# Noncancer Oral Reference Dose for Uranium, Soluble Salts

## Summary

The Washington State Department of Ecology's (Ecology) Cleanup Levels and Risk Calculation (CLARC)[1] online database contains toxicity information and presents pre-calculated Method B and C formula values for establishing cleanup standards. In consultation with the Environmental Protection Agency (EPA Region 10) and the Washington State Department of Health (DOH), Ecology is updating CLARC to reflect one of the intermediate oral minimum risk levels (MRL) found in the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR is a federal public health agency under the U.S. Department of Health and Human Services that works to protect communities from harmful health effects related to exposure to natural and man-made hazardous substances.

CLARC will now reflect the ATSDR's oral MRL for making cleanup level and risk calculations for uranium, soluble salts under Washington's Model Toxics Control Act (MTCA). Both EPA and DOH concurred with our decision to use the ATSDR oral MRL (see **Attachment A**). The rationale and scientific justification for using the ATSDR MRL are provided below.

In 2002, EPA's National Center for Environmental Assessment (NCEA), which manages the Integrated Risk Information System (IRIS), conducted a literature review for uranium. They identified new relevant toxicological studies that may yield a change in the oral reference dose (RfDo) for soluble uranium. The existing RfDo in IRIS (0.003 mg/kg-day for soluble uranium) is based on a single-dose response study from 1949.

In 2013, ATSDR conducted a comprehensive review and evaluation of available toxicity studies and derived an intermediate MRL of 0.0002 mg/kg-day for soluble uranium. ATSDR's Toxicological Profile for uranium[2] is available online. Their worksheet for developing the MRL is in **Attachment B** of this guidance document and on page A-20 of the Toxicological Profile (ATSDR 2013). The MRL is a dose that is likely to be without an appreciable risk of adverse noncancer health effects over a specified duration of exposure. ATSDR concluded that continued exposure beyond an intermediate duration is not likely to induce more severe effects, and may be adequately protective of chronic exposures. The MRL derived by ATSDR for soluble uranium is 15 times lower (this yields lower cleanup levels) than the RfDo published in IRIS.

In a memo dated December 21, 2016, the EPA Superfund Program recommended that the ATSDR MRL be used in place of the RfDo in IRIS without any further adjustment to assess chronic oral exposures. EPA's memo is provided herein as **Attachment C** (EPA 2016). We agree with EPA that ATSDR's MRL was derived using better and more relevant data than the study that formed the basis for the RfDo in IRIS, and is scientifically defensible. The techniques used by ATSDR to derive its RfDo are consistent with

[1] https://ecology.wa.gov/Regulations-Permits/Guidance-technical-assistance/Contamination-clean-up-tools/CLARC
[2] https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=440&tid=77

those used by EPA's IRIS program and those recommended in Washington's MTCA Cleanup Rule (WAC 173-340-708(7)(f)).[3]

IRIS is undertaking a reassessment of the noncancer (nonradiological) health effects of uranium via oral exposure. Uranium was included on the December 2015 IRIS Program multiyear agenda as a chemical having high priority for assessment development. In January 2018, EPA released IRIS Assessment Plan for Uranium (Oral Reference Dose) (Scoping and Problem Formulation Materials).[4] We will re-evaluate using the ATSDR oral MRL for soluble uranium if and when IRIS is updated with a new noncancer RfDo.

Below are the MTCA Method B and C cleanup levels protective of soil direct contact and ingestion of potable groundwater for uranium, soluble salts using the ATSDR oral MRL of 0.0002 mg/kg-day.

| Soil | Groundwater |
|---|---|
| • **Method B** – 16 mg/kg | • **Method B** – 3.2 µg/L |
| • **Method C** – 700 mg/kg | • **Method C** – 7 µg/L |

## I. Uranium, soluble salts Oral RfD currently in EPA's IRIS Database

EPA's published RfDo for uranium, soluble salts in IRIS is 0.003 mg/kg-day (last revised October 1, 1989). EPA's IRIS assessment[5] is based on a 1949 one-dose response study (Maynard, E.A. and H.C. Hodge 1949). The Lowest Observed Adverse Effect Level (LOAEL)[6] from the study—which was 2.8 mg/kg-day, based on a 30-day exposure period to rabbits—was used to develop the RfDo. Rabbits were fed dietary levels of uranyl nitrate. Rats and dogs were also administered uranium compounds, however rabbits showed the greatest sensitivity to the toxic effects. Critical toxic effects included changes to body weight and kidneys. An uncertainty factor of 10 was applied based on using an LOAEL instead of a No Observed Adverse Effect Level (NOAEL[7]; not determined), and 10 for both interspecies (animal-to-human extrapolation) and intraspecies (human variability) variability to the toxicity of the chemical. As a result, the RfDo was derived from the LOAEL (2.8 mg/kg-day) which was divided by 1,000 (10 x 10 x 10) to build in a margin of safety, such that doses equal to or less than this value are not likely to cause an adverse effect. Applying an uncertainty factor of 1,000 to the LOAEL (and rounding) generated an RfDo of 0.003 mg/kg-day.

[3] https://app.leg.wa.gov/wac/default.aspx?cite=173-340-708
[4] https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=338655
[5] https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=421

[6] The LOAEL is the lowest dose which produces an effect, following some specified duration of exposure.

[7] The NOAEL is the highest dose that does not produce an observable adverse effect.

## II. Uranium, soluble salts Oral MRL Developed by ATSDR

ATSDR reviewed numerous toxicity studies when developing its MRL based on intermediate-duration oral exposure (15 to 364 days; see **Attachment 2**). These studies used the NOAEL/LOAEL approach and evaluated a range of effects including kidney, neurological, reproductive, and developmental. ATSDR used the Gilman et al. 1998 studies to derive an intermediate oral MRL of 0.0002 mg/kg-day for soluble uranium compounds. Separate studies were conducted based on exposure to rats (Gilman et al. 1998a) and rabbits (Gilman et al. 1998b; Gilman et al. 1998c). Both of these species were exposed to soluble uranium as uranyl nitrate in drinking water for 91 days. The LOAELs developed from these studies were comparable (rabbit – 0.05 mg/kg-day; rat – 0.06 mg/kg-day) based on effects to the kidney, which is the most sensitive target organ. The LOAEL for the rat study (0.06 mg/kg-day) was selected as the point of departure for development of the oral MRL because of a subclinical infection found in the rabbit study. An uncertainty factor of 3 was applied based on using a minimal LOAEL (adverse effects considered minimal and a NOAEL was not identified) and 10 for both interspecies (animal-to-human extrapolation) and intraspecies (human variability) variability to the toxicity of the chemical. As a result, the oral MRL was derived from the LOAEL (0.06 mg/kg-day) which was divided by 300 (3 x 10 x 10) to build in a margin of safety, such that doses equal to or less than this value are not likely to cause an adverse effect. Application of the uncertainty factor yielded an oral MRL of 0.0002 mg/kg-day for soluble uranium.

In their toxicological assessment, ATSDR indicated that, owing to regeneration (a reparative response) of the kidney's renal tubule epithelium at low doses, continued exposure beyond an intermediate duration is not likely to induce more severe effects. As a result, ATSDR concluded that the intermediate MRL may be adequately protective for chronic exposures.

## III. EPA's 2016 Memorandum from the Office of Superfund Remediation and Technology Innovation (OSRTI)

EPA's December 21, 2016, memorandum (see **Attachment 3**) provides information and recommendations about using the ATSDR oral intermediate MRL for soluble uranium as part of an environmental investigation and cleanup conducted under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). After review and consideration of the available toxicological information for this chemical, EPA's Office of Superfund Remediation and Technology Innovation (OSRTI) recommended using of the ATSDR intermediate MRL for soluble uranium without further adjustment, in lieu of the RfDo currently published in IRIS, for assessment of chronic exposures. EPA's assessment of noncancer toxicological data for uranium from the December 2016 memorandum is summarized below:

- EPA's 2003 toxicity hierarchy guidance says that EPA and state personnel may use and accept other technically sound approaches for developing toxicity data for use in risk assessments, and use best science available. As such, EPA may deviate from their hierarchy when appropriate based on best science available.
- EPA's NCEA reviewed ATSDR's derivation of an intermediate-duration oral MRL for soluble uranium. They concluded it is reliable and was derived based on similar methods and procedures as those used by the IRIS and EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) programs.
- EPA said that the ATSDR oral MRL generally reflects a better scientific basis for assessing the chronic health risks of soluble uranium than the RfDo currently available in IRIS. One reason for this conclusion is that it provides more recent, credible, and relevant information.
- EPA considers the Gilman et al. 1998 studies to be reliable for hazard identification and dose-response assessment, based on current standard EPA methodology and practice.
- The Gilman et al. 1998 studies tested a larger number of animals per dose group, used a larger number of dose groups, was of longer duration (i.e., 91 days as opposed to 30 days), and evaluated more endpoints than did the Maynard and Hodge 1949 study. On this basis, the Gilman et al. 1998 studies are scientifically superior to the Maynard and Hodge study for characterizing the hazards and dose response relationship for soluble uranium.
- The Gilman et al. 1998 studies encompassed lower administered doses than did the Maynard and Hodge study that resulted in a lower value for the LOAEL.
- ATSDR's oral MRL is significantly lower than the chronic RfDo currently available in IRIS. ATSDR concluded that continued exposure beyond an intermediate duration is not likely to induce more severe effects, and may be adequately protective of chronic exposures.

## Acronyms and Abbreviations

| Acronym or Abbreviation | Definition |
|---|---|
| ATSDR | Agency for Toxic Substances and Disease Registry |
| CLARC | Cleanup Levels and Risk Calculation |
| DOH | Washington State Department of Health |
| Ecology | Washington State Department of Ecology |
| EPA | Environmental Protection Agency |
| IRIS | Integrated Risk Information System |
| LOAEL | Lowest Observed Adverse Effect Level |
| µg/L | microgram per liter |
| mg/kg-day | milligram per kilogram per day |
| MRL | Minimum Risk Level |
| MTCA | Model Toxics Control Act |
| NCEA | National Center for Environmental Assessment |
| NOAEL | No Observed Adverse Effect Level |
| OSRTI | Office of Superfund Remediation and Technology Innovation |
| PPRTV | Provisional Peer-Reviewed Toxicity Value |
| RfD | Reference Dose |
| RfDo | Oral Reference Dose |

## References

**Agency for Toxic Substances and Disease Registry (ATSDR)**. Toxicological Profile for Uranium. February 2013. Retrieved from https://www.atsdr.cdc.gov/

**Environmental Protection Agency (EPA). (2016)**. EPA Memorandum: *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. December 21, 2016.

**Gilman, A.P., Villeneuve D.C., Secours V.E., et al. (1998a)**. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. *Toxicological Sciences 41(1)*, 117–128.

**Gilman, A.P., Villeneuve D.C., Secours V.E., et al. (1998b)**. Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. *Toxicological Sciences 41(1)*, 129–137.

**Gilman, A.P., Moss, M.A., Villeneuve, D.C., et al. (1998c)**. Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit. *Toxicological Sciences 41(1)*, 138–151.

**Maynard, E.A. and Hodge, H.C. (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, Ed. McGraw Hill, New York, NY, pp. 309–376.

# ATTACHMENT A
# EPA and DOH Consultations

STATE OF WASHINGTON

DEPARTMENT OF HEALTH

OFFICE OF ENVIRONMENTAL PUBLIC HEALTH SCIENCES

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# Memorandum

**DATE:** February 20, 2020

**TO:** Andy Kallus, Toxicologist

**FROM:** Lenford O'Garro, Toxicologist

**Re:** Non-cancer Oral Reference Dose for Uranium Soluble Salts

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This memorandum (memo) provides feedback from the Washington State Department of Health (DOH) Office of Environmental Public Health Sciences to the Washington State Department of Ecology (Ecology). Ecology requested DOH's review and consultation on the supporting materials for updating the Cleanup Levels and Risk Calculation (CLARC) Non-cancer Oral Reference Dose (RfD) for Uranium Soluble Salts.

After reviewing the supporting materials provided by Ecology, DOH agrees that Ecology should use the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL) for Uranium Soluble Salts instead of the U.S. Environmental Protection Agency (EPA) RfD for Uranium Soluble Salts.

The ATSDR derived MRL for uranium is based on sound and defensible science. Furthermore, the data are of better quality and more applicable than that used to derive the RfD. DOH suggests adding a reference to the ATSDR Toxicological Profile for Uranium. Specifically, the MRL worksheet in Appendix A on page A-20 or a copy of the worksheet to the supporting materials.

## Kallus, Andrew (ECY)

**From:** Kissinger, Lon <Kissinger.Lon@epa.gov>
**Sent:** Monday, July 20, 2020 2:34 PM
**To:** Kallus, Andrew (ECY)
**Cc:** Stifelman, Marc; Bachman, Brenda
**Subject:** EPA R10 Approval of Ecology Toxics Cleanup Program Use of the 2013 ATSDR Uranium MRL for Human Health Risk Assessment Activities
**Attachments:** OSRTI-U-Final-Dec-21-2016-196808.pdf

Dear Mr. Kallus,

We have reviewed the February 2020 Ecology Toxics Cleanup Program memo documenting the decision to use the 2013 ATSDR soluble uranium MRL (0.0002 mg U/kg-day) rather than the EPA Integrated Risk Information System uranium oral reference dose (0.003 mg U/kg-day) for human health risk assessment. We find the memo to be consistent with EPA Region 10 and EPA HQ Office of Land and Emergency Management (OLEM) (See attached memo) approaches for determining soluble uranium health risks. We, as EPA Region 10 risk assessors, support use of the 2013 soluble uranium ATSDR MRL for Ecology's Clean up Level and Risk Calculations effort.

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# ATTACHMENT B
# ATSDR Toxicological Profile MRL Worksheet (Appendix A, Page A-20)

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Uranium (soluble forms)
CAS Numbers: Multiple
Date: July 2012
Profile Status: Draft 2, Postpublic Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: 0.0002 [X] mg/kg/day [ ] ppm [ ] $mg/m^3$

Reference: Gilman AP, Villeneuve DC, Secours VE, et al. 1998a. Uranyl nitrate 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicol Sci 41(1):117-128.

Experimental design: Five groups of Sprague-Dawley rats (15/sex/dose, 60 g) were exposed to uranium as uranyl nitrate in drinking water (0, 0.96, 4.8, 24, 120, and 600 mg/L) for 91 days. Time-weighted average doses calculated by the authors from fluid intake data were <0.0001 (control group), 0.06, 0.31, 1.52, 7.54, and 36.73 mg U/kg/day in males and <0.0001 (control), 0.09, 0.42, 2.01, 9.98, and 53.56 mg U/kg/day in females. Clinical signs were monitored daily and body weights were measured weekly; fluid intake and feed consumption were also measured, but the frequency was not reported. Hematological parameters serum clinical chemistry (sodium, potassium, phosphate, bilirubin, alkaline phosphatase, aspirate aminotransferase, total protein, calcium, cholesterol, glucose, uric acid, lactate dehydrogenase, sorbitol dehydrogenase), organ weights, and histopathology (tissues examined: adrenal, brain [three sections], bone marrow, bronchi, colon, duodenum, epididymis, stomach [gastric cardia, fundus, and pylorus], heart, kidney, liver, lungs, mesenteric and mediastinal lymph nodes, ovary, pancreas, parathyroid, pituitary, salivary glands, skeletal muscle, spleen, testes, thoracic aorta, thymus, thyroid, trachea, and uterus) were assessed at termination. Uranium residues were measured in samples of brain, liver, spleen, liver, kidney, and bone in the control and two highest dose groups.

Effect noted in study and corresponding doses: Hematological and biochemical parameters were not affected in a significant exposure-related manner. Statistically significant increases in renal lesions included cytoplasmic vacuolization (0/15, 9/15, 7/15, 12/15, 9/15, 7/15), tubular dilation (0/15, 4/15, 5/15, 10/15, 4/15, 5/15), and lymphoid cuffing (0/15, 6/15, 6/15, 2/15, 7/15, 10/15) in males at ≥0.06 mg U/kg/day; capsular sclerosis (0/15, 5/15, 4/15, 3/15, 6/14, 5/14), tubular anisokaryosis (0/15, 5/15, 4/15, 3/15, 6/14, 5/14; not significant at 2.01 mg U/kg/day), and interstitial reticulin sclerosis (1/15, 9/15, 8/15, 7/15, 6/14, 5/14) in females at ≥0.09 mg U/kg/day; nuclear vesiculation in males (0/15, 6/15, 10/15, 6/15, 8/15) and females (0/15, 6/15, 6/15, 7/15, 4/14, 7/14) at ≥0.06/0.09 mg U/kg/day; and glomerular adhesions (2/15, 4/15, 10/15, 10/15, 10/15, 11/15) and cytoplasmic degeneration (0/15, 2/15, 11/15, 13/15, 7/15, 7/15) in males at ≥0.31 mg U/kg/day. Lesions were also observed in the liver at all doses including anisokaryosis, vesiculation, increased portal density, perivenous vacuolation, and homogeneity; the investigators considered these adaptive and likely reversible. Thyroid lesions were observed in both sexes (multifocal reduction of follicular size, increased epithelial height in males at 0.31 mg/kg/day and females at 2.01 mg/kg/day). A decreased amount and density of colloid in the thyroid was observed in males only. Sinus hyperplasia of the spleen was observed in males and females at 36.73/53.56 mg/kg/day.

Dose and end point used for MRL derivation: 0.06 mg U/kg/day, renal toxicity. This is considered a minimal LOAEL.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

- [x] 3 for use of a minimal LOAEL
- [x] 10 for extrapolation from animals to humans
- [x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No, doses were calculated by the authors on the basis of measured water intake.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: No studies have been identified that examined the toxicity of uranium in humans following an intermediate-duration oral exposure. A number of studies have examined the intermediate-duration oral toxicity of uranium in laboratory animals. Most of these studies involved exposure to soluble uranium compounds such as uranyl nitrate and uranyl acetate; there are limited data on moderately soluble or insoluble uranium compounds. The available data suggest that the kidney is the most sensitive target of uranium toxicity; at higher dose levels, neurological, reproductive, and developmental effects have been reported. At lower concentrations, histological alterations have been observed in the proximal tubules, glomerulus, and/or renal interstitium in rats and mice exposed to uranyl nitrate in drinking water (Berradi et al. 2008; Gilman et al. 1998a, 1998b, 1998c; McDonald-Taylor et al. 1992, 1997). At higher concentrations (40.38 mg U/kg/day), evidence of renal dysfunction (e.g., glycosuria, proteinuria) has also been observed (Gilman et al. 1998c). The Gilman et al. (1998a, 1998b) studies identified the LOAELs of 0.06 and 0.05 mg U/kg/day for renal effects in rats and rabbits, respectively; neither study identified NOAEL values.

The LOAELs for neurological, reproductive, and developmental effects are similar and are about 50-fold higher than the LOAEL for renal effects. Neurological effects such as sleep and behavior alterations and decreased spatial memory were observed in rats exposed to 2.5–2.7 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2005, 2007b). However, no neurological effects were observed in rats similarly exposed to the same dose of depleted uranyl nitrate (Houpert et al. 2005). The investigators suggest that the observed effects may have been related to radiological activity. The reproductive effects consisted of decreases in male fertility in rats and mice following exposure to ≥5.6 mg U/kg/day as uranyl acetate (Linares et al. 2005; Llobet et al. 1991) and alterations in ovarian folliculogenesis in mice at ≥1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008; Feugier et al. 2008; Kundt et al. 2009). A recent study by Raymond-Whish et al. (2007) also reported alterations in ovarian folliculogenesis in mice, but the effects were at an extremely low dose (0.00039 mg U/kg/day). Additional data are needed to support whether reproductive effects occur at this dose level and to evaluate the toxicological significance of the observed effect (reduced number of small primary follicles, but no effect on primordial, secondary/growing, healthy, or atretic follicle populations). Developmental effects have been observed in rats and mice; most effects occurred at maternally toxic doses. The observed effects included neurobehavioral effects in the offspring of rats exposed premating and during gestation and lactation to 4.3 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2007a), decreases in pup body weight at ≥2.8 mg U/kg/day as uranyl acetate (Paternain et al. 1989; Sanchez et al. 2006), decreases in litter size, live fetuses, or viability at ≥14 mg

U/kg/day as uranyl acetate (Domingo et al. 1989b; Paternain et al. 1989), and altered ovarian folliculogenesis in 3-month-old pups of dams exposed to 1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008).

The LOAELs of 0.05 and 0.06 mg U/kg/day for kidney effects in rats and rabbits (Gilman et al. 1998a, 1998b) were considered as possible points of departure for an intermediate-duration oral MRL for soluble uranium compounds. Although the rabbit study identified the slightly lower LOAEL, the rat LOAEL was selected as the point of departure for the MRL due to possible subclinical infection in the rabbits. Gilman et al. (1998b, 1998c) conducted two 91-day studies in rabbits. The kidney uranium levels for the two studies were not comparable; rabbits in the first study (Gilman et al. 1998b) had higher kidney uranium levels than in the second study (Gilman et al. 1998c) even though the dose was lower in the first study (28.70 mg U/kg/day dose and 4.98 µg U/g kidney level in the Gilman et al. 1998b study compared to 40.98 mg U/kg/day dose and 3.48 µg U/g kidney level in the Gilman et al. 1998c study). In the Gilman et al. (1998b) study, the male rabbits were not SPF derived and four animals developed *Pasteurella multocida* infections during the study; Gilman et al. (1998c) suggested that even though the affected rabbits were removed from the study, it is possible that other animals had a subclinical infection and that this may have increased sensitivity. Thus, the rat study was selected as the basis of the MRL; the rats used in the Gilman et al. (1998a) study were SPF derived. The Raymond-Whish et al. (2007) study was not selected as the point of departure because there are no other data to support this extremely low value and the toxicological significance of this slight change in one follicle population is not known.

Other Issues

The results of a serial study in which rats were exposed to several doses of uranyl nitrate in the diet for up to one year (Maynard et al. 1953) coupled with the rat 2-year study (Maynard and Hodge 1949; Maynard et al. 1953) suggest that at low exposures the renal tubular epithelium is regenerated and continued exposure does not result in more severe effects. However, at higher doses, the capacity to regenerate the renal tubular epithelium is exceeded and tubular atrophy is observed. In the serial study (Maynard et al. 1953), exposure to 170 mg U/kg/day as uranyl nitrate in the diet resulted in regeneration of the renal tubular epithelium after 2 weeks of exposure; there was no progression of renal damage with continued exposure and the renal tubules in rats exposed for 2 weeks were similar to those exposed for 1 year. Additionally, a 2 year exposure to 170 mg U/kg/day did not result in any further damage to the kidneys (Maynard and Hodge 1949; Maynard et al. 1953). In contrast, regeneration was observed in the first month of the exposure to 660 mg U/kg/day, however, with continued exposure, tubular atrophy was observed at 6–8 weeks. The severity of the atrophy and the areas of the kidney affected by uranium increased with duration. Given these data on the ability of the kidney to repair renal damage at low doses, the intermediate-duration oral MRL may be protective for chronic exposures.

Agency Contacts (Chemical Managers): Sam Keith, Obaid Faroon, Nickolette Roney, Franco Scinicariello, Sharon Wilbur

# ATTACHMENT C
# EPA December 21, 2016, Memorandum on Uranium Noncancer Oral RfD (images of scanned documents)

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

OFFICE OF
LAND AND EMERGENCY
MANAGEMENT

*formerly*
OFFICE OF
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

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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:<br>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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U.S. Environmental Protection Agency Contract No. EP-C-13-007

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

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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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