provided in the *Federal Register* notice about the Final Rule).

Acronyms: LOAEL = lowest observed adverse effects level; MRL = Minimal Risk Level; NOAEL = no observed adverse effects level; OGWDW = Office of Ground Water and Drinking Water; UF = uncertainty factor; UF_A= uncertainty factor for animal-to-human extrapolation (inter-species variability); UF_H = uncertainty factor for human (intra-species) variability; UF_L = uncertainty factor for use of a minimal LOAEL.

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