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IRIS Assessment Plan for Uranium (Oral Reference Dose) (Scoping and Problem Formulation Materials)

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CONTENTS

TABLES

ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
EPA	Environmental Protection Agency
IRIS	Integrated Risk Information System
LOAEL	lowest-observed-adverse-effect level
MCL	maximum contaminant limit
MRL	minimal risk level
OW	Office of Water
PECO	populations, exposures, comparators, and outcomes
RfD	oral reference dose

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program 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 (https://www.epa.gov/iris/iris-agenda) as a chemical having high priority for assessment development.

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations, but provide a critical part of the scientific foundation for decisions made in Environmental Protection Agency (EPA) program and regional offices to protect public health.

Before beginning an assessment, the IRIS Program consults with EPA program and regional offices to define the scope of the assessment, including the nature of the hazard characterization needed, identification of the most important exposure pathways, and level of detail needed to inform Agency decisions. Based on the scope defined by EPA, the IRIS Program develops problem formulations to frame the scientific questions that will be the focus of the assessment, which is conducted using systematic review methodology.

This document presents the draft assessment plan for uranium, including a summary of the IRIS Program's scoping and initial problem formulation conclusions, objectives, and specific aims of the assessment; draft populations, exposures, comparators, and outcomes (PECO) criteria outlining the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

2. SCOPING AND INITIAL PROBLEM FORMULATION SUMMARY

2.1. BACKGROUND

Uranium is a naturally occurring radioactive element, which in nature is a mixture of three isotopes: ^{234}U, ^{235}U, and ^{238}U. The most common isotope, ^{238}U, makes up about 99% of natural uranium, and due to that predominance, is thought to be primarily responsible for the chemical toxicity of uranium. Uranium is "enriched" by processes that remove and concentrate ^{235}U, with the remaining uranium being termed "depleted." Depleted uranium has an even greater concentration of ^{238}U than natural uranium and the chemical toxicity of the two are believed to be essentially identical (ATSDR, 2013). Enriched uranium is used in nuclear reactor fuel and in nuclear weapons; it is not a subject of this assessment. Uranium metal is almost as hard as steel and much denser than lead. Due to its physical properties, depleted uranium is used as counterweights in aircraft applications, for shielding against ionizing radiation, as military armor, and in armor-penetrating munitions.

Uranium is naturally present in many soils with an average concentration in the United States of about 3 ppm; some areas, particularly in the western United States, have higher concentrations. Uranium mining, milling, and processing operations have released uranium into the environment leading to elevated levels of uranium in affected soils and dusts (ATSDR, 2013). In response to the presence of hundreds of abandoned uranium mines in the Navajo Nation in the southwest United States, EPA has commitments for major risk assessment and remediation projects in that area (US EPA, 2018). Commercially viable phosphate ore deposits in the United States and elsewhere contain uranium (Ulrich et al., 2014; Sattouf et al., 2007) and cleanup sites at former phosphate mines in, for example, the northwest United States have elevated soil concentrations of uranium. Evaluation of cleanup needs at sites with uranium contamination generally entails assessment of both the risks from the chemical toxicity of uranium and the radiological risks multiple elements, where both may contribute importantly to total risk.

The general population is primarily exposed to uranium through food and drinking water. In most areas of the United States, low levels of uranium are found in drinking water, with a population mean concentration of about 1 µg U/L. Higher levels of uranium are seen in water from wells in uranium-rich rock. Approximately 4% of reporting US drinking water systems (serving 8 million people in total) reported some exceedance of the EPA maximum contaminant limit (MCL) for uranium of 30 µg/L (US EPA, 2016). Large aquifers in the United States great plains and in California's central valley have locally elevated uranium concentrations (Nolan and Weber, 2015).

Human daily intake of uranium from typical diets has been estimated to range from 0.9 to 1.5 µg/day. Uranium from soil is adsorbed onto the roots of plants; root crops including potatoes, radishes, and other root vegetables are a source of uranium in the diet (ATSDR, 2013).

Environmental exposures to uranium from contaminated sites can involve multiple pathways including ingestion of soil, foods, surface water, or ground water as well as consumption of locally grown or foraged food. Multiple routes of exposure may be particularly important at sites that are located on or near Indian Nations (Arnold, 2014; ATSDR, 2013; Middlecamp et al., 2006; Brugge and Goble, 2002).

Depending on the chemical form of uranium and circumstances of intake, about 0.1–6% of ingested uranium is absorbed by the gastrointestinal tract and enters the systemic circulation in humans, with soluble uranium compounds being more readily absorbed. Urinary excretion is the principal elimination pathway for absorbed uranium. Absorbed uranium is retained in many organ systems, with the highest levels found in the bones, liver, and kidneys. It is estimated that 66% of the typical human body burden of uranium is found in the skeleton. Uranium in the skeleton is retained for a longer period, with a half-life on the order of 70–200 days; most of the uranium in other tissues leaves the body in 1–2 weeks following exposure (ATSDR, 2013).

2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that are interested in an IRIS assessment for uranium to discuss specific assessment needs. Table 1 provides a summary of input from this outreach.

Table 1. EPA program and regional office interest in an assessment of uranium

Program or regional office	Oral	Inhalation	Statues/regulations	Anticipated uses/interest
Office of Land and Emergency Management	✓		CERCLA	Uranium toxicological information may be used to make risk determinations for response or remedial actions (e.g., short-term removals, long-term remedial response actions). CERCLA authorizes EPA to conduct short- or long-term cleanups at Superfund sites and later recover cleanup costs from potentially responsible parties. Uranium is listed as a hazardous substance under CERCLA and is commonly found at National Priorities List facilities.
Region 10[a]	✓			

Program or regional office	Oral	Inhalation	Statues/regulations	Anticipated uses/interest
OW	✓		Safe Drinking Water Act	Uranium toxicological information may be used to inform risk determinations associated with contaminants commonly found in water. The maximum contaminant level goals of 0 µg/L and maximum contaminant level of 30 µg/L for uranium were published in 2000 (65 FR 76707).

CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; OW = Office of Water
[a] Pacific Northwest States.

Oral exposure to uranium is of concern to the Superfund Program as this element has been found at approximately 60 Superfund sites, with oral intake driving site exposure assessments. EPA regulated uranium as a drinking water contaminant in 2000 based primarily on radiological exposures, but also considered kidney toxicity. The EPA's Office of Water (OW) periodically updates drinking water regulations and needs an IRIS assessment of uranium that examines the more recent literature (U.S. EPA, 2017).

This reassessment focuses on nonradiological, noncancer effects associated with uranium exposure because (1) IRIS assessments historically focus on the nonradiological effects of chemicals and (2) cancer risks from uranium have generally been attributed to and assessed as the result of radiation exposures. In addition, this reassessment focuses only on oral exposure because the oral pathway has been the primary route of exposure for nonradiological environmental exposures to uranium (e.g., drinking water, soils at contaminated sites). Studies on both natural uranium and depleted uranium will be considered in this reassessment; studies of enriched uranium or the radiological effects of uranium are not within the assessment scope. This update will include examination of potentially susceptible populations, including women of child-bearing age, pregnant women, infants, and children.

2.3. PROBLEM FORMULATION

EPA's IRIS assessment of uranium dates from 1989 (U.S. EPA, 1989). Much research on the health effects of uranium has been subsequently published. In 2013, the Agency for Toxic Substances and Disease Registry (ATSDR) completed its *Toxicological Profile for Uranium* (ATSDR, 2013), which includes a detailed review of the available human epidemiology and experimental toxicology data. The ATSDR assessment examines the substantial data available on the kidney, reproductive, developmental, and other effects of uranium and recommends an intermediate-duration oral minimal risk level (MRL) of 2×10^{-4} mg U/kg-day for soluble uranium compounds based on 90-day studies in rats (Gilman et al., 1998). This MRL calculation uses a

lowest-observed-adverse-effect level (LOAEL) value of 0.06 mg U/kg-day for renal effects in rats, divided by an uncertainty factor of 300. This includes a factor of 3 due to the use of a LOAEL, a factor of 10 for animal-to-human extrapolation, and a factor of 10 for human variability. For comparison, in EPA's 1989 IRIS assessment, an oral reference dose (RfD) of 3×10^{-3} mg/kg-day was based on kidney toxicity and body weight loss with a LOAEL of 2.8 mg U/kg-day in a 30-day oral study in rabbits (Maynard and Hodge, 1949) and used a composite uncertainty factor of 1,000 (U.S. EPA, 1989).

In this reassessment, EPA will heavily rely on the literature review and scientific analysis contained in ATSDR's toxicological profile (ATSDR, 2013). In addition, EPA will perform a review of literature published since the development of ATSDR's assessment (literature since 2012) and will seek to develop an updated RfD based on the noncancer, nonradiological effects from oral exposure to uranium.

The ATSDR toxicological profile identified kidney, reproductive, and developmental effects of uranium as being of principal concern, and data on these effects provided the bases for that assessment's MRL values for different durations of exposure. The IRIS assessment will examine whether newly available data indicate a need to revise the conclusions for these hazards. Newly available data will also be examined to see whether additional health hazards of uranium have been identified that may provide a basis for developing new toxicity values. As described below, the review of the new literature will be integrated with the evidence compiled in the ATSDR toxicological profile to develop a revised characterization of health hazards and provide the basis for the derivation of an RfD for uranium.

2.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues have been identified that warrant evaluation in this assessment.

- Uranium occurs in the environment in a variety of forms to which humans may be exposed, including metallic uranium, soluble uranium salts, and poorly soluble uranium compounds. In developing the IRIS assessment, consideration will be given to the approach used by ATSDR of providing toxicity values suitable for all soluble forms of uranium versus possible alternatives, addressing specific forms of uranium (e.g., more soluble versus poorly soluble versus insoluble species). Taking into account any new research, the assessment will develop and use a rationale for the specific categories of uranium compounds assessed.

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT PECO (POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES) CRITERIA

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for noncancer, nonradiological effects from ingestion of uranium to support development of toxicity values (e.g., an RfD). This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for uranium. Given the extent of human and animal toxicology studies, in vitro and other mechanistic studies will not be a focus of the systematic review because toxicity values for uranium are likely to be based directly on human and mammalian studies of uranium's apical effects. The evaluation conducted in this assessment will be consistent with relevant EPA guidance.[1] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and the PECO criteria in response to public input.

3.1. SPECIFIC AIMS

- Building on findings from the *Toxicological Profile for Uranium* (ATSDR, 2013), identify new epidemiological and experimental animal studies of the health hazards of uranium as outlined in the PECO criteria. The literature search will be focused on publications since the ATSDR literature search was conducted (i.e., publications from 2012–2017).

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies identified in the literature search. The results of this review will allow subsequent analyses to be focused on those new studies that are most informative for the assessment's needs.

- Examine whether newly available data indicate a need to update evidence conclusions and toxicity values for principal health outcomes from the ATSDR toxicological profile (i.e., kidney toxicity, and reproductive and developmental effects of uranium). Also, this review will examine whether newly available data on other health outcomes support identification

[1]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

of additional uranium health hazards and may plausibly support deriving an RfD for uranium.

- If newer PECO-relevant studies on health outcomes are identified, these findings will be considered along with key studies[2] cited in the ATSDR toxicological profile for evidence synthesis/integration and RfD derivation purposes. In this case, both new studies and key studies used from the ATSDR toxicological profile will be summarized and evaluated jointly using the methods described below.

- Extract data on relevant health outcomes from epidemiological and toxicological studies considered informative.

- For the identified outcomes with important new data, synthesize evidence across studies (including both new and key older studies) within the human and animal evidence streams, using a narrative approach or meta-analysis (if appropriate). For health outcomes examined by ATSDR where important new studies are *not* identified, EPA will seek to base its hazard conclusions on ATSDR's findings unless compelling reasons for further review are identified.

- For each of the selected health outcomes, express confidence in conclusions from across studies within human and animal evidence streams, evaluating each evidence stream (human and animal) separately.

- For each health outcome, integrate results across evidence streams (human and animal) to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages. Biological support from mechanistic studies will be summarized primarily by relying on other published sources and targeted literature searches, if warranted, to address specific topics that may arise when conducting the assessment.

- Derive an RfD as supported by the available data. System- and organ-specific RfD values will be derived where supported by the database.

- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence base, limitations of the systematic review, and dose relevance and pharmacokinetic differences when extrapolating findings from higher dose animal studies to lower levels of human exposure.

[2]Key earlier studies on relevant toxicological endpoints will be identified through the study summaries and analysis developed by ATSDR. Considerations include: studies providing data in dose ranges proximate to toxicological findings considered in ATSDR MRL derivation and/or used in important newly identified literature; studies of relevant durations for toxicity value development (generally studies of subchronic or chronic duration as well as developmental or reproductive studies using relevant shorter exposure durations); and studies, which as summarized, were not identified to have major methodological shortcomings. Accordingly, key studies are generally those that appear to provide informative data on the health outcomes and may plausibly support deriving toxicity values for uranium.

3.2. DRAFT PECO (POPULATIONS, COMPARATORS, EXPOSURES, AND OUTCOMES) CRITERIA

A PECO statement is used as an aid to focus the research questions, search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO criteria for the uranium assessment (see Table 2) were based on (1) nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for uranium (primarily reviews and authoritative health assessment documents) to identify the major health hazards associated with exposure to uranium and key areas of scientific complexity.

Table 2. Draft PECO (populations, comparators, exposures, and outcomes) criteria for the uranium assessment

PECO element	Evidence
Population[a]	*Human*: Any population and all life stages (e.g., children, general population, occupational, or high exposure from an environmental source). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few more informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposure	Exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental, or occupational-setting measures (e.g., air, water levels), or job title or residence. Studies on natural uranium and depleted uranium will be included, studies on enriched uranium or those specific to radiation exposure from uranium will not be included. Mixture studies for animals will be included if they have an arm with a uranium compound only.
	Human and animal: Oral exposure will be examined. Other exposure routes, including dermal, inhalation, or injection, will be tracked during title and abstract as "supplemental information."
Comparator	*Human*: A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) of uranium or to uranium for shorter periods.
	Animal: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcomes	All noncancer health outcomes. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures.

[a] Evaluating individual mechanistic studies for uranium is not anticipated to be critical given the extent of the experimental animal evidence for noncancer outcomes and findings of earlier reviews. For mechanistic information, this assessment will primarily rely on other published authoritative sources, such as public health agency reports and expert review articles.

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