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Protocol
for the Uranium IRIS Assessment (Oral)
(Preliminary Assessment Materials)

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Integrated Risk Information System
Center for Public Health and Environmental Assessment
Office of Research and Development
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ABBREVIATIONS

AC50	activity concentration at 50%
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike's information criterion
ALT	alanine aminotransferase
AOP	adverse outcome pathway
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
$BW^{3/4}$	body weight scaling to the 3/4 power
CA	chromosomal aberration
CAA	Clean Air Act
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CHO	Chinese hamster ovary (cell line cells)
CI	confidence interval
CL	confidence limit
CNS	central nervous system
COI	conflict of interest
COPD	chronic obstructive pulimary disease
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
EPA	Environmental Protection Agency
ER	extra risk
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
FSH	follicle-stimulating hormone
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GLP	Good Laboratory Practice
GSH	glutathione
GST	glutathione-*S*-transferase
HAP	hazardous air pollutant
HAWC	Health Assessment Workspace Collaborative
Hb/g-A	animal blood:gas partition coefficient
Hb/g-H	human blood:gas partition coefficient
HBCD	hexabromocyclododecane
HEC	human equivalent concentration
HED	human equivalent dose
HERO	Health and Environmental Research Online
HPV	high production volume
i.p.	intraperitoneal
i.v.	intravenous
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MAC	maximum acceptable concentration
MeSH	Medical Subject Headings
MLE	maximum likelihood estimation
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MRL	minimal risk level
MTD	maximum tolerated dose
NCI	National Cancer Institute
NMD	normalized mean difference
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OAR	Office of Air and Radiation
OECD	Organisation for Economic Co-operation and Development
OLEM	Office of Land and Emergency Management
ORD	Office of Research and Development
OSF	oral slope factor
OW	Office of Water

PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PK	pharmacokinetic
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QAPP	quality assurance project plan
QSAR	quantitative structure-activity relationship
RD	relative deviation
RfC	inhalation reference concentration
RfD	oral reference dose
RfV	reference value
RGDR	regional gas dose ratio
RNA	ribonucleic acid
ROBINS I	Risk of Bias in Nonrandomized Studies of Interventions
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SEM	systematic evidence map
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
TDI	tolerable daily intake
TIAB	title and abstract
TK	toxicokinetic
TSCA	Toxic Substances Control Act
TSCATS	Toxic Substances Control Act Test Submissions
TWA	time-weighted average
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_D	database deficiencies uncertainty factor
UF_H	human variation uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOS	Web of Science

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the noncancer health effects of natural and/or depleted uranium via oral exposure. Enriched uranium is not a subject of this assessment.

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These science assessments are not regulations and do not constitute U.S. Environmental Protection Agency (EPA) policy. Science assessments such as these provide a critical part of the scientific foundation for subsequent risk assessment and risk management decisions made by EPA program and regional offices to protect public health. IRIS assessments are also used by states and local health agencies, Tribes, other federal agencies, international health organizations, and other external stakeholders.

This protocol document includes the IAP content, revised in response to public input and updated EPA scoping needs, and presents the methods for conducting the systematic review and dose-response analysis for the assessment. While the IAP described *what* the assessment will cover, this protocol describes *how* the assessment will be conducted (see Figure 1-1).

The systematic review methods described in this protocol are based on the Office of Research and Development (ORD) Staff Standard Operating Procedures for Developing Integrated Risk Information System (IRIS) Assessments (Version 2.0, referred to as the "IRIS Handbook") (U.S. EPA, 2022a).

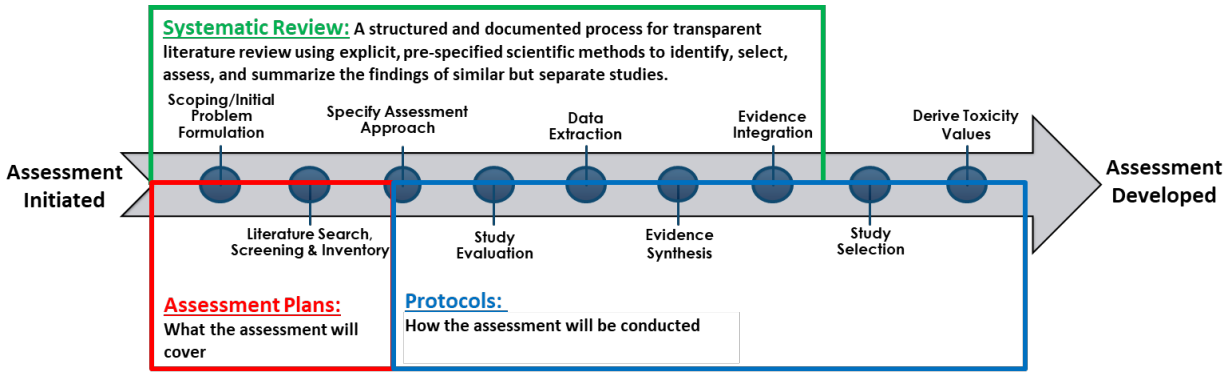


Figure 1-1. Integrated Risk Information System systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION SUMMARY

2.1. BACKGROUND

2.1.1. Physical and Chemical Properties

Uranium (U), the 92nd element in the periodic table, is a naturally occurring radioactive actinide element,[1] which has the highest atomic mass among naturally occurring elements. The half-life of naturally occurring uranium ranges between 159,200 and 4.5 billion years. It is a silvery-gray metal in the actinide series of elements, and a uranium atom has 92 protons and 92 electrons of which 6 are valence electrons. In nature, uranium can be found in rock and ores. In the United States it can be naturally found in greatest concentrations in western states (including Arizona, Colorado, New Mexico, Texas, Utah, and Wyoming) (U.S. EPA, 2023a; ATSDR, 2013). Table 2-1 lists the properties of elemental uranium and the most common uranium compounds used in toxicological studies (uranyl nitrate, uranyl acetate, uranyl fluoride, uranium tetrachloride, and uranyl fluoride).

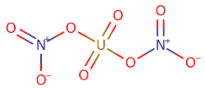
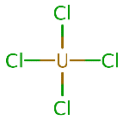
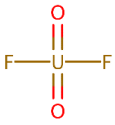
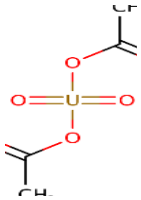
In nature uranium exists as a mixture of three isotopes: ^{234}U, ^{235}U, and ^{238}U, with ^{238}U being the most abundant. By weight, natural uranium is mostly (99.27%) ^{238}U, with 0.72% ^{235}U and 0.006% ^{234}U (USEPA OGWDW, 2000). The specific activities of U-238, U-235, and U-234 in natural uranium are about 12.4, 80, and 231,000 becquerels [Bq]/mg, respectively (Kim et al., 2012), or 0.34, 2.2, and 6,253 pCi/kg. The specific activity of natural uranium in rock is 0.68 pCi/µg (USEPA OGWDW, 2000). Uranium is "enriched" by processes that remove and concentrate ^{235}U from 0.72% to 2–4%, with the remaining uranium being termed "depleted." Depleted uranium has a greater concentration of ^{238}U than natural uranium, but the toxicity of the two are believed to be essentially identical. In its refined state uranium is malleable, dense, ductile, and slightly paramagnetic (UNSCEAR, 2017; ATSDR, 2013).

Uranium is chemically reactive and can combine with most elements. In air, the metal easily oxidizes and becomes coated with a layer of oxide (Bleise et al., 2003). Uranium forms compounds in which the valence of the element can range between +3 and +6. The most prevalent form of uranium in the environment is the uranyl ion UO22+ (the +6-oxidation state). It can form complexes with phosphate, carbonate, and sulfur ions (Sheppard et al., 2005). In aqueous solutions, only the +4 and +6 compounds are sufficiently stable, both thermodynamically and kinetically, to be

[1]Actinide elements are 15 metallic chemical elements that are all radioactive and found in the f-block of the periodic table.

of biological importance. These are the compounds that are commonly identified in and transported by ground and surface waters (NRC, 1988).

Table 2-1. Chemical identity and physiochemical properties of selected uranium compounds as curated by EPA's CompTox Chemicals Dashboard

Name	Elemental uranium	Uranyl nitrate	Uranium tetrachloride	Uranyl fluoride	Uranyl acetate
CASRN	7440-61-1	10102-06-4	10026-10-5	13536-84-0	541-09-3
DTXSID[a]	1042522	2037136	1064906		3060243
Structure					
Molecular weight (g/mol)	238.029	394.035	379.83	308.024	388.115
Molecular formula	U	$UO_2(NO_3)_2$	UCl_4	F_2O_2U	$C_4H_6O_6U$
Selected synonyms	238U	Uranium dinitrate dioxide, uranyl dinitrate	Uranium chloride	Uranium difluoride dioxide, Difluoride [bis(oxido)] uranium	Uranium, bis(acetato-.kappa.O)dioxo-, (T-4)
Water solubility (mol/L)[b]	–	–	–	–	–
LogKow: Octanol – Water[b]	–	–	–	–	–
Melting point (°C)[b]	1.13×10^3	–	–	–	–
Boiling point (°C)[b]	3.82×10^3	–	–	–	–

[a]DTXSIDs are unique substance identifiers used for curation by EPA's Distributed Structure-Searchable Toxicity (DSSTox) project (https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database).

[b]Experimental average values for physiochemical properties are shown here. Median values and ranges for physiochemical properties are also provided on EPA's Chemicals Dashboard at https://comptox.epa.gov/dashboard/ (U.S. EPA, 2023a). If no experimental or predicted values were available on the Chemicals Dashboard, "–" is shown.

2.1.2. Sources, Production, and Use

Uranium is naturally present in many soils with an average concentration in the United States and worldwide of about 3 ppm; some areas, particularly in the western US, have higher concentrations. Uranium is found as a component of various minerals (e.g., uraninite, pitchblende, and carnotite) in its natural state, but not in its metallic state (ATSDR, 2013). Commercially viable phosphate ore deposits contain uranium (Ulrich et al., 2014; Sattouf et al., 2007). The major producers of uranium in the world are the US, China, Australia, Kazakhstan, Namibia, Niger, Russia,

and Uzbekistan (Keith et al., 2015). In the United States higher concentrations in rocks and ores occur in westerns states including Arizona, Colorado, New Mexico, Texas, Wyoming, and Utah (ATSDR, 2013).

The main commercial use for uranium is to create fuel for electricity (NRC, 2012). Uranium is mined primarily for the U^{235} isotope, and the process of enrichment adjusts the ratio of U^{234}, U^{235}, and U^{238} to an increased amount of U^{235} (Yelamanchili and Fox, 2010). In addition to energy and weapons production, uranium is also used in a variety of products such as X-ray targets, glass tinting agents, gyroscope wheels, ceramic glazes, and shields for radioactive sources. Enriched uranium[2] is used in nuclear reactor fuel and in nuclear weapons.

Depleted uranium is the by-product of the uranium enrichment process. It is less radioactive than natural uranium (approximately 60%) and it has a density higher than lead (UNEP, 2022; U.S. EPA, 2006a). Because of its physical properties depleted uranium is used for several applications including: as a counterbalance in aircraft, for shielding against ionizing radiation, as a gyroscope component, and both in military armor and in armor penetrating munitions (UNEP, 2022; ATSDR, 2013).

2.1.3. Environmental Fate and Transport

Uranium is naturally mobilized from the Earth's crust by chemical and mechanical weathering of rocks. Uranium mining, milling, and processing operations can release it into the environment leading to elevated levels of uranium in affected soils, dusts, and surface and ground water (U.S. EPA, 2023b; ATSDR, 2013). Uranium mining and the treatment of uranium ore creates waste in the form of tailings which contain uranium and other radioactive elements such as radium and plutonium (Brugge and Buchner, 2011; Yelamanchili and Fox, 2010). Depleted uranium has also been introduced into the environment because of its use in military conflicts (WHO, 2001), and can be found in soil, water, biota, and airborne particles (U.S. EPA, 2006a).

2.1.4. Potential Human Exposure (Oral)

The general population is primarily exposed to uranium through intake of food and drinking water. Higher levels of uranium are seen in water from wells in uranium-rich rock. Human daily intake from water and food has been estimated to range from 0.9 to 1.5 µg U/day depending on the drinking water source and type of diet (Keith et al., 2015). Uranium from soil is adsorbed onto the roots of plants; root crops including potatoes, onions, and other root vegetables are a source of uranium in the diet (ATSDR, 2013).

Environmental exposures to uranium include ingestion of soil, foods, surface water, or ground water including ingestion of locally grown or foraged food. Such routes of exposure may be important at a number of Superfund sites with uranium contamination that are located on or near Indian Country (Arnold, 2014; ATSDR, 2013; Middlecamp et al., 2006; Brugge and Goble, 2002).

[2]Enriched uranium is not a subject of this assessment.

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 (e.g., uranyl nitrate and uranyl acetate) being more readily absorbed (Keith et al., 2015). Urinary excretion is the principal elimination pathway for absorbed uranium. Absorbed uranium is retained in many organ systems with the highest levels found in 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 within 1–2 weeks following exposure (ATSDR, 2013).

2.1.5. Previous Assessments of Oral Exposure to Uranium by the Environmental Protection Agency and Other Health Agencies

Existing human health oral reference values for uranium from federal, state, and international agencies were searched in October 2022 as described in Appendix B and are depicted in Figure 2-1, and Table 2-2. IRIS published health effect assessments on uranium soluble salts in 1989, which included a reference dose (RfD) for lifetime oral exposure to uranium (U.S. EPA, 1989). The RfD was based on a study by Maynard and Hodge (1949) in which rabbits were administered uranyl nitrate hexahydrate in the diet at 0%, 0.02%, 0.1%, or 0.5% (2.8, 14, or 71 mg/kg-day) for 30 days. An RfD of 0.003 mg/kg-day for uranium was derived based on the Lowest Observed Adverse Effects Level (LOAEL) of 2.8 mg/kg-day for renal histopathological damage. The RfD was calculated by applying an uncertainty factor of 1,000 (a factor of 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 10 for use of a LOAEL).

The EPA Office of Water (OW) also developed an RfD for chronic (lifetime) exposure to uranium (USEPA OGWDW, 2000). These values were based on renal histopathology (dilation of tubules, apical displacement, vesiculation of tubular nuclei, and cytoplasmic vacuolation and degranulation in kidneys of male rats exposed to uranyl nitrate) observed in a subchronic exposure study in which Sprague-Dawley (SD) rats were exposed to uranyl nitrate at 0.06, 0.31, 1.52, 7.54, 36.73 mg/kg-day for 91 days (Gilman et al., 1998). A chronic RfD of 0.0006 mg/kg-day was derived based on a LOAEL of 0.06 mg/kg-day and applying a UF of 100 (3 for animal to human extrapolation, 10 for interhuman variability, 3 for LOAEL to NOAEL extrapolation, and 1 for subchronic to chronic adjustment).

Health Canada calculated a tolerable daily intake (TDI), health-based value (HBV), and a maximum acceptable concentration (MAC) for chronic exposure to uranium in drinking water. Their analysis was also based on renal lesions reported in the Gilman et al. 1998 study, which exposed male rats to uranyl nitrate for 91 days (Health Canada, 2019; Gilman et al., 1998). This study was selected for the Health Canada risk assessment point of departure as it reported the lowest LOAEL for kidney effects. A total uncertainty of 100 (10 for animal to human extrapolation, and 10 for interhuman variability) was applied to the selected LOAEL of 0.06 mg U/kg-day. The TDI

of 0.0006 mg/kg-bw was used to determine an HBV for total uranium in drinking water of 0.014 mg/L and a MAC of 0.02 mg/L total natural uranium in drinking water (Health Canada, 2019).

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 Toxicological Profile 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. This intermediate-duration MRL is also based on the 91-day study in rats by Gilman et al. 1998 (Gilman et al., 1998). This MRL calculation uses a 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 because of the use of a "minimal" LOAEL, a factor of 10 for animal to human extrapolation, and a factor of 10 for human variability.

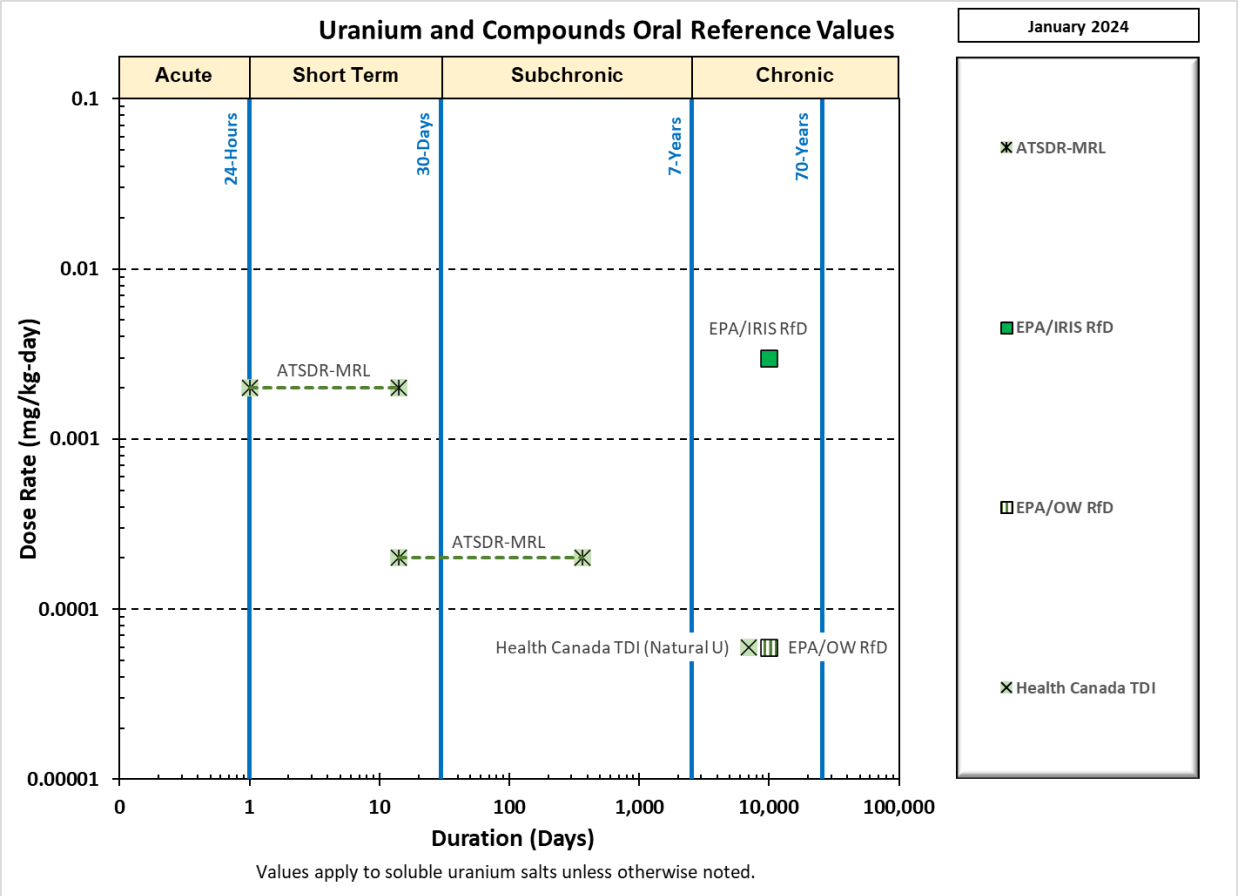


Figure 2-1. Available health effect reference values for oral exposure to uranium (current as of November 2022).

Table 2-2. Details on derivation of the available health effect reference values for oral exposure to uranium[a]

Reference value name	Duration	Uranium form(s)	Reference value (mg/kg-d)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
EPA RfD (IRIS)	Chronic	Soluble uranium salts	0.003	Initial BW loss and mild nephrotoxicity in rabbits exposed to uranyl nitrate hexahydrate for 30 d	2.8 mg U/kg-d	LOAEL	Maynard and Hodge (1949)	Total UF = 1,000 UF_A = 10 UF_H = 10 UF_L = 10	NA	Final NCEA (1989)
EPA RfD (OW)	Chronic	Soluble uranium salts	0.0006	Renal histological lesions in male rats exposed to uranyl nitrate hexahydrate for 91 d	0.06 mg U/kg-d	LOAEL	Gilman et al. (1998)	Total UF = 100 UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 1	NA	Final USEPA OGWDW (2000)
ATSDR MRL	Acute (1–14 d)	Soluble uranium salts	0.002	Cleft palate and other developmental effects in fetal mice exposed to uranyl acetate dihydrate in utero	0.2 mg U/kg-d	$BMDL_{05}$	Domingo et al. (1989)	Total UF = 100 UF_A = 10 UF_H = 10	NA	Final ATSDR (2013)

Reference value name	Duration	Uranium form(s)	Reference value (mg/kg-d)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
	Intermediate (15–365 d)		0.0002	Renal histological lesions in male rats exposed to uranyl nitrate hexahydrate for 91 d	0.06 mg U/kg-d	LOAEL	Gilman et al. (1998)	Total UF = 300 UF_A = 10 UF_H = 10 UF_L = 3		
Health Canada TDI	Chronic	Natural uranium	0.0006	Renal histological lesions in male rats exposed to uranyl nitrate hexahydrate for 91 d	0.06 mg U/kg-d	LOAEL	Gilman et al. (1998)	Total UF = 100 UF_A = 10 UF_H = 10	NA	Final Health Canada (2019)

ATSDR = Agency for Toxic Substances and Disease Registry; BMDL = benchmark dose level; BW = body weight; EPA = U.S. Environmental Protection Agency; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; OGWDW = Office of Groundwater and Drinking Water; OW = Office of Water; RfD = reference dose; TDI = tolerable daily intake; UF = uncertainty factor; UF_A = animal to human variability; UF_H = interhuman variability; UF_L = LOAEL-to-NOAEL adjustment; UF_S = subchronic-to-chronic adjustment**.**

[a]Current as of January 2020; please consult citation source entities and other entities in Appendix Table B-1 for current values.

2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for uranium to discuss specific assessment needs. Table 2-3 below provides a summary of input from this outreach.

Table 2-3. EPA Program and Regional Office interest in an assessment of uranium

EPA program or regional office	Oral	Inhalation	Anticipated uses/interest
OW	✓		Uranium is found as a natural contaminant of ground water in certain geologic situations. OW periodically updates drinking water standards under the Safe Drinking Water Act.
OLEM	✓		Uranium is found at approximately 60 Superfund sites across the United States. Uranium is a hazardous constituent at Resource Conservation and Recovery Act (RCRA) sites. Uranium is also found at a number of Federal Facility sites that are managed under CERCLA or RCRA. Sites include uranium and phosphate mines and the Hanford Nuclear Reservation (non-enriched uranium).
Region 10	✓		Updated uranium reference values are needed to conduct regional risk assessment-related activities at contaminated sites.

Oral exposure to uranium is of concern to several EPA Program and Regional Office, including the Office of Water (OW), Office of Land and Emergency Management (OLEM), and Region 10. Uranium is of concern to the OLEM-administered Superfund Program (approximately 60 Superfund sites) and Federal Facility sites managed under the Comprehensive Environmental Response and Liability Act (CERCLA) or the Resource Conservation and Recovery Act (RCRA), with oral intake driving site exposure assessments. EPA regulated uranium as a drinking water contaminant in 2000 based primarily on radiological exposures, but also considering kidney toxicity. The EPA's Office of Water (OW) periodically updates drinking water regulations and has need for an IRIS assessment of uranium that examines the more recent literature, and the EPA's Office of Land and Emergency Management (OLEM) manages Superfund sites (see Table 2-3). The EPA has been involved in the cleanup or of abandoned uranium mines in Utah, New Mexico, and Arizona; and Navajo and Hopi lands (U.S. EPA, 2021).

An IRIS assessment plan (IAP) for uranium (IRIS, 2018) was presented at a public science meeting on March 14, 2018 (https://www.epa.gov/iris/iris-public-science-meeting-mar-2018) to seek input on the problem formulation components of the assessment plan. The 2018 IAP specifies why uranium was selected for evaluation, specifies the objectives and specific aims of the

assessment, provides draft populations, exposures, comparators, and outcomes (PECO) criteria, and identifies key areas of scientific complexity. However, in April 2019 the uranium assessment was suspended because of changes in how EPA identified priorities for the IRIS Program (April 2019 IRIS Program Outlook). In June 2021, the assessment work was restarted after interest was expressed by the EPA Office of Land and Emergency Management (OLEM), Office of Water (OW), and Region 10. This assessment may also be used to support actions in other EPA programs and regions and can inform efforts to address uranium by tribes, states, and international health agencies.

This reassessment focuses on noncancer effects associated with uranium exposure because 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 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 reassessment will include examination of potentially susceptible populations including women of childbearing age, pregnant women, infants, and children.

2.3. PROBLEM FORMULATION

EPA's IRIS assessment of uranium dates from 1989 (IRIS, 2018). Much research on the health effects of uranium has been subsequently published. Systematic review methods were used to identify a preliminary literature inventory for uranium compounds using the literature search and screening methods described in Section 4. The ATSDR Toxicological Profile for Uranium (ATSDR, 2013), was selected as the starting point for the literature search. All references from the ATSDR Toxicological Profile were retrieved and stored in the EPA's Health and Environmental Research Online (HERO) database (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/3609),[3] and a literature search was conducted to identify studies published since the end of the period covered by the ATSDR Toxicological Profile (see Section 4).

In this reassessment, EPA will include the literature review and scientific analysis contained in ATSDR's Toxicological Profile. (ATSDR, 2013) identified urinary, hepatic, neurological, reproductive, and developmental effects of uranium as being of possible concern. Data on these effects provided the basis for the Toxicological Profile's MRL values for different durations of exposure (ATSDR, 2013). The IRIS assessment will examine whether newly available data could be considered for dose-response analysis for these hazards. Newly available studies and data will also

[3]EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes more than 600,000 scientific references and data from the peer-reviewed literature used by EPA to develop its health assessment documents.

be examined to determine whether there are additional health hazards related to uranium exposure that have been reported and may provide a basis for hazard evaluation and the development of toxicity values. As described below, the review of the new literature will be integrated with the studies and evidence compiled in the ATSDR Toxicological Profile to develop an updated characterization of health hazards and provide the basis for the derivation of an oral RfD for uranium.

These methods were implemented in accordance with EPA Quality Assurance policies and procedures [Quality Policy Procedures[4] and CIO 2105.0 (formerly 5360.1 A2)[5]]. The results obtained from this systematic compilation of the evidence helped inform the specific aims and key science issues that will be the focus of the assessment (see Section 2.4 below).

2.4. KEY SCIENCE ISSUE

The preliminary literature survey identified the following key scientific issue, which warrants evaluation in this assessment.

- Earlier life stages appear to be more susceptible to uranium-induced musculoskeletal effects in experimental studies (Arzuaga et al., 2015). A toxicological study using SD rats suggests that newborns are more sensitive than sexually mature animals to uranium-induced effects in the skeletal system such as decreased cortical bone diameter and trabecular bone development in the femur (Wade-Gueye et al., 2012). To evaluate potentially increased susceptibility in younger individuals the available epidemiological and animal evidence will be evaluated and synthesized according to the recommendations presented in the EPA's Framework for Assessing Health Risk of Environmental Exposures to Children (Brown et al., 2008; Makris et al., 2008; U.S. EPA, 2006b)

[4]U.S. Environmental Protection Agency Procedures for Quality Policy: https://www.epa.gov/sites/production/files/2015-10/documents/21060.pdf.
[5]Policy and Program Requirements for the Mandatory Agency-Wide Quality System: https://www.epa.gov/sites/production/files/2015-09/documents/epa_order_cio_21050.pdf.

3. OVERALL OBJECTIVES AND SPECIFIC AIMS

The overall objectives of this assessment are to identify adverse health effects and characterize oral exposure-response relationships for noncancer effects from ingestion of uranium to support development of oral toxicity values (RfD). This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for uranium, including consideration of relevant supplemental material. The assessment methods described in this protocol utilize EPA guidelines.[6]

3.1. SPECIFIC AIMS

- Develop a systematic evidence map (SEM) to identify an initial literature inventory of epidemiological studies (i.e., human), toxicological studies (i.e., experimental animal), PBPK models, and supplemental literature pertinent to characterizing the noncancer, health effects of oral uranium exposure, according to the methods for literature search, screening, and inventory described in Section 4. The literature search will build on findings from the ATSDR Toxicological Profile (ATSDR, 2013) and will focus on publications published since the ATSDR literature search was conducted; the current search addresses publications from 2011 to 2022.

    - Epidemiological studies, toxicological studies, and PBPK models are identified for inclusion based on the predefined populations, exposure, comparators, and outcomes (PECO) criteria (referred to as the "problem formulation PECO").

    - Supplemental material content includes: mechanistic studies, including in vivo, in vitro, ex vivo, or in silico models; pharmacokinetic and *absorption, distribution, metabolism, and excretion* (ADME) studies; studies with routes of exposure other than oral; case studies; studies that evaluate exposure and health effects associated with exposure to enriched uranium; studies in non-PECO animal models, such as nonmammalian systems; mixture studies; case reports or case series; records with no original data; and studies that are abstract-only or did not have the full text available.

- Examine whether newly available data indicate a need to update evidence conclusions and (or) toxicity values for principal health systems from the ATSDR Toxicological Profile. Also examine whether newly available data on other health systems support identification of additional uranium health hazards and may plausibly support deriving a toxicity value (RfD) for uranium.

    - Informed by these examinations: (1) develop "assessment PECO" criteria that define the subset of health systems that will be the focus of the systematic review; (2) define the unit(s) of analysis at the level of endpoint or health system for hazard characterization; and

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

(3) identify priority analyses of supplemental material to address the specific aims, uncertainties in hazard characterization, susceptibility, and dose-response analysis.

- If important newer studies on relevant health systems are identified, these findings will be considered along with key studies[7] cited in the ATSDR Toxicological Profile for evidence synthesis/integration and RfD derivation purposes using the methods described below.

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies that meet the assessment PECO criteria.

- Conduct a scientific and technical review of available PBPK models and their use. If a PBPK or PK model is selected for use, the most reliable dose metric will be applied based on analyses of the available dose metrics and the outcomes to which they are being applied.

- Conduct data extraction (summarizing study methods and results) from epidemiological and animal toxicological studies that meet the assessment PECO criteria.

- For the identified health effect categories with important new data, synthesize evidence across studies (including both new and older studies cited in ATSDR Toxicological Profile) within the human and animal evidence streams, using a structured framework to develop and describe weight of evidence judgments across evidence streams and the supporting rationale for those judgments ("evidence integration"). The evidence integration analysis presents inferences and conclusions on human relevance of findings in animals, cross-evidence stream coherence, potentially susceptible populations and lifestages, and other critical inferences supported by mechanistic, or ADME, or PK/PBPK data (e.g., biological plausibility). For health systems examined by ATSDR where important new studies are *not* identified, EPA will seek to base its hazard conclusions on ATSDR's findings.

- For each health effect category, summarize evidence synthesis and evidence integration conclusions in an evidence profile table (see Section 8).

- As supported by the currently available evidence, derive noncancer chronic and subchronic oral reference doses (RfDs) and organ- or system-specific RfDs. Apply pharmacokinetic and dosimetry modeling (possibly including PBPK modeling) to account for interspecies differences, as appropriate. Characterize confidence in any toxicity values that are derived.

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

[7]Key studies cited in the ATSDR Toxicological Profile document are those that appear to provide informative data on relevant health outcomes and may plausibly support deriving noncancer toxicity values for uranium. These will be identified through the study summaries and analysis in the ATSDR Toxicological Profile. Considerations include studies providing data in dose ranges proximate to toxicological findings considered in ATSDR's 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 that were not determined by ATSDR to have major methodological shortcomings.

4. LITERATURE SEARCH AND SCREENING STRATEGIES

The literature search and screening processes described in this section were used to conduct a systematic evidence map (SEM) and identify an initial literature inventory for uranium, using problem formulation PECO criteria (see Section 4.2) and supplemental screening criteria (see Section 4.3) to guide the inclusion of studies. The resulting initial literature inventory was used to develop assessment PECO criteria (described in Section 5). The initial literature search as well as all subsequent literature search updates are conducted using the processes described in this section, and therefore for the purposes of this assessment the literature inventory developed as part of the SEM will be continually updated with new studies as the assessment progresses.

4.1. USE OF EXISTING ASSESSMENTS

The IRIS assessment of uranium will build on findings from the ATSDR Toxicological Profile for Uranium, (ATSDR, 2013) which included an extensive search of the existing literature. The literature search for the current uranium assessment will focus on publications since the ATSDR literature search was conducted (i.e., publications from 2011 to 2022). The United Nations Scientific Committee on the Effects of Atomic Radiation published a review of uranium that included examination of toxicological and epidemiological studies (UNSCEAR, 2017), so this reference will also be consulted to aid in identification of literature. Finally, any unique references from the 1989 U.S. EPA IRIS summary will also be incorporated (U.S. EPA, 1989).

4.2. POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES CRITERIA FOR THE SYSTEMATIC EVIDENCE MAP

PECO (Populations, Exposures, Comparators, and Outcomes) criteria are used to focus the research question(s), search terms, and inclusion/exclusion criteria. The PECO criteria used to develop the SEM are referred to hereafter as the "problem formulation PECO" (see Table 4-1) and were intentionally broad to identify the available evidence in humans and animal models. During problem formulation, exposure to uranium from routes other than ingestion were determined to be out of scope for this assessment.

Table 4-1. Problem formulation populations, exposures, comparators, and outcomes criteria used for the systematic evidence map

PECO element	Evidence
Population	**Human**: Any population and lifestage (occupational or general population, including children and other sensitive populations). Note: Case reports and case series will be tracked during study screening as potentially relevant supplemental material
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposure	Exposure to natural or depleted uranium 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 specific to radiation exposure from uranium will not be included but will be tracked as potentially relevant supplemental information. Oral exposure will be examined. Other exposure routes, such as those that are clearly dermal, or inhalation will be tracked during title and abstract screening as "supplemental information." Animal studies involving exposures to mixtures will be included only if they include an arm with exposure to uranium alone.
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. Any study with a comparison group, control group, or referent group, including: • A comparison group that does not have the disease or outcome of interest (such as a case-control study); or • Any study comparing exposed individuals to unexposed or lower-exposed individuals including: • A comparison group with no exposure to the chemical of interest or exposure below detection limits, or • A comparison group exposed to lower levels of the chemical of interest; or • A comparison group exposed to the chemical of interest for shorter periods of time; or • Any study assessing the association between a continuous measure of exposure and a health outcome; or For studies in which humans are intentionally exposed to the chemical of interest, an individual can serve as their own control.
	Animal: A concurrent control group exposed to vehicle-only treatment and/or untreated control. The control could be a baseline measurement (e.g., acute toxicity studies of mortality) or a repeated measure design.
Outcomes	All noncancer health effect categories. 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.

4.3. SUPPLEMENTAL CONTENT SCREENING CRITERIA

During the literature screening process, studies containing information that may be potentially relevant to the specific aims of the assessment are tagged as supplemental material by category. Because the major health effect categories and units of analysis are not fully identified when screening is initially conducted, the broad tagging categorization, described in Table 4-2, was used to characterize the available evidence base and facilitate further screening and analysis of the supplemental material after PECO refinement. Some studies could emerge as being critically important to the assessment and may need to be evaluated and summarized at the individual study level (e.g., certain MOA or ADME studies), or might be helpful to provide context (e.g., provide hazard evidence from routes or durations of exposure not meeting the PECO), or might not be cited at all in the assessment (e.g., individual studies that contribute to a well-established scientific conclusion). The categories are designed to help the assessment team prioritize citations for consideration in the assessment based on the likelihood of impacting assessment conclusions.

Table 4-2. Categories of potentially relevant supplemental material

Category	Evidence	Typical assessment use
Mechanistic	Studies that do not meet PECO criteria but report measurements that inform the biological or chemical events associated with phenotypic effects related to a health outcome. Experimental design may include in vitro, in vivo (by various routes of exposure; includes all transgenic models), ex vivo, and in silico studies in mammalian and nonmammalian model systems. Studies using new approach methodologies (NAMs, e.g., high-throughput testing strategies, read-across applications) are also categorized here. Studies where the chemical is used as a laboratory reagent (e.g., as a chemical probe used to measure antibody response) generally are not considered relevant and should be excluded).	Prioritized studies of mechanistic endpoints are described in the mechanistic synthesis sections; subsets of the most informative studies may become part of the units of analysis. Mechanistic evidence can provide support for the relevance of animal effects to humans and biological plausibility for evidence integration judgments (including MOA analyses, e.g., using the MOA framework in the U.S. EPA Cancer Guidelines). (U.S. EPA, 2005a)
Enriched uranium	Studies that evaluate health effects caused by the enriched fissionable uranium isotope. Uranium is enriched by processes that concentrate ^{235}U. Enriched uranium is used in nuclear reactor fuel and in nuclear weapons; it is not a subject of this assessment.	Studies of non-PECO animals, exposures, or durations can be summarized to inform evaluations of consistency (e.g., across species, routes, or duration), coherence, or adversity; subsets of the most informative studies may be included in the unit of analysis. These studies may also be used to inform evidence integration judgments of biological plausibility and/or MOA analyses and thus may be summarized as part of the mechanistic evidence synthesis.
Non-PECO animal model (i.e., nonmammalian systems)	Studies reporting outcomes in animal models that meet the outcome criteria but do not meet the "P" in the PECO criteria. Depending on the endpoints measured in these studies, they can also provide mechanistic information (in these cases studies should also be tagged "mechanistic or MOA").	
Non-PECO route of exposure	Epidemiological or animal studies that use a non-PECO route of exposure, (e.g., injection studies or dermal studies if the dermal route is not part of the exposure criteria). This categorization generally does not apply to epidemiological studies where the exposure route is unclear; such studies are considered to meet PECO criteria if the relevant route(s) of exposure are plausible, with exposure being more thoroughly evaluated at later steps.	
Non-PECO exposure duration	For assessments that focus on chronic exposure, acute exposure durations (defined as animal studies of less than 1 d in duration) are generally considered supplemental. In rare cases and for very large	

Category	Evidence	Typical assessment use
	evidence bases, short-term (i.e., less than subchronic) exposure durations could also be categorized as supplemental. Some assessment teams might prefer to keep these studies as PECO relevant and summarize them in the literature inventory rather than track them as supplemental.	
Susceptible populations	Studies that help identify potentially susceptible subgroups, including citations investigating how intrinsic factors such as sex, lifestage, genotype, or other factors (e.g., health status) that can influence toxicity. These are often co-tagged with other supplemental material categories, such as mechanistic or ADME. Studies meeting PECO criteria that also address susceptibility should be co-tagged as supplemental. Susceptibility based on most extrinsic factors, such as increased exposure due to residential proximity to exposure sources, is not considered an indicator of susceptible populations for the purposes of IRIS assessments.	Provides information on factors that might predispose sensitive populations or lifestages to a higher risk of adverse health effects following exposure to the chemical. This information is summarized during evidence integration for each health effect and is considered during dose-response, where it can directly impact modeling decisions.
Classical pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) model studies	**Classical pharmacokinetic or dosimetry model studies:** Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, wherein movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to absorption, distribution, metabolism, and excretion (ADME) data. This category is for papers that provide detailed descriptions of PK models that are not physiologically based PK (PBPK) models. • The data are typically the concentration time course in blood or plasma after oral and or intravenous exposure, but other exposure routes can be described. • A classical PK model might be elaborated from the basic structure applied in standard PK software, for example to include dermal or inhalation exposure, or growth of body mass over time, but otherwise does not use specific tissue volumes or blood flow rates as model parameters.	PBPK and PK model studies are included in the assessment and evaluated for possible use in conducting quantitative extrapolations. PBPK/PK models are categorized as supplemental material with the expectation that each one will be evaluated for applicability to address assessment extrapolation needs and technical conduct. Specialized expertise is required for their evaluation. Standard operating procedures for PBPK/PK model evaluation and the identification, organization, and evaluation of ADME studies are outlined in *An Umbrella Quality Assurance Project Plan (QAPP) for PBPK models* (U.S. EPA, 2018b).

Category	Evidence	Typical assessment use
	• Such models can be used for extrapolation similar to PBPK models, although such use might be more limited. • Note: ADME studies often report classical PK parameters, such as bioavailability (fraction of an oral dose absorbed), volume of distribution, clearance rate, and/or half-life or half-lives. If a paper provides such results only in tables with minimal description of the underlying model or software (i.e., uses standard PK software without elaboration), including "noncompartmental analysis," it should only be listed as a supplemental material ADME study. **Physiologically based pharmacokinetic or mechanistic dosimetry model studies:** PBPK models represent the body as various compartments (e.g., liver, lung, slowly perfused tissue, richly perfused tissue) to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism, and elimination, and thereby estimate concentrations in blood or target tissues. • Usually specific to humans or defined animal species; often a single model structure is calibrated for multiple species. • Some mechanistic dosimetry models might not be compartmental PBPK models but predict dose to the body or specific regions or tissues based on mechanistic data, such as ventilation rate and airway geometry. • A defining characteristic is that key parameters are determined from a substance's physicochemical parameters (e.g., particle size and distribution, octanol-water partition coefficient) and physiological parameters (e.g., ventilation rate, tissue volumes); that is, data that are independent of in vivo ADME data that are otherwise used to estimate model parameters.	
Pharmacokinetic (ADME)	Pharmacokinetic (ADME) studies are primarily controlled experiments in which defined exposures usually occur by intravenous, oral, inhalation, or dermal routes, and the concentration of particles, a	ADME studies are inventoried and prioritized for possible inclusion in an ADME synthesis section on the chemical's PK properties and for conducting quantitative adjustments or extrapolations (e.g., animal to human).

Category	Evidence	Typical assessment use
	chemical, or its metabolites in blood or serum, other body tissues, or excreta are then measured. • These data are used to estimate the amount absorbed (A), distributed to different organs (D), metabolized (M), and/or excreted (E) through urine, breath, or feces. • The most informative studies involve measurements over time such that the initial increase and subsequent concentration decline is observed, preferably at multiple exposure levels. • Data collected from multiple tissues or excreta at a single time point also inform distribution. • ADME data can also be collected from human subjects who have had environmental or workplace exposures that are not quantified or fully defined. However, to be useful such data must involve either repeated measurements over a time period when exposure is known (e.g., is zero because previous exposure ended) or time- and subject-matched tissue or excreta concentrations (e.g., plasma and urine, or maternal and cord blood). • ADME data, especially metabolism and tissue partition coefficient information, can be generated using in vitro model systems. Although in vitro data may not be as definitive as in vivo data, these studies should also be tracked as ADME. For large evidence bases it may be appropriate to separately track the in vitro ADME studies. Note: Studies describing environmental fate and transport or metabolism in bacteria or model systems not applicable to humans or animals should not be tagged.	Specialized expertise in PK is necessary for inventory and prioritization. Standard operating procedures for PBPK/PK model evaluation and the identification, organization, and evaluation of ADME studies is outlined in *An Umbrella Quality Assurance Project Plan (QAPP) for PBPK models* (U.S. EPA, 2018b).
Exposure and biomonitoring (no health outcome)	Exposure characteristic studies include data that are unrelated to toxicological endpoints, but which provide information on exposure sources or measurement properties of the environmental agent (e.g., demonstrate a biomarker of exposure).	This information may be useful for developing exposure criteria for study evaluation or refining problem formulation decisions.

Category	Evidence	Typical assessment use
Mixture studies	Mixture studies that are not considered PECO relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. This categorization generally does not apply to epidemiological studies in which the exposure source might be unclear.	Mixture studies are tracked to help inform cumulative risk analyses, which may provide useful context for risk assessment but fall outside the scope of an IRIS assessment.
Case reports or case series	All study designs such as case reports, case series, and case studies without a comparison group in any setting (e.g., occupational, general population).	Tracking case studies can facilitate awareness of potential human health issues missed by other types of studies during problem formulation.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.	Studies that are tracked for potential use in identifying missing studies, background information, or current scientific opinions (e.g., hypothesized MOAs).
Conference abstracts / proceedings, abstract-only	Records that do not contain sufficient documentation to support study evaluation and data extraction.	

ADME = absorption, distribution, metabolism, and excretion; MOA = mode of action; NAM = new approach methodology; PECO = populations, exposures, comparators, and outcomes; PK = pharmacokinetic; PBPK = physiologically based pharmacokinetic.

4.4. LITERATURE SEARCH STRATEGIES

4.4.1. Database Search Term Development

In accordance with the Uranium IAP (IRIS, 2018), the EPA conducted an in-depth literature search to identify relevant studies published since the completion of the ATSDR literature search. EPA's search strategy for the literature published since 2011 was developed using key terms and words related to the PECO criteria.

4.4.2. Database Searches

The literature search focused on studies published after the period covered by the ATSDR Toxicological Profile for Uranium, covering the period January 2011 to November 2022. No language restrictions were applied. The detailed search strategies are presented in Appendix A. Literature searches were conducted using EPA's Health and Environmental Research Online (HERO) database.[8] The following databases were searched:

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- Scopus
- Toxline[9]

After deduplication in HERO, records were imported into SWIFT Review software (Howard et al., 2016) to identify those references most likely to be applicable to a human health assessment. In brief, SWIFT Review has preset literature search strategies ("filters") developed and applied by information specialists to identify studies more likely to be useful for identifying human health content from those that likely are not (e.g., analytical methods). The filters function like a typical search strategy in which studies are tagged as belonging to a certain filter if the terms appear in title, abstract, keyword or *MeSH*. The applied SWIFT Review filters focused on lines of evidence: human, animal models for human health, and in vitro studies. The details of the search strategies that underlie the filters are available online (Sciome, 2019). Studies not retrieved using these filters were not considered further. Studies that included one or more of the search terms in the title, abstract, keyword, or *MeSH* fields were exported as a RIS (Research Information System) file for screening in SWIFT-Active Screener (Sciome, 2019) and then DistillerSR, as described below in Section 4.5 (Evidence Partners, 2022).

The literature searches are updated annually throughout the assessment's development and review process to identify newly published literature. During this period, the literature search

[8]Health and Environmental Research Online: https://hero.epa.gov/hero/.
[9]The Toxline database was migrated to PubMed after the 2019 literature search update, thus it was not included in subsequent literature search updates.

terms do not change from those used in the initial search and studies are screened according to both the problem formulation PECO criteria. Thus, the SEM literature inventory is updated during the process of developing the draft assessment. The last full literature search update is conducted several months prior to the planned release of the draft document for public comment. Studies identified after peer review begins are only considered for inclusion if they are directly relevant to the assessment PECO criteria and are expected to fundamentally alter the draft assessment conclusions.

4.4.3. Searching Other Sources

The literature search strategy described above was designed to be broad, but like any search strategy, studies can be missed [e.g., cases where the specific chemical is not mentioned in title, abstract, or keyword content; ability to capture "gray" literature (studies not reported in the peer-reviewed literature) that is not indexed in the databases listed above]. Thus, in addition to the database searches, the sources below were used to identify studies that could have been missed based on the database search. Searching of these resources occurs during preparation of the SEM literature inventory. After preparation of the SEM literature inventory, references can be identified during public comment periods, by technical consultants, and during peer review. Records that appeared to meet the problem formulation PECO criteria and that had not been previously identified in the literature search are uploaded into DistillerSR, annotated with respect to source of the record, and screened using the methods described in Section 4.5. Appendix C describes the specific methods and results for searching the sources below. Searching of these sources is summarized to include the source type or name, the search string (when applicable), number of results present within the resource, and the URL (uniform resource locator, when available and applicable). The list of other sources consulted includes:

- Manual review (at the title level) of the reference list from other publicly available final or draft assessments from other non-EPA Agencies (e.g., 2016 UNSCEAR Report to the United Nations General Assembly) or published journal review specifically focused on human health. Reviews can be identified from the database search or from the resources listed in Appendix B.

- European Chemicals Agency (ECHA) registration dossiers to identify data submitted by registrants http://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation.

- EPA ChemView database (U.S. EPA, 2019) to identify unpublished studies, information submitted to EPA under Toxic Substances Control Act (TSCA) Section 4 (chemical testing results), Section 8(d) (health and safety studies), Section 8I (substantial risk of injury to health or the environment notices), and FYI (For Your Information, voluntary documents). Other databases accessible via ChemView include the EPA High Production Volume (HPV) Challenge database and the Toxic Release Inventory database.

- The National Toxicology Program (NTP) database of study results and research projects (https://ntp.niehs.nih.gov/results/index.html).

- The Organization for Economic Cooperation and Development (OECD) Screening Information DataSet (SIDS) High Production Volume Chemicals https://www.echemportal.org/echemportal/substancesearch/page.action?pageID=9

- References identified during public comment periods by technical consultants, and during peer review.

- References that had been previously added to the HERO database for the uranium assessment during the development of the IAP.

4.4.4. Non-Peer-Reviewed Data

IRIS assessments rely mainly on publicly accessible, peer-reviewed studies. However, it is possible that unpublished data directly relevant to the PECO may be identified during assessment development. In these instances, the EPA will try to get permission to make the data publicly available (e.g., in HERO); data that cannot be made publicly available are not used in IRIS assessments. In addition, on rare occasions where unpublished data would be used to support key assessment decisions (e.g., deriving a toxicity value), EPA may obtain external peer review if the owners of the data are willing to have the study details and results made publicly accessible, or if an unpublished report is publicly accessible (or submitted to EPA in a non-confidential manner) (U.S. EPA, 2015). This independent, contractor driven, peer review would include an evaluation of the study similar to that for peer review of a journal publication. The contractor would identify and typically select three scientists knowledgeable in scientific disciplines relevant to the topic as potential peer reviewers. Persons invited to serve as peer reviewers would be screened for conflict of interest. In most instances, the peer review would be conducted by letter review. The study and its related information, if used in the IRIS assessment, would become publicly available. In the assessment, EPA would acknowledge that the document underwent external peer review managed by the EPA, and the names of the peer reviewers would be identified. In certain cases, IRIS will assess the utility of a data analysis of accessible raw data (with descriptive methods) that has undergone rigorous quality assurance/quality control review (e.g., ToxCast/Tox21 data, results of NTP studies not yet published) but that have not yet undergone external peer review.

Unpublished data from personal author communication can supplement a peer-reviewed study as long as the information is made publicly available. If such ancillary information is acquired, it will be documented in the Health Assessment Workspace Collaborative (HAWC) or HERO project page (depending on the nature of the information received).

4.5. LITERATURE SCREENING

The problem formulation PECO criteria described in Section 4.2 are used to determine inclusion or exclusion of a reference as a primary source of health effects data or a published PBPK model. In general, records identified from the literature searches are housed in the HERO system and imported into SWIFT-Active Screener (https://www.sciome.com/swift-activescreener/) for an

initial title and abstract (TIAB) screen using machine learning, followed by import into DistillerSR (Evidence Partners; https://distillercer.com/products/distillersr-systematic-review-software/) for manual TIAB screening and full-text screening by two independent reviewers. One batch of literature search results corresponding to the literature search update was imported directly into DistillerSR for title-abstract screening without the initial import into SWIFT-Active Screener (see Figure 4-1).

In addition to the inclusion of studies that meet the problem formulation PECO criteria, studies containing supplemental material that is potentially relevant to the specific aims are tracked during the screening process. Although not considered to directly meet PECO criteria, these studies are not strictly excluded unless otherwise specified. Unlike studies that meet PECO criteria, supplemental studies may not be subject to systematic review unless specifically defined questions are identified that focus the mechanistic (or other) analysis to inform the specific aims.

4.5.1. Title and Abstract Screening

The studies identified from the searches described above are imported into SWIFT-Active Screener for TIAB screening. SWIFT-Active Screener is a web-based collaborative software application that utilizes active machine learning approaches to reduce the screening effort (Howard et al., 2020). Following a pilot phase to calibrate screening guidance, two screeners independently perform a TIAB screen using a structured form. Studies considered "relevant" or "unclear" based on meeting all problem formulation PECO criteria at the TIAB level are considered for inclusion and advanced to full-text screening. TIAB screening is conducted by two independent reviewers and any screening conflicts are resolved by discussion between the primary screeners with consultation by a third reviewer, if needed. For citations with no abstract, articles are initially screened based on the following: title relevance (title should indicate clear relevance), and page length (articles two pages in length or less are assumed to be conference reports, editorials, or letters). Eligibility status of non-English studies is assessed using the same approach with online translation tools or engagement with a native speaker.

The machine learning screening process is designed to prioritize references that appear to meet the problem formulation PECO criteria or supplemental material content for manual review (i.e., both types of references are screened as "include" for machine learning purposes). Screening continues until SWIFT-Active Screener indicates that it was likely at least 95% of the relevant studies are identified, a percent identification often used to evaluate the performance of machine learning applications and considered comparable to human error rates (Bannach-Brown et al., 2018; Howard et al., 2016; Cohen et al., 2006). Any studies with "partially screened" status at the time of reaching the 95% threshold are then fully screened. Studies identified as meeting the problem formulation PECO criteria, unclear, or supplemental material by SWIFT-Active Screener are then imported into DistillerSR software either for conflict resolution or for an additional round of more specific TIAB tagging (i.e., to separate studies meeting PECO criteria versus supplemental content and to tag the evidence stream or specific type of supplemental content). In DistillerSR,

TIAB screening is conducted manually by two independent reviewers and any screening conflicts resolved by discussion between the primary screeners with consultation by a third reviewer, if needed. Conflicts between screeners in applying the supplemental tags, which primarily occur at the TIAB level, are resolved similarly, erring on the side of over-tagging based on TIAB content.

4.5.2. Full-Text Screening

Full-text references are sought through the EPA's HERO database for studies screened as meeting the problem formulation PECO criteria or "unclear" based on the TIAB screening. Full-text screening occurs in DistillerSR. Full-text copies of these records are retrieved, stored in the HERO database, and independently assessed by two screeners using a structured form in DistillerSR to confirm eligibility. Screening conflicts are resolved by discussion among the primary screeners with consultation by a third reviewer or technical advisor (as needed to resolve any remaining disagreements). Rationales for excluding studies are documented, e.g., study did not meet PECO, full-text not available. Approaches for language translation include online translation tools or engagement of a native speaker. Fee-based translation services for non-English studies are typically reserved for studies that are anticipated as being useful for toxicity value derivation.

4.5.3. Multiple Publications of the Same Data

When there are multiple publications using the same or overlapping data, all publications are included, with one selected for use as the primary study; the others are considered as secondary publications with annotation in HAWC and HERO indicating their relationship to the primary record during data extraction. For epidemiology studies, the primary publication is generally the one with the longest follow-up, the largest number of cases, or the most recent publication date. For animal studies, the primary publication is typically the one with the longest duration of exposure, the largest sample size, or with the outcome(s) most informative to the PECO criteria. For both epidemiology and animal studies, the assessments include relevant data from all publications of the study, although if the same data are reported in more than one study, the data are only extracted once (see Section 7). For corrections, retractions, and other companion documents to the included publications, a similar approach to annotation is taken and the most recently published data are incorporated into the assessments.

4.5.4. Literature Flow Diagram

The results of the screening process are posted on the project page for the assessment in the HERO database (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/2970). Results are also summarized in a literature flow diagram (see Figure 4-1) and interactive HAWC literature trees (where additional sub-tagging beyond what is presented in HERO is documented and visualized, e.g., more details on the nature of mechanistic or ADME studies).

The literature flow diagram represents the results of the original literature searches as well as several updates. The original literature search was conducted preceding the absorption of the

Toxline database into PubMed. Most of the literature was initially screening in SWIFT-Active Screener prior to being screened in DistillerSR. However, the gray literature and one of the literature updates was directly imported into DistillerSR for screening. For large datasets, the use of SWIFT-Active Screener before DistillerSR allowed for more efficient screening via the use of the inherent predictive relevance component. Less than 10% of the references screened at the TIAB screening level made it to the full-text screening phase and of those, only about half (143 out of 257) were deemed PECO relevant. In addition to identifying references that were PECO relevant, the screening process identified nearly 1,000 references that can be categorized as supplemental material.

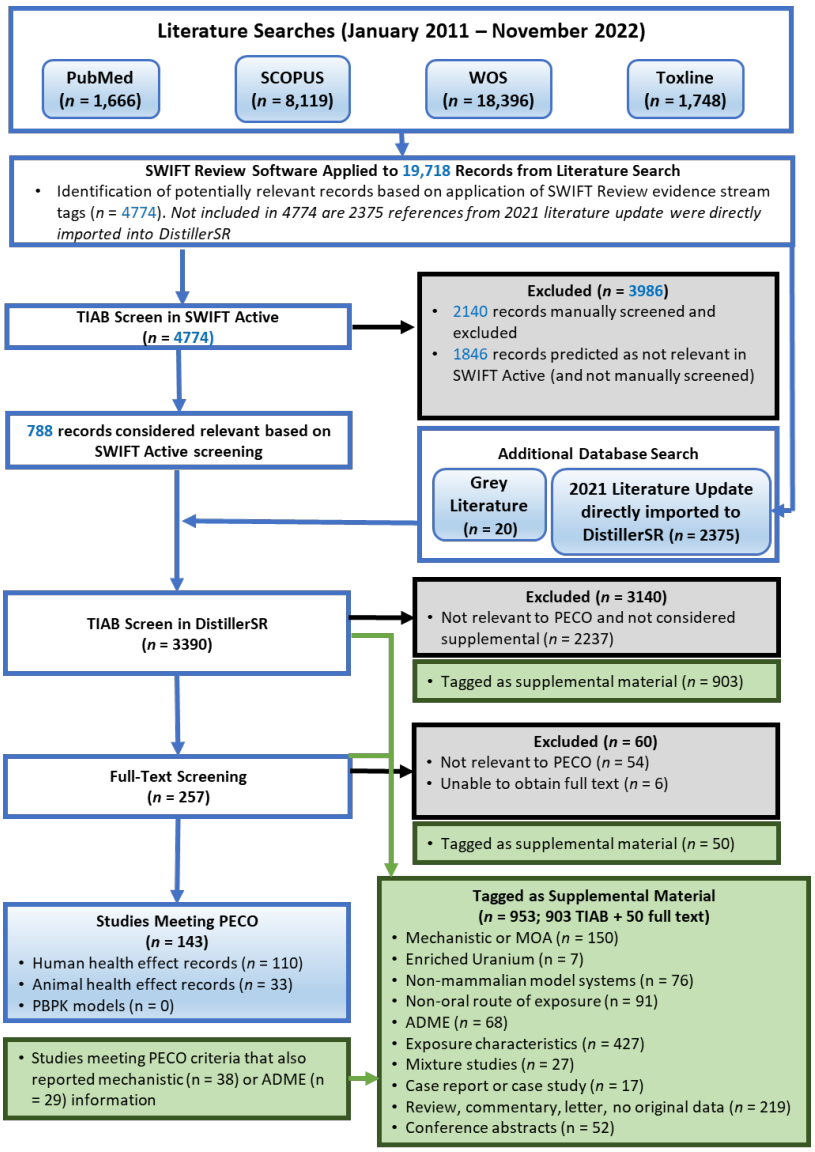


Figure 4-1. IRIS literature search flow diagram for uranium.

The Toxline database was migrated to PubMed after the 2019 literature search update, thus it was not included in subsequent literature search updates.
Tagged as Supplemental Material: these numbers represent the total number of unique citations that were identified; because some citations are given multiple tags, the sum of the individual material tags is greater than the total number of citations.

4.6. LITERATURE INVENTORY

During TIAB or full-text level screening, studies that meet the problem formulation PECO criteria are categorized by evidence type (human, or animal) or category of supplemental information (e.g., mechanistic, ADME, PK/PBPK, reviews). Next, study design details for studies that meet the problem formulation PECO criteria are summarized. The results of this categorization are referred to as the literature inventory and is the key analysis output of the SEM. Literature inventories for PECO-relevant studies were created to develop summary level, sortable lists that include some basic study design information (e.g., study population, exposure information such as doses administered or biomarkers analyzed, age/life stage of exposure, endpoints examined). These literature inventories facilitated subsequent review of individual studies and effects for comparison with the ATSDR Toxicological Profile.

4.6.1. Studies That Meet Problem Formulation PECO Criteria

Human and animal studies that meet the problem formulation PECO criteria after TIAB and full-text review are briefly summarized using structured DistillerSR Hierarchical Data Extraction forms to create literature evidence inventories, which were used to display the extent and nature of the available evidence (see Section 4.2). The literature inventories are used to inform the assessment PECO criteria and evaluation plan. Studies were extracted by one team member and the extracted data were qualitatively reviewed by at least one other team member. The extraction fields in the forms are available in Microsoft (MS) Excel format upon request. See https://www.epa.gov/iris/forms/contact-us-about-iris for requests. The literature inventories were exported from Distiller SR in MS Excel format.

For experimental animal studies, which are typically studies in rodents, the following information is captured: chemical form, study type (acute [<24 hours], short term [<7 days], short term [7–27 days], subchronic [28–90 days], chronic [>90 days[10]] and developmental, which includes multigeneration studies), duration of treatment, route, species, strain, sex, dose or concentration levels tested, dose units, health system and specific endpoints assessed, and a summary of the results reported in the study.

For epidemiological studies the following information was summarized: uranium compound, population type (e.g., residential/school based, occupational, other), sex, study design (e.g., cross-sectional, cohort, case-control, ecological, case-report, controlled trial, meta-analysis),

[10]EPA considers chronic exposure to be more than approximately 10% of the life span in humans. For typical laboratory rodent species, this can lead to consideration of exposure durations of approximately 90 days to 2 years. However, studies in duration of 1–2 years are typical of what is considered representative of chronic exposure rather than durations just over 90 days.

study location, life stage (adults, children/infants), exposure measurement (air sampling, occupational history, other), biomonitoring matrix, health system studied, endpoints assessed, and a brief description of the observed effects. More detail on the process of summarizing studies is presented in Sections 5 and 7.

4.6.2. Organizational Approach for Supplemental Material

The results of the supplemental material tagging conducted in DistillerSR are imported into the literature review module in HAWC, where more granular sub-tagging within a type of supplemental material content category is conducted. A publication can have multiple tags, including PECO studies that also contain supplemental material. The degree of sub-tagging depends on the extent of content for a given type of supplemental material and needs of the assessment with respect to developing human health hazard conclusions and derivation of toxicity values. Tagging judgments in DistillerSR and HAWC are made by one assessment member and confirmed during the screening step by another member of the assessment team. The overall approach for supplemental material content is presented in Figure 4-2, with details on subtagging presented in the following sections under the specific type of supplemental content (see Table 4-2).

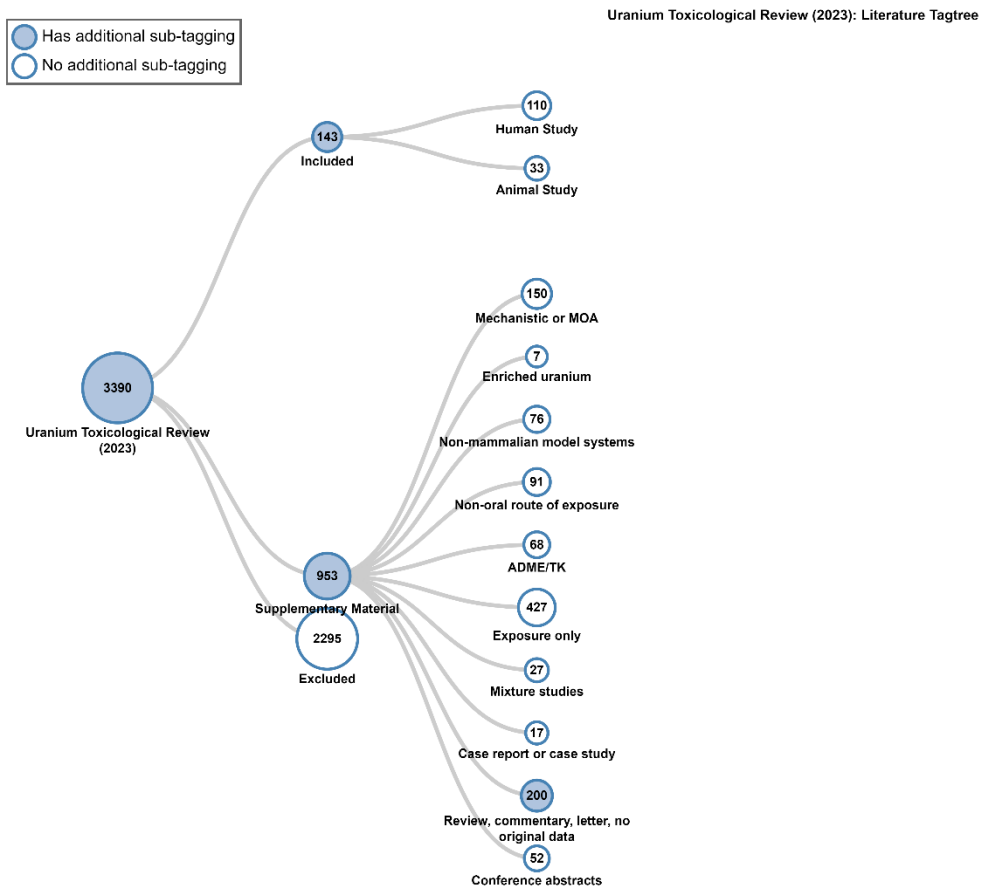


Figure 4-2. Visual summary of approach for tagging major categories of supplemental material. See interactive HAWC link: Uranium Literature Tagtree.

Organization of Mechanistic Information

If a mechanistic analysis is considered necessary to assist with the interpretation and integration of the epidemiological and experimental evidence of a specific hazard or health effect, EPA will rely on previously published reviews and analyses to identify potential pathways of toxicity and identify critical studies through forward/backward searches. To facilitate this analysis, publications tagged as reviews or commentaries that included a mechanistic analysis were sub-tagged according to health system/target tissue. With respect to health system/target tissue tagging, the following organizational categories were applied: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematologic, hepatic, immune, metabolic, musculoskeletal/connective tissue, multi-system, nervous, ocular, reproductive, respiratory, sensory, urinary, or whole body. The same publication could have multiple tags and studies that address broad physiological processes were tagged as systemic.

Depending on the extent of evidence for a given health system target tissue/cellular response category (e.g., liver, nervous system, immune), an additional level of sub-tagging describing the biological processes presented in the studies may be utilized. This level of sub-

tagging is based on the content of the available studies (e.g., specific receptor interaction, inflammation pathway).

5. REFINED PROBLEM FORMULATION AND ASSESSMENT APPROACH

The primary purpose of this step is to provide further specification to the assessment methods based on characterization of the extent and nature of the evidence identified from the literature inventory. This includes refinements to PECO criteria and defining the unit(s) of analysis for health endpoints/outcomes during evidence synthesis, and presenting analysis approaches for mechanistic, ADME or other types of supplemental material content. A unit of analysis is an outcome or group of related outcomes within a health effect category that are considered together during evidence synthesis (see Section 8). The systematic review will focus on the health outcome categories that appear to have sufficient information available to support hazard identification, based upon the availability of animal and human studies as cited in ATSDR Toxicological Profile (ATSDR, 2013), and the updated literature search conducted by EPA.

5.1. COMPARISON WITH ATSDR TOXICOLOGICAL PROFILE (2013)

In this reassessment, EPA builds on the scientific review and analysis from the ATSDR Toxicological Profile for Uranium (ATSDR, 2013). The following categories of health effects of oral uranium exposure were identified in ATSDR 2013: urinary, hepatic, neurological, reproductive, and developmental.[11] While ATSDR 2013 did not identify the following as hazards, they also considered uranium-induced body weight changes, mortality, metabolic alterations, and effects on the endocrine, musculoskeletal, cardiovascular, gastrointestinal, hematological, immune, and respiratory systems.

This protocol examines newly available literature since the publishing of ATSDR 2013. The newly available literature as determined by the IRIS literature search (i.e., studies that met problem formulation PECO criteria) was examined to determine whether the data warranted a revision of ATSDR health effect categories and their hazard findings or identified additional noncancer health effect categories for examination in the IRIS assessment. The proposed approach to compare ATSDR 2013 with the IRIS literature search results is shown in Figure 5-1:

[11]These were identified by EPA based on the "Summary of Health Effects" section of the Profile (see Section 1.2) and were confirmed by ATSDR staff in a meeting with EPA in August 2023. Furthermore, urinary, and developmental effects of uranium were considered the bases for MRL values for intermediate and acute duration oral exposures, respectively (ATSDR, 2013).

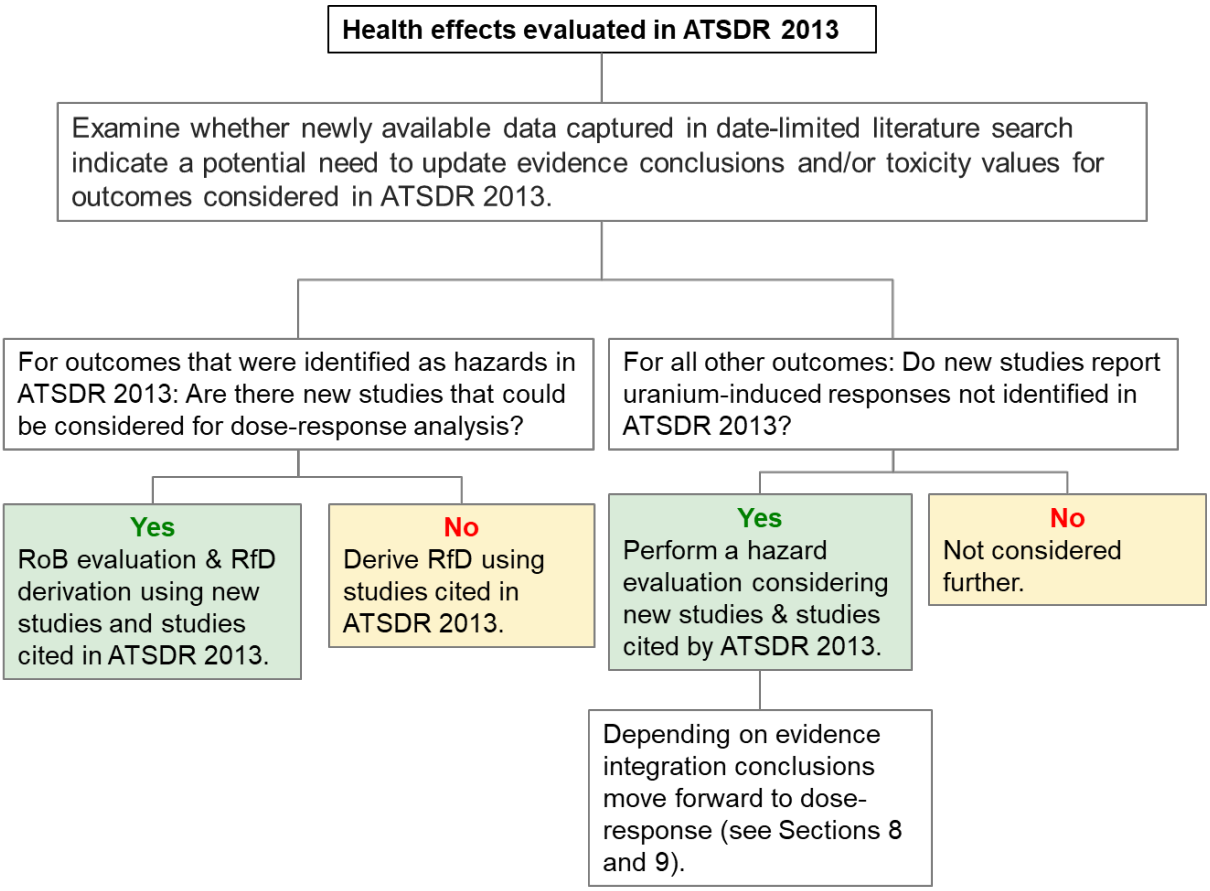


Figure 5-1. Approach and decision tree used to compare ATSDR 2013 (ATSDR, 2013) with IRIS literature search results.

PECO-relevant studies were examined by two reviewers who compared the IRIS literature search results with ATSDR 2013 conclusions for each health effect category. The initial examination was done independently, followed by discussion. Expert judgment from the reviewers was used to look for associations between uranium exposure and health effects, noting potential study limitations. Appendix D contains the review for each health effect category: summary of the ATSDR 2013 conclusion; description of the new epidemiological data; and description of the new toxicological data.

As described in Appendix D and Table 5-1 below, health effect categories that will undergo full evaluation by EPA according to the methods described in Sections 6, 7, 8, and 9 are: cardiovascular, endocrine, immune, musculoskeletal, and respiratory effects. Health systems with hazards previously identified by ATSDR 2013 that will *not* undergo hazard re-evaluation by EPA but will be considered for dose-response analysis include: developmental, hepatic, neurological, reproductive, and urinary effects.

Table 5-1. Health effect categories from ATSDR 2013 (ATSDR, 2013) selected for hazard ID, dose response, or no further consideration

Hazard evaluation	
Update ATSDR Toxicological Profile hazard conclusions by performing new hazard identification for health effect categories, using studies from both the IRIS literature search and ATSDR 2013.	• Cardiovascular • Endocrine • Immune • Musculoskeletal • Respiratory
Dose-response	
Accept ATSDR Toxicological Profile hazard conclusion[a] and conduct dose-response analysis for health effect categories using studies from both the IRIS literature search and ATSDR 2013.	• Developmental • Hepatic • Neurological • Reproductive • Urinary
No further consideration	
Accept ATSDR Toxicological Profile conclusion with no further consideration for health effect categories.	• Body weight • Gastrointestinal • Hematological • Metabolic

[a]For the purposes of this IRIS Assessment, the evidence for the health effects identified as hazards by ATSDR 2013 were considered to support an evidence integration judgment of at least "*evidence indicates [likely],*" as defined in Section 8.

Because of a lack of evidence in epidemiological studies and/or lack of evidence from experimental studies, EPA will not consider the following health effect categories effects for hazard evaluation or dose-response (see Table 5-1): body weight, due to new animal studies, the majority of which reported no effect, and no new epidemiological studies (see Appendix D.1.); gastrointestinal, due to no new animal studies and two epidemiological studies that did not show a negative effect (see Appendix D.5.); hematological, due to two animal studies reporting null evidence and two epidemiological studies with potential limitations (see Appendix D.6.); or metabolic, due to no new animal studies and only one new epidemiological study that observed an association (see Appendix D.9.). EPA will continue to monitor the literature and these decisions will be re-evaluated when the literature search is annually updated.

5.2. REFINEMENTS TO PECO CRITERIA

The problem formulation PECO criteria were refined based on the analysis of the literature inventory and comparison with the ATSDR Toxicological Profile to develop the assessment PECO criteria (see Table 5-2 with changes underlined). The assessment PECO criteria focused on the health systems listed below which EPA determined to have new available data that indicated a need to revise hazard evaluation conclusions or derive new toxicity values (see Appendix D, and

Table 5-1). The hazards listed from ATSDR 2013 were triaged for evaluation in the IRIS assessment as follows:

- For the hazards previously identified by ATSDR (2013) (urinary, hepatic, neurological, reproductive, and developmental), EPA considered the evidence to be sufficient to support reference value derivation. For the purposes of this IRIS Assessment, the evidence for the health effects identified as hazards by ATSDR 2013 were considered to support an evidence integration judgment of at least "evidence indicates [likely]," as defined in Section 8. EPA will not conduct a de novo hazard synthesize the evidence for these outcomes. EPA will perform study evaluations (see Section 6) on the studies considered for dose response, based on the considerations in Section 9, from both the IRIS literature search and studies cited in (ATSDR, 2013) (see Table 5-1).

  For other health effect categories, if the newly available evidence from PECO-relevant toxicological and epidemiological studies suggests a need to update hazard conclusions, EPA will perform a complete evaluation of the studies identified in the IRIS literature search plus the studies cited in (ATSDR, 2013). In such cases, both new studies and the studies cited in ATSDR (2013) will be summarized and evaluated jointly using the methods described in Sections 6, 7, 8, and 9 (see Table 5-1).

Table 5-2. Assessment populations, exposures, comparators, and outcomes criteria for uranium

PECO element	Evidence
Population	**Human**: Any population and lifestage (occupational or general population, including children and other sensitive populations). Note: Case reports and case series will be tracked during study screening as potentially relevant supplemental material.
	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 specific to radiation exposure from uranium will not be included but will be tracked as potentially relevant supplemental information. Oral exposure will be examined. Other exposure routes, such as those that are clearly dermal, or inhalation will be tracked during title and abstract screening as "supplemental information." Animal studies involving exposures to mixtures will be included only if they include an arm with exposure to uranium alone.
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. Any study with a comparison group, control group, or referent group, including: • A comparison group that does not have the disease or outcome of interest (such as a case-control study); or • Any study comparing exposed individuals to unexposed or lower-exposed individuals including: • A comparison group with no exposure to the chemical of interest or exposure below detection limits, or • A comparison group exposed to lower levels of the chemical of interest; or • A comparison group exposed to the chemical of interest for shorter periods of time; or • Any study assessing the association between a continuous measure of exposure and a health outcome; or • For studies in which humans are intentionally exposed to the chemical of interest, an individual can serve as their own control.
	Animal: A concurrent control group exposed to vehicle-only treatment and/or untreated control. The control could be a baseline measurement (e.g., acute toxicity studies of mortality) or a repeated measure design.
Outcomes	Outcomes considered for hazard evaluation by EPA: cardiovascular, endocrine, immune, musculoskeletal, and respiratory effects. These outcomes may also be considered for dose response after evidence synthesis and integration (see Sections 8 and 9) Outcomes for which EPA will rely on ATSDR's hazard conclusions but will be considered for dose-response analysis: developmental, hepatic, neurological, reproductive, and urinary effects. 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.

5.2.1. Other Exclusions Based on Full-Text Content

In addition to failure to meet PECO criteria (described above), epidemiological and toxicological studies may be excluded at the full-text level due to critical reporting limitations. Reporting limitations can be identified during full-text screening but are more commonly identified during subsequent phases of the assessment (e.g., literature inventory, data extraction, study evaluation). Regardless of when the limitation is identified, exclusions based on full-text content are documented at the level of full-text exclusions in literature flow diagrams with a rationale of "critical reporting limitation." Critical reporting information for different study types are summarized below. For each piece of information, if the information can be inferred (when not directly stated) for an exposure/endpoint combination, the study should be included.

Epidemiology studies

- Sample size
- Exposure characterization and/or measurement method
- Outcome ascertainment method
- Study design

Animal studies

- Species
- Test article name
- Levels and duration of exposure
- Route of exposure
- Quantitative or qualitative (e.g., photomicrographs; author-reported lack of an effect on the outcome) results for at least one endpoint of interest

5.3. UNITS OF ANALYSES FOR DEVELOPING EVIDENCE SYNTHESIS AND INTEGRATION JUDGMENTS FOR HEALTH EFFECT CATEGORIES

The planned units of analysis based on health systems identified in the assessment PECO are summarized in Tables 5-3 and 5-4. General considerations for defining the units of analysis are presented in the IRIS Handbook. For dose-response analysis units of analysis captured in Table 5-3 will be analyzed as described in Section 9. For hazard evaluation each unit of analysis captured in Table 5-4 is initially synthesized and judged separately within an evidence stream (see Section 8.1). Depending on the specific health endpoint or outcome, PK data, mechanistic information, and other supporting evidence (e.g., from studies of non-PECO routes of exposure) may be included in a unit of analysis.

The units of analysis can also include or be framed to focus on precursor events (e.g., biomarkers). Evidence integration judgments focus on the stronger within evidence stream synthesis when multiple units of analysis are synthesized. The evidence synthesis judgments are used alongside other key considerations (i.e., human relevance of findings in animal evidence, coherence across evidence streams, information on susceptible populations or lifestages, and other critical inferences that draw on mechanistic evidence) to draw an overall evidence integration judgment for each health effect category or more granular health outcome grouping (see Section 8.2).

Table 5-3. Dose-response: Health effect categories and human and animal evidence unit of analysis endpoint groupings for dose response

Health effect categories for dose response	Units of analysis for dose-response analysis (each bullet represents a unit of analysis)	
	Human evidence	**Animal evidence**
Developmental	• Pregnancy outcomes • Congenital malformations	• Fetal viability/survival or other birth parameters (e.g., resorptions, number of pups per litter) • Fetal/pup growth (e.g., weight or length) • Note: An analysis of dam health (e.g., weight gain, food consumption) is also conducted to support conclusions of specificity of the effects as being developmental (versus derivative of maternal toxicity)
Hepatic	• Liver disease	• Organ weight • Clinical measures of liver function (including liver enzymes) • Clinical measures of biliary function • Organ morphology/histopathology
Neurological	• Cognitive function • Brain disorders	• Learning/memory • Brain morphology/histopathology • Neurodegenerative disease • Neurotransmitter levels/function • Organ weights
Reproductive	• Semen quality	• Organ morphology/histopathology • Developmental measures • Reproductive hormone measures • Functional measures
Urinary	• Kidney disease • Markers of kidney function	• Urinary and serum markers of renal disease/function • Organ weights • Organ morphology/histopathology

Table 5-4. Hazard evaluation: Health effect categories and human and animal evidence unit of analysis endpoint groupings for hazard evaluation

Health effect categories for evidence integration	Units of analysis for evidence synthesis that inform evidence integration (each bullet represents a unit of analysis)	
	Human evidence	**Animal evidence**
Cardiovascular	• Cardiovascular disease • Blood pressure	• Blood and arteriole pressure, peripheral resistance, and other measures of cardiovascular function • Heart and vessel morphology and histopathology • Organ weights
Endocrine	• Thyroid hormone measures • Diabetes	• Hormone measures • Organ morphology/histopathology • Organ weights
Immune	• Autoimmune disease and measures • Immunotoxicity	• Clinical endpoints (e.g., immune cell counts/responses) • Organ weights • Organ morphology/histopathology • Immune functional measures
Musculoskeletal	• Musculoskeletal conditions • Muscle and bone health	• Muscular & skeletal morphology/histopathology • Clinical markers of musculoskeletal disease • Parameters/measures of bone development and function
Respiratory	• Respiratory disease • Pulmonary symptoms	• Organ weights • Organ morphology/histopathology • Functional measures

5.4. CONSIDERATIONS OF SUPPLEMENTAL MATERIAL

5.4.1. Noncancer MOA Mechanistic Information

For uranium, evaluating individual mechanistic studies is not anticipated to be critical for this noncancer assessment given the extent of the epidemiological and experimental animal evidence for included outcomes well as the availability of earlier reviews that include mechanistic analyses (Ma et al., 2020; Shaki et al., 2019; IRIS, 2018; Yue et al., 2018). For mechanistic information, this assessment will primarily rely on other published sources, such as public health agency reports and expert review articles (see Section 4.6.2).

5.4.2. ADME and PK/PBPK Model Information

Studies containing ADME and PK/PBPK content were screened and tagged as described in Section 4.5. Oral pharmacokinetics of uranium compounds are the primary focus since the current

assessment focuses on the derivation of oral toxicity values. However, pharmacokinetic studies from alternate routes of exposure can still inform various aspects of ADME and are also considered. The ATSDR Toxicological Profile identified two PK/PBPK models for inhalation exposure (ICRP, 1995, 1993) and oral exposure (1995); (ATSDR, 2013). These models do not include dosimetric adjustments from animals to humans, and therefore could not be used for human extrapolation. The ATSDR Toxicological Profile did not incorporate these models into their dose-response analysis. Furthermore, no new PK/PBPK models were identified in the date-limited IRIS literature search. These decisions will be re-evaluated when the literature search is annually updated.

5.4.3. Other Supplemental Material Content

Structured approaches to organize evidence were not developed for the supplemental material. Instead, the tagged material was reviewed during preparation of the draft to determine whether the available studies addressed specific uncertainties of the health study evidence base, inform susceptibility conclusions, and ensure completeness of identifying primary data papers most pertinent to the assessment.

- Titles of studies tagged as exposure-only are reviewed to see if they provided information pertinent to establish study evaluation considerations for the exposure domain.

- Titles of review articles are reviewed to identify those that are directly pertinent to the scope of the assessment. The reference lists of such reviews are scanned to identify primary data studies that might have been missed from database search queries. The reviews may also be used to provide perspective on interpretation of foundational science cited in the assessment.

- Other types of supplemental material did not undergo additional analysis because the information was not considered likely to impact toxicity value development (including application of uncertainty factors). The specific categories are case reports, enriched uranium, nonmammalian model systems, mixtures, or conference abstracts.

6. STUDY EVALUATION (RISK OF BIAS AND SENSITIVITY)

The general approach for evaluating primary health effect studies that meet assessment PECO criteria is described in Section 6.1. Instructional and informational materials for study evaluations are available at https://hawcprd.epa.gov/assessment/100000039/. The approach is conceptually the same for epidemiology, animal toxicology, and in vitro studies but the application specifics differ; thus, they are described separately in Sections 6.2, 6.3, and 6.4, respectively. Any PBPK models used in the assessment are evaluated using methods described in the Quality Assurance Project Plan for PBPK models (U.S. EPA, 2018b), which is summarized below (see Section 6.5).

6.1. STUDY EVALUATION OVERVIEW FOR HEALTH EFFECT STUDIES

The IRIS Program uses a domain-based approach to evaluate studies. Key concerns for the review of epidemiology and animal toxicology studies are potential bias (factors that affect the magnitude or direction of an effect in either direction) and insensitivity (factors that limit the ability of a study to detect a true effect; low sensitivity is a bias toward the null when an effect exists). The study evaluations are aimed at discerning the expected magnitude of any identified limitations (focusing on limitations that could substantively change a result), considering the expected direction of the bias. The study evaluation approach is designed to address a range of study designs, health effects, and chemicals. The general approach for reaching an overall judgment regarding confidence in the reliability of the results is illustrated in Figure 6-1.

(a) Individual evaluation domains

Epidemiology	Animal	In vitro
• Exposure measurement • Outcome ascertainment • Participant selection • Confounding • Analysis • Selective reporting • Sensitivity	• Allocation • Observational bias/blinding • Confounding • Attrition • Chemical administration and characterization • Endpoint measurement • Results presentation • Selective reporting • Sensitivity	• Observational bias/blinding • Variable control • Selective reporting • Chemical administration and characterization • Endpoint measurement • Results presentation • Sensitivity

(b) Domain level judgements and overall study rating

Domain judgments

Judgment	Interpretation
Good	Appropriate study conduct relating to the domain and minor deficiencies not expected to influence results.
Adequate	A study that may have some limitations relating to the domain, but they are not likely to be severe or to have a notable impact on results.
Deficient	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
Critically Deficient	A serious flaw identified that makes the observed effect(s) uninterpretable. Studies with a critical deficiency are considered "uninformative" overall.

Overall study rating for an outcome

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted but they are unlikely to have a significant impact on results.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results uninterpretable but may be used to highlight possible research gaps.

Figure 6-1. Overview of Integrated Risk Information System study evaluation approach. (a) individual evaluation domains organized by evidence type, and (b) individual evaluation domains judgments and definitions for overall ratings (i.e., domain and overall judgments are performed on an outcome-specific basis).

To calibrate the assessment-specific considerations, the study evaluation process includes a pilot phase to assess and refine the evaluation process. Following this pilot, at least two reviewers

independently evaluate studies to identify characteristics that bear on the informativeness (i.e., validity and sensitivity) of the results. The independent reviewers use structured web-based forms for study evaluation housed within the EPA's version of HAWC to record separate judgments for each domain and the overall study for each outcome and unit of analysis, to reach consensus between reviewers, and when necessary, resolve differences by discussion between the reviewers or consultation with additional independent reviewers. As reviewers examine a group of studies, additional chemical-specific knowledge or methodological concerns could emerge, and a second pass of all pertinent studies might become necessary.

In general, considerations for reviewing a study with regard to its conduct for specific health outcomes are based on considerations presented in the IRIS Handbook (U.S. EPA, 2022a) and use of existing guideline documents when available, including EPA guidelines for carcinogenicity, neurotoxicity, reproductive toxicity, and developmental toxicity (U.S. EPA, 2005a, 1998, 1996, 1991).

Authors might be queried to obtain critical information, particularly that involving missing key study design or results information, or additional analyses that could address potential study limitations. During study evaluation, the decision on whether to seek missing information focuses on information that could result in a re-evaluation of the overall study confidence for an outcome. Any information obtained through personal correspondence with the authors must be made public to be used in the assessment. If this information cannot be obtained, the study will be rated Deficient in the "Chemical administration and characterization" domain and Low confidence overall. Outreach to study authors is documented in HAWC and considered unsuccessful if researchers do not respond to an email or phone request within 1 month of the attempt to contact. Only information or data that can be made publicly available (e.g., within HAWC or HERO) will be considered.

When evaluating studies that examine more than one outcome, the evaluation process is explicitly conducted at the individual outcome level within the study. Thus, the same study may have different outcome domain judgments for different outcomes. These measures could still be grouped for evidence synthesis.

During review, for each evaluation domain, reviewers reach a consensus judgment of *good*, *adequate, deficient, not reported*, or *critically deficient*. If a consensus is not reached, a third reviewer performs conflict resolution. It is important to emphasize that evaluations are performed in the context of the study's utility for identifying individual hazards. Limitations specific to the usability of the study for dose-response analysis are useful to note and applicable to selecting studies for that purpose (see Section 9), but they do not contribute to the study confidence classifications. These four categories are applied to each evaluation domain for each outcome considered within a study, as follows:

- *Good* represents a judgment that the study was conducted appropriately in relation to the evaluation domain, and any minor deficiencies noted are not expected to influence the study results or interpretation of the study findings.

- *Adequate* indicates a judgment that methodological limitations related to the evaluation domain are (or are likely to be) present, but those limitations are unlikely to be severe or to notably impact the study results or interpretation of the study findings.

- *Deficient* denotes identified biases or deficiencies interpreted as likely to have had a notable impact on the results, or that limit interpretation of the study findings.

- *Not reported* indicates the information necessary to evaluate the domain question was not available in the study. Depending on the expected impact, the domain may be interpreted as adequate or deficient for the purposes of the study confidence rating.

- *Critically deficient* reflects a judgment that the study conduct relating to the evaluation domain introduced a serious flaw that is interpreted to be the primary driver of any observed effect(s) or makes the study uninterpretable. Studies with critically deficient judgments in any evaluation domain are almost always classified as overall *uninformative* for the relevant outcome(s).

Once the evaluation domains are rated, the identified strengths and limitations are considered collectively to reach a study confidence classification of *high*, *medium*, or *low* confidence, or *uninformative* for each specific health outcome(s). This classification is based on the reviewer judgments across the evaluation domains and considers the likely impact that the noted deficiencies in bias and sensitivity have on the outcome-specific results. There are no pre-defined weights for the domains, and the reviewers are responsible for applying expert judgment to make this determination. The study confidence classifications, which reflect a consensus judgment between reviewers, are defined as follows:

1) *High confidence*: No notable deficiencies or concerns were identified; the potential for bias is unlikely or minimal, and the study used sensitive methodology. *High* confidence studies generally reflect judgments of good across all or most evaluation domains.

2) *Medium confidence*: Possible deficiencies or concerns were identified, but the limitations are unlikely to have a significant impact on the study results or their interpretation. Generally, *medium c*onfidence studies include adequate or good judgments across most domains, with the impact of any identified limitation not being judged as severe.

3) *Low confidence*: Deficiencies or concerns are identified, and the potential for bias or inadequate sensitivity is expected to have a significant impact on the study results or their interpretation. Typically, *low* confidence studies have a deficient evaluation for one or more domains, although some *medium* confidence studies might have a deficient rating in domain(s) considered to have less influence on the magnitude or direction of effect estimates. Low confidence results are given less weight compared to *high* or *medium* confidence results during evidence synthesis and integration (see Sections 7 and 8) and are generally not used as the primary sources of information for hazard identification or derivation of toxicity values unless they are the only studies available (in which case, this significant uncertainty would be emphasized during dose-response analysis). Studies rated

low confidence only because of sensitivity concerns are asterisked or otherwise noted because they often require additional consideration during evidence synthesis. Effects observed in studies that are biased toward the null may increase confidence in the results, assuming the study is otherwise well-conducted (see Section 8).

4) *Uninformative*: Serious flaw(s) are judged to make the study results uninterpretable for use in the assessment. Studies with critically deficient judgments in any evaluation domain are almost always rated uninformative. Studies with multiple deficient judgments across domains may also be considered *uninformative*. Given that the findings of interest are considered uninterpretable based on the identified flaws (see above definition of *critically deficient*) and do not provide information of use to assessment interpretations, these studies have no impact on evidence synthesis or integration judgments and are not usable for dose-response analyses but may be used to highlight research gaps.

As previously noted, study evaluation determinations reached by each reviewer and the consensus judgment between reviewers are recorded in HAWC. Final study evaluations housed in HAWC are made available when the draft is publicly released. The study confidence classifications and their rationales are carried forward and considered as part of evidence synthesis (see Section 8) to help interpret the results across studies.

6.2. EPIDEMIOLOGY STUDY EVALUATION

Evaluation of epidemiology studies of health effects to assess risk of bias and study sensitivity are conducted for the following domains: exposure measurement, outcome ascertainment, participant selection, potential confounding, analysis, study sensitivity, and selective reporting. Bias can result in false positives and negatives, whereas study sensitivity is typically concerned with identifying the latter.

The principles and framework used for evaluating epidemiology studies are adapted from the principles in the Cochrane Risk of Bias in Nonrandomized Studies of Interventions [ROBINS-I; (Sterne et al., 2016)], modified to address environmental and occupational exposures. Core and prompting questions, presented in Table 6-1, are used to collect information to guide evaluation of each domain. Core questions represent key concepts while the prompting questions help the reviewer focus on relevant details under each key domain. Exposure- and outcome-specific criteria to use during study evaluation are developed using the core and prompting questions and refined during a pilot phase with engagement from topic-specific experts.

Table 6-1. Questions to guide the development of criteria for each domain in epidemiology studies

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
<u>Exposure measurement</u> Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	For all: • Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency, and duration of exposure? • Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? • Was the exposure measurement likely to be affected by knowledge of the outcome? • Was the exposure measurement likely to be affected by the presence of the outcome (i.e., reverse causality)? For case-control studies of occupational exposures: • Is exposure based on a comprehensive job history describing tasks, setting, period, and use of specific materials? For biomarkers of exposure, general population: • Is a standard assay used? What are the intra- and interassay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? • What exposure period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between exposure measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurements? If potential for bias is a concern, is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good** • Valid exposure assessment methods used, which represent the etiologically relevant period of interest. • Exposure misclassification is expected to be minimal. **Adequate** • Valid exposure assessment methods used, which represent the etiologically relevant period of interest. • Exposure misclassification could exist but is not expected to greatly change the effect estimate. **Deficient** • Valid exposure assessment methods used, which represent the etiologically relevant time period of interest. Specific knowledge about the exposure and outcome raises concerns about reverse causality, but whether it is influencing the effect estimate is uncertain. • Exposed groups are expected to contain a notable proportion of unexposed or minimally exposed individuals, the method did not capture important temporal or spatial variation, or other evidence of exposure misclassification would be expected to notably change the effect estimate. **Critically deficient** • Exposure measurement does not characterize the etiologically relevant period of exposure or is not valid. • Evidence exists that reverse causality is very likely to account for the observed association. • Exposure measurement was not independent of outcome status.

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
<u>Outcome ascertainment</u> Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	For all: • Is outcome ascertainment likely affected by knowledge, or presence, of exposure (e.g., consider access to healthcare, if based on self-reported history of diagnosis)? For case-control studies: • Is the comparison group without the outcome (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? For mortality measures: • How well does cause-of-death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? For diagnosis of disease measures: • Is the diagnosis based on standard clinical criteria? If it is based on self-report of the diagnosis, what is the validity of this measure? For laboratory-based measures (e.g., hormone levels): • Is a standard assay used? Does the assay have an acceptable level of interassay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population?	Is there a concern that any outcome misclassification is nondifferential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good** • High certainty in the outcome definition (i.e., specificity and sensitivity), minimal concerns with respect to misclassification. • Assessment instrument was validated in a population comparable to the one from which the study group was selected. **Adequate** • Moderate confidence that outcome definition was specific and sensitive, some uncertainty with respect to misclassification but not expected to greatly change the effect estimate. • Assessment instrument was validated but not necessarily in a population comparable to the study group. **Deficient** • Outcome definition was not specific or sensitive. • Uncertainty regarding validity of assessment instrument. • Critically deficient • Invalid/insensitive marker of outcome. • Outcome ascertainment is very likely to be affected by knowledge of, or presence of, exposure. Note: Lack of blinding should not be automatically construed to be *critically deficient*.

<u>Participant selection</u> Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?	For longitudinal cohort: • Did participants volunteer for the cohort on the basis of knowledge of exposure or preclinical disease symptoms? Was entry into, or continuation in, the cohort related to exposure and outcome? For occupational cohort: • Did entry into the cohort begin with the start of the exposure? • Was follow-up or outcome assessment incomplete, and if so, was follow-up related to both exposure and outcome status? • Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")? For case-control study: • Were controls representative of population and periods from which cases were drawn? • Are hospital controls selected from a group whose reason for admission is independent of exposure? • Could recruitment strategies, eligibility criteria, or participation rates result in differential participation relating to both disease and exposure? For population-based survey: • Was recruitment based on advertisement to people with knowledge of exposure, outcome, and hypothesis?	Were differences in participant enrollment and follow-up evaluated to assess bias? If potential for bias is a concern, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)? Were appropriate analyses performed to address changing exposures over time relative to symptoms? Is there a comparison of participants and nonparticipants to address whether differential selection or study retention/continuation is likely?	**Good** • Minimal concern for selection bias based on description of recruitment process and follow-up (e.g., selection of comparison population, population-based random sample selection, recruitment from sampling frame including current and previous employees). • Exclusion and inclusion criteria specified and would not induce bias. • Participation rate is reported at all steps of study (e.g., initial enrollment, follow-up, selection into analysis sample). If rate is not high, appropriate rationale is given for why it is unlikely to be related to exposure (e.g., comparison between participants and nonparticipants or other available information indicates differential selection is not likely). **Adequate** • Enough of a description of the recruitment process to be comfortable that there is no serious risk of bias. • Inclusion and exclusion criteria specified and would not induce bias. • Participation rate is incompletely reported but available information indicates participation is unlikely to be related to exposure. **Deficient** • Little information on recruitment process, selection strategy, sampling framework, and participation OR aspects of these processes raises the potential for bias (e.g., healthy worker effect, survivor bias). **Critically deficient** • Aspects of the processes for recruitment, selection strategy, sampling framework, or participation result in concern that selection bias is likely to have had a large impact on effect estimates (e.g., convenience sample with no information about recruitment and selection,

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
			cases and controls are recruited from different sources with different likelihood of exposure, recruitment materials stated outcome of interest and potential participants are aware of or are concerned about specific exposures).
<u>Confounding</u> Is confounding of the effect of the exposure likely?	Is confounding adequately addressed by considerations in: • Participant selection (matching or restriction)? • Accurate information on potential confounders and statistical adjustment procedures? • Lack of association between confounder and outcome, or confounder and exposure in the study? • Information from other sources? Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing), and minimizing potential overcontrol (e.g., inclusion of a variable on the pathway between exposure and outcome)?	If potential for bias is a concern, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good** • Conveys strategy for identifying key confounders, including co-exposures. This may include a priori biological consideration, published literature, causal diagrams, or statistical analyses, with the recognition that not all "risk factors" are confounders. • Inclusion of potential confounders in statistical models not based solely on statistical significance criteria (e.g., $p < 0.05$ from stepwise regression). • Does not include variables in the models likely to be influential colliders or intermediates on the causal pathway. • Key confounders are evaluated appropriately and considered unlikely sources of substantial confounding. This often will include: o Presenting the distribution of potential confounders by levels of the exposure of interest or the outcomes of interest (with amount of missing data noted); o Consideration that potential confounders were rare among the study population, or were expected to be poorly correlated with exposure of interest; o Consideration of the most relevant functional forms of potential confounders; o Examination of the potential impact of measurement error or missing data on confounder adjustment; or

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
			○ Presenting a progression of model results with adjustments for different potential confounders, if warranted. **Adequate** • Similar to *good* but might not have included all key confounders, or less detail might be available on the evaluation of confounders (e.g., sub bullets in *good*). That residual confounding could explain part of the observed effect is possible, but concern is minimal. **Deficient** • Does not include variables in the models shown to be influential colliders or intermediates on the causal pathway. • And any of the following: ○ The potential for bias to explain some results is high based on an inability to rule out residual confounding, such as a lack of demonstration that key confounders of the exposure-outcome relationships were considered; ○ Descriptive information on key confounders (e.g., their relationship relative to the outcomes and exposure levels) are not presented; or ○ Strategy of evaluating confounding is unclear or is not recommended (e.g., only based on statistical significance criteria or stepwise regression [forward or backward elimination]). **Critically deficient** • Includes variables in the models that are colliders or intermediates in the causal pathway, indicating that substantial bias is likely from this adjustment; or

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
			• Confounding is likely present and not accounted for, indicating that all results were most likely due to bias.
Analysis Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?	• Are missing outcome, exposure, and covariate data recognized, and if necessary, accounted for in the analysis? • Does the analysis appropriately consider variable distributions and modeling assumptions? • Does the analysis appropriately consider subgroups or lifestages of interest (e.g., based on variability in exposure level or duration or susceptibility)? • Is an appropriate analysis used for the study design? • Is effect modification considered, based on considerations developed a priori? • Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	If potential for bias is a concern, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good** • Use of an optimal characterization of the outcome variable, including presentation of subgroup- or lifestage-specific comparisons (as appropriate for the outcome). • Quantitative results presented (effect estimates and confidence limits or variability in estimates) (i.e., not presented only as a p-value or "significant"/"not significant"). • Descriptive information about outcome and exposure provided (where applicable). • Amount of missing data noted and addressed appropriately (discussion of selection issues—missing at random vs. differential). • Where applicable, for exposure, includes LOD (and percentage below the LOD), and decision to use log transformation. • Includes analyses that address robustness of findings, e.g., examination of exposure-response (explicit consideration of nonlinear possibilities, quadratic, spline, or threshold/ceiling effects included, when feasible); relevant sensitivity analyses; effect modification examined based only on a priori rationale with sufficient numbers. • No deficiencies in analysis evident. Discussion of some details might be absent (e.g., examination of outliers). **Adequate** • Same as "Good," except: • Descriptive information about exposure provided (where applicable) but might be incomplete; might not

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
			have discussed missing data, cut points, or shape of distribution(s). • Includes analyses that address robustness of findings (examples in 'Good'), but some important analyses are not performed. **Deficient** • Does not conduct analysis using optimal characterization of the outcome variable. • Descriptive information about exposure levels not provided (where applicable). • Effect estimates and p-value presented, without standard error or confidence interval. • Results presented as statistically "significant"/"not significant." **Critically deficient** • Analysis methods are not appropriate for design or data of the study.
<u>Selective reporting</u> Is there reason to be concerned about selective reporting?	• Were results provided for all the primary analyses described in the methods section? • Is appropriate justification given for restricting the amount and type of results shown? • Are only statistically significant results presented?	If potential for bias is a concern, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good** • The results reported by study authors are consistent with the primary and secondary analyses described in a registered protocol or methods paper. **Adequate** • The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses. **Deficient** • Concerns were raised based on previous publications, a methods paper, or a registered protocol indicating that analyses were planned or conducted that were not reported, or that hypotheses originally considered to

Domain and core question	Prompting questions	Follow-up questions	Criteria that apply to most exposures and outcomes
			be secondary were represented as primary in the reviewed paper. • Only subgroup analyses were reported, suggesting that results for the entire group were omitted. • Only statistically significant results were reported.
<u>Sensitivity</u> Is there a concern that sensitivity of the study is not adequate to detect an effect?	• Is the exposure contrast adequate to detect associations and exposure-response relationships? • Was the appropriate population or lifestage included? • Was the length of follow-up adequate? Is the time/age of outcome ascertainment optimal given the interval of exposure and the health outcome? • Do other aspects related to risk of bias or otherwise raise concerns about sensitivity?		**Good** • There is sufficient variability/contrast in exposure to evaluate primary hypotheses. • The study population was sensitive to the development of the outcomes of interest (e.g., ages, lifestage, sex). • The timing of outcome ascertainment was appropriate given expected latency for outcome development (i.e., adequate follow-up interval). • The study was adequately powered to observe an effect. • No other concerns raised regarding study sensitivity. **Adequate** • Same considerations as *Good*, except: • There may be issues identified that could reduce sensitivity, but they are considered unlikely to substantially impact the overall findings of the study. **Deficient** • Concerns were raised about the considerations described for *Good* that are expected to notably decrease the sensitivity of the study to detect associations for the outcome. **Critically deficient** • Severe concerns were raised about the sensitivity of the study such that any observed associations are likely to be explained by bias.

6.3. EXPERIMENTAL ANIMAL STUDY EVALUATION

Using the principles described in Section 6.1, the identified animal studies are evaluated for the following domains to assess risk of bias and sensitivity: allocation, observational bias/blinding, confounding, selective reporting, attrition, chemical administration and characterization, endpoint measurement and validity, results presentation and comparisons, and sensitivity (see Table 6-2).

The rationale for judgments is documented at the outcome level. The evaluation documentation in HAWC includes the identified limitations and their expected impact on the overall confidence level. To the extent possible, the rationale will reflect an interpretation of the potential influence on the outcome-specific results, including the direction or magnitude of influence (or both).

Table 6-2. Questions to guide the development of criteria for each domain in experimental animal toxicology studies

Domain and core question	Prompting questions	General considerations
Allocation Were animals assigned to experimental groups using a method that minimizes selection bias?	For each study: Did each animal or litter have an equal chance of being assigned to any experimental group (i.e., random allocation)? Is the allocation method described? Aside from randomization, were any steps taken to balance variables across experimental groups during allocation?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. **Good** • Experimental groups were randomized, and any specific randomization procedure was described or inferable (e.g., computer-generated scheme. Note that normalization is not the same as randomization [see response for *adequate*]). **Adequate** • Authors report that groups were randomized but do not describe the specific procedure used (e.g.," animals were randomized"). Alternatively, authors used a nonrandom method to control for important modifying factors across experimental groups (e.g., body-weight normalization). **Not reported** • (Interpreted as *deficient*): No indication of randomization of groups or other methods (e.g., normalization) to control for important modifying factors across experimental groups. **Critically deficient** • Bias in the animal allocations was reported or inferable.
Observational bias/blinding Did the study implement measures to reduce observational bias?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Does the study report blinding or other procedures for reducing observational bias? If not, did the study use a design or approach for which such procedures can be inferred?	These considerations typically do not need to be refined by the assessment teams. (Note that it can be useful for teams to identify highly subjective measures of endpoints/outcomes where observational bias may strongly influence results prior to performing evaluations.) A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study.

Domain and core question	Prompting questions	General considerations
	What is the expected impact of failure to implement (or report implementation) of these procedures on results?	**Good** • Measures to reduce observational bias were described (e.g., blinding to conceal treatment groups during endpoint evaluation; consensus-based evaluations of histopathology-lesions). [a] **Adequate** • Methods for reducing observational bias (e.g., blinding) can be inferred or were reported but described incompletely. **Not reported** • Measures to reduce observational bias were not described. **Interpreted** • (Interpreted as *adequate*) The potential concern for bias was mitigated based on use of automated/computer driven systems, standard laboratory kits, relatively simple, objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology. • (Interpreted as *deficient*) The potential impact on the results is major (e.g., outcome measures are highly subjective). **Critically deficient** • Strong evidence for observational bias that impacted the results.
Confounding Are variables with the potential to confound or modify results controlled for and consistent across experimental groups? *Note:* *Consideration of overt toxicity (possibly masking more specific effects) is addressed under endpoint measurement reliability.*	For each study: Are there differences across the treatment groups, considering both differences related to the exposure (e.g., co-exposures, vehicle, diet, palatability) and other aspects of the study design or animal groups (e.g., animal source, husbandry, or health status), that could bias the results? If differences are identified, to what extent are they expected, based on a specific scientific understanding, to impact the results?	These considerations may need to be refined by assessment teams, as the specific variables of concern can vary by experiment or chemical. A judgment and rationale for this domain should be given for each cohort or experiment in the study, noting when the potential for confounding is restricted to specific endpoints/outcomes. **Good** • Outside of the exposure of interest, variables that are likely to confound or modify results appear to be controlled for and consistent across experimental groups. **Adequate** • Some concern that variables that were likely to confound or modify results were uncontrolled or inconsistent across groups but are expected to have a minimal impact on the results.

Domain and core question	Prompting questions	General considerations
		Deficient • Notable concern that potentially confounding variables were uncontrolled or inconsistent across groups and are expected based on to substantially impact the results. **Critically deficient** • Confounding variables were presumed to be uncontrolled or inconsistent across groups and are expected to be a primary driver of the results.
Attrition Did the study report the results for all tested animals?	For each study: Are all animals accounted for in the results? If there is attrition, do authors provide an explanation (e.g., death or unscheduled sacrifice during the study)? If unexplained attrition of animals for outcome assessment is identified, what is the expected impact on the interpretation of the results?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. **Good** • Results were reported for all animals. If animal attrition is identified, the authors provide an explanation, and these are not expected to impact the interpretation of the results. **Adequate** • Results are reported for most animals. Attrition is not explained but this is not expected to significantly impact the interpretation of the results. **Deficient** • Moderate to high level of animal attrition that is not explained and may significantly impact the interpretation of the results. **Critically deficient** • Extensive animal attrition that prevents comparisons of results across treatment groups.
Chemical administration and characterization Did the study adequately characterize exposure to the chemical of interest and the exposure administration methods?	For each study: Are there concerns [specific to this chemical] regarding the source and purity and/or composition (e.g., identity and percent distribution of different isomers) of the chemical? Was independent analytical verification of the test article (e.g.,	It is essential that these considerations are considered, and potentially refined, by assessment teams, as the specific variables of concern can vary by chemical (e.g., stability may be an issue for one chemical but not another). A judgment and rationale for this domain should be given for each cohort or experiment in the study.

Domain and core question	Prompting questions	General considerations
Note: *Consideration of the appropriateness of the route of exposure (not the administration method) is not a risk of bias consideration. Relevance and utility of the routes of exposure are considered in the PECO criteria for study inclusion and during evidence synthesis.* *Relatedly, consideration of exposure level selection (e.g., were levels sufficiently high to elicit effects) is addressed during evidence synthesis and is not a risk of bias consideration.*	composition, homogeneity, and purity) performed? Were nominal exposure levels verified analytically? Are there concerns about the methods used to administer the chemical (e.g., inhalation chamber type, gavage volume)?	**Good** • Chemical administration and characterization are complete (i.e., source and purity are provided or can be obtained from the supplier and test article is analytically verified). There are no notable concerns about the composition, stability, or purity of the administered chemical, or the specific methods of administration. Exposure levels are verified using reliable analytical methods. **Adequate** • Some uncertainties in the chemical administration and characterization are identified but these are expected to have minimal impact on interpretation of the results (e.g., purity of the test article is suboptimal but interpreted as unlikely to have a significant impact; analytical verification of exposure levels is not reported or verified with nonpreferred methods). **Deficient** • Uncertainties in the exposure characterization are identified and expected to substantially impact the results (e.g., source of the test article is not reported, and composition is not independently verified; impurities are substantial or concerning; administration methods are considered likely to introduce confounders, such as use of static inhalation chambers or a gavage volume considered too large for the species or lifestage at exposure). **Critically deficient** • Uncertainties in the exposure characterization are identified and there is reasonable certainty that the study results are largely attributable to factors other than exposure to the chemical of interest (e.g., identified impurities are expected to be a primary driver of the results).
Endpoint measurement Are the selected procedures, protocols, and animal models adequately described and appropriate for the endpoint(s)/outcome(s) of interest? *Notes:*	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Are the evaluation methods and animal model adequately described and appropriate? Are there concerns regarding the methodology selected for endpoint evaluation?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and typically must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Some considerations include the following: **Good** • Adequate description of methods and animal models.

Domain and core question	Prompting questions	General considerations
Considerations related to the sensitivity of the animal model and timing of endpoint measurement are evaluated under Sensitivity *Considerations related to adjustments/corrections to endpoint measurements (e.g., organ weight corrected for body weight) are addressed under results presentation.*	Are there concerns about the specificity of the experimental design? Are there serious concerns regarding the sample size or how endpoints were sampled? Are appropriate control groups for the study/assay type included?	• Use of generally accepted and reliable endpoint methods. • Sample sizes are generally considered adequate for the assay or protocol of interest and there are no notable concerns about sampling in the context of the endpoint protocol (e.g., sampling procedures for histological analysis). • Includes appropriate control groups and any use of nonconcurrent or historical control data (e.g., for evaluation of rare tumors) is justified (e.g., authors or evaluators considered the similarity between current experimental animals and laboratory conditions to historical controls). Ratings of **Adequate, Deficient,** and **Critically Deficient** are generally defined as follows: **Adequate** • Issues are identified that may affect endpoint measurement but are considered unlikely to substantially impact the overall findings or the ability to reliably interpret those findings. **Deficient** • Concerns are raised that are expected to notably affect endpoint measurement and reduce the reliability of the study findings. **Critically deficient** • Severe concerns are raised about endpoint measurement and any findings are likely to be largely explained by these limitations. The following specific examples of relevant concerns are typically associated with a **Deficient** rating, but **Adequate** or **Critically Deficient** might be applied depending on the expected impact of limitations on the reliability and interpretation of the results: • Study report lacks important details that are necessary to evaluate the appropriateness of the study design (e.g., description of the assays or protocols; information on the strain, sex, or lifestage of the animals). • Selection of protocols that are nonpreferred or lack specificity for investigating the endpoint of interest. This includes omission of additional experimental criteria (e.g., inclusion of a positive control or dosing up to levels causing minimal toxicity) when required by specific testing guidelines/protocols.* • Over toxicity (e.g., mortality, extreme weight loss) is observed or expected based on findings from similarly designed studies and may mask interpretation of outcome(s) of interest.

Domain and core question	Prompting questions	General considerations
		• Sample sizes are smaller than is generally considered adequate for the assay or protocol of interest. Inadequate sampling can also be raised within the context of the endpoint protocol (e.g., in a pathology study, bias that is introduced by only sampling a single tissue depth or an inadequate number of slides per animal). • Control groups are not included, considered inappropriate, or comparisons to non-concurrent or historical controls are not adequately justified. *These limitations typically also raise a concern for insensitivity **Sample size alone is not a reason to conclude an individual study is critically deficient.
Results presentation Are the results presented and compared in a way that is appropriate and transparent?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Does the level of detail allow for an informed interpretation of the results? Are the data compared, or presented, in a way that is inappropriate or misleading?	Considerations for this domain are highly variable depending on the outcomes of interest and typically must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Some considerations include the following: **Good** • No concerns with how the data are presented. • Results are quantified or otherwise presented in a manner that allows for an independent consideration of the data (assessments do not rely on author interpretations). • No concerns with completeness of the results reporting.* Ratings of **Adequate**, **Deficient**, and **Critically Deficient** are generally defined as follows: **Adequate** • Concerns are identified that may affect results presentation but are considered unlikely to substantially impact the overall findings or the ability to reliably interpret those findings. **Deficient** • Concerns with results presentation are identified and expected to substantially impact results interpretation and reduce the reliability of the study findings. **Critically deficient** • Severe concerns about results presentation were identified and study findings are likely to be largely explained by these limitations.

Domain and core question	Prompting questions	General considerations
		The following specific examples of relevant concerns are typically associated with a **Deficient** rating but **Adequate** or **Critically Deficient** might be applied depending on expected impact of limitations on the reliability and interpretation of the results: • Nonpreferred presentation of data (e.g., developmental toxicity data averaged across pups in a treatment group, when litter responses are more appropriate; presentation of only absolute organ weight data when relative weights are more appropriate). • Pooling data when responses are known or expected to differ substantially (e.g., across sexes or ages). • Incomplete presentation of the data* (e.g., presentation of mean without variance data; concurrent control data are not presented; dichotomizing or truncating continuous data). *Failure to describe *any* findings for assessed outcomes (i.e., report lacks any qualitative or quantitative description of the results in tables, figures, or text) is addressed under Selective Reporting.
Selective reporting Did the study report the results for all prespecified outcomes? *Note:* *This domain does not consider the appropriateness of the analysis/results presentation. This aspect of study quality is evaluated in another domain.*	For each study: Are results presented for all endpoints/outcomes described in the methods (see note)? If unexplained results omissions are identified, what is the expected impact on the interpretation of the results?	These considerations typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. **Good** • Quantitative or qualitative results were reported for all prespecified outcomes (explicitly stated or inferred), exposure groups and evaluation time points. Data not reported in the primary article is available from supplemental material. If results omissions are identified, the authors provide an explanation, and these are not expected to impact the interpretation of the results. **Adequate** • Quantitative or qualitative results are reported for most prespecified outcomes (explicitly stated or inferred) and evaluation time points. Omissions and are not explained but are not expected to significantly impact the interpretation of the results.

Domain and core question	Prompting questions	General considerations
		Deficient • Quantitative or qualitative results are missing for many prespecified outcomes (explicitly stated or inferred), omissions are not explained and may significantly impact the interpretation of the results. **Critically deficient** • Extensive results omission is identified and prevents comparisons of results across treatment groups.
Sensitivity Are there concerns that sensitivity in the study is not adequate to detect an effect? *Note:* *Consideration of exposure level selection (e.g., were levels sufficiently high to elicit effects) is addressed during evidence synthesis and is not a study sensitivity consideration.*	Was the exposure period, timing (e.g., lifestage), frequency, and duration sensitive for the outcome(s) of interest? Given knowledge of the health hazard of concern, did the selection of species, strain, and/or sex of the animal model reduce study sensitivity? Are there concerns regarding the timing (e.g., lifestage) of the outcome evaluation? Are there aspects related to risk of bias domains that raise concerns about insensitivity (e.g., selection of protocols that are known to be insensitive or nonspecific for the outcome(s) of interest)	These considerations may require customization to the specific exposure and outcomes. Some study design features that affect study sensitivity may have already been included in the other evaluation domains; these should be noted in this domain, along with any features that have not been addressed elsewhere. Some considerations include: **Good** • The experimental design (considering exposure period, timing, frequency, and duration) is appropriate and sensitive for evaluating the outcome(s) of interest. • The selected animal model (considering species, strain, sex, and/or lifestage) is known or assumed to be appropriate and sensitive for evaluating the outcome(s) of interest. • No significant concerns with the ability of the experimental design to detect the specific outcome(s) of interest. (e.g., outcomes evaluated at the appropriate lifestage; study designed to address known endpoint variability that is unrelated to treatment, such as estrous cyclicity or time of day). • Timing of endpoint measurement in relation to the chemical exposure is appropriate and sensitive (e.g., behavioral testing is not performed during a transient period of test chemical-induced depressant or irritant effects; endpoint testing does not occur only after a prolonged period, such as weeks or months, of non-exposure) • Potential sources of bias toward the null are not a substantial concern. **Adequate** Same considerations as *Good*, except: • The duration and frequency of the exposure was appropriate, and the exposure covered most of the critical window (if known) for the outcome(s) of interest.

Domain and core question	Prompting questions	General considerations
		• Potential issues are identified that could reduce sensitivity, but they are unlikely to impact the overall findings of the study. **Deficient** • Concerns were raised about the considerations described for Good or Adequate that are expected to notably decrease the sensitivity of the study to detect a response in the exposed group(s). **Critically deficient** • Severe concerns were raised about the sensitivity of the study and experimental design such that any observed associations are likely to be explained by bias. The rationale should indicate the specific concern(s).
Overall confidence Considering the identified strengths and limitations, what is the overall confidence rating for the endpoint(s)/outcome(s) of interest?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: Were concerns (i.e., limitations or uncertainties) related to the risk of bias or sensitivity identified? If yes, what is their expected impact on the overall interpretation of the reliability and validity of the study results, including (when possible) interpretations of impacts on the magnitude or direction of the reported effects?	The overall confidence rating considers the likely impact of the noted concerns (i.e., limitations or uncertainties) in reporting, bias, and sensitivity on the results. Reviewers should mark studies that are rated lower than high confidence only due to low sensitivity (i.e., bias toward the null) for additional consideration during evidence synthesis. If the study is otherwise well conducted and an effect is observed, it may increase the strength of evidence judgment. A confidence rating and rationale should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Confidence ratings are described above (see Section 6.1).

[a]For nontargeted or screening-level histopathological outcomes often used in guideline studies, blinding during the initial evaluation of tissues is generally not recommended, as masked evaluation can make "the task of separating treatment-related changes from normal variation more difficult" and "there is concern that masked review during the initial evaluation may result in missing subtle lesions." Generally, blinded evaluations are recommended for targeted secondary review of specific tissues or in instances when there is a predefined set of outcomes that is known or predicted to occur (Crissman et al., 2004).

6.4. MECHANISTIC AND OTHER NON-PECO STUDY EVALUATION

As described in Sections 4.4, 4.5, and 4.6, the initial literature screening identifies sets of other potentially informative studies, including mechanistic studies, as potentially relevant supplemental information that do not meet the assessment PECO criteria. The approach for the prioritization and evaluation of mechanistic and other non-PECO studies is targeted to the assessment needs, depending on the extent and nature of the human and animal evidence. An intensive analysis may not be warranted for health outcomes or specific mechanistic events not expected to meaningfully impact assessment approaches or conclusions or for those already well accepted scientifically. Given the literature inventory and findings from the ATSDR assessment used as a starting point for the IRIS assessment, evaluating individual mechanistic studies is not anticipated to be impactful for most, if not all, health effects identified for review for this assessment. As described in Section 5.4, this assessment will primarily rely on other published authoritative sources, such as public health agency reports and literature reviews, to summarize the available mechanistic information (when such context aids the evidence synthesis narrative) unless substantial scientific issues or new, impactful studies are identified during the course of developing the assessment.

6.5. PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL DESCRIPTIVE SUMMARY AND EVALUATION

PBPK (or classical pharmacokinetic [PK]) models should be used in an assessment when an applicable one exists and no equal or better alternative for dosimetric extrapolation is available. Any models used should represent current scientific knowledge and accurately translate the science into computational code in a reproducible, transparent manner. For a specific target organ/tissue, it may be possible to employ or adapt an existing PBPK model or develop a new PBPK model or an alternate quantitative approach. Data for PBPK models may come from studies across various species and may be in vitro or in vivo in design.

Note that the terms “pharmacokinetic” (adjective) and “pharmacokinetics” (noun), which are both abbreviated as “PK,” are used in this document when discussing absorption, distribution, metabolism, and excretion (ADME) of a substance by an organism or any related quantities, experiments, or models. The terms “toxicokinetic” and “toxicokinetics,” which are both abbreviated as “TK,” are frequently used as synonyms for “pharmacokinetic” and “pharmacokinetics” in the literature, but the latter terms are used preferentially here for document-wide consistency. Also, PBPK models are sometimes described as “physiologically based toxicokinetic models” (abbreviated “PBTK models”) or even as “physiologically based kinetic models” (abbreviated “PBK models”) in the literature, but in this document the term “PBPK model” is used preferentially for purposes of consistency.

As described in Section 5.4.2, the ATSDR Toxicological Profile identified two PK/PBPK models for inhalation and oral exposures, but these models do not include a dosimetric adjustments from animals to humans and were not considered further. No PBPK models for uranium have been identified in the preliminary survey of the date-limited literature search.

7. DATA EXTRACTION OF STUDY METHODS AND RESULTS

The process of summarizing study methods and results is referred to as data extraction. Studies that met initial PECO criteria after full-text review are briefly summarized in data extraction forms available in the Distiller and serve as a literature inventory. These study summaries are exported from DistillerSR in Excel format to create interactive literature inventory used for analysis of the available evidence. For experimental animal studies, which are typically studies in rodents, the following information is captured: chemical form, study type (acute [<24 hours], short term [<7 days], short term [7–27 days], subchronic [28–90 days], chronic [>90 days] and developmental, which includes multigeneration studies), duration of treatment, route, species, strain, sex, dose or concentration levels tested, dose units, health system and specific endpoints assessed, and the no-observed-effect level/low-observed-effect level (NOEL/LOEL) based on author-reported statistical significance. Expert judgment may be used to identify NOEL/LOELs in cases where only qualitative results are reported (e.g., "no effects on liver weight were observed at any dose level") or when the findings indicate an apparent clear and strong effect of exposure (e.g., large magnitude of change) but the authors did not present a statistical comparison. When findings are not analyzed by the authors and are not readily interpretable, then NOEL/LOELs are not identified, and the extraction field entry indicates "not reported." For human studies, the following information is summarized in DistillerSR forms: chemical form, population type (e.g., general population-adult, occupational, pregnant women, infants and children), study type (e.g., cross-sectional, cohort, case-control), sex, major route of exposure (if known), description of how exposure was assessed, health system studied, specific endpoints assessed and a quantitative summary of findings at the endpoint level (or narrative only if the finding was qualitatively presented).

For epidemiology and animal studies that met the assessment PECO criteria, the HAWC is used for study evaluation and for full extraction of study methods and results. Compared with the literature inventory, full data extraction in HAWC includes summarizing more details of study design and gathering effect size information. For animal studies, compared with the literature inventory forms used to described studies that meet problem formulation PECO criteria, full data extraction in HAWC includes summarizing more details of study design (e.g., diet, chemical purity) and gathering effect size information. Instructions on how to conduct data extraction in HAWC are available at https://hawcproject.org/resources/. An additional resource used to implement use of a consistent vocabulary to summarize endpoints assessed in animal studies is available in HAWC (the Environmental Health Vocabulary (EHV); https://hawc.epa.gov/vocab/ehv/.

In some cases, EPA may conduct their own statistical analysis of human and animal toxicology data (assuming the data are amenable to doing so and the study is otherwise well-conducted) during evidence synthesis.

If necessary, data extraction for mechanistic studies (including in vivo and in vitro studies) will be conducted in Distiller SR or Microsoft Excel and presented in tabular format. The extracted evidence is available in MS Excel format upon request. See https://www.epa.gov/iris/forms/contact-us-about-iris for requests.

All findings are considered for extraction, regardless of statistical significance. The level of extraction for specific outcomes within a study could differ (i.e., narrative only if the finding was qualitative). For quality control, studies were extracted by one member of the evaluation team and independently verified by at least one other member. Discrepancies were resolved by discussion or consultation within the evaluation team. Data extraction results are presented via figures, tables, or interactive web-based graphics in the assessment. The information is also made available for download in Excel format when the draft is publicly released. Download of full data extraction for animal studies is done directly from HAWC.

For non-English studies online translation tools (e.g., Google translator) or engagement with a native speaker can be used to summarize studies at the level of the literature inventory. Fee-based translation services for non-English studies are typically reserved for studies considered potentially informative for dose response, a consideration that occurs after preparation of the initial literature inventory during draft assessment development. Digital rulers, such as WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/), are used to extract numerical information from figures, and their use is be documented during extraction. For studies that evaluate endpoints at multiple time points (e.g., 7 days, 3 weeks, 3 months) data are generally summarized for the longest duration in the study report, but other durations may be summarized if they provide important contextual information for hazard characterization (e.g., an effect was present at an interim time point but did not appear to persist or the magnitude of the effect diminished). A free text field is available in HAWC to describe cases when the approach for summarizing results requires explanation.

Author queries may be conducted for studies considered for hazard identification or dose-response to facilitate study evaluation and quantitative analysis (e.g., information on variability or availability of individual animal data). Outreach to study authors or designated contact persons is documented and considered unsuccessful if researchers do not respond to email or phone requests within 1 month of initial attempt(s) to contact. Only information or data that can be made publicly available (e.g., within HAWC or HERO) will be considered.

Exposures are standardized to common units when possible. For hazard characterization, exposure levels are typically presented as reported in the study and standardized to common units.

7.1. STANDARDIZING ADMINISTERED DOSE LEVELS/CONCENTRATIONS

Exposures are standardized to common units. Exposure levels in oral studies are expressed in units of mg uranium/kg-day. When study authors provide exposure levels in concentrations in the diet or drinking water, dose conversions are made using study-specific food or water consumption rates and body weights when available. Otherwise, EPA defaults are used (U.S. EPA, 1988), addressing age and study duration as relevant for the species/strain and sex of the animal of interest. Exposure levels are converted to uranium equivalents. For example, doses administered as uranyl nitrate are expressed as uranium using a molecular weight conversion. Unless otherwise reported by study authors, the background level in experimental animal studies is assumed to be 0 ppm (0 mg/kg-day).

8. EVIDENCE SYNTHESIS AND INTEGRATION

As described in Sections 5.1 and 5.2 if the newly available evidence from PECO-relevant toxicological and epidemiological studies suggests a need to update hazard conclusions, EPA will perform a complete evaluation of the studies identified in the IRIS literature search plus the studies cited in (ATSDR, 2013).[12] Within-stream evidence synthesis is conducted separately for human, animal, and mechanistic evidence to directly inform the integration across the streams of evidence and draw overall conclusions for each of the assessed human health effects. The phrases "evidence synthesis" and "evidence integration" used here are analogous to the phrases "strength of evidence" and "weight of evidence," respectively, used in some other assessment processes (EFSA, 2017; U.S. EPA, 2017; NRC, 2014; U.S. EPA, 2005a). A structured framework approach is used to guide both evidence synthesis and integration. This structured framework includes consideration of mechanistic information during both evidence synthesis and integration, although the focus of the analysis differs. Similarly other types of supplemental information (e.g., ADME, non-PECO route of exposure) can also inform evidence synthesis and integration analyses.

- Evidence synthesis: Judgment(s) regarding the strength of the evidence for hazard for each unit of analysis from the available human and animal studies are made in parallel, but separately. These judgments can incorporate PK, mechanistic, and other supplemental evidence when the unit of analysis is defined as such (see Section 5.2). The units of analysis can also include or be framed to focus on precursor events (e.g., biomarkers). In addition, this includes an evaluation of coherence across units of analysis within an evidence stream. At this stage, the animal evidence judgment(s) does not yet consider the human relevance of that evidence.

- Evidence integration: The animal and human evidence judgments are combined to draw an overall evidence integration judgment(s) that incorporates inferences drawn based on information on the human relevance of the animal evidence, coherence across evidence streams, potential susceptibility, and other critical inferences (e.g., biological plausibility) informed by mechanistic, ADME, or other supplemental data.

Evidence synthesis and integration judgments are expressed both narratively in the assessment and summarized in tabular format in evidence profile tables (see Table 8-1). Key findings and analyses of mechanistic and other supplemental content are also summarized in narrative and tabular format to inform evidence synthesis and integration judgments (see Table 8-2). In brief, a synthesis (strength of evidence) judgment is drawn for each unit of analysis summarized as *robust*, *moderate*, *slight*, *indeterminate,* or *compelling evidence of no effect* (see

[12]Health systems that will undergo full evaluation by EPA: cardiovascular (see Appendix D.2), endocrine (see Appendix D.4), immune (see Appendix D.8), musculoskeletal (see Appendix D.10), and respiratory (see Appendix D.13).

Section 8.1). Next, evidence synthesis judgments are used to inform evidence integration (weight of evidence) judgments summarized as *evidence demonstrates, evidence indicates, evidence suggests, evidence inadequate,* or *strong evidence supports no effect*) (see Section 8.2). These summary judgments are included as part of the evidence synthesis and integration narratives. When multiple units of analysis are synthesized, the main evidence integration judgments[13] typically focus on the unit of analysis with the strongest evidence synthesis judgments, although exceptions may occur. Structured evidence profile tables are used to summarize these analyses and foster consistency within and across assessments. Instructions for using HAWC to create these tables are available at the HAWC project "IRIS PPRTV SEM Template Figures and Resources" (see "Attachments," then select the "Creating Evidence Profile Tables in HAWC")

[13]In some cases, as discussed in Section 8.2, it will be appropriate to draw multiple evidence integration judgments within a given health effect category. This is generally dependent on data availability (i.e., more narrowly defined categories may be possible with more evidence) and the ability to integrate the different evidence streams at the level of these more granular categories. More granular categories will generally be organized by pre-defined manifestations of potential toxicity. For example, within the health effect category of immune effects, separate and different evidence integration judgments might be appropriate for immunosuppression, immunostimulation, and sensitization and allergic response (i.e., the three types of immunotoxicity described in the 2012 WHO Guidance for immunotoxicity risk assessment for chemicals (WHO, 2012)). Likewise, within the category of developmental effects, it may be appropriate to draw separate judgments for potential effects on fetal death, structural abnormality, altered growth, and functional deficits (i.e., the four manifestations of developmental toxicity described in EPA guidelines (U.S. EPA, 1991)). These separate judgments are particularly important when the evidence supports that the different manifestations might be based on different toxicological mechanisms. As described for the evidence synthesis judgments, the strongest evidence integration judgment will typically be used to reflect certainty in the broader health effect category.

Table 8-1. Generalized evidence profile table to show the relationship between evidence synthesis and evidence integration to reach judgment of the evidence for hazard

Evidence synthesis (strength of evidence) judgments (note that many factors and judgments require elaboration or evidence-based justification; see IRIS Handbook for details)					Evidence integration (weight of evidence) judgment(s)
Studies	**Summary of key findings**	**Factors that increase certainty (applied to each unit of analysis)**	**Factors that decrease certainty (applied to each unit of analysis)**	**Evidence synthesis judgment(s)**	Describe overall evidence integration judgment(s): ⊕⊕⊕ *Evidence demonstrates* ⊕⊕⊙ *Evidence indicates (likely)* ⊕⊙⊙ *Evidence suggests* ⊙⊙⊙ *Evidence inadequate* *– – – Strong evidence supports no effect* Highlight the primary supporting evidence for each integration judgment[a] Present inferences and conclusions on: • Human relevance of findings in animals[a] • Cross-stream coherence[a] • Potential susceptibility[a] • Understanding of biological plausibility and MOA[a] • Other critical inferences[a]
Evidence from human studies					
Unit of analysis #1 Studies considered and study confidence	Description of the primary results	• All/Mostly medium or high confidence studies • Consistency • Dose-response gradient • Large or concerning magnitude of effect • Coherence[a]	• All/Mostly low confidence studies • Unexplained inconsistency • Imprecision • Concerns about biological significance[a] • Indirect outcome measures[a] • Lack of expected coherence[a]	Judgment reached for each unit of analysis[a] ⊕⊕⊕ *Robust* ⊕⊕⊙ *Moderate* ⊕⊙⊙ *Slight* ⊙⊙⊙ *Indeterminate* *– – – Compelling evidence of no effect*	
Unit of analysis #2 Studies considered and study confidence	Description of the primary results				
Evidence from animal studies					
Unit of analysis #1 Studies considered and study confidence	Description of the primary results	• All/Mostly medium or high confidence studies • Consistency • Dose-response gradient • Large or concerning magnitude of effect • Coherence[a]	• All/Mostly low confidence studies • Unexplained inconsistency • Imprecision • Concerns about biological significance[a] • Indirect outcome measures[a] • Lack of expected coherence[a]	Judgment reached for each unit of analysis ⊕⊕⊕ *Robust* ⊕⊕⊙ *Moderate* ⊕⊙⊙ *Slight* ⊙⊙⊙ *Indeterminate* *– – – Compelling evidence of no effect*	
Unit of analysis #2 Studies considered and study confidence	Description of the primary results				

[a]Can be informed by key findings from the mechanistic analyses (see Table 8-2).

Table 8-2. Generalized evidence profile table to show the key findings and supporting rationale from mechanistic analyses

Mechanistic analyses		
Biological events or pathways (or other relevant evidence grouping)	**Summary of key findings and interpretation**	**Judgment(s) and rationale**
Different analyses can be presented separately, **e.g., by exposure route or key uncertainty addressed.** Each analysis can include multiple rows separated by biological events or other feature of the approach used for the analysis • Generally, will cite mechanistic synthesis (e.g., for references; for detailed analysis). • Does not have to be chemical-specific (e.g., read-across).	Can include separate summaries, for example by study type (e.g., new approach methods vs. in vivo biomarkers), dose, or design. *Interpretation*: Summary of expert interpretation for the body of evidence and supporting rationale. *Key findings*: Summary of findings across the body of evidence (may focus on or emphasize highly informative designs or findings), including key sources of uncertainty or identified limitations of the study designs tested (e.g., regarding the biological event or pathway being examined).	Overall summary of expert interpretation across the assessed set of biological events, potential mechanisms of toxicity, or other analysis approach (e.g., AOP). • Includes the primary evidence supporting the interpretation(s). • Describes and informs the extent to which the evidence influences inferences across evidence streams. • Characterizes the limitations of the evaluation and highlights existing data gaps. • May have overlap with factors summarized for other streams.

8.1. EVIDENCE SYNTHESIS

IRIS assessments synthesize the evidence separately for each unit of analysis by focusing on factors that increase or decrease certainty in the reported findings as evidence for hazard (see Table 8-1). These factors are adapted from considerations for causality introduced by Austin Bradford Hill (Hill, 1965) with some expansion and adaptation of how they are applied to facilitate transparent application to chemical assessments that consider multiple streams of evidence. Specifically, the factors considered are confidence in study findings (risk of bias [RoB] and sensitivity), consistency across studies or experiments, dose/exposure-response gradient, strength (effect magnitude) of the association, directness of outcome or endpoint measures, and coherence [see Table 8-3; see additional discussion in (U.S. EPA, 2022a, 2005a, 1994)]. These factors are similar to the domains considered in the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Quality of Evidence framework (Schünemann et al., 2013). Each of the considered factors and the certainty of evidence judgments requires elaboration or evidence-based justification in the synthesis narrative. Analysis of evidence synthesis considerations is qualitative (i.e., numerical scores are not developed, summed, or subtracted).

As previously described, the units of analysis may include predefined categories of mechanistic evidence or other supplemental information (e.g., from studies of non-PECO routes of exposure). This may include consideration of biomarkers or precursor events. Biological understanding (e.g., knowledge of how an effect is manifest or progresses) or mechanistic inference (e.g., dependency on a conserved key event across outcomes) can also be used to define which related outcomes are considered as a unit of analysis. These considerations also inform the evaluation of coherence and adversity within a unit of analysis and coherence with other units of analyses. Mechanistic analyses outside the context of defining and evaluating the units of analysis during evidence synthesis are considered as part of across stream evidence integration (see Section 8.2).

Typically, human and animal evidence synthesis sections are structured similarly across different units of analysis, health effects, and assessments. In contrast, the presentation, and analyses of mechanistic and other types of supplemental information often differs within and across assessments. This is due to the diversity of supplemental data that may be available and the complexity of conducting supplemental analyses. For example, these data may inform unit of analysis considerations, evidence integration judgments, or both. Each of the key analyses informing the synthesis judgments are described in the narrative and summarized in an evidence profile table.

Five levels of certainty in the evidence for (or against) a hazard are used to summarize evidence synthesis judgments: *robust* (⊕⊕⊕, very little uncertainty exists), *moderate* (⊕⊕⊙, some uncertainty exists), *slight* (⊕⊙⊙, large uncertainty exists), *indeterminate* (⊙⊙⊙), or *compelling evidence of no effect* (- - -, little to no uncertainty exists for lack of hazard) (see

Tables 8-3 and 8-4 for descriptions). Conceptually, before the evidence synthesis framework is applied, certainty in the evidence is neutral (i.e., functionally equivalent to indeterminate). Next, the level of certainty regarding the evidence for (or against) hazard is increased or decreased depending on interpretations using the factors described in Table 8-3. Observations that increase certainty are having consistency across *high* or *medium* confidence studies or experiments, the presence of *medium* or *high* confidence studies with a strong dose-response gradient or observing a large or concerning magnitude of effect, and coherent findings across *medium* or *high* confidence studies for closely related endpoints (can include mechanistic endpoints) within the unit of analysis within an evidence stream. Evidence from *low* confidence studies can further strengthen observations from *medium* or *high* confidence studies but do not increase certainty on their own. Observations that decrease certainty are having an evidence base of mostly *low* confidence studies, unexplained inconsistency, lack of expected coherence, imprecision, unclear biological significance, null findings with concerns for insensitivity (which decreases certainty in the lack of an effect), or indirect measures of outcomes. Table 8-3 provides additional detail on how these factors are considered when evaluating units of analysis.

Table 8-3. Considerations that inform evaluations and judgments of the strength of the evidence for hazard

Consideration	Increased evidence certainty (of the human or animal evidence for hazard[a])	Decreased evidence certainty (of the human or animal evidence for hazard[a])
Risk of bias and sensitivity (across studies)	• An evidence base of mostly (or all) *high* or *medium* confidence studies is interpreted as being only minimally affected by bias and insensitivity. • This factor should not be used if no other factors would increase or decrease the confidence for a given unit of analysis. • In addition, consideration of risk of bias and sensitivity should inform how other factors are evaluated, i.e., can inconsistency be potentially explained by variation in confidence judgments?	• An evidence base of mostly (or all) low confidence studies decreases strength. An exception to this is an evidence base of studies in which the issues resulting in low confidence are related to insensitivity. This may increase evidence certainty in cases where an association is identified because the expected impact of study insensitivity is toward the null. • An evidence base of mostly null findings where insensitivity is a serious concern decreases certainty that the evidence is sufficient to support a lack of health effect or association. • Decisions to increase certainty for other considerations in this table should generally not be made if there are serious concerns for risk of bias.
Consistency	• Similarity of findings for a given outcome (e.g., of a similar direction) across independent studies or experiments, especially when medium or high confidence, increases certainty. The increase in certainty is larger when consistency is observed across populations (e.g., geographical location) or exposure scenarios in human studies, and across laboratories, species, or exposure scenarios (e.g., route; timing) in animal studies. When seemingly inconsistent findings are identified, patterns should be further analyzed to discern if the inconsistencies can potentially be explained based on study confidence, dose or exposure levels, population, or experimental model differences, etc. This factor is typically given the most attention during evidence synthesis.	• Unexplained inconsistency [i.e., conflicting evidence; see (U.S. EPA, 2005a)] decreases certainty. Generally, certainty should not be decreased if discrepant findings can be reasonably explained by considerations such as study confidence conclusions (including sensitivity); variation in population or species, sex, or lifestage (including understanding of differences in pharmacokinetics); or exposure patterns (e.g., intermittent versus continuous), levels (low versus high), or duration. Similar to current recommendations in the Cochrane Handbook [(Higgins et al., 2022), see Section 7.8.6], clear conflicts of interest (COI) related to funding source can be considered as a factor to explain apparent inconsistency. For small evidence bases, it might be hard to assess consistency. An evidence base of a single or a few studies where consistency cannot be accurately assessed does not, alone, increase or decrease evidence certainty. Similarly, a reasonable explanation for inconsistency does not necessarily result in an increase in evidence certainty.

Consideration	Increased evidence certainty (of the human or animal evidence for hazard[a])	Decreased evidence certainty (of the human or animal evidence for hazard[a])
Effect magnitude and imprecision	• Evidence of a large or concerning magnitude of effect can increase strength (generally only when observed in medium or high confidence studies). • Judgments on effect magnitude and imprecision consider the rarity and severity of the effect.	• Certainty could be decreased if the findings are considered not likely to be biologically significant. Effects that are small in magnitude might not be considered biologically significant (adverseb) based on information such as historical responses and variability. However, effects that appear to be of small magnitude could be meaningful at the population level e.g., IQ shifts); in such cases, certainty would not be decreased. • Certainty might also be decreased for imprecision, particularly if there are only a few studies available to evaluate consistency in effect magnitude across studies.
Dose-response	• Evidence of dose-response or exposure-response in high or medium confidence studies increases certainty. Dose-response can be demonstrated across studies or within studies and it can be dose- or duration-dependent. It could also not be a monotonic dose-response (monotonicity should not necessarily be expected as different outcomes might be expected at low vs. high doses due to factors such as activation of different mechanistic pathways, systemic toxicity at high doses or tolerance/acclimation). Sometimes, grouping studies by level of exposure is helpful to identify the dose-response pattern. • Decreases in a response (e.g., symptoms of current asthma) after a documented cessation of exposure also might increase certainty in a relationship between exposure and outcome (this is primarily applicable to epidemiology studies because of their observational nature).	• A lack of dose-response when expected on the basis of biological understanding can decrease certainty in the evidence. If the data are not adequate to evaluate a dose-response pattern, however, certainty is neither increased nor decreased. • In some cases, duration-dependent patterns in the dose-response can decrease evidence certainty. Such patterns are generally only observable in experimental studies. Specifically, the magnitude of effects at a given exposure level might decrease with longer exposures (e.g., due to tolerance or acclimation). Or effects might rapidly resolve under certain experimental conditions (e.g., reversibility after removal of exposure). As many reversible and short-lived effects can be of high concern, decisions about whether such patterns decrease evidence certainty depend on considering the pharmacokinetics of the chemical and the conditions of exposure [see U.S. EPA (1998)], endpoint severity, judgments regarding the potential for delayed or secondary effects, the underlying mechanism(s) involved, and the exposure context focus of the assessment (e.g., addressing intermittent or short-term exposures).
Directness of outcome/endpoint measures	• Not applicable	• If the evidence base primarily includes outcomes or endpoints that are indirect measures (e.g., biomarkers) of the unit of analysis, certainty (for that unit of analysis) is typically decreased. Judgments to decrease certainty based on indirectness should focus on findings

Consideration	Increased evidence certainty (of the human or animal evidence for hazard[a])	Decreased evidence certainty (of the human or animal evidence for hazard[a])
		for measures that have an unclear linkage to an apical or clinical (adverseb) outcome. Scenarios where the magnitude of the response is not considered to reflect a biologically meaningful level of change (i.e., biological significance; see "effect magnitude and imprecision" row, above) are not considered under indirectness of outcome measures. • Related to indirectness, certainty in the evidence can be decreased when the findings are determined to be nonspecific to the hazard under evaluation. This consideration is generally only applicable to animal evidence and the most common example is effects only with exposures (level, duration) shown to cause excessive toxicity in that species and lifestage (including consideration of maternal toxicity in developmental evaluations). This does not apply when an effect is viewed as secondary to other changes (e.g., effects on pulmonary function because of disrupted immune responses).
Coherence	• Biologically related findings within or across studies, within an organ system or across populations (e.g., sex), increase certainty (generally only when observed in medium or high confidence studies). Certainty is further increased when a temporal or dose-dependent progression of related effects is observed within or across studies, or when related findings of increasing severity are observed with increasing exposure. • Coherence across findings within a unit of analysis (e.g., consistent changes in disease markers and biological precursors in exposed humans) can increase certainty in the evidence for an effect. • Coherence within or across biologically related units of analysis can also increase certainty for a given (or multiple) unit(s) of analysis. This considers certainty in the biological	• An observed lack of expected coherent changes (e.g., in well-established biological relationships) within or across biologically related units of analysis will typically decrease evidence certainty. This includes mechanistic changes when included in the unit of analysis. However, as described for decisions to increase certainty, confidence in the understanding of the biological relationships between the endpoints being compared, and the sensitivity and specificity of the measures used, need to be carefully examined. The decision to decrease certainty depends on the availability of evidence across multiple related endpoints for which changes would be anticipated, and it considers factors (e.g., dose and duration of exposure, strength of expected relationship) across the studies of related changes.

Consideration	Increased evidence certainty (of the human or animal evidence for hazard[a])	Decreased evidence certainty (of the human or animal evidence for hazard[a])
	relationships between the endpoints being compared, and the sensitivity and specificity of the measures used. • Mechanistic support for, or biological understanding of, the relatedness between different endpoints within (or across different) units of analysis, can inform an understanding of coherence.	
Other factors	• Unusual scenarios that cannot be addressed by the considerations above, e.g., read-across inferences supporting the adversity of observed changes.	• Unusual scenarios that cannot be addressed by the considerations above, e.g., strong evidence of publication bias.c

[a]Although the focus is on identifying potential adverse human health effects (hazards) of exposure, these factors can also be used to increase or decrease certainty in the evidence supporting lack of an effect (e.g., leading to a judgment of compelling evidence of no effect). The latter application is not explicitly outlined here.

[b]Within this framework, evidence synthesis judgments reflect an interpretation of the evidence for a hazard; thus, consideration of the adversity of the findings is an explicit aspect of the analyses. To better define how adversity is evaluated, the consideration of adversity is broken into the two, sometimes related, considerations of the indirectness of the outcome measures and the interpreted biological significance of the effect magnitude.

[c]Publication bias involves the influence of the direction, magnitude, or statistical significance of the results on the likelihood of a paper being published; it can result from decisions made, consciously or unconsciously, by study authors, journal reviewers, and journal editors (Dickersin, 1990). This could make the available evidence base unrepresentative. However, publication bias can be difficult to evaluate (NTP, 2019) and should not be used as a factor that decreases certainty unless there is strong evidence.

A structured framework approach is used to draw evidence synthesis judgments for human and animal evidence. Tables 8-4 and 8-5 (for human and animal evidence, respectively) provide the criteria that guide how to draw the strength of evidence judgments for each unit of analysis within a health effect category and the terms used to summarize those judgments. These terms are applied to human and animal evidence separately. The terms *robust* and *moderate* are characterizations for judgments that the evidence (across studies) supports a conclusion that the effect(s) results from the exposure being assessed. These two terms are differentiated by the quality and amount of information available to rule out alternative explanations for the results. For example, repeated observations of effects by independent studies or experiments examining various aspects of exposure or response (e.g., different exposure settings, dose levels or patterns, populations or species, biologically related endpoints) result in increased certainty in the evidence for hazard. The term *slight* indicates situations in which there is some evidence supporting an association within the evidence stream, but substantial uncertainties in the data exist to prevent judgments that the effect(s) can be reliably attributed to the exposure being assessed. *Indeterminate* reflects judgments for a wide variety of evidence scenarios, including when no studies are available or when the evidence from studies of similar confidence has a high degree of unexplained inconsistency. *Compelling evidence of no effect* represents a rare situation in which extensive evidence across a range of populations and exposures has demonstrated that no effects are likely attributable to the exposure being assessed. This category is applied at the health effect level (e.g., hepatic effects) rather than more granular units of analysis level to avoid giving the impression of confidence in lack of a health effect when aspects of potential toxicity have not been adequately examined. Reaching this judgment is infrequent because it requires both a high degree of confidence in the conduct of individual studies, including consideration of study sensitivity, as well as comprehensive assessments of outcomes and lifestages of exposure that adequately address concern for the hazard under evaluation.

Table 8-4. Framework for strength of evidence judgments from studies in humans

Evidence synthesis judgment	Description
Robust (⊕⊕⊕) …evidence in human studies *(strong signal of effect with very little uncertainty)*	A set of *high* or *medium* confidence independent studies (e.g., in different populations) reporting an association between the exposure and the health outcome(s), with reasonable confidence that alternative explanations, including chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; the findings are considered adverse (i.e., biologically significant and without notable concern for indirectness); and an exposure-response gradient is demonstrated. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk or severity of the response, can increase certainty but are not required. Supplemental evidence included in the unit of analysis (e.g., mechanistic studies in exposed humans or human cells) could raise the certainty in the evidence to *robust* for a set of studies that otherwise would be described as *moderate*. Such evidence not included in the unit of analysis can also inform evaluations of the coherence of the human evidence, the directness of the outcome measures, and the biological significance of the findings. Causality is inferred for a human evidence base of robust.
Moderate (⊕⊕⊙) …evidence in human studies *(signal of effect with some uncertainty)*	A set of evidence that does not reach the degree of certainty required for robust, but which includes at least one *high* or *medium* confidence study reporting an association and additional information increasing certainty in the evidence. For multiple studies, there is primarily consistent evidence of an association with reasonable support for adversity, but there might be some uncertainty due to potential chance, bias, or confounding or because of the indirectness of some measures. When only a single study is available in the unit of analysis, there is a large magnitude or severity of the effect, or a dose-response gradient, or other supporting evidence, and there are no serious residual methodological uncertainties. Supplemental evidence included in the unit of analysis might address the above factors and raise certainty in the evidence to *moderate* for a set of studies that otherwise would be described as slight or, in exceptional cases, could support raising to moderate evidence that would otherwise be described as *indeterminate*. Mechanistic evidence not included in the unit of analysis can also inform evaluations of the coherence of the human evidence, the directness of the outcome measures, and the biological significance of the findings.
Slight (⊕⊙⊙) …evidence in human studies *(signal of effect with large amount of uncertainty)*	One or more studies reporting an association between exposure and the health outcome, but considerable uncertainty exists and supporting coherent evidence is sparse. In general, the evidence is limited to a set of consistent *low* confidence studies, or *higher* confidence studies with significant unexplained heterogeneity or other serious residual uncertainties. It also applies when one *medium* or *high* confidence study is available within the unit of analysis without additional information strengthening the likelihood of a causal association (e.g., coherent findings within the same study or from other studies). This category serves primarily to encourage additional study where evidence does exist that might provide some support for an association, but for which the evidence does not reach the degree of confidence required for *moderate*.

Evidence synthesis judgment	Description
Indeterminate (⊙⊙⊙) …evidence in human studies *(signal cannot be determined for or against an effect)*	No studies available in humans or situations when the evidence is inconsistent and primarily of *low* confidence. In addition, this might include situations where higher confidence studies exist, but there are major concerns with the evidence base such as unexplained inconsistency, a lack of expected coherence from a stronger set of studies, very small effect magnitude (i.e., major concerns about biological significance), or uncertainties or methodological limitations that result in an inability to discern effects from exposure. It also applies for a single *low* confidence study in the absence of factors that increase certainty. A set of largely null studies could be concluded to be *indeterminate* if the evidence does not reach the level required for *compelling evidence of no effect*.
Compelling evidence of no effect (- - -) …in human studies *(strong signal for lack of an effect with little uncertainty)*	A set of *high* confidence studies examining a reasonable spectrum of endpoints showing null results (e.g., an odds ratio of 1.0), ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for susceptible populations). The set as a whole should include diverse sampling (across sexes [if applicable] and different populations) and include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure-response gradient, and an examination of at-risk populations and lifestages. Supplemental evidence can help to address the above considerations or, when included in the unit of analysis, provide additional support for this judgment.

Table 8-5. Framework for strength of evidence judgments from studies in animals

Evidence synthesis judgment	Description
Robust (⊕⊕⊕) …evidence in animal studies *(strong signal of effect with very little uncertainty)*	The set of *high* or *medium* confidence, independent experiments (i.e., across laboratories, exposure routes, experimental designs [for example, a subchronic study and a multigenerational study], or species) reporting effects of exposure on the health outcome(s). The set of studies is primarily consistent, with reasonable explanations when results differ (i.e., due to differences in study design, exposure level, animal model, or study confidence), and the findings are considered adverse (i.e., biologically significant and without notable concern for indirectness). At least two of the following additional factors in the set of experiments increase certainty in the evidence: coherent effects across multiple related endpoints (within or across biologically related units of analysis); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across animal lifestages, sexes, or strains. Supplemental evidence included in the unit of analysis (e.g., mechanistic studies in exposed animals or animal cells) might raise the certainty of evidence to *robust* for a set of studies that otherwise would be described as *moderate*. Such evidence not included in the unit of analysis can also inform evaluations of the coherence of the animal evidence, the directness of the outcome measures, and the biological significance of the findings.

Evidence synthesis judgment	Description
Moderate (⊕⊕⊙) …evidence in animal studies *(signal of effect with some uncertainty)*	A set of evidence that does not reach the degree of certainty required for *robust*, but which includes at least one *high* or *medium* confidence study and additional information increasing certainty in the evidence. For multiple studies or a single study, the evidence is primarily consistent or coherent with reasonable support for adversity, but there are notable remaining uncertainties (e.g., difficulty interpreting the findings due to concerns for indirectness of some measures); however, these uncertainties are not sufficient to reduce or discount the level of concern regarding the positive findings and any conflicting findings are from a set of experiments of lower confidence. The set of experiments supporting the effect provide additional information increasing certainty in the evidence, such as consistent effects across laboratories or species; coherent effects across multiple related endpoints (can include mechanistic endpoints within the unit of analysis); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across exposure scenarios (e.g., route, timing, duration), sexes, or animal strains. Supplemental evidence included in the unit of analysis could address the above factors and raise certainty in the evidence to *moderate* for a set of studies that otherwise would be described as *slight* or, in exceptional cases, might support raising to *moderate* evidence that would otherwise be described as *indeterminate*. Mechanistic evidence not included in the unit of analysis can also inform evaluations of the coherence of the animal evidence, the directness of the outcome measures, and the biological significance of the findings.
Slight (⊕⊙⊙) …evidence in animal studies *(signal of effect with large amount of uncertainty)*	One or more studies reporting an effect on an exposure on the health outcome, but considerable uncertainty exists and supporting coherent evidence is sparse. In general, the evidence is limited to a set of consistent *low* confidence studies, or higher confidence studies with significant unexplained heterogeneity or other serious uncertainties (e.g., concerns about adversity) across studies. It also applies when one *medium* or *high* confidence experiment is available within the unit of analysis without additional information increasing certainty in the evidence (e.g., coherent findings within the same study or from other studies). Biological evidence from mechanistic studies could also be independently interpreted as s*light*. This category serves primarily to encourage additional study where evidence does exist that might provide some support for an association, but for which the evidence does not reach the degree of confidence required for *moderate*.
Indeterminate (⊙⊙⊙) …evidence in animal studies *(signal cannot be determined for or against an effect)*	No studies available in animals or situations when the evidence is inconsistent and primarily of *low* confidence. In addition, this might include situations where higher confidence studies exist, but there are major concerns with the evidence base such as unexplained inconsistency, a lack of expected coherence from a stronger set of studies, very small effect magnitude (i.e., major concerns about biological significance), or uncertainties or methodological limitations that result in an inability to discern effects from exposure. It also applies for a single *low* confidence study in the absence of factors that increase certainty. A set of largely null studies could be concluded to be *indeterminate* if the evidence does not reach the level required for c*ompelling evidence of no effect*.

Evidence synthesis judgment	Description
Compelling evidence of no effect (- - -) …in animal studies *(strong signal for lack of an effect with little uncertainty)*	A set of *high* confidence experiments examining a reasonable spectrum of endpoints that demonstrate a lack of biologically significant effects across multiple species, both sexes, and a broad range of exposure levels. The data are compelling in that the experiments have examined the range of scenarios across which health effects in animals could be observed, and an alternative explanation (e.g., inadequately controlled features of the studies' experimental designs; inadequate sample sizes) for the observed lack of effects is not available. Each of the studies should have used an optimal endpoint and exposure assessment and adequate sample size. The evidence base should represent both sexes and address potentially susceptible populations and lifestages. Supplemental evidence can help to address the above considerations or, when included in the unit of analysis, provide additional support for this judgment.

8.2. EVIDENCE INTEGRATION

The phase of evidence integration combines animal and human evidence synthesis judgments while also considering information on the human relevance of findings in animal evidence, coherence across evidence streams ("cross-stream coherence"), information on susceptible populations or lifestages, understanding of biological plausibility or MOA, and potentially other critical inferences (e.g., read-across analyses) that generally draw on mechanistic and other supplemental evidence (see Table 8-6). This analysis culminates in an evidence integration judgment and narrative for each potential health effect category (i.e., each noncancer health effect and specific type of cancer, or broader grouping of related outcomes as defined during problem formulation). To the extent it can be characterized prior to conducting dose-response analyses, exposure context is also provided.

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 noncancer toxicity values for uranium are likely to be based directly on human and mammalian studies of uranium's apical effects. If a mechanistic analysis is considered necessary to assist with the interpretation and integration of the epidemiological and experimental evidence of a specific hazard or health effect, EPA will rely on previous reviews and analyses to identify relevant pathways and key studies (see Section 4.5).

With respect to susceptibility, the assessment describes the evidence (i.e., human, animal, mechanistic) on populations and lifestages most likely to be susceptible to the hazards identified and, to the extent possible, the factors that increase their risk for the hazards. In addition to assessment-specific health effects evidence, background information about biological mechanisms or ADME, as well as biochemical and physiological differences among lifestages and sexes, may be used. At a minimum, particular consideration is given to infants and children, pregnant women, and women of childbearing age. Many of the foundational analyses for summarizing susceptibility in the evidence integration narrative are undertaken during evidence synthesis as patterns across studies are evaluated with respect to consistency, coherence, and the magnitude and direction of effect measures. Relevant factors for exploring patterns may include intrinsic factors (e.g., age, sex,

genetics, health status, behaviors) and certain extrinsic factors (e.g., socioeconomic status, access to healthcare), although information on the latter is rarely available in human health studies of environmental chemicals.

Table 8-6. Considerations that inform evidence integration judgments

Judgment	Description
Human relevance of findings	Used to describe and justify the interpreted relevance of the data from experimental animals (or other model systems) to humans. In the absence of chemical-specific evidence informing human relevance, the evidence integration narrative will briefly describe the interpreted underlying biological similarity across species. As noted in EPA guidelines (U.S. EPA, 2005a), there needs to be evidence or a biological explanation to support an interpreted lack of human relevance for findings in animals, and site concordance is neither expected nor required. Thus, in the absence of specific evidence or cross-species understanding of the underlying biology, it is appropriate to use a statement such as, "without evidence to the contrary, [health effect] responses in animals are presumed relevant to humans."
Cross-stream coherence	Used to address the concordance of biologically related findings across human, animal, and mechanistic studies, considering features of the available evidence such as exposure timing and cancer), it is not necessary or expected that effects manifest in humans are identical to those observed in animals (e.g., tumors in animals can be predictive of carcinogenic potential in humans, but not necessarily at the same site), although this typically provides stronger evidence. Biological understanding of the manner in which the outcomes are manifest in different species can inform cross-stream coherence. Evidence supporting a biologically plausible mechanistic pathway across species adds coherence (see below).
Susceptible populations and lifestages	Used to summarize analyses relating to individual and social factors that may increase susceptibility to exposure-related health effects in certain populations or lifestages, or to highlight the lack of such information. These analyses are based on knowledge about the health outcome or organ system affected and focus on the influence of intrinsic biological factors but can also include consideration of mechanistic and ADME evidence.
Biological plausibility and MOA considerations	Used to summarize the interpreted biological plausibility of an association between exposure and the health effect, based primarily on the extent to which the available evidence comports with the known development and characteristics of the health effect (and thus dependent on sufficient information being available to draw such an interpretation). Importantly, because this interpretation is dependent on canonical scientific knowledge about the health effect, the lack of such understanding does not provide a rationale to decrease certainty in the evidence for an effect (NTP, 2015; NRC, 2014). These analyses can be detailed (e.g., when attempting to establish MOA understanding) and, if so, are typically conducted separately (e.g., as part of the mechanistic evidence synthesis) and then referenced in the evidence integration narrative.
Other critical inferences (optional)	Can be used to describe the consideration of other evidence or non-chemical-specific information that informs evidence integration judgments (e.g., use of read-across analyses or ADME understanding used to inform the other considerations described below; judgments on other health effects expected to be linked to the health effect under evaluation).

ADME = absorption, distribution, metabolism, and excretion; MOA = mode of action.

Using a structured framework approach, one of five phrases is used to summarize the evidence integration judgment based on the integration of the evidence synthesis judgments, taking into account the additional considerations assessed across evidence streams: *evidence demonstrates*, *evidence indicates (likely)*, *evidence suggests*, *evidence is inadequate*, or *strong evidence supports no effect* (see Table 8-7). The five evidence integration judgment levels reflect the differences in the amount and quality of the data that inform the evaluation of whether exposure is interpreted as capable of causing the health effect(s). As it is assumed that any identified health hazards will only be manifest given exposures of a certain type and amount (e.g., a specific route; a minimal duration, periodicity, and level), the evidence integration narrative and summary judgment levels include the generic phrase, "given sufficient exposure conditions." This highlights that, for those assessment-specific health effects identified as potential hazards, the exposure conditions associated with those health effects will be defined (as will the uncertainties in the ability to define those conditions) during dose-response analysis (see Section 9). More than one evidence integration judgment level can be used when the evidence base is able to support that a chemical's effects differ by exposure level or route (U.S. EPA, 2005a). The analyses and judgments are summarized in the evidence profile table (see Table 8-1).

Similar to the description for summarizing noncancer judgments above, the cancer descriptor and evidence integration narrative for carcinogenicity also consider the conditions of carcinogenicity, including exposure (e.g., route; level) and susceptibility (e.g., genetics; lifestage), as the data allow (Farland, 2005; U.S. EPA, 2005a, b). As with noncancer effects, the specific exposure conditions necessary for carcinogenicity are further defined during dose-response analysis.

Table 8-7. Framework for summary evidence integration judgments in the evidence integration narrative

Summary evidence integration judgment[a] in narrative	Evidence integration judgment level	Explanation and example scenarios[b]
The currently available ***evidence demonstrates*** that [chemical] causes [health effect] in humans[c] given sufficient exposure conditions. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration[d]].	**Evidence demonstrates**	A strong evidence base demonstrating that [chemical] exposure causes [health effect] in humans. • This conclusion level is used if there is *robust* human evidence supporting an effect. • This conclusion level could also be used with *moderate* human evidence and robust animal evidence if there is strong mechanistic evidence that MOAs and key precursors identified in animals are anticipated to occur and progress in humans.
The currently available **evidence indicates** that [chemical] likely causes [health effect] in humans given sufficient exposure conditions. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration].	**Evidence indicates (likely[e])**	An evidence base that indicates that [chemical] exposure likely causes [health effect] in humans, although there may be outstanding questions or limitations that remain, and the evidence is insufficient for the higher conclusion level. • This conclusion level is used if there is *robust* animal evidence supporting an effect and *slight-to-indeterminate* human evidence, or with *moderate* human evidence when strong mechanistic evidence is lacking. • This conclusion level could also be used with *moderate* human evidence supporting an effect and *moderate-to-indeterminate* animal evidence, or with *moderate* animal evidence supporting an effect and *moderate-to-indeterminate* human evidence. In these scenarios, any uncertainties in the *moderate* evidence are not sufficient to substantially reduce confidence in the reliability of the evidence, or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., precursors) exists to increase confidence in the reliability of the moderate evidence.

Summary evidence integration judgment[a] in narrative	**Evidence integration judgment level**	**Explanation and example scenarios[b]**
The currently available evidence suggests that [chemical] may cause [health effect] in humans given sufficient exposure conditions. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration].	**Evidence suggests**	An evidence base that suggests that [chemical] exposure may cause [health effect] in humans, but there are very few studies that contributed to the evaluation, the evidence is very weak or conflicting, and/or the methodological conduct of the studies is poor. • This conclusion level is used if there is *slight* human evidence and i*ndeterminate-to-slight* animal evidence. • This conclusion level is also used with slight animal evidence and *indeterminate-to-slight* human evidence. • This conclusion level could also be used with *moderate* human evidence and s*light* or *indeterminate* animal evidence, or with *moderate* animal evidence and slight or indeterminate human evidence. In these scenarios, there are outstanding issues or uncertainties regarding the *moderate* evidence (i.e., the synthesis judgment was borderline with *slight*), or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., null results in well-conducted evaluations of precursors) exists to decrease confidence in the reliability of the *moderate* evidence. • Exceptionally, when there is general scientific understanding of mechanistic events that result in a health effect, this conclusion level could also be used if there is strong mechanistic evidence that is sufficient to highlight potential human toxicity[f]—in the absence of informative conventional studies in humans or in animals (i.e., *indeterminate* evidence in both).

Summary evidence integration judgment[a] in narrative	Evidence integration judgment level	Explanation and example scenarios[b]
The currently available evidence is inadequate to assess whether [chemical] may cause [health effect] in humans.	**Evidence inadequate**	his conveys either a lack of information or an inability to interpret the available evidence for [health effect]. On an assessment-specific basis, a single use of this "*inadequate*" conclusion level might be used to characterize the evidence for multiple health effect categories (i.e., all health effects that were examined and did not support other conclusion levels).[g] • This conclusion level is used if there is *indeterminate* human and animal evidence. • This conclusion level is also used with *slight* animal evidence and compelling evidence of no effect human evidence. • This conclusion level could also be used with *slight-to-robust* animal evidence and *indeterminate* human evidence if strong mechanistic information indicated that the animal evidence is unlikely to be relevant to humans. A conclusion of ***inadequate*** is not a determination that the agent does not cause the indicated health effect(s). It simply indicates that the available evidence is insufficient to reach conclusions.

Summary evidence integration judgment[a] in narrative	Evidence integration judgment level	Explanation and example scenarios[b]
Strong evidence supports no effect in humans. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations].	**Strong evidence supports no effect** in humans. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations].	This represents a situation in which extensive evidence across a range of populations and exposure levels has identified no effects/associations. This scenario requires a *high* degree of confidence in the conduct of individual studies, including consideration of study sensitivity, and comprehensive assessments of the endpoints and lifestages of exposure relevant to the heath effect of interest. • This conclusion level is used if there is compelling evidence of no effect in human studies and compelling evidence of no effect to indeterminate in animals. • This conclusion level is also used if there is *indeterminate* human evidence and *compelling evidence of no effect* animal evidence in models concluded to be relevant to humans. • This conclusion level could also be used with compelling evidence of no effect in human studies and *moderate-to-robust* animal evidence if strong mechanistic information indicated that the animal evidence is unlikely to be relevant to humans.

[a]Evidence integration judgments are typically developed at the level of the health effect when there are sufficient studies on the topic to evaluate the evidence at that level; this should always be the case for "evidence demonstrates" and "strong evidence supports no effect," and typically for "evidence indicates (likely)." However, some databases only allow for evaluations at the category of health effects examined; this will more frequently be the case for conclusion levels of "evidence suggests" and "evidence inadequate." A judgment of "strong evidence supports no effect" is drawn at the health effect level.

[b]Terminology of "is" refers to the default option; terminology of "could also be" refers to situational options dependent on mechanistic understanding.

[c]In some assessments, these conclusions might be based on data specific to a particular lifestage of exposure, sex, or population (or another specific group). In such cases, this would be specified in the narrative conclusion, with additional detail provided in the narrative text. This applies to all conclusion levels.

[d]If concentrations cannot be estimated, an alternative expression of exposure level such as "occupational exposure levels," are provided. This applies to all conclusion levels.

[e]For some applications, such as benefit-cost analysis, categories of "evidence demonstrates" and "evidence indicates," should be interpreted as evidence that supports an exposure-effect linkage that is likely to be causal.

[f]Scientific understanding of adverse outcome pathway (AOPs) and of the human implications of new toxicity testing methods (e.g., from high-throughput screening, from short-term in vivo testing of alternative species or from new in vitro testing) will continue to increase. This may make possible the development of hazard conclusions when there are mechanistic or other relevant data that can be interpreted with a similar level of confidence to positive animal results in the absence of conventional studies in humans or in animals.

[g]Specific narratives for each of these health effects may also be deemed unnecessary.

9. DOSE-RESPONSE ASSESSMENT: STUDY SELECTION AND QUANTITATIVE ANALYSIS

9.1. OVERVIEW

Selection of specific datasets for dose-response assessment and performance of the dose-response assessment is conducted after hazard identification is complete and involves database- and chemical-specific biological judgments. A number of EPA guidance and support documents detail data requirements and other considerations for dose-response modeling, especially EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b), EPA's *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2005a, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). This section of the protocol provides an overview of considerations for conducting the dose-response assessment, particularly statistical considerations specific to dose-response analysis that support quantitative risk assessment. Importantly, these considerations do not supersede existing EPA guidance.

The focus of this assessment is to develop an oral noncancer reference dose (RfD). An RfD-is an estimate, with uncertainty spanning perhaps an order of magnitude, of an exposure to the human population (including susceptible populations and life stages) that is likely to be without an appreciable risk of deleterious health effects over a lifetime (U.S. EPA, 2002). A reference concentration (RfC) for inhalation noncancer will not be derived, nor will inhalation unit risk and oral slop factors to characterize cancer dose response.

The derivation of noncancer toxicity values depends on the nature of the hazard conclusion. For noncancer outcomes dose-response is conducted based on having stronger evidence of a hazard (generally, "*evidence demonstrates*" and "*evidence indicates [likely].*" When the noncancer outcome is considered "*evidence suggests*" of potential hazard to humans, EPA generally would not conduct a dose-response assessment and derive a RfD. Cases where suggestive evidence might be used to develop a noncancer toxicity value include when the evidence base includes a well-conducted study (overall *medium* or *high* confidence for the outcome), quantitative analyses may be useful for some purposes, (e.g., providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities) (U.S. EPA, 2005a).

Dose-response assessments for noncancer hazards are typically performed following chronic exposure[14] to the chemical of interest, if supported by existing data. In addition to an RfD,

[14]Dose-response assessments may also be conducted for shorter durations, particularly if the evidence base for a chemical indicates risks associated with shorter exposures to the chemical (U.S. EPA, 2002).

this assessment will attempt to derive organ- or system-specific RfDs (osRfDs) when the data are sufficiently strong (i.e., noncancer conclusions of *evidence demonstrate* or *evidence indicates [likely]*). If the available data are appropriate for doing so, the assessments will derive a less-than-lifetime toxicity value (a "subchronic" reference dose) for noncancer hazards. Both less-than-lifetime and hazard-specific values may be useful to EPA risk assessors within specific decision contexts.

9.2. SELECTING STUDIES FOR DOSE-RESPONSE ASSESSMENT

The assessment presents a summary of hazard identification conclusions to transition to dose response considerations, highlighting the feasibility of extracting, or deriving, a dose-response function corresponding to each identified hazard. If PODs are based on modeled internal dose levels, there will need to be physiologically based pharmacokinetic (PBPK) modeling to convert internal POD into human equivalent doses ($POD_{(HED)}$s). If such PBPK models have not been established, then it may not be feasible to derive $POD_{(HED)}$s. Once the feasibility of using dose-response information to derive PODs has been established, the next step is to identify and justify the selection of one or more benchmark response (BMR) levels for the derivation of points of departure (PODs).

The pool of outcomes and study-specific endpoints is discussed to identify which categories of effects and study designs are considered the strongest and most appropriate for quantitative assessment of a given health effect, particularly among the studies that exemplify the study attributes summarized in Table 9-1. Consideration will also be given as to whether toxicity values can be derived to protect specific populations or life stages.

Also considered is whether there are opportunities for quantitative evidence integration. Examples of quantitative integration, from simplest to more complex, include (1) combining results for an outcome across sex (within a study); (2) characterizing overall toxicity, as in combining effects that comprise a syndrome, or occur on a continuum (e.g., precursors and eventual overt toxicity, benign tumors that progress to malignant tumors); and (3) conducting a meta-analysis or meta-regression of all studies addressing a category of important health effects.

Some studies that are used qualitatively for hazard identification may or may not be useful quantitatively for dose-response assessment due to such factors as the lack of quantitative measures of exposure or lack of variability measures for response data. If the needed information cannot be located, semiquantitative analysis may be feasible (e.g., via NOAEL/LOAEL). In the draft and final assessments, specific endpoints considered for dose response are summarized in a tabular format that includes rationales for decisions to proceed (or not) for POD derivation. In addition, mechanistic evidence that influences the dose-response analyses is highlighted, for example, evidence related to susceptibility or other uncertainty factors, or if MOA may influence the potential shape of the dose-response curve (i.e., linear, nonlinear, or threshold model).

Table 9-1. Attributes used to evaluate studies for derivation of toxicity values

Study attributes		Considerations	
		Human studies	**Animal studies**
Study confidence		*High* or *medium* confidence studies are highly preferred over *low* confidence studies. The selection of low confidence studies should include an additional explanatory justification (e.g., only low confidence studies had adequate data for toxicity value derivation). The available *high* and *medium* confidence studies are further differentiated on the basis of the study attributes below, as well as a reconsideration of the specific limitations identified and their potential impact on dose-response analyses.	
Rationale for choice of species		Human data are preferred over animal data to **eliminate interspecies extrapolation uncertainties** (e.g., in pharmacodynamics, dose-response pattern in relevant dose range, relevance of specific health outcomes to humans).	Animal studies provide supporting evidence when adequate human studies are available, and they are considered the studies of primary interest when adequate human studies are not available. For some hazards, studies of particular animal species known to respond similarly to humans would be preferred over studies of other species.
Relevance of exposure paradigm	Exposure route	Studies involving **human environmental exposures** (oral, inhalation).	Studies by a route of administration relevant to human environmental exposure are preferred. A validated pharmacokinetic or PBPK model can also be used to extrapolate across exposure routes.
	Exposure durations	When developing a chronic toxicity value, chronic or subchronic studies are preferred over studies of acute exposure durations. Exceptions exist, such as when a susceptible population or life stage is more sensitive in a particular time window (e.g., developmental exposure).	
	Exposure levels	Exposures near the range of typical environmental human exposures are preferred. Studies with a broad exposure range and multiple exposure levels are preferred to the extent that they can provide information about the shape of the exposure-response relationship (see the EPA *Benchmark Dose Technical Guidance*, §2.1.1) and facilitate extrapolation to more relevant (generally lower) exposures.	
Subject selection		Studies that provide risk estimates in the most susceptible groups are preferred.	
Controls for possible confounding[a]		Studies with a design (e.g., matching procedures, blocking) or analysis (e.g., covariates or other procedures for statistical adjustment) that adequately address the relevant sources of potential critical confounding for a given outcome are preferred.	

Study attributes	Considerations	
	Human studies	**Animal studies**
Measurement of exposure	Studies that can reliably distinguish between levels of exposure in a time window considered most relevant for development of a causal effect are preferred. Exposure assessment methods that provide measurements at the level of the individual and that reduce measurement error are preferred. Measurements of exposure should not be influenced by knowledge of health outcome status.	Studies providing actual measurements of exposure (e.g., analytical inhalation concentrations vs. target concentrations) are preferred. Relevant internal dose measures may facilitate extrapolation to humans, as would availability of a suitable animal PBPK model in conjunction with an animal study reported in terms of administered exposure.
Health outcome(s)	Studies that can reliably distinguish the presence or absence (or degree of severity) of the outcome are preferred. Outcome ascertainment methods using generally accepted or standardized approaches are preferred.	
	Studies with individual data are preferred in general. For example, individual data allow you to characterize experimental variability more realistically and to characterize overall incidence of individuals affected by related outcomes (e.g., phthalate syndrome).	
	Among several relevant health outcomes, preference is generally given to those outcomes with less concern for indirectness or with greater biological significance.	
Study size and design	Preference is given to studies using designs reasonably expected to have power to detect responses of suitable magnitude.[b] This does not mean that studies with substantial responses, but low power would be ignored, but that they should be interpreted in light of a confidence interval or variance for the response. Studies that address changes in the number at risk (through decreased survival, loss to follow-up) are preferred.	

[a]An exposure or other variable that is associated with both exposure and outcome but is not an intermediary between the two.

[b]Power is an attribute of the design and population parameters, based on a concept of repeatedly sampling a population; it cannot be inferred post hoc using data from one experiment (Hoenig and Heisey, 2001).

9.3. CONDUCTING DOSE-RESPONSE ASSESSMENTS

EPA uses a two-step approach for dose-response assessment that begins with analysis of the dose-response data in the range of observation. However, when data are available, they often cover only a portion of the possible range of the dose-response relationship, in which case some extrapolation must be done in order to estimate the effects of exposures that are lower than the range of data obtained from scientific studies (U.S. EPA, 2012b, 2005a):

1) **Step 1:** Take an assessment of all data that are available from selected studies or can be gathered through experiments. This is in order to document the dose-response relationship(s) over the range of observed doses (i.e., the doses that are reported in the data collected) to derive an estimated POD). See Section 9.3.1 for more details. However, frequently this range of observation may not include sufficient data to identify a dose where the adverse effect is not observed in the human population (U.S. EPA, 2022b, 2000).

2) **Step 2:** This consists of extrapolations to estimate the risk of adverse effects beyond the lower range of available observed data. This is in order to make inferences about the critical region where the dose level begins to cause the adverse effect in the human population (U.S. EPA, 2022b, 2000). See Section 9.3.2.

When sufficient and appropriate human data and laboratory animal data are both available for the same outcome, human data are generally preferred for the dose-response assessment because their use eliminates the need to perform interspecies extrapolations.

For noncancer analyses, IRIS assessments typically derive a candidate value from each suitable dataset, whether for human or animal. Evaluating these candidate values grouped within a particular organ/system yields a single organ/system-specific reference value for each organ/system under consideration. Next, evaluation of these organ/system-specific reference values results in the selection of a single overall reference value to cover all health outcomes across all organs/systems. While this overall reference value is the focus of the assessment, the organ/system-specific reference values can be useful for subsequent cumulative risk assessments that consider the combined effect of multiple agents acting at a common organ/system.

9.3.1. Dose-Response Analysis in the Range of Observation

For conducting a dose response assessment, pharmacodynamic ("biologically based") modeling can be used when there are sufficient data to ascertain the mode of action and quantitatively support model parameters that represent rates and other quantities associated with the key precursor events of the modes of action. If there is not an applicable pharmacodynamic model available to assess health effects associated with oral exposure to uranium, empirical dose-response modeling is used to fit the data (on the apical outcomes or a key precursor events) in the ranges of observation. For this purpose of empirical dose-response modeling, EPA has developed a standard set of models (http://www.epa.gov/ncea/bmds) that can be applied to typical dichotomous and continuous datasets, including those that are nonlinear. In situations where there

are alternative models with significant biological support, the users of the assessment can be informed by the presentation of these alternatives along with the models' strengths and uncertainties. The EPA has developed guidelines on modeling dose-response data, assessing model fit, selecting suitable models, and reporting modeling results [see the *EPA Benchmark Dose Technical Guidance* (U.S. EPA, 2012b)].

U.S. EPA Benchmark Dose Software (BMDS) is designed to model dose-response datasets in accordance with EPA *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). For noncancer effects, a benchmark dose lower confidence limit (BMDL) is computed from a model selected from the BMDS suite of models using statistical and graphical criteria. Additional judgments or alternative analyses may be used if initial modeling procedures fail to yield results in reasonable agreement with the data. For example, modeling may be restricted to the lower doses, especially if there is competing toxicity at higher doses. Modeling may also need to accommodate cases of nonlinear dose-response data.

For noncancer datasets, EPA recommends (1) application of a preferred set of models that use maximum likelihood estimation (MLE) methods (default models in BMDS) and (2) selection of a POD from a single model based on criteria designed to limit model selection subjectivity (auto implemented in BMDS version 3 and higher). For the linear analysis of cancer datasets, EPA recommends (1) application of the Multistage MLE model; (2) selection of a single Multistage degree; and (3) in cases where tumors are observed in multiple organ systems, use of a multi-tumor model (i.e., MS-Combo) that appropriately estimates combined tumor risk (both (2) and (3) are available in BMDS).[15]

Version 3.2 and higher of BMDS also provides an alternative modeling approach that uses Bayesian model averaging for dichotomous modeling average (DMA). EPA makes DMA available as an alternative approach but has not yet finalized guidelines for their use. DMA may be applied to uranium as a supplemental analysis.

For each modeled dataset for an outcome, a POD from the observed data should be estimated to mark the beginning of extrapolation to lower doses. The POD is an estimated dose (expressed in human equivalent terms) near the lower end of the observed range without significant extrapolation to lower doses. For linear extrapolation of cancer risk, the POD is used to calculate an OSF, and for nonlinear extrapolation, the POD is used in calculating an RfD.

The selection of the response level at which the POD is calculated is guided by the severity of the endpoint. Nonlinear approaches consider both statistical and biologic considerations. For dichotomous data, a response level of 10% extra risk is generally used for minimally adverse effects, 5% or lower for more severe effects or effects observed in studies with increased statistical sensitivity. Lower BMRs are often supported for developmental toxicity studies. For continuous

[15]The Multistage degree selection process outlined in the memo is auto-implemented in the BMDS multi tumor model, which can be run on one or more tumor datasets, but only the noncancer model selection process is auto-implemented for individual Multistage model runs in the current version, BMDS 3.2).

data, a response level is ideally based on an established definition of biologic significance. In the absence of such definition, one control standard deviation from the control mean is often used for minimally adverse effects, one-half standard deviation for more severe effects. As with dichotomous endpoints, lower BMRs may also be supported for endpoints observed in studies with greater statistical sensitivity (e.g., developmental toxicity studies). The POD is the 95% lower bound on the dose associated with the selected response level.

EPA has developed standard approaches for determining the relevant dose to be used in the dose-response modeling in the absence of appropriate pharmacokinetic modeling. These standard approaches also facilitate comparison across exposure patterns and species:

- Intermittent study exposures are standardized to a daily average over the duration of exposure. For chronic effects, daily exposures are averaged over the lifespan. Exposures during a critical period, however, are not averaged over a longer duration ((U.S. EPA, 2005a), see §3.1.1; (U.S. EPA, 1991), see §3.2). Note that this will typically be done after modeling because the conversion is linear.

- Doses are standardized to equivalent human terms to facilitate comparison of results from different species. Oral doses are scaled allometrically using $mg/kg^{3/4}day$ as the equivalent dose metric across species. Allometric scaling pertains to equivalence across species, not across life stages, and is not used to scale doses from adult humans or mature animals to infants or children (U.S. EPA, 2011a, 2005a), §3.1.3. Inhalation exposures are scaled using dosimetry models that apply species-specific physiologic and anatomic factors and consider whether the effect occurs at the site of first contact or after systemic circulation (U.S. EPA, 2012a, 1994), §3.

- It can be informative to convert doses across exposure routes. If this is done, the assessment describes the underlying data, algorithms, and assumptions (U.S. EPA, 2005a), §3.1.4.

- In the absence of study specific data on, for example, intake rates or body weight, the EPA has developed recommended values for use in dose response analysis (U.S. EPA, 1988).

- The preferred approach for dosimetry extrapolation from animals to humans is through PBPK modeling. Elements of more than one published model can be combined if the effort involved is minimal and no one model has all the features desired.

Briefly, PBPK model simulations are used to estimate internal dose metrics corresponding to the applied doses for each experimental animal bioassay. By simulating the exposure scenario for each toxicity study, the resulting internal metric effectively accounts for the difference between the pattern and a nominal daily exposure. The set of internal dose metrics for each toxicity study and endpoint can then be used in dose-response analysis to identify a BMDL or other POD for individual animal toxicity studies. In this assessment, the internal dose metric is either the tissue-specific rate of oxidative metabolism or a daily average blood concentration. The human version of the PBPK model can then be used to estimate the exposure dose that would result in an internal dose at the POD. Any remaining uncertainty factors, including the factor of 10 for human interindividual variability (UFH) will then be applied for derivation of the HECs.

9.3.2. Extrapolation: Reference Values

Reference value derivation is EPA's most frequently used type of nonlinear extrapolation method. For each dataset selected for reference value derivation, reference values are estimated by applying relevant adjustments to the PODs to account for the conditions of the reference value definition—for human variation, extrapolation from animals to humans, extrapolation to chronic exposure duration, and extrapolation to a minimal level of risk (if not observed in the dataset). Increasingly, data-based adjustments (U.S. EPA, 2014) and Bayesian methods for characterizing population variability (NRC, 2014) are feasible and may be distinguished from the UF considerations outlined below. The assessment discusses the scientific bases for estimating these data-based adjustments and UFs:

- *Animal-to-human extrapolation*: If animal results are used to make inferences about humans, the reference value derivation incorporates the potential for cross-species differences, which may arise from differences in pharmacokinetics or toxicodynamics. If available, a biologically based model that adjusts fully for pharmacokinetic and toxicodynamic differences across species may be used. Otherwise, the POD is standardized to equivalent human terms or is based on pharmacokinetic or dosimetry modeling, that may range from detailed chemical-specific to default approaches (U.S. EPA, 2014, 2011a), and a factor of $10^{1/2}$ (rounded to 3) is applied to account for the remaining uncertainty involving pharmacokinetic and toxicodynamic differences.

- *Human variation*: The assessment accounts for variation in susceptibility across the human population and the possibility that the available data may not represent individuals who are most susceptible to the effect, by using a data-based adjustment, a UF, or a combination of the two. Where appropriate data or models for the effect or for characterizing the internal dose are available, the potential for data-based adjustments for toxicodynamics or pharmacokinetics is considered (U.S. EPA, 2014, 2002).[16] [17] When sufficient data are available, an intraspecies UF either less than or greater than 10-fold may be justified (U.S. EPA, 2002). This factor may be reduced if the POD is derived from or adjusted specifically for susceptible individuals [not for a general population that includes both susceptible and non-susceptible individuals (U.S. EPA, 2002), §4.4.5; (U.S. EPA, 1998), §4.2; (U.S. EPA, 1996), §4; (U.S. EPA, 1994), §4.3.9.1; (U.S. EPA, 1991), §3.4]. When the use of such data or modeling is not supported, a UF with a default value of 10 is considered.

- *LOAEL-to-NOAEL*: If a POD is based on a LOAEL, the assessment includes an adjustment to an exposure level where such effects are not expected. This can be a matter of great uncertainty if there is no evidence available at lower exposures. A factor of 10 is generally applied to extrapolate to a lower exposure expected to be without appreciable effects. A factor other than

[16]Examples of adjusting the pharmacokinetic portion of interhuman variability include the IRIS boron assessment's use of nonchemical-specific kinetic data [e.g., glomerular filtration rate in pregnant humans as a surrogate for boron clearance (U.S. EPA, 2004)] and the IRIS trichloroethylene assessment's use of population variability in trichloroethylene metabolism, via a PBPK model, to estimate the lower 1st percentile of the dose metric distribution for each POD (U.S. EPA, 2011b).

[17]Note that when a PBPK model is available for relating human internal dose to environmental exposure, relevant portions of this UF may be more usefully applied prior to animal-to-human extrapolation, depending on the correspondence of any nonlinearities (e.g., saturation levels) between species.

10 may be used depending on the magnitude and nature of the response and the shape of the dose-response curve (U.S. EPA, 2002, 1998, 1996, 1994, 1991).

- *Subchronic-to-chronic exposure*: When using subchronic studies to make inferences about chronic/lifetime exposure, the assessment considers whether lifetime exposure could have effects at lower levels of exposure. A factor of up to 10 may be applied to the POD, depending on the duration of the studies and the nature of the response (U.S. EPA, 2002, 1998, 1994).

- *Database deficiencies*: In addition to the adjustments above, if database deficiencies raise concern that further studies might identify a more sensitive effect, organ system, or life stage, the assessment may apply a database UF (U.S. EPA, 2002, 1998, 1996, 1994, 1991). The size of the factor depends on the nature of the database deficiency. For example, the EPA typically follows the recommendation that a factor of 10 be applied if both a prenatal toxicity study and a two-generation reproduction study are missing and a factor of $10^{1/2}$ (i.e., 3) if either one or the other is missing (U.S. EPA, 2002).

The POD for a reference value (RfV) is divided by the product of these factors. (U.S. EPA, 2002) recommends that any composite factor that exceeds 3,000 represents excessive uncertainty and recommends against relying on the associated RfV.

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APPENDIX A. ELECTRONIC DATABASE SEARCH STRATEGIES

Table A-1. Database search strategy

Database	Search string	Results[a]
Scopus	((TITLE-ABS-KEY-AUTH("Uranium tetrachloride*") OR TITLE-ABS-KEY-AUTH("Uranium chloride*") OR TITLE-ABS-KEY-AUTH("Sodium diuranate*") OR TITLE-ABS-KEY-AUTH("Sodium uranate*") OR TITLE-ABS-KEY-AUTH("Sodium uranium oxide*") OR TITLE-ABS-KEY-AUTH("Disodium heptaoxodiuranate*") OR TITLE-ABS-KEY-AUTH("Ammonium uranyl tricarbonate*") OR TITLE-ABS-KEY-AUTH("Ammonium uranium carbonate*") OR TITLE-ABS-KEY-AUTH("Tetraammonium uranyl tricarbonate*") OR TITLE("uranium*") OR TITLE("diuranium*") OR TITLE("triuranium*") OR TITLE("uranic") OR TITLE("uranous") OR TITLE("uranyl") OR TITLE("uranate") OR TITLE("uranates") OR TITLE("diuranate") OR TITLE("diuranates") OR TITLE("dioxouranium") OR TITLE("uranyldifluoride") OR TITLE("uranyldifluorides") OR TITLE("diacetatodioxouranium") OR TITLE("difluorodioxouranium") OR TITLE("dinitratodioxouranium") OR TITLE("yellowcake") OR TITLE("234U") OR TITLE("235U") OR TITLE("238U") OR TITLE("u-234") OR TITLE("u-235") OR TITLE("u-238")) OR ((TITLE-ABS-KEY-AUTH("uranium*") OR TITLE-ABS-KEY-AUTH("diuranium*") OR TITLE-ABS-KEY-AUTH("triuranium*") OR TITLE-ABS-KEY-AUTH("uranic") OR TITLE-ABS-KEY-AUTH("uranous") OR TITLE-ABS-KEY-AUTH("uranyl") OR TITLE-ABS-KEY-AUTH("uranate") OR TITLE-ABS-KEY-AUTH("uranates") OR TITLE-ABS-KEY-AUTH("diuranate") OR TITLE-ABS-KEY-AUTH("diuranates") OR TITLE-ABS-KEY-AUTH("dioxouranium") OR TITLE-ABS-KEY-AUTH("uranyldifluoride") OR TITLE-ABS-KEY-AUTH("uranyldifluorides") OR TITLE-ABS-KEY-AUTH("diacetatodioxouranium") OR TITLE-ABS-KEY-AUTH("difluorodioxouranium") OR TITLE-ABS-KEY-AUTH("dinitratodioxouranium") OR TITLE-ABS-KEY-AUTH("yellowcake")) AND (((TITLE-ABS-KEY-AUTH("occupational disease*") OR TITLE-ABS-KEY-AUTH("human") OR TITLE-ABS-KEY-AUTH("humans") OR TITLE-ABS-KEY-AUTH("mammals") OR TITLE-ABS-KEY-AUTH("mammals")) AND ((TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("adverse effects")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("blood")) OR (TITLE-ABS-KEY-AUTH("Heavy") AND TITLE-ABS-KEY-AUTH("cerebrospinal fluid")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("metabolism")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("pharmacokinetics")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("poisoning")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("toxicity")) OR (TITLE-ABS-KEY-AUTH("Heavy Metals") AND TITLE-ABS-KEY-AUTH("urine")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("adverse effects")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("blood")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("metabolism")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("pharmacokinetics")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("poisoning")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-	**8,119**

Database	Search string	Results[a]
	KEY-AUTH("toxicity")) OR (TITLE-ABS-KEY-AUTH("Metals") AND TITLE-ABS-KEY-AUTH("urine")))) OR (TITLE-ABS-KEY-AUTH("chronic") OR TITLE-ABS-KEY-AUTH("immun*") OR TITLE-ABS-KEY-AUTH("lymph*") OR TITLE-ABS-KEY-AUTH("neurotox*") OR TITLE-ABS-KEY-AUTH("toxicokin*") OR TITLE-ABS-KEY-AUTH("pharmacokin*") OR TITLE-ABS-KEY-AUTH("biomarker*") OR TITLE-ABS-KEY-AUTH("neurolog*") OR TITLE-ABS-KEY-AUTH("subchronic") OR TITLE-ABS-KEY-AUTH("epidemiolog*") OR TITLE-ABS-KEY-AUTH("acute") OR TITLE-ABS-KEY-AUTH("subacute") OR TITLE-ABS-KEY-AUTH("ld50") OR TITLE-ABS-KEY-AUTH("lc50") OR TITLE-ABS-KEY-AUTH("inhal*") OR TITLE-ABS-KEY-AUTH("pulmon*") OR TITLE-ABS-KEY-AUTH("nasal") OR TITLE-ABS-KEY-AUTH("lung*") OR TITLE-ABS-KEY-AUTH("respir*") OR TITLE-ABS-KEY-AUTH("occupation*") OR TITLE-ABS-KEY-AUTH("workplace") OR TITLE-ABS-KEY-AUTH("worker*") OR TITLE-ABS-KEY-AUTH("oral") OR TITLE-ABS-KEY-AUTH("orally") OR TITLE-ABS-KEY-AUTH("ingest*") OR TITLE-ABS-KEY-AUTH("gavage") OR TITLE-ABS-KEY-AUTH("diet") OR TITLE-ABS-KEY-AUTH("diets") OR TITLE-ABS-KEY-AUTH("dietary") OR TITLE-ABS-KEY-AUTH("drinking") OR TITLE-ABS-KEY-AUTH("gastr*") OR TITLE-ABS-KEY-AUTH("intestin*") OR TITLE-ABS-KEY-AUTH("gut") OR TITLE-ABS-KEY-AUTH("sensitiz*") OR TITLE-ABS-KEY-AUTH("abort*") OR TITLE-ABS-KEY-AUTH("abnormalit*") OR TITLE-ABS-KEY-AUTH("embryo*") OR TITLE-ABS-KEY-AUTH("cleft*") OR TITLE-ABS-KEY-AUTH("fetus*") OR TITLE-ABS-KEY-AUTH("foetus*") OR TITLE-ABS-KEY-AUTH("fetal*") OR TITLE-ABS-KEY-AUTH("foetal*") OR TITLE-ABS-KEY-AUTH("fertilit*") OR TITLE-ABS-KEY-AUTH("infertil*") OR TITLE-ABS-KEY-AUTH("malform*") OR TITLE-ABS-KEY-AUTH("ovum") OR TITLE-ABS-KEY-AUTH("ova") OR TITLE-ABS-KEY-AUTH("ovary") OR TITLE-ABS-KEY-AUTH("placenta*") OR TITLE-ABS-KEY-AUTH("pregnan*") OR TITLE-ABS-KEY-AUTH("sperm") OR TITLE-ABS-KEY-AUTH("testic*") OR TITLE-ABS-KEY-AUTH("testosterone") OR TITLE-ABS-KEY-AUTH("testis") OR TITLE-ABS-KEY-AUTH("testes") OR TITLE-ABS-KEY-AUTH("epididym*") OR TITLE-ABS-KEY-AUTH("seminiferous") OR TITLE-ABS-KEY-AUTH("cervix") OR TITLE-ABS-KEY-AUTH("ovaries") OR TITLE-ABS-KEY-AUTH("ovarian") OR TITLE-ABS-KEY-AUTH("corpora lutea") OR TITLE-ABS-KEY-AUTH("corpus luteum") OR TITLE-ABS-KEY-AUTH("estrous") OR TITLE-ABS-KEY-AUTH("estrus") OR TITLE-ABS-KEY-AUTH("dermal*") OR TITLE-ABS-KEY-AUTH("dermis") OR TITLE-ABS-KEY-AUTH("skin") OR TITLE-ABS-KEY-AUTH("epiderm*") OR TITLE-ABS-KEY-AUTH("cutaneous") OR TITLE-ABS-KEY-AUTH("carcinog*") OR TITLE-ABS-KEY-AUTH("cocarcinog*") OR TITLE-ABS-KEY-AUTH("cancer") OR TITLE-ABS-KEY-AUTH("precancer") OR TITLE-ABS-KEY-AUTH("neoplas*") OR TITLE-ABS-KEY-AUTH("tumor*") OR TITLE-ABS-KEY-AUTH("tumour*") OR TITLE-ABS-KEY-AUTH("oncogen*") OR TITLE-ABS-KEY-AUTH("lymphoma*") OR TITLE-ABS-KEY-AUTH("carcinom*") OR TITLE-ABS-KEY-AUTH("genetox*") OR TITLE-ABS-KEY-AUTH("genotox*") OR TITLE-ABS-KEY-AUTH("mutagen*") OR TITLE-ABS-KEY-AUTH("nephrotox*") OR TITLE-ABS-KEY-AUTH("hepatotox*") OR TITLE-ABS-KEY-AUTH("endocrin*") OR TITLE-ABS-KEY-AUTH("estrogen*") OR TITLE-ABS-KEY-AUTH("androgen*") OR TITLE-ABS-KEY-AUTH("hormon*") OR TITLE-ABS-KEY-AUTH("blood") OR TITLE-ABS-KEY-AUTH("serum") OR TITLE-ABS-KEY-AUTH("urine") OR TITLE-ABS-KEY-AUTH("bone") OR TITLE-ABS-KEY-AUTH("bones") OR TITLE-ABS-KEY-AUTH("skelet*") OR TITLE-ABS-KEY-AUTH("rat") OR TITLE-ABS-KEY-AUTH("rats") OR TITLE-ABS-KEY-AUTH("mouse") OR TITLE-ABS-KEY-AUTH("mice") OR TITLE-ABS-KEY-AUTH("guinea") OR TITLE-ABS-KEY-AUTH("muridae") OR TITLE-ABS-KEY-AUTH("rabbit*") OR TITLE-ABS-KEY-AUTH("lagomorph*") OR TITLE-ABS-	

Database	Search string	Results[a]
	KEY-AUTH("hamster*") OR TITLE-ABS-KEY-AUTH("ferret*") OR TITLE-ABS-KEY-AUTH("gerbil*") OR TITLE-ABS-KEY-AUTH("rodent*") OR TITLE-ABS-KEY-AUTH("dog") OR TITLE-ABS-KEY-AUTH("dogs") OR TITLE-ABS-KEY-AUTH("beagle*") OR TITLE-ABS-KEY-AUTH("canine") OR TITLE-ABS-KEY-AUTH("cats") OR TITLE-ABS-KEY-AUTH("feline") OR TITLE-ABS-KEY-AUTH("pig") OR TITLE-ABS-KEY-AUTH("pigs") OR TITLE-ABS-KEY-AUTH("swine") OR TITLE-ABS-KEY-AUTH("porcine") OR TITLE-ABS-KEY-AUTH("monkey*") OR TITLE-ABS-KEY-AUTH("macaque*") OR TITLE-ABS-KEY-AUTH("baboon*") OR TITLE-ABS-KEY-AUTH("marmoset*") OR TITLE-ABS-KEY-AUTH("toxic*") OR TITLE-ABS-KEY-AUTH("adverse") OR TITLE-ABS-KEY-AUTH("poisoning") OR TITLE-ABS-KEY-AUTH("prenatal") OR TITLE-ABS-KEY-AUTH("perinatal") OR TITLE-ABS-KEY-AUTH("postnatal") OR TITLE-ABS-KEY-AUTH("reproduc*") OR TITLE-ABS-KEY-AUTH("steril*") OR TITLE-ABS-KEY-AUTH("teratogen*") OR TITLE-ABS-KEY-AUTH("sperm*") OR TITLE-ABS-KEY-AUTH("neonat*") OR TITLE-ABS-KEY-AUTH("newborn*") OR TITLE-ABS-KEY-AUTH("development*") OR TITLE-ABS-KEY-AUTH("zygote*") OR TITLE-ABS-KEY-AUTH("child") OR TITLE-ABS-KEY-AUTH("children") OR TITLE-ABS-KEY-AUTH("adolescen*") OR TITLE-ABS-KEY-AUTH("infant*") OR TITLE-ABS-KEY-AUTH("wean*") OR TITLE-ABS-KEY-AUTH("offspring") OR TITLE-ABS-KEY-AUTH("age factor") OR TITLE-ABS-KEY-AUTH("age factors") OR TITLE-ABS-KEY-AUTH("Genomics") OR TITLE-ABS-KEY-AUTH("Proteomics") OR TITLE-ABS-KEY-AUTH("Metabolic Profile") OR TITLE-ABS-KEY-AUTH("Metabolome") OR TITLE-ABS-KEY-AUTH("Metabolomics") OR TITLE-ABS-KEY-AUTH("Microarray") OR TITLE-ABS-KEY-AUTH("Nanoarray") OR TITLE-ABS-KEY-AUTH("Gene expression") OR TITLE-ABS-KEY-AUTH("Transcript expression") OR TITLE-ABS-KEY-AUTH("transcriptomes") OR TITLE-ABS-KEY-AUTH("transcriptome") OR TITLE-ABS-KEY-AUTH("Phenotype") OR TITLE-ABS-KEY-AUTH("Transcription") OR TITLE-ABS-KEY-AUTH("Trans-act*") OR TITLE-ABS-KEY-AUTH("transact*") OR TITLE-ABS-KEY-AUTH("trans act*") OR TITLE-ABS-KEY-AUTH("genetic") OR TITLE-ABS-KEY-AUTH("genetics") OR TITLE-ABS-KEY-AUTH("genotype") OR TITLE-ABS-KEY-AUTH("messenger RNA") OR TITLE-ABS-KEY-AUTH("transfer RNA") OR TITLE-ABS-KEY-AUTH("peptide biosynthesis") OR TITLE-ABS-KEY-AUTH("protein biosynthesis") OR TITLE-ABS-KEY-AUTH("protein synthesis") OR TITLE-ABS-KEY-AUTH("RT-PCR") OR TITLE-ABS-KEY-AUTH("RTPCR") OR TITLE-ABS-KEY-AUTH("Reverse Transcriptase Polymerase Chain Reaction") OR TITLE-ABS-KEY-AUTH("DNA sequence") OR TITLE-ABS-KEY-AUTH("renal") OR TITLE-ABS-KEY-AUTH("kidney*") OR TITLE-ABS-KEY-AUTH("urinary") OR TITLE-ABS-KEY-AUTH("liver") OR TITLE-ABS-KEY-AUTH("hepat*") OR TITLE-ABS-KEY-AUTH("osseous") OR TITLE-ABS-KEY-AUTH("ossif*") OR TITLE-ABS-KEY-AUTH("behavioral") OR TITLE-ABS-KEY-AUTH("behavioural") OR TITLE-ABS-KEY-AUTH("brain") OR TITLE-ABS-KEY-AUTH("nervous system") OR ((TITLE-ABS-KEY-AUTH("Genetic transcription") OR TITLE-ABS-KEY-AUTH("Gene transcription") OR TITLE-ABS-KEY-AUTH("Gene Activation") OR TITLE-ABS-KEY-AUTH("Genetic induction") OR TITLE-ABS-KEY-AUTH("Reverse transcription") OR TITLE-ABS-KEY-AUTH("Transcriptional activation") OR TITLE-ABS-KEY-AUTH("Transcription factors") OR TITLE-ABS-KEY-AUTH("Biosynthesis"))AND (TITLE-ABS-KEY-AUTH("RNA") OR TITLE-ABS-KEY-AUTH("DNA") OR TITLE-ABS-KEY-AUTH("mRNA"))) OR ((TITLE-ABS-KEY-AUTH("Informatics") OR TITLE-ABS-KEY-AUTH("Information Science") OR TITLE-ABS-KEY-AUTH("Medical") OR TITLE-ABS-KEY-AUTH("Systems biology") OR TITLE-ABS-KEY-AUTH("Biological systems"))AND(TITLE-ABS-KEY-AUTH("monit*") OR TITLE-ABS-KEY-AUTH("data") OR TITLE-ABS-KEY-AUTH("analysis"))))))) AND (LIMIT-TO(SUBJAREA,"BIOC") OR LIMIT-TO(SUBJAREA, "ENVI") OR LIMIT-TO(SUBJAREA,	

Database	Search string	Results[a]
	"MEDI") OR LIMIT-TO(SUBJAREA, "AGRI") OR LIMIT-TO(SUBJAREA, "PHAR") OR LIMIT-TO (SUBJAREA, "IMMU") OR LIMIT-TO(SUBJAREA, "NEUR") OR LIMIT-TO(SUBJAREA, "VETE")) AND PUBYEAR AFT 2010	
WoS	((TS="Uranium tetrachloride*" OR TS="Uranium chloride*" OR TS="Sodium diuranate*" OR TS="Sodium uranate*" OR TS="Sodium uranium oxide*" OR TS="Disodium heptaoxodiuranate*" OR TS="Ammonium uranyl tricarbonate*" OR TS="Ammonium uranium carbonate*" OR TS="Tetraammonium uranyl tricarbonate*" OR TI="uranium*" OR TI="diuranium*" OR TI="triuranium*" OR TI="uranic" OR TI="uranous" OR TI="uranyl" OR TI="uranate" OR TI="uranates" OR TI="diuranate" OR TI="diuranates" OR TI="dioxouranium" OR TI="uranyldifluoride*" OR TI="uranyldifluorides" OR TI="diacetatodioxouranium" OR TI="difluorodioxouranium" OR TI="dinitratodioxouranium" OR TI="yellowcake" OR TI="234U" OR TI="235U" OR TI="238U" OR TI="u-234" OR TI="u-235" OR TI="u-238") OR ((TS="uranium*" OR TS="diuranium*" OR TS="triuranium*" OR TS="uranic" OR TS="uranous" OR TS="uranyl" OR TS="uranate" OR TS="uranates" OR TS="diuranate" OR TS="diuranates" OR TS="dioxouranium" OR TS="uranyldifluoride" OR TS="uranyldifluorides" OR TS="diacetatodioxouranium" OR TS="difluorodioxouranium" OR TS="dinitratodioxouranium" OR TS="yellowcake") AND (((TS="occupational disease*" OR TS="humans" OR TS="human" OR TS="mammals" OR TS="mammal") AND ((TS="Heavy Metals" AND TS="adverse effects") OR (TS="Heavy Metals" AND TS="blood") OR (TS="Heavy" AND TS="cerebrospinal fluid") OR (TS="Heavy Metals" AND TS="metabolism") OR (TS="Heavy Metals" AND TS="pharmacokinetics") OR (TS="Heavy Metals" AND TS="poisoning") OR (TS="Heavy Metals" AND TS="toxicity") OR (TS="Heavy Metals" AND TS="urine") OR (TS="Metals" AND TS="adverse effects") OR (TS="Metals" AND TS="blood") OR (TS="Metals" AND TS="metabolism") OR (TS="Metals" AND TS="pharmacokinetics") OR (TS="Metals" AND TS="poisoning") OR (TS="Metals" AND TS="toxicity") OR (TS="Metals" AND TS="urine"))) OR (TS="chronic" OR TS="immun*" OR TS="lymph*" OR TS="neurotox*" OR TS="toxicokin*" OR TS="pharmacokin*" OR TS="biomarker*" OR TS="neurolog*" OR TS="subchronic" OR TS="epidemiolog*" OR TS="acute" OR TS="subacute" OR TS="ld50" OR TS="lc50" OR TS="inhal*" OR TS="pulmon*" OR TS="nasal" OR TS="lung*" OR TS="respir*" OR TS="occupation*" OR TS="workplace" OR TS="worker*" OR TS="oral" OR TS="orally" OR TS="ingest*" OR TS="gavage" OR TS="diet" OR TS="diets" OR TS="dietary" OR TS="drinking" OR TS="gastr*" OR TS="intestin*" OR TS="gut" OR TS="sensitiz*" OR TS="abort*" OR TS="abnormalit*" OR TS="embryo*" OR TS="cleft*" OR TS="fetus*" OR TS="foetus*" OR TS="fetal*" OR TS="foetal*" OR TS="fertilit*" OR TS="infertil*" OR TS="malform*" OR TS="ovum" OR TS="ova" OR TS="ovary" OR TS="placenta*" OR TS="pregnan*" OR TS="sperm" OR TS="testic*" OR TS="testosterone" OR TS="testis" OR TS="testes" OR TS="epididym*" OR TS="seminiferous" OR TS="cervix" OR TS="ovaries" OR TS="ovarian" OR TS="corpora lutea" OR TS="corpus luteum" OR TS="estrous" OR TS="estrus" OR TS="dermal*" OR TS="dermis" OR TS="skin" OR TS="epiderm*" OR TS="cutaneous" OR TS="carcinog*" OR TS="cocarcinog*" OR TS="cancer" OR TS="precancer" OR TS="neoplas*" OR TS="tumor*" OR TS="tumour*" OR TS="oncogen*" OR TS="lymphoma*" OR TS="carcinom*" OR TS="genetox*" OR TS="genotox*" OR TS="mutagen*" OR TS="nephrotox*" OR TS="hepatotox*" OR TS="endocrin*" OR TS="estrogen*" OR TS="androgen*" OR TS="hormon*" OR TS="blood" OR TS="serum" OR TS="urine" OR TS="bone" OR TS="bones" OR TS="skelet*" OR TS="rat" OR TS="rats" OR TS="mouse" OR TS="mice" OR TS="guinea" OR	**18,396**

Database	Search string	Results[a]
	TS="muridae" OR TS="rabbit*" OR TS="lagomorph*" OR TS="hamster*" OR TS="ferret*" OR TS="gerbil*" OR TS="rodent*" OR TS="dog" OR TS="dogs" OR TS="beagle*" OR TS="canine" OR TS="cats" OR TS="feline" OR TS="pig" OR TS="pigs" OR TS="swine" OR TS="porcine" OR TS="monkey*" OR TS="macaque*" OR TS="baboon*" OR TS="marmoset*" OR TS="toxic*" OR TS="adverse" OR TS="poisoning" OR TS="prenatal" OR TS="perinatal" OR TS="postnatal" OR TS="reproduc*" OR TS="steril*" OR TS="teratogen*" OR TS="sperm*" OR TS="neonat*" OR TS="newborn*" OR TS="development*" OR TS="zygote*" OR TS="child" OR TS="children" OR TS="adolescen*" OR TS="infant*" OR TS="wean*" OR TS="offspring" OR TS="age factor" OR TS="age factors" OR TS="Genomics" OR TS="Proteomics" OR TS="Metabolic Profile" OR TS="Metabolome" OR TS="Metabolomics" OR TS="Microarray" OR TS="Nanoarray" OR TS="Gene expression" OR TS="Transcript expression" OR TS="transcriptomes" OR TS="transcriptome" OR TS="Phenotype" OR TS="Transcription" OR TS="Trans-act*" OR TS="transact*" OR TS="trans act*" OR TS="genetic" OR TS="genetics" OR TS="genotype" OR TS="messenger RNA" OR TS="transfer RNA" OR TS="peptide biosynthesis" OR TS="protein biosynthesis" OR TS="protein synthesis" OR TS="RT-PCR" OR TS="RTPCR" OR TS="Reverse Transcriptase Polymerase Chain Reaction" OR TS="DNA sequence" OR TS="renal" OR TS="kidney*" OR TS="urinary" OR TS="liver" OR TS="hepat*" OR TS="osseous" OR TS="ossif*" OR TS="behavioral" OR TS="behavioural" OR TS="brain" OR TS="nervous system" OR ((TS="Genetic transcription" OR TS="Gene transcription" OR TS="Gene Activation" OR TS="Genetic induction" OR TS="Reverse transcription" OR TS="Transcriptional activation" OR TS="Transcription factors" OR TS="Biosynthesis")AND (TS="RNA" OR TS="DNA" OR TS="mRNA")) OR ((TS="Informatics" OR TS="Information Science" OR TS="Medical" OR TS="Systems biology" OR TS="Biological systems")AND(TS="monit*" OR TS="data" OR TS="analysis"))))))AND PY=(2011-2021)	
PubMed	("uranium"[MeSH Terms] OR "Uranyl Nitrate"[mh] OR "uranium compounds"[MeSH Terms] OR 7440-61-1[rn] OR 1344-57-6[rn] OR 1344-58-7[EC/RN Number] OR 12036-71-4[EC/RN Number] OR 1344-59-8[EC/RN Number] OR 10049-14-6[EC/RN Number] OR 7783-81-5[EC/RN Number] OR 13536-84-0[EC/RN Number] OR 541-09-3[rn] OR 6159-44-0[rn] OR 10102-06-4[rn] OR 7783-22-4[EC/RN Number] OR 18378-88-6[rn] OR 12179-35-0[rn] OR 23243-55-2[rn]) AND ("Uranium/adverse effects"[Mesh] OR "Uranium/antagonists and inhibitors"[Mesh] OR "Uranium/blood"[Mesh] OR "Uranium/immunology"[Mesh] OR "Uranium/metabolism"[Mesh] OR "Uranium/pharmacokinetics"[Mesh] OR "Uranium/poisoning"[Mesh] OR "Uranium/radiation effects"[Mesh] OR "Uranium/toxicity"[Mesh] OR "Uranium/urine"[Mesh] OR "Oxides/adverse effects"[Mesh] OR "Oxides/antagonists and inhibitors"[Mesh] OR "Oxides/blood"[Mesh] OR "Oxides/cerebrospinal fluid"[Mesh] OR "Oxides/metabolism"[Mesh] OR "Oxides/pharmacokinetics"[Mesh] OR "Oxides/poisoning"[Mesh] OR "Oxides/radiation effects"[Mesh] OR "Oxides/toxicity"[Mesh] OR "Oxides/urine"[Mesh] OR "chemically induced"[Subheading] OR "environmental exposure"[mh] OR cancer[sb] OR "endocrine system"[mh] OR "endocrine disruptors"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR endocrine[tw] OR "dose-response relationship, drug"[mh] OR "risk"[MeSH Terms] OR "toxicity tests"[mh] OR (("pharmacokinetics"[MeSH Terms] OR "metabolism"[MeSH Terms] OR "metabolic networks and pathways"[MeSH Terms]) AND "humans"[MeSH Terms] OR	1,**666**

Database	Search string	Results[a]
	"animals"[MeSH Terms]) OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR "genomics"[MeSH Terms] OR "genome"[MeSH Terms] OR "proteomics"[MeSH Terms] OR "proteome"[MeSH Terms] OR "metabolomics"[MeSH Terms] OR "metabolome"[MeSH Terms] OR "genes"[MeSH Terms] OR "Gene expression"[mh] OR "phenotype"[MeSH Terms] OR "genetics"[MeSH Terms] OR "genotype"[MeSH Terms] OR "transcriptome"[MeSH Terms] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR "analysis"[Subheading])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND ("rna"[MeSH Terms] OR "dna"[MeSH Terms])) OR "RNA, Messenger "[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR "Organometallic Compounds/adverse effects"[Mesh] OR "Organometallic Compounds/antagonists and inhibitors"[Mesh] OR "Organometallic Compounds/blood"[Mesh] OR "Organometallic Compounds/cerebrospinal fluid"[Mesh] OR "Organometallic Compounds/metabolism"[Mesh] OR "Organometallic Compounds/pharmacokinetics"[Mesh] OR "Organometallic Compounds/poisoning"[Mesh] OR "Organometallic Compounds/radiation effects"[Mesh] OR "Organometallic Compounds/toxicity"[Mesh] OR "Organometallic Compounds/urine"[Mesh]) AND ("2011/01/01"[PDAT] : "2021/09/01"[PDAT])	
Toxnet	@OR+(@term+@rn+7440-61-1+@term+@rn+1344-57-6+@term+@rn+1344-58-7+@term+@rn+19525-15-6+@term+@rn+12036-71-4+@term+@rn+171236-10-5+@term+@rn+1344-59-8+@term+@rn+10049-14-6+@term+@rn+7783-81-5+@term+@rn+10026-10-5+@term+@rn+13536-84-0)+@AND+@org+tscats @OR+(@term+@rn+7440-61-1+@term+@rn+1344-57-6+@term+@rn+1344-58-7+@term+@rn+19525-15-6+@term+@rn+12036-71-4+@term+@rn+171236-10-5+@term+@rn+1344-59-8+@term+@rn+10049-14-6+@term+@rn+7783-81-5+@term+@rn+10026-10-5+@term+@rn+13536-84-0)+@NOT+@org+pubmed+pubdart+crisp+tscats @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Gene+expression"+"Transcript+expression"+"transcriptomes"+"transcriptome"+"Phenotype"+"Transcription"+"transact*"+genetic+"genetics"+"genotype")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Gene+expression"+"Transcript+expression"+"transcriptomes"+"transcriptome"+"Phenotype"+"Transcription"+"transact*"+genetic+"genetics"+"genotype")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Genomics"+"Proteomics"+"Metabolic+Profile"+"Metabolome"+"Metabolomics"+"Microarray"+"Nanoarray")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Genomics"+"Proteomics"+"	

Database	Search string	Results[a]
	Metabolic+Profile"+"Metabolome"+"Metabolomics"+"Microarray"+"Nanoarray")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("messenger+RNA"+"transfer+RNA"+"peptide+biosynthesis"+"protein+biosynthesis"+"protein+synthesis"+"RT+PCR"+"RTPCR"+"Reverse+Transcriptase+Polymerase+Chain+Reaction"+"DNA+sequence")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("messenger+RNA"+"transfer+RNA"+"peptide+biosynthesis"+"protein+biosynthesis"+"protein+synthesis"+"RT+PCR"+"RTPCR"+"Reverse+Transcriptase+Polymerase+Chain+Reaction"+"DNA+sequence")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Transcriptional+activation"+"Transcription+factors"+RNA+DNA+"mRNA")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+("Transcriptional+activation"+"Transcription+factors"+RNA+DNA+"mRNA")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(chronic+lymph*+neurotox*+toxicokin*+pharmacokin*+biomarker*+neurolog*+subchronic+pbpk+epidemiolog*+acute+subacute+ld50)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(chronic+lymph*+neurotox*+toxicokin*+pharmacokin*+biomarker*+neurolog*+subchronic+pbpk+epidemiolog*+acute+subacute+ld50)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(dermal*+dermis+skin+epiderm*+cutaneous+carcinog*+cocarcinog*+cancer+precancer+neoplas*+tumor*+tumour*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(dermal*+dermis+skin+epiderm*+cutaneous+carcinog*+cocarcinog*+cancer+precancer+neoplas*+tumor*+tumour*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(gut+sensitiz*+abort*+abnormalit*+embryo*+cleft*+fetus*+foetus*+fetal*+foetal*+fertilit*+infertil*+malform*+ovum+ova+ovary+placenta*+pregnan*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(gut+sensitiz*+abort*+abnor	

Database	Search string	Results[a]
	malit*+embryo*+cleft*+fetus*+foetus*+fetal*+foetal*+fertilit*+infertil*+malform*+ovum+ova+ovary+placenta*+pregnan*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(hamster*+ferret*+gerbil*+rodent*+dog+dogs+beagle*+canine+cats+feline+pig+pigs+swine+porcine+monkey*+macaque*+baboon*+marmoset*+toxic*+adverse+poisoning)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(hamster*+ferret*+gerbil*+rodent*+dog+dogs+beagle*+canine+cats+feline+pig+pigs+swine+porcine+monkey*+macaque*+baboon*+marmoset*+toxic*+adverse+poisoning)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(hormon*+blood+serum+urine+bone+bones+skelet*+rat+rats+mouse+mice+guinea+muridae+rabbit*+lagomorph*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(hormon*+blood+serum+urine+bone+bones+skelet*+rat+rats+mouse+mice+guinea+muridae+rabbit*+lagomorph*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(immune+autoimmun*+immunosuppress*+immunolog*+immunotox*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(immune+autoimmun*+immunosuppress*+immunolog*+immunotox*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(informatics+"systems+biology"+"biological+systems"+"information+science")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(lc50+inhal*+pulmon*+nasal+lung*+respir*+occupation*+workplace+worker*+oral+orally+ingest*+gavage+diet+diets+dietary+drinking+gastr*+intestin*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(lc50+inhal*+pulmon*+nasal+lung*+respir*+occupation*+workplace+worker*+oral+orally+ingest*+gavage+diet+diets+dietary+drinking+gastr*+intestin*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(microarray+"Genetic+transcription"+"Gene+transcription"+"Gene+Activation"+"Genetic+induction"+"Reverse+transcription")+@range+yr+2013+2017	

Database	Search string	Results[a]
	@OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(microarray+"Genetic+transcription"+"Gene+transcription"+"Gene+Activation"+"Genetic+induction"+"Reverse+transcription")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(oncogen*+lymphoma*+carcinom*+genetox*+genotox*+mutagen*+nephrotox*+hepatotox*+endocrin*+estrogen*+androgen*)+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(oncogen*+lymphoma*+carcinom*+genetox*+genotox*+mutagen*+nephrotox*+hepatotox*+endocrin*+estrogen*+androgen*)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(prenatal+perinatal+postnatal+reproduct*+steril*+teratogen*+sperm*+neonat*+newborn*+development*+zygote*+child+children+adolescen*+infant*+wean*+offspring+"age factor"+"age factors")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(prenatal+perinatal+postnatal+reproduct*+steril*+teratogen*+sperm*+neonat*+newborn*+development*+zygote*+child+children+adolescen*+infant*+wean*+offspring+"age factor"+"age factors")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(renal+kidney*+urinary+liver+hepat*+osseous+ossif*+behavioral+behavioural+brain+"nervous+system")+@range+yr+2013+2017 @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(renal+kidney*+urinary+liver+hepat*+osseous+ossif*+behavioral+behavioural+brain+"nervous+system")+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl*+uranate*+diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@AND+@OR+(sperm+testic*+testosterone+testis+testes+epididym*+seminiferous+cervix+ovaries+ovarian+corpora lutea+corpus luteum+estrous+estrus)+@AND+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl+uranate*+ diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@NOT+@org+pubmed+pubdart+crisp+tscats+ntis @OR+(uranium+diuranium+triuranium+uranic+uranous+uranyl+uranate*+ diuranate*+dioxouranium+uranyldifluoride*+diacetatodioxouranium+difluorodioxouranium+dinitratodioxouranium+yellowcake)+@range+yr+2013+2017	

[a] Searchesdates covered in this document are current as of November 2022.

APPENDIX B. SURVEY OF EXISTING TOXICITY VALUES

Table B-1 lists websites that are searched for relevant human health reference values. In addition to these sources, the ToxVal database on the Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/TOXVAL_V5) is searched for both reference values and PODs as described in Appendix D. ToxVal is searched in the EPA CompTox Chemicals Dashboard (U.S. EPA, 2018a).

Table B-1. Sources searched for existing human health reference values

Source[a]	Query and/or link
ATSDR	http://www.atsdr.cdc.gov/toxprofiles/index.asp
CalEPA	http://www.oehha.ca.gov/tcdb/index.asp
DWSHA	https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf
Health Canada	https://www.canada.ca/en/services/health/publications/healthy-living.html
	https://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/collection_2012/sc-hc/H128-1-11-638-eng.pdf
	https://publications.gc.ca/site/archivee-archived.html?url=https://publications.gc.ca/collections/Collection/H46-2-96-194E.pdf
HEAST	https://epa-heast.ornl.gov/heast.php
	https://nepis.epa.gov/Exe/ZyPDF.cgi/2000O0GZ.PDF?Dockey=2000O0GZ.PDF
IRIS	https://www.epa.gov/iris
MI EGLE	https://www.michigan.gov/documents/deq/deq-rrd-chem-CleanupCriteriaTSD_527410_7.pdf
MDH	https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html
NHMRC	https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines
NY DEC	https://www.dec.ny.gov/docs/remediation_hudson_pdf/techsuppdoc.pdf
OPP	https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1
PPRTV	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
RIVM	https://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf

Source[a]	Query and/or link
TCEQ	https://www.tceq.texas.gov/remediation/trrp/trrppcls.html
WHO	http://www.who.int/ipcs/publications/ehc/en/

[a]ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IRIS = Integrated Risk Information System; MDH = Minnesota Department of Health; MI EGLE = Michigan Department of Environment, Great Lakes & Energy; NHMRC = National Health and Medical Research Council; NY DEC = New York State Department of Environmental Conservation; OPP = Office of Pesticide Programs; PPRTV = Provisional Peer-Reviewed Toxicity Values; RIVM = Rijksinstituut voor Volksgezondheid en Milieu, the Netherlands Institute for Public Health and the Environment; TCEQ = Texas Commission on Environmental Quality; WHO = World Health Organization.

APPENDIX C. PROCESS FOR SEARCHING AND COLLECTING EVIDENCE FROM SELECTED OTHER RESOURCES

C.1. REVIEW OF REFERENCE LISTS FROM EXISTING ASSESSMENTS (FINAL OR PUBLICLY AVAILABLE DRAFT), JOURNAL REVIEWS ARTICLES, AND STUDIES CONSIDERED RELEVANT TO PECO BASED ON FULL-TEXT SCREENING

Review of the citation reference lists is typically done manually because they are not available in a file format (e.g., RIS) that permits uploading into screening software applications. Manual review entails scanning the title, study summary, or study details as presented in the resource for those that appear to meet the populations, exposures, comparators, and outcomes (PECO) criteria. Any records identified that are not identified from the other sources are annotated with respect to source and screened as outlined in Section 4.

C.2. EUROPEAN CHEMICALS AGENCY

A search of the European Chemicals Agency registered substances database was conducted using the chemical names. The registration dossier associated with the chemical name was retrieved by navigating to and clicking the eye-shaped view icon displayed in the chemical summary panel. The general information page and all subpages included under the Toxicological Information tab were reviewed to identify any human or animal health effects information from 2016 onward that would be eligible for inclusion based on PECO criteria.

C.3. EPA CHEMVIEW

The EPA ChemView database (U.S. EPA, 2019) using the chemical CASRN is searched. The prepopulated CASRN match and the "Information Submitted to EPA" output option filter are selected before generating results. If results are available, the square-shaped icon under the "Data Submitted to EPA" column is selected, and the following records are included:

- High Production Volume Challenge Database (HPVIS)
- Human Health studies (Substantial Risk Reports)
- Monitoring (includes environmental, occupational, and general entries)
- TSCA Section 4 (chemical testing results)

- TSCA Section 8(d) (health and safety studies)
- TSCA Section 8(e) (substantial risk)
- FYI (voluntary documents)

All records for ecotoxicology and physical and chemical property entries were excluded. When results were available, extractors navigated into each record until a substantial risk report link was identified and saved as a PDF file. If the report could not be saved, due to file corruption or broken links, the record was excluded during full-text review as "unable to obtain record." Most substantial risk reports contained multiple document IDs, so citations were derived by concatenating the unique report numbers (OTS; 8EHD Num; DCN; TSCATS RefID; and CIS) associated with each document along with the typical author organization, year, and title. Once a citation was generated, the study moved forward to DistillerSR with which it was screened according to PECO and supplemental material criteria.

C.4. NTP CHEMICAL EFFECTS IN BIOLOGICAL SYSTEMS

This database is searched using the chemical CASRN (https://manticore.niehs.nih.gov/cebssearch). All non-NTP data were excluded using the "NTP Data Only" filter. Data tables for reports undergoing peer review are also searched for studies that have not been finalized (https://ntp.niehs.nih.gov/data/tables/index.html) based on a manual review of chemical names.

C.5. OECD ECHEMPORTAL

The OECD eChemPortal (https://hpvchemicals.oecd.org/UI/Search.aspx) is searched using the chemical CASRN. Only database entries from the following sources are included and entries from all other databases are excluded in the search. Final assessment reports and other relevant SIDS reports embedded in the links are captured and saved as PDF files.

- OECD HPV
- OECD SIDS IUCLID
- SIDS United Nations Environment Programme (UNEP)

C.6. ECOTOX DATABASE

EPA's ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/search.cfm) was searched using the chemical names. Results were refined to terrestrial mammalian studies by selecting the terrestrial tab at the top of the search page and sorting the results by species group. Results were reviewed to verify that it was not already identified from the database search (or searches of "other sources consulted") search prior to moving forward to screening.

Table C-1. Summary table for other sources search results

Source	Source address	Search terms	Search date	Total unique number of results retrieved	Records not otherwise identified that were screened in DistillerSR
Review of reference lists studies considered relevant to PECO-based on full-text screening	NA	NA	NA	67	65
Review of reference lists from existing assessments (final or publicly available draft) or journal review articles that focused on human health	NA	NA	NA	3	0
EPA CompTox (Computational Toxicology Program) Chemicals Dashboard (ToxVal)	https://comptox.epa.gov/dashboard/dsstoxdb/results?abbreviation=TOXVAL_V5&search=DTXSID6021793#toxicity-values	90-15-3 (results from human health: POD, toxicity value, lethality effect level)	12/10/2019	21	5
ECHA	https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation	90-15-3	10/8/2019	53	24
EPA ChemView	https://chemview.epa.gov/chemview?tf=0&ch=90-15-3&su=2-5-6-7-37574985&as=3-10-9-8&ac=1-15-16-6378999&ma=4-11-1981377&tds=0&tdl=10&tas1=1&tas2=asc&tas3=undefined&tss=	90-15-3	9/19/2019	3	1

Source	Source address	Search terms	Search date	Total unique number of results retrieved	Records not otherwise identified that were screened in DistillerSR
High Production Volume Information System (HPVIS)	https://ofmpub.epa.gov/oppthpv/quicksearch.display?pChem=101850	90-15-3	9/19/2019	4	4
NTP CEBS	https://manticore.niehs.nih.gov/cebssearch/search?q=90-15-3	90-15-3	9/19/2019	0	0
OECD eChemPortal	https://hpvchemicals.oecd.org/UI/Search.aspx	90-15-3	9/19/2019	0	0
ECOTOX database	https://cfpub.epa.gov/ecotox/search.cfm	90-15-3	9/19/2019	4	3
EPA CompTox Chemicals Dashboard version to retrieve a summary of any ToxCast or Tox21 high-throughput screening information	https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6021793	90-15-3	9/19/2019	1	1
Comparative Toxicogenomics Database (CTDB)	http://ctdbase.org/	90-15-3	12/9/2019	57	30
ArrayExpress	https://www.ebi.ac.uk/arrayexpress/	90-15-3 and “naphthol”	12/9/2019	1	1

Source	Source address	Search terms	Search date	Total unique number of results retrieved	Records not otherwise identified that were screened in DistillerSR
Gene Expression Omnibus	https://www.ncbi.nlm.nih.gov/geo/	(90-15-3[rn] OR "1-Naphthol"[tw] OR "Naphthalen-1-ol"[tw] OR "1-Naphthalenol"[tw] OR "1-naphthalenol"[tw]) AND ("Expression profiling by RT-PCR"[Filter] OR "Expression profiling by MPSS"[Filter] OR "Expression profiling by SAGE"[Filter] OR "Expression profiling by SNP array"[Filter] OR "Expression profiling by array"[Filter] OR "Expression profiling by genome tiling array"[Filter] OR "Expression profiling by high throughput sequencing"[Filter] OR "Protein profiling by Mass Spec"[Filter] OR "Protein profiling by protein array"[Filter]).	12/9/2019	2	1

CEBS = Chemical Effects in Biological Systems; ECHA = European Chemicals Agency; NA = not applicable; NTP = National Toxicology Program; OECD = Organisation for Economic Co-operation and Development; PECO = populations, exposures, comparators, and outcomes; POD = point of departure.

APPENDIX D. COMPARISON BETWEEN ATSDR 2013 AND IRIS LITERATURE SEARCH INVENTORY

In this appendix, the following is presented for each health effect category:

- Summary of findings from studies used in ATSDR 2013;
- Description of newly identified studies, human and animal, from the IRIS literature search, in both narrative and tabular format;
- Conclusions of whether the newly available studies identified in the literature search update provide further support of the evidence considered by ATSDR 2013 and their interpretation;
- Units of analysis, if applicable.

D.1. BODY WEIGHT EFFECTS

ATSDR Summary

ATSDR 2013 stated that no body weight effects were reported in the available human studies. ATSDR 2013 also provide a summary of the animal evidence, but state that body weight "effects are not necessarily the result of systemic toxicity." This is because the observed decreases in body weight are accompanied by a reduction in food consumption, which in turn could be caused by the palatability of uranium in the food. ATSDR 2013 also states the same aversive taste issue may influence water consumption. They cited studies using rats, mice, and dogs exposed to high doses of uranium for subchronic and chronic durations, which reported no significant changes in body weight.

Newly Identified Human Studies

No new human studies were identified in the IRIS literature search.

Newly Identified Animal Studies

Three studies using mice and seven studies using SD rats were identified in the IRIS literature search. In adult C57BL/6J mice and ApoE null mice, subchronic exposures to uranium did not have a significant impact on body weights (Medina et al., 2020; Bolt et al., 2019; Souidi et al., 2012). In adult SD rats most of the available studies reported no significant effects on body weight or food and water consumption (Grison et al., 2016; Dublineau et al., 2014; Gueguen et al., 2014; Poisson et al., 2014b; Hao et al., 2013a; Rouas et al., 2011). One study reported decreased body weight after exposure to uranyl nitrate for 11 or 22 weeks, but the study authors also noted that water consumption was also decreased in exposed animals (Vicente-Vicente et al., 2013). These findings are consistent with ATSDR's interpretation.

Conclusion

The available toxicological studies identified in the literature search update provide further support of the evidence considered by ATSDR 2013 and their interpretation. EPA will not consider body weight effects in sexually mature animals for hazard evaluation or dose-response as the majority of the available studies report no effects on body weight or food and water consumption and the study that observed uranium-induced changes in body weight also reported decreased water consumption, which may be a potential confounder.

Units of Analysis

N/A

D.2. CARDIOVASCULAR EFFECTS

ATSDR Summary

ATSDR 2013 concluded that "cardiovascular effects following intake of uranium are unlikely." ATSDR cited animal toxicity studies using rats or New Zealand rabbits and two epidemiological studies (one case study and one cohort study). The animal toxicity studies cited in ATSDR 2013 measured organ weights and histopathology, and none reported significant uranium-induced effects. ATSDR examined a case report, which documented a patient who suffered from myocarditis after ingestion of a large dose uranyl acetate (approximately 15 g), and an observational study, which reported a small positive association between urinary uranium concentrations and blood pressure.

Newly Identified Human Studies

Twenty-two (n = 22) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for cardiovascular outcomes (see Table D-1). Blood pressure was commonly examined. Some studies reported significant associations: dilated cardiomyopathy (Malamba-Lez et al., 2021), and high blood pressure in NHANES (Shiue and Hristova, 2014), using urinary biomarkers to assess exposure. For a few studies there were potential limitations, including with exposure assessment, such as judging exposure by job classification with no biomarker or other exposure measurement (Al Rashida et al., 2019; Shumate et al., 2017; Guseva Canu et al., 2014). Additionally, some studies only reported exposure averages by outcome group.

Newly Identified Animal Studies

Four animal toxicity studies that meet PECO criteria were identified in the IRIS literature search (see Table D-2). These studies used SD rats, and wild type and ApoE null mice exposed to uranyl nitrate in drinking water for 11 weeks to 9 months. No effects were observed for markers of cardiovascular disease including total cholesterol, LDL and HDL, and triglycerides. Exposure to uranium in drinking water for 11 and 21 weeks increased systolic blood pressure in SD rats (Vicente-Vicente et al., 2013). However, these effects may be confounded by apparent palatability issues causing large decrease in water intake (54% decrease) at the only dose tested (Vicente-Vicente et al., 2013).

Conclusion

Potentially impactful epidemiological studies report on a potential association with uranium exposure and high blood pressure and cardiomyopathy. Based on these findings, plus animal study findings, EPA will perform a hazard evaluation of uranium-induced cardiovascular effects. This analysis will consider studies cited in ATSDR and studies that met problem formulation PECO criteria in the IRIS literature search.

Units of Analysis

Humans: blood pressure, cardiovascular disease.

Animals: Heart and vessel morphology and histopathology, blood and arteriole pressure, peripheral resistance, and other measures of cardiovascular function.

Table D-1. Studies of cardiovascular endpoints in humans identified 2011–2021

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Choi et al. (2019)	Korea Cross-sectional	Hair	Atherosclerotic cardiovascular disease	Significant inverse association.
Duan et al. (2020)	U.S. Cross-sectional	Urine	CVD mortality	No effects observed.
Feng et al. (2014)	China Cohort	Urine	Heart rate variability indices	Significant association.
Harmon et al. (2018)	Population-based U.S. cross-sectional	Blood, urine	CVD biomarkers (oxLDL, CRP)	No effects observed.
Long et al. (2019)	China Cohort	Blood	Incident CVD	No effects observed.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Malamba-Lez et al. (2021)	DR Congo Case-control	Urine	Dilated cardiomyopathy (DCM)	Significant association.
Mendy et al. (2012)	U.S. (NHANES) Cross-sectional	Urine	Heart failure, coronary heart disease, heart attack, stroke	No effects observed.
Richardson et al. (2021)	Occupational North America/Europe Cohort	Occupational	Circulatory disease mortality	Significant association (suggesting benefit).
Shiue and Hristova (2014)	U.S. (NHANES) cross-sectional	Urine	Blood pressure	Significant association.
Sankar et al. (2014)	U.S. (NHANES) cross-sectional	Urine	Blood pressure	Significant association.
Wu et al. (2018a)	China Cross-sectional	Urine	Systolic and diastolic blood pressure, diagnosis of hypertension	No effects observed.
Ass'ad et al. (2021)	Occupational U.S. Cross-sectional	Blood	Biomarkers of inflammation (soluble vascular cell adhesion molecule 1)	Biomarker levels differed between uranium miners and non-uranium miners.
Butler-Dawson et al. (2021)	Occupational Guatemala cohort	Urine	Hypertension	No effects observed.
Guseva Canu et al. (2014)	Occupational France cohort	Occupational history and employment-exposure-matrix	Mortality (diseases of the circulatory system, ischemic myocardial disease, cerebrovascular diseases)	Significant increased mortality.
Karakis et al. (2021)	Israel Cohort	Urine	Pediatric cardiovascular-related morbidity	No effects observed.
Pavlyushchik et al. (2017)	Hypertensive patients	Hair sample	Blood pressure	No effects observed.
Al Rashida et al. (2019)	Occupational U.S. Cross-sectional	Occupational	Angina	Significant association.
Samson et al. (2016)	Occupational France Cohort	Occupational	Diseases of the circulatory system	Significant deficits in deaths.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Shumate et al. (2017)	Occupational U.S. Cross-sectional	Occupational	Angina, heart attack	No effects reported.
Sulibursk a et al. (2016)	Poland Cross-sectional	Amniotic fluid	Maternal systolic blood pressure, diastolic blood pressure	No effects reported.
Tret'iakov et al. (2011)	Occupational Russia	Occupational	Arterial hypertension, coronary heart disease	Unclear findings.
Zablotska et al. (2013)	Occupational Canada Cohort	Occupational	Mortality from CVD	No effects reported.

Table D-2. Summary of animal studies reporting on uranium-induced cardiovascular effects

Reference	Experimental design	Author-reported findings
Vicente-Vicente et al. (2013)	Male SD rats exposed to 5.4 g/L for 11 wk (243 mg/kg-d)	Increased systolic blood pressure.
Vicente-Vicente et al. (2013)	Male SD rats exposed to 5.4 g/L for 21 wk (229.5 mg/kg-d)	Increased systolic blood pressure.
Grison et al. (2013)	Male SD rats exposed to 40 mg/L (2.7 mg/kg-d) for 9 mo	No effect on plasma markers (total cholesterol, triglycerides, phospholipids, HDL & LDL cholesterol).
Lestaevel et al. (2014)	Male wild type & ApoE null mice exposed to 20 mg/L (4 mg/kg-d) for 14 wk	
Dublineau et al. (2014)	Male SD rats exposed to 0, 0.009, 0.09, 0.23, 0.45, 0.9, 7.8, or 5.4 mg/kg-d for 9 mo	
Souidi et al. (2012)	Male ApoE null mice exposed to 0, 20 mg/L (4 mg/kg-d)	

D.3. DEVELOPMENTAL EFFECTS

ATSDR Summary

ATSDR 2013 did not identify human studies reporting on the potential developmental effects caused by uranium exposure. In their hazard evaluation ATSDR considered animal toxicity studies using rats or mice as experimental models and identified developmental effects as a health response to uranium exposure. Experimental designs used in these studies included gestational and early postnatal exposures to uranium and they measured litter size, numbers of resorptions, live fetuses, pup survival, body weight and length, internal and external malformations, and

developmental milestones (e.g., tooth eruption, pinnae unfolding, and eye opening). In Swiss mice gestational exposure to uranium resulted in decreased pup weight, increased neonatal death and incidence of external malformations, and reduced litter size, viability index and lactation index. In SD rats gestational treatment with uranium resulted in decreased pup weight, but there were no effects on tooth eruption, pinna detachment or eye opening. In 7-day-old Wistar rats, uranium exposure resulted in delayed tooth eruption and elevated bone resorption. ATSDR 2013 considered the developmental effects reported in (Domingo et al., 1989) for derivation of an acute minimal risk level.

Newly Identified Human Studies

Nineteen (n = 19) epidemiological studies meeting PECO criteria were identified in the IRIS literature search (see Table D-3). Studies examined developmental-related endpoints including preterm birth, birth weight, neural tube defects, and orofacial cleft. For preterm birth, one study found an association between maternal urinary uranium and preterm birth (Zhang et al., 2020), whereas a nested case-control study from the U.S. observed no statistically significant associations between maternal urinary uranium and preterm birth (Kim et al., 2018). For birth weight, no association was seen between umbilical cord blood uranium and birth weight in a Chinese cohort (Yang et al., 2020) or in toenail uranium levels in mother-infant pairs from the U.S. (Deyssenroth et al., 2018). Bloom et al. (2015) found reduced anthropometric measurements, including birth weight in a U.S. cohort. In a case-control study in China, (Yin et al., 2022) observed increased risk of neural tube defects associated with placental tissue uranium concentration. For orofacial cleft (OFC), no association was observed (Wei et al., 2019), but another study did see associations with OFC, and with cleft lip with cleft palate (Guo et al., 2020).

Some studies had potential limitations due to deficiencies in analyses by only reporting exposure averages by outcome group or correlations; deficiencies in participant selection with no information on recruitment or inclusion criteria, with major concern for selection bias; and lack of contrast between the low- and high-exposure groups with concerns for study sensitivity.

Newly Identified Animal Studies

Ten rat studies that met PECO criteria were identified in the IRIS literature search. In SD rats, uranium exposure led to decreases in body weight without changes in food or water consumption. However, several studies reported no effects on body weight of developing animals (see Table D-4). In Wistar rats there was a decrease in pregnancy rate, labor rate, and pup survival rate (from birth to adulthood). The study using Wistar rats also measured pup weights, and malformations (including incidence of cleft palate, skeletal variations, or hematomas). Overall, the results from the (Hao et al., 2012) study are consistent with the studies and evidence summarized in ATSDR 2013.

Conclusion

The available toxicological and epidemiological studies identified in the IRIS literature search update provide further support of the studies and evidence considered by ATSDR 2013 in its evaluation of uranium-induced developmental effects. Furthermore, newly identified epidemiological studies provide evidence that may be considered for dose response. Based on these findings, EPA will perform a dose-response analysis on uranium-induced developmental effects that includes epidemiological and toxicological evidence. This will include studies identified in the IRIS literature search and studies cited in ATSDR 2013.

Units of Analysis

Humans: Pregnancy outcomes, congenital malformations.

Animals: Fetal viability/survival or other birth parameters (e.g., resorptions, number of pups per litter), fetal/pup growth (e.g., weight or length).

Note: An analysis of dam health (e.g., weight gain, food consumption) is also conducted to support conclusions of specificity of the effects as being developmental (versus derivative of maternal toxicity).

Table D-3. Studies of developmental endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Bloom et al. (2015)	U.S. Cohort	Urine	Birth weight, birth length, head circumference, gestational age	Significant associations reported for paternal uranium and endpoints.
Deyssenroth et al. (2018)	U.S. Cohort	Nail	Gestational age	No effects reported.
Guo et al. (2020)	China Case-control	Umbilical cord tissue	Orofacial clefts, cleft lip with cleft palate	Significant associations.
Howe et al. (2022)	U.S. Cohort	Urine	Body weight for gestational age	No effects reported.
Kim et al. (2018)	U.S. Cohort	Urine	Pre-term birth	No effects reported.
Wei et al. (2019)	China Case-control	Hair	Orofacial cleft	No effects observed.
Wu et al. (2020)	China Cohort	Urine	Tooth eruption	Significant association.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Yang et al. (2020)	China Cohort	Umbilical cord blood	Birth weight	No effects observed.
Yin et al. (2022)	China Case-control	Placental tissue	Neural tube defects	Significant association.
Zhang et al. (2020)	China Cohort	Urine	Preterm birth	Significant association.
Alaani et al. (2011)	Case-report/series Iraq	Hair	Congenital anomalies	No effects reported.
Al-Sahlanee et al. (2017)	Cross-sectional, Iraq	Blood, umbilical cord blood	Birth weight, birth length, head circumference	Significant associations.
Karakis et al. (2021)	Cohort, Israel	Urine	Preterm delivery	Significant association.
Kocylowski et al. (2019)	Cohort, Poland	Blood, amniotic fluid	Birth defects	No effects reported.
Manduca et al. (2014)	Palestine Cohort	Hair	Neural tube defects, polycystic kidney defect, congenital heart disease, cleft lift/palate	No effects reported.
Mckeating et al. (2021)	Australia Cross-sectional	Blood, urine	Placental weight	No effects reported.
Rhaifal-Sahlanee et al. (2016)	Iraq Cohort	Blood, umbilical cord blood	"Deformed and dead infants."	No effects reported.
Savabieasfahani et al. (2020)	Iraq Case-control	Hair	Congenital abnormalities	No effects reported.
Suliburska et al. (2016)	Poland Cross-sectional	Amniotic fluid	Biparietal diameter, abdominal and head circumference, femur length	No effects reported.

Table D-4. Summary of toxicological studies reporting on uranium-induced developmental effects

Reference	Experimental design	Author-reported findings
Legendre et al. (2016)	F0 female SD rats exposed to uranyl nitrate (0, 40, 120 mg/L in drinking water) from GD 1 to PND 168	No effect on body weight or food and water consumption.
Lestaevel et al. (2015)	Male SD rats exposed to uranyl nitrate (0, 10, 40 mg/L in drinking water) for 10 wk starting at birth	No effects on bodyweight or food and water consumption.
Elmhiri et al. (2018)	Male and female SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) from GD 1 to 9 mo of age	Decreased body weight in F1 male animals, but no effect on F2 animals. No effect of food or water consumption.
Grison et al. (2013)	Male rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo starting at birth	Decreased body weight, but no effect on food and water consumption.
Grison et al. (2018)	Male and female F0 generation SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo	Increased body weight in F1 generation males; and ↓ body weight in F2 generation males. No effects on water consumption & no effects in F1 or F2 females.
Grison et al. (2019)	Male and female SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo starting at birth	No effect on body weight.
Lestaevel et al. (2016)	Male & female SD rats exposed to uranyl nitrate (0, 10, 40 mg/L in drinking water) for 9 mo starting at birth	No effects on bodyweight or food and water consumption.
Dinocourt et al. (2017)	Pregnant SD rats exposed to uranium (0, 2, 6 mg/kg-d in drinking water) during gestation	No effects on bodyweight or food and water consumption.
Legrand et al. (2016a)	Pregnant SD rats exposed to depleted uranium (0, 10, 120 mg/L in drinking water) during gestation	Decreased body weight on PND0 and increased body weight on PND5 and PND21.
Hao et al. (2012)	Male and Female Wistar rats exposed to depleted uranyl nitrate (0, 4, 40 mg/kg-d, in food) for 4 mo starting at weaning	Decreased pregnancy rate, labor rate, pup survival rate (at birth and adulthood), and number of pups produced. No effect on pup weights, incidence of cleft palate, skeletal variations, or hematomas.

D.4. ENDOCRINE EFFECTS

ATSDR Summary

ATSDR 2013 did not identify human studies informing potential uranium-induced endocrine effects. ATSDR 2013 did identify several experimental studies in animal models.

Although two studies using rats report histopathological effects in the thyroid, the majority of the available evidence from experiments using rats or rabbits did not report an association between uranium exposure and endocrine effects in the adrenal, pancreas, thyroid, thymus, parathyroid, or pituitary.

Newly Identified Human Studies

Ten (n = 10) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for endocrine outcomes (see Table D-5). Many studies were conducted using NHANES data. Significant associations were observed between urinary uranium and measures of thyroid hormones (Kim et al., 2022; Christensen, 2012); thyroid antibodies (van Gerwen et al., 2020); and diabetes (Menke et al., 2016). No effects were reported for thyroid problems (Mendy et al., 2012) and diabetes (Yang et al., 2022). A few studies had potential limitations, including due to reporting the exposure-outcome association only as exposure averages for outcomes groups.

Newly Identified Animal Studies

No new animal studies informing endocrine effects after oral exposure to uranium were identified in the literature search update. Studies that evaluated uranium-induced effects on reproductive hormones are described in the reproductive effects section.

Conclusion

The epidemiological studies identified in the IRIS literature search suggests that uranium exposure may impact the endocrine system. Based on these findings, EPA will perform a hazard evaluation of uranium-induced endocrine effects. This analysis will consider studies cited in ATSDR and studies that met PECO criteria in the IRIS literature search.

Units of Analysis

Humans: Thyroid hormone measures, diabetes.

Animals: Hormone measures, organ weights, organ morphology/histopathology.

Table D-5. Studies of endocrine endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Christensen (2012)	U.S. (NHANES) Cross-sectional	Urine	Thyroid hormones	Significant association.
Kim et al. (2022)	U.S. (NHANES) Cross-sectional	Urine	Thyroid hormones	Significant association.
Mendy et al. (2012)	U.S. (NHANES) Cross-sectional	Urine	Thyroid problems	No effects reported.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Menke et al. (2016)	U.S. (NHANES) Cross-sectional	Urine	Diabetes	Significant association.
van Gerwen et al. (2020)	U.S. (NHANES) Cross-sectional	Urine	Thyroid antibodies	Significant association.
Yang et al. (2022)	U.S. (NHANES) Cross-sectional	Urine	Type 2 diabetes	No effects reported.
Samson et al. (2016)	Occupational France Cohort	Occupational	Endocrine, metabolic disease mortality	Significant deficits in deaths.
Stojsavljević et al. (2019)	Serbia Cross-sectional	Thyroid tissue	Thyroid disease	No effects observed.
Stojsavljević et al. (2020b)	Serbia Case-control	Thyroid tissue	Colloid goiter disease	No effects observed.
Stojsavljević et al. (2020a)	Serbia Cross-sectional	Thyroid tissue, blood, urine	Hashimoto's thyroiditis	No effects observed.

D.5. GASTROINTESTINAL EFFECTS

ATSDR Summary

ATSDR cited two case studies where individuals were acutely exposed to uranyl nitrate (14.3 mg/kg) or uranyl acetate (131 mg/kg) and reported nausea, diarrhea, vomiting, and paralytic ileus. They also cited animal studies using rats or rabbits that measured organ weight changes and histopathology of the gastrointestinal system. In male and female SD rats and New Zealand white rabbits, exposure to uranium up to 91 days did not affect organ weight or histopathology.

Newly Identified Human Studies

Two (n = 2) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for gastrointestinal effects. Both were occupational studies. One (Richardson et al., 2021) examined mortality from noncancer diseases of the digestive system and did not find an association. The other (Samson et al., 2016) also examined mortality from noncancer diseases of the digestive system. The study found a reduced standardized mortality ratio but had a potential limitation due to selection bias from the healthy worker effect.

Newly Identified Animal Studies

No new animal studies were identified in the literature search update.

Conclusion

EPA will not consider gastrointestinal effects for hazard evaluation or dose response.

Units of Analysis

N/A

D.6. HEMATOLOGICAL EFFECTS

ATSDR Summary

ATSDR 2013 considered one case study in which an individual was exposed to a large dose of uranium (15 g) plus benzodiazepine. The study reported anemia over a period of 8 weeks. ATSDR also identified experimental studies using SD rats or New Zealand white rabbits and concluded that most animal studies show no uranium-induced effects on hematological parameters.

Newly Identified Human Studies

Two (n = 2) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for hematological effects (see Table D-6). Both had potential limitations due to reporting the exposure-outcome association only as exposure averages for outcome groups or concern for selection bias.

Newly Identified Animal Studies

Two animal chronic exposure toxicity studies were identified in the literature search. (Grison et al., 2013) and (Dublineau et al., 2014) used SD rats exposed to UN for 9 months. Both studies report that uranium exposure had no significant effects on hematological parameters including platelets, RBC and WBC counts, hemoglobin, lymphocytes hematocrit, granulocytes, or monocytes. (Dublineau et al., 2014) observed alterations on cytokines indicative of changes in hematopoiesis, but blood cell production was unaltered in the bone marrow and spleen.

Conclusion

Because of null evidence from experimental and epidemiological studies EPA will not consider hematological effects for hazard evaluation or dose response.

Units of Analysis

N/A

Table D-6. Studies of hematological endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Henríquez-Hernández et al. (2017)	Cross-sectional Gran Canaria	Blood sample	Anemia	No effects observed.
Samson et al. (2016)	Occupational France cohort	Occupational	Mortality: Diseases of the blood and blood-forming organs	No effects observed.

D.7. HEPATIC EFFECTS

ATSDR Summary

ATSDR 2013 considered human and animal toxicological study evidence in their evaluation of uranium-induced liver effects. A case report in which a patient had elevated serum liver enzymes levels after exposure to a large dose of uranyl acetate (approximately 15 g) was considered. ATSDR also considered animal toxicity studies performed in dogs, rats, and rabbits. ATSDR 2013 concluded that "in the available animal studies, the existing data provide evidence that uranium exposure can damage the liver," and that "few human data are available on the hepatic effects of uranium."

Newly Identified Human Studies

One study meeting PECO criteria was identified in the IRIS literature search (Samson et al., 2016). It had a potential limitation over the ability of the outcome measure to correctly classify liver disease, as it examined liver disease combined with "psychosis and other diseases due [sic]—alcohol."

Newly Identified Animal Studies

Ten animal toxicity studies that meet PECO criteria were identified in the IRIS literature search (see Table D-7). These studies used SD rats, several strains of mice (including C57BL/6J, Kunming, and CBA), and genetically modified ApoE null mice. Studies using mice exposed animals to uranium for 30 days to 4 months. Studies using SD rats exposed animals for 1 to 18 months. Outcomes considered in the available studies included organ weight measures, macroscopic appearance, serum markers of liver damage, and histology. In mice, uranium exposure did not affect liver macroscopic appearance, or clinical markers of liver disease, but one study reported altered hepatic lipid composition. In SD rats several studies reported alterations in serum markers of liver disease and one study reported increased liver weight. However, these effects were not accompanied by histopathological responses, and there was no increase in severity after chronic exposures (9 to 18 months).

Conclusion

The available toxicological studies identified in the literature search update provide further support of the studies and evidence considered by ATSDR 2013 in its evaluation of uranium-induced liver effects. Based on these findings, EPA will perform a dose-response analysis on uranium-induced liver effects. This will include studies identified in the IRIS literature search and studies cited in ATSDR 2013 (ATSDR, 2013).

Units of Analysis

Humans: Liver disease.

Animals: Organ weight, organ morphology/histopathology, clinical measures of biliary function, clinical measures of liver function (including liver enzymes).

Table D-7. Summary of toxicological studies reporting on uranium-induced hepatic effects

Reference	Experimental design	Author-reported findings
Mouse studies		
Bolt et al. (2019)	Male & female C57BL/6J mice exposed to uranyl acetate (0, 5, 50 mg/L in drinking water) for 60 d	No effect on serum markers of liver disease (ALT and ALP).
Hao et al. (2013b)	Male Kunming mice exposed to uranyl nitrate (0, 0.4, 4, 40 mg/kg-d in food) for 4 mo	No effect on markers of liver damage (ALT, AST).
Kudyasheva et al. (2020)	Male CBA mice exposed to uranyl nitrate (0, 2 mg/L in drinking water) for 60 d	Altered hepatic lipid composition.
Souidi et al. (2012)	Male ApoE null mice exposed to uranyl nitrate (0, 20 mg/L in drinking water) for 3 mo	No effects on markers of liver damage (ALT, AST), liver weight, or macroscopic appearance.
Rat studies		
Dublineau et al. (2014)	Male SD rats exposed to uranyl nitrate (0.009, 0.09, 0.23, 0.45, 0.9, 1.8, 5.4 mg/kg-d in drinking water) for 9 mo	No macroscopic or histological effects. Increased ALT and AST at high dose, but effect not statistically significant. No effects on bilirubin.
Grison et al. (2013)	Male rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo starting at birth	Increased AST, but no effect on ALP, ALT, or bilirubin.
Grison et al. (2019)	Male rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo starting at birth	No effect on plasma markers of liver damage.

Reference	Experimental design	Author-reported findings
Gueguen et al. (2014)	Male SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 1–18 mo	No effects on liver weight, histopathology, or markers of liver damage (ALT, AST, or bilirubin).
	Male SD rats exposed to uranyl nitrate (0, 10, 40, 120 mg/L in drinking water) for 9 mo	Increased relative liver weight, but no effect on markers of liver damage (ALT, AST, or bilirubin).
Legendre et al. (2016)	Male SD rats exposed to uranyl nitrate (0, 40, 120 mg/L in drinking water) from GD 1 to PND 168	Increased ALT and AST/ALT, but no effect on AST.
Poisson et al. (2014b)	Male SD rats exposed to uranyl nitrate (0, 40, 120, 400 mg/L in drinking water) for 3 mo	No effects on liver histopathology or markers of liver disease.
	Male SD rats exposed to uranyl nitrate (0, 40, 120, 600 mg/L in drinking water) for 9 mo	No effects on liver histopathology or markers of liver disease.

D.8. IMMUNE EFFECTS

ATSDR Summary

ATSDR 2013 did not identify human studies informing potential uranium-induced immunological effects. ATSDR 2013 did identify experimental studies using rats, mice or New Zealand white rabbits and concluded that exposure "to uranium had no significant effect on immune system function."

Newly Identified Human Studies

Eleven (n = 11) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for immunological outcomes (see Table D-8). A number of studies observed significant associations, including with ankylosing spondylitis, lupus, immunotoxicity, and rheumatoid arthritis. The remaining studies observed no significant associations with autoimmunity or arthritis. One study had potential limitations due to reporting exposure-outcome associations only as exposure averages for outcome groups.

Newly Identified Animal Studies

Five animal toxicity studies (two using rats and three using mice) were identified in the IRIS literature search. Outcomes considered in these studies include organ weights, histopathology, hematological endpoints, and immune function measures. In rat studies exposure was associated with decreased thymus and spleen weight, alterations in immune cell composition and functions, and bone marrow and spleen histopathology (see Table D-9). In mice uranium treatment altered

natural killer and macrophage functions, increased cytokine production, changes in immune cell numbers and functions (see Table D-9).

Conclusion

The toxicological and epidemiological studies identified in the IRIS literature search suggests that uranium exposure may impact the immune system. Based on these findings, EPA will perform a hazard evaluation of uranium-induced immunological effects. This analysis will consider studies cited in ATSDR 2013 and studies that met PECO criteria in the IRIS literature search.

Units of Analysis

Humans: Autoimmune disease and measures, immunotoxicity.

Animals: Organ weights, clinical endpoints (e.g., immune cell counts/responses), immune functional measures, organ morphology/histopathology.

Table D-8. Studies of immunological endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Aung et al. (2019)	U.S. Cross-sectional	Urine	Immune markers of inflammation	Significant association.
Chen et al. (2022a)	U.S. (NHANES) Cross-sectional	Urine	Rheumatoid arthritis	Significant association.
Chen et al. (2022b)	U.S. (NHANES) Cross-sectional	Urine	Osteoarthritis	No effect reported.
Erdei et al. (2019)	U.S. Cross-sectional	Urine	Autoimmunity	Significant association.
Greene et al. (2019)	U.S. Case-control	Blood	Chemokines (endometriosis cases)	Significant association.
Lourenço et al. (2013)	Portugal Cross-sectional	Blood	Immune cell count	Significant association.
Lu-Fritts et al. (2014)	U.S. Case-control	Air	Lupus	Significant association.
Mendy et al. (2012)	U.S. (NHANES) Cross-sectional	Urine	Arthritis	No effects reported.
Scammell et al. (2020)	U.S., Nicaragua Cross-sectional	Urine	Autoimmunity	No effects reported.
Shiue (2014)	U.S. (NHANES)	Urine	Ankylosing spondylitis	Significant association.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
	Cross-sectional			
Denisova et al. (2020)	Russia Case-control	Lung tissue	Sarcoidosis	No effects observed.

Table D-9. Summary of toxicological studies reporting on uranium-induced immunological effects

Reference	Experimental design	Author-reported findings
Mouse studies		
Bolt et al. (2019)	Male and female C57BL/6J mice exposed uranyl acetate (0, 5, 50 ppm in drinking water) for 60 d	Decreased percent macrophages and natural killer cells in male spleen. No effect on immune tissue weights, immune cell recoveries or viability, or immune responses.
Medina et al. (2020)	Male and female C57BL/6J mice exposed to uranyl acetate (0, 5, 50 ppm in drinking water) for 45 d	Decreased intraepithelial lymphocyte subsets in small intestine of males but no effect in females. No effect on innate immune cells.
Hao et al. (2013b)	Male Kunming mice exposed to uranyl nitrate (0, 0.4, 4, 40 mg/kg-d in food)	Decreased natural killer cell and macrophage functions; ↑ IgG and IgE levels; altered splenic T and B cells proliferation; ↑ delayed-type hypersensitivity; altered T cell and B cell subtypes and cytokine production in splenic cells.
Rat studies		
Hao et al. (2013a)	Female SD rats exposed to depleted uranyl nitrate (0, 1.3, 13, 130 mg/kg in food) for 4 mo	Decreased thymus and spleen weight. Altered immune cell composition and functions, and bone marrow, and spleen histopathology.
Dublineau et al. (2014)	Male SD rats exposed to uranyl nitrate (0.009, 0.09, 0.23, 0.45, 0.9, 1.8, 5.4 mg/kg-d in drinking water) for 9 mo	Decreased intestinal macrophages by 50% but effect was not dose-dependent and not statistically significant.

D.9. METABOLIC EFFECTS

ATSDR Summary

ATSDR 2013 cited two acute exposure studies that report altered levels of 1,25(OH)2D3, the active form of vitamin D, after a single exposure to depleted uranyl nitrate. Vitamin D levels were measured at 1- or 3-days post exposure. No subchronic or chronic experimental studies and no epidemiological studies on metabolic effects were identified in ATSDR 2013.

Newly Identified Human Studies

Six (n = 6) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for metabolic outcomes (see Table D-10). Urinary uranium was significantly associated with increased risk of metabolic syndrome in a cross-sectional study (Xu et al., 2020). No associations were observed in studies examining urinary uranium and diabetes (Wang et al., 2020; Chafe et al., 2018; Liu et al., 2016). Two studies had potential limitations including concern for exposure assessment misclassification and only reporting the exposure-outcome association as exposure averages for outcome groups.

Newly Identified Animal Studies

No new animal studies were identified in the literature search update.

Conclusion

Use of a lack of evidence from experimental studies, and only one epidemiological study that observed an association cross-sectionally, EPA will not consider hematological effects for hazard evaluation or dose response.

Units of Analysis

N/A

Table D-10. Studies of metabolic endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Liu et al. (2016)	Occupational China Cross-sectional	Urine	Diabetes	No effects reported.
Chafe et al. (2018)	Canada Case-control	Drinking water	Type 1 diabetes	No effects reported.
Xu et al. (2020)	China Cross-sectional	Urine	Metabolic syndrome	Significant association.
Wang et al. (2020)	United States Cohort	Urine	Diabetes	No association observed.
Su et al. (2012)	China Case-control	Blood	Gouty arthritis	No effects reported.
Zablotska et al. (2013)	Occupational Canada Cohort	Occupational	Mortality–diabetes	No effects reported.

D.10. MUSCULOSKELETAL EFFECTS

ATSDR Summary

ATSDR 2013 considered one case study in which an individual was exposed to a large dose of uranium plus benzodiazepine, and a case-control study reporting a significant association between uranium exposure and serum type I collagen carboxy-terminal telopeptide (a marker of bone resorption). They also cite three animal toxicity studies that include acute, short-term, and subchronic studies using rats, mice, or rabbits. In mice, uranium exposure resulted in decreased percent metaphyseal activity in bone formation and increased bone resorption, but in SD rats and New Zealand rabbits there were no effects in histological measures of bone damage. ATSDR concluded that "there are limited data on the potential of uranium to induce bone or muscle damage." (ATSDR, 2013)[18]

Newly Identified Human Studies

Five (n = 5) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for musculoskeletal outcomes (see Table D-11). No associations were observed in studies examining systemic sclerosis, muscle strength, or mortality from diseases of the musculoskeletal system. Significant findings were seen in an NHANES study examining the association with bone density (Park and An, 2022). One study had potential limitations including selection bias.

Newly Identified Animal Studies

Three animal toxicity studies (one short-term and two chronic exposures) were identified in the literature search. They exposed young SD rats for 3 to 28 days or 9 months and reported alterations in cortical bone parameters, reduced bone mineral density, and altered mRNA levels of genes associated with bone development and functions (see Table D-12). One study (Wade-Gueye et al., 2012) compared responses in young and sexually mature animals and observed that younger individuals appear to be more susceptible to uranium-induced bone effects.

Conclusion

The toxicological and epidemiological studies identified in the IRIS literature search suggest that uranium exposure may impact the skeletal system and that early lifestages may represent a susceptible population. Based on these findings, EPA will perform a hazard evaluation of uranium-induced musculoskeletal effects. This analysis will consider studies cited in ATSDR 2013 and studies that met PECO criteria in the IRIS literature search.

[18](ATSDR, 2013) also considered uranium-induced skeletal effects after gestational exposure in mice (see Domingo et al. 1989, and ATSDR 2013 Developmental Effects section 3.2.2.6).

Units of Analysis

Human: Musculoskeletal conditions, muscle, and bone health.

Animal: Muscular & skeletal morphology/histopathology, clinical markers of musculoskeletal disease, and parameters/measures of bone development and function.

Table D-11. Studies of musculoskeletal endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Marie et al. (2017)	Case-control France	Hair	Systemic sclerosis	No associations observed.
Park and An (2022)	U.S. (NHANES) Cross-sectional	Urine	Bone density	Significant association.
Wu et al. (2022)	Cross-sectional U.S.	Urine	Muscle strength	No effects reported.
Shumate et al. (2017)	Occupational Cross-sectional U.S.	Urine	Arthritis/back pain	Significant association.
Samson et al. (2016)	Occupational France cohort	Occupational	Diseases of the musculoskeletal system–mortality	No effects reported.

Table D-12. Summary of toxicological studies reporting on uranium-induced musculoskeletal effects

Reference	Experimental design	Author-reported findings
Wade-Gueye et al. (2012)	Newborn and mature male SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo	Cortical bone parameters were affected in the young animals. No effect in adults. No effect on clinical markers.
Rodrigues et al. (2013)	Weaning female Wistar rats exposed to uranyl nitrate (0, 50 ppm in food) for 3, 7, 11, 14, 21, or 28 d	Decreased femoral bone mineral density.
Souidi et al. (2018)	Newborn male SD rats exposed to 0, 1.5, 10, 40 ppm (0, 0.18, 1.2, 4.8 mg/kg-d)	Decreased cortical bone diameter in the femur. No effect on microarchitecture parameters, bone mineral density, or serum markers.

D.11. NEUROLOGICAL EFFECTS

ATSDR Summary

ATSDR 2013 identified neurobehavioral health effects as a response to uranium exposure. ATSDR 2013 did not identify human studies reporting on neurological effects, but considered toxicological studies using several rat strains, mice, or New Zealand rabbits. In SD and Long-Evans rats and in Swiss mice exposure to uranium lead to altered behaviors such as line crossing and rearing behaviors, and motor activity. Brain neurotransmitter levels and sleep cycles were also altered in exposed rats. However, brain histopathology was not affected in rats or rabbits.

Newly Identified Human Studies

Thirteen (n = 13) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for neurological outcomes (see Table D-13). One study observed a significant association with schizophrenia (Ma et al., 2018), but the two other studies saw no association with cognitive performance. Many studies had potential limitations, including due to not accounting for confounding and reporting the exposure-outcome association only as exposure average for outcomes groups.

Newly Identified Animal Studies

Nine animal toxicity studies (eight using rats and one using mice) were identified in the IRIS literature search. Outcomes considered in these subchronic and chronic exposure studies include behavioral and functional measures, histopathology, and neurotransmitter levels. Experimental studies using rats report alterations in behaviors (e.g., depressive, and anxiety-like behaviors) and functions (e.g., decreased locomotor activity), and increased neurocellular damage (e.g., apoptosis, and reduced spinal motor neurons) after oral exposure to uranium (see Table D-14). In both mice and rats, uranium exposure was associated with impaired memory.

Conclusion

The available toxicological studies identified in the literature search update provide further support of the studies and evidence considered by ATSDR 2013. Based on these findings, EPA will evaluate the available evidence (studies identified in the IRIS literature search and studies cited in ATSDR 2013) for dose-response analysis on uranium-induced neurological effects.

Units of Analysis

Humans: Cognitive function, brain disorders.

Animals: Learning/memory, brain morphology/histopathology, neurodegenerative disease, neurotransmitter levels/function, organ weights.

Table D-13. Studies of neurological endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Ma et al. (2018)	China Case-control	Blood	Schizophrenia	Statistically significant.
Nozadi et al. (2021)	U.S. Cohort	Blood, urine	Gross motor, fine motor, problem solving, personal-social	No effects(s) reported.
Wang et al. (2022)	U.S. (NHANES) Cross-sectional	Urine	Cognitive performance	No effect(s) reported.
Adams et al. (2013)	U.S. Case-control	Blood, urine	Autism	Significant association.
De Benedetti et al. (2017)	Italy Case-control	Blood	Amyotrophic lateral sclerosis (ALS)	No effect(s) reported.
Fiore et al. (2020)	Italy Cross-sectional	Hair	Autism	No effect(s) reported.
Harchaoui et al. (2020)	Case-control	Hair	Autism	No effect(s) reported.
Karakis et al. (2021)	Israel Cohort	Urine	Developmental disorders	No effect(s) reported.
Lin et al. (2022)	Taiwan Cross-sectional	Blood	Alzheimer's disease	Statistically significant (suggesting benefit).
Roos et al. (2013)	Norway Case-control	Blood	Amyotrophic lateral sclerosis (ALS)	No effects(s) reported.
Samson et al. (2016)	Occupational France Cohort	Occupational	Non-malignant tumors of the central nervous system	No effect(s) reported.
Torrente et al. (2013)	Spain Cohort	Hair	Motor function, behavioral outcomes in children	No effect(s) reported.
Tretyakov et al. (2011)	Occupational Russia	Unclear	Cognitive function	No effect(s) reported.

Table D-14. Summary of toxicological studies reporting on uranium-induced neurological effects

Reference	Experimental design	Author-reported findings
Mouse studies		

Reference	Experimental design	Author-reported findings
Lestaevel et al. (2014)	Male C57BL/6J and ApoE null mice exposed uranyl nitrate (0, 20 mg/L in drinking water) for 14 wk	In ApoE null animals, uranium impaired working memory, but no effect on anxiety-like behavior or cerebral cortex levels of acetylcholine.
Rat studies		
Dublineau et al. (2014)	Male SD rats exposed to uranyl nitrate (0.009, 0.09, 0.23, 0.45, 0.9, 1.8, 5.4 mg/kg-d in drinking water) for 9 mo	No effect on brain acetylcholine levels.
Lestaevel et al. (2015)	Male SD rats exposed to uranyl nitrate (0, 10, 40 mg/L in drinking water) for 10 wk starting at birth	Decreased locomotor activity, but no effect on rearing movements; increased anxiety-like behavior and decreased depressive-like behavior and rotarod.
Lestaevel et al. (2013)	Male SD rats exposed to uranyl nitrate (0, 10, 40 mg/L in drinking water) during gestation plus 10 wk	Decreased object recognition memory. No effect on sleep-wake cycle or spatial working memory.
Saint-Marc et al. (2016)	Male SD rats exposed to uranyl nitrate (0, 1, 40, 120 mg/L in drinking water) for 9 mo	Decreased in the number of spinal motor neurons.
Lestaevel et al. (2016)	Male & female SD rats exposed to uranyl nitrate (0, 10, 40 mg/L in drinking water) from PND 1–250)	Altered behaviors (motor activity, spatial working memory, anxiety, depressive-like behavior).
Legrand et al. (2016a)	Pregnant SD rats exposed to depleted uranium (0, 10, 120 mg/L in drinking water) during gestation	Increased cell death and apoptosis and reduced dividing cells in dentate gyrus. Increased cell proliferation in dentate neuroepithelium.
Legrand et al. (2016b)	Pregnant SD rats exposed to uranium (0, 6 mg/kg-d in drinking water) during gestation	Altered neuronal cell differentiation in hippocampal dentate gyrus, and depression behavior. No effect on locomotor activity, exploratory activity, or spatial memory.
Dinocourt et al. (2017)	Pregnant SD rats exposed to uranium (0, 2, 6 mg/kg-d in drinking water) during gestation	Altered behaviors (depressive-like behavior, spatial memory) No effect on hippocampal morphology. Altered pyramidal cells in hippocampus.

D.12. REPRODUCTIVE EFFECTS

ATSDR Summary

ATSDR 2013 did not identify human studies reporting on the potential reproductive effects caused by uranium exposure, but they identified and evaluated animal toxicity studies using rats or mice as experimental models and evaluated male and female reproductive outcomes. ATSDR 2013

identified reproductive effects as a health response to uranium exposure. Reproductive effects observed in studies evaluating male mice and rats include reduced pregnancy rates, numbers of spermatozoa and epididymal weight after uranium treatment. Female reproductive effects were reported in studies using murine models and include altered ovarian folliculogenesis, increased percentage of dysmorphic oocytes, reduced mitotoxic index in oocyte supporting cells, and reduced proportion of healthy oocytes in exposed mice.

Newly Identified Human Studies

Five (n = 5) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for reproductive outcomes (see Table D-15). A cohort study from Lebanon found uranium in seminal fluid was significantly associated with low progressive motility, low normal morphology, and low sperm viability (Sukhn et al., 2018). In the U.S., (Branch et al., 2021) observed urinary uranium to be significantly positively associated with DNA fragmentation index, while (Wang et al., 2016) observed no effects in a Chinese cohort. A few studies had potential limitations due to a limited exposure contrast and reporting the exposure-outcome association only as exposure averages for outcome groups.

Newly Identified Animal Studies

Six animal toxicity studies that meet PECO criteria were identified in the IRIS literature search (see Table D-16). These studies used SD or Wistar rats to evaluate potential U-induced male and female reproductive effects. Two studies evaluated effects in the male reproductive system after gestational or chronic exposures. Chronic (6- or 12-month) exposures lead to increased nuclear pyknosis in testis, decreased spermatocytes and spermatids, and reduced serum testosterone but no effects on follicle-stimulating hormone levels. Gestational plus postnatal exposures resulted in altered reproductive hormone levels (decreased plasma testosterone and intratesticular estradiol, and increased plasma luteinizing hormone and follicle-stimulating hormone) and increased absolute testicular weight (without changes in relative weight).

Four studies evaluated reproductive outcomes after exposing male and female rats and evaluated effects in F0, F1, or F2 generation animals (see Table D-16). Effects reported include uranium-induced changes in reproductive organ weights and alterations in reproductive hormone levels after exposure. Sperm measures were also measured. Uranium treatment for 9 months altered sperm morphology in F0, F1, and F2 SD animals. Finally, pregnancy rates were considered, and exposure was associated with decreased pregnancy rate in F0 and F1 animals.

Conclusion

The available toxicological and epidemiological studies identified in the IRIS literature search update provide further support of the studies and evidence considered by ATSDR 2013 in its evaluation of uranium-induced reproductive effects. Furthermore, newly identified toxicological and epidemiological studies provide evidence that may be considered for dose response. Based on

these findings, EPA will perform a dose-response analysis on uranium-induced male and female effects that includes toxicological evidence identified by ATSDR 2013 and epidemiological and toxicological evidence captured in the IRIS literature search.

Units of Analysis

Humans: Semen quality.

Animals: Organ morphology/histopathology, developmental measures, reproductive hormone measures, functional measures.

Table D-15. Studies of reproductive endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Branch et al. (2021)	Cohort U.S.	Urine	Semen quality	Significant association (suggesting benefit).
Sukhn et al. (2018)	Cohort Lebanon	Blood, seminal fluid	Semen quality markers	Significant associations.
Wang et al. (2016)	Cohort China	Urine	Spermatozoa apoptosis measures, Sperm DNA damage parameters	No effect(s) reported.
McKeating et al. (2020)	Cohort Australia	Cord blood	Pregnancy complications	No effect(s) reported.
Wang et al. (2017)	Cohort China	Seminal plasma	Sperm apoptosis	Uranium not analyzed further except for exploratory purposes.

Table D-16. Summary of toxicological studies reporting on uranium-induced reproductive effects

Reference	Experimental design	Author-reported findings
Studies evaluating male repro toxicity		
Lu et al. (2021)	Male SD exposed to depleted uranium (0, 3, 30, 300 ppm in food) for 60 d	Increased nuclear pyknosis in testis. Decreased spermatocytes and spermatids, and decreased serum testosterone.
Legendre et al. (2016)	Female SD rats exposed to uranyl nitrate (0, 40, 120 mg/L in drinking water) from GD 1 to PND 168	Increased absolute testis weight, but no effect on relative weight. No effect on epididymis weight or sperm measures. Decreased plasma testosterone and intratesticular estradiol. Increased plasma LH and FSH.
Studies exposing males and females		
Hao et al. (2012)	Male and female Wistar rats exposed to depleted uranyl nitrate (0, 0.3, 3 mg/kg-d in food) for 4 mo	Decreased pregnancy rate. In F0 and F1 males: increased serum T and decreased serum FSH. In F0 males: Increased serum LH. In F1 males: decreased serum LH.
Grison et al. (2022)	Male and female SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo; animals mated at 6 mo	Decreased pregnancy rate in F1 generation animals. No effect on the number of pups per litter or the male female ratio in F0, F1, or F2 generation animals.
Elmhiri et al. (2018)	Male and female SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo and then mated	Increased testes and ovaries weights. These effects were not apparent in F0 and F1 animals.
Legendre et al. (2019)	Male and female SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo	Altered sperm morphology in F0, F1, and F2 generation animals. Decreased pregnancy rate and epididymis weight in F1 generation animals only.

LH = luteinizing hormone; FSH = follicle stimulating hormone.

D.13. RESPIRATORY EFFECTS

ATSDR Summary

ATSDR 2013 considered human and animal toxicological study evidence in their evaluation of uranium-induced respiratory effects after oral exposure. A case report in which a patient had elevated serum liver enzymes levels after exposure to a large dose of uranyl acetate (approximately 15 g) was considered. ATSDR also considered animal toxicity studies performed in dogs, rats, and rabbits. Experimental designs used in these studies included chronic, subchronic, and short-term exposures and measured histopathological endpoints. ATSDR concluded that respiratory effects from oral exposure to uranium are unlikely.

Newly Identified Human Studies

Sixteen (n = 16) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for respiratory outcomes (see Table D-17). Three studies observed urinary uranium to be significantly associated with asthma or emphysema prevalence (Li et al., 2021; Huang et al., 2016; Mendy et al., 2012); and one occupational study observed increased risk of breathless and pulmonary symptoms (Shumate et al., 2017). Several studies had potential limitations, including concerns over confounding, selection bias, exposure assessment misclassification, and lack of contrast.

Newly Identified Animal Studies

No new animal studies informing respiratory effects after oral exposure to uranium were identified in the literature search update.

Conclusion

The epidemiological studies identified in the IRIS literature search suggests that uranium oral exposure may impact the respiratory system. Based on these findings, EPA will perform a hazard evaluation of uranium-induced respiratory effects. This analysis will consider studies cited in ATSDR 2013 and studies that met PECO criteria in the IRIS literature search.

Units of Analysis

Humans: Respiratory disease, pulmonary symptoms.

Animals: Organ weights, organ morphology/histopathology, functional measures.

Table D-17. Studies of respiratory endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Feng et al. (2015)	Cross-sectional China	Urine	Pulmonary function	No effects observed.
Huang et al. (2016)	Case-control China	Urine	Asthma	Significant association.
Li et al. (2021)	U.S. (NHANES) Cross-sectional	Urine	Asthma	Significant association.
Mendy et al. (2012)	U.S. (NHANES) Cross-sectional	Urine	Asthma, emphysema	Significant association.
Rahman et al. (2022a)	U.S. (NHANES) Cross-sectional	Urine	COPD	No effects reported.
Rahman et al. (2022c)	U.S. (NHANES) Cross-sectional	Urine	Emphysema	No effects reported.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Rahman et al. (2022d)	U.S. (NHANES) Cross-sectional	Urine	Emphysema	No effects reported.
Rahman et al. (2022b)	U.S. (NHANES) Cross-sectional	Urine	Chronic bronchitis	No effects reported.
Richardson et al. (2021)	Occupational North America/Europe Cohort	Occupational	Noncancer disease of the respiratory system (mortality)	Significant association.
Shumate et al. (2017)	Occupational U.S. Cross-sectional	Occupational	Pulmonary symptoms	Significant association.
Samson et al. (2016)	Occupational France Cohort	Occupational	Respiratory disease mortality	Significant deficits in deaths.
Denisova et al. (2018)	Russia Cross-sectional	Lung tissue	Sarcoidosis	No effects observed.
Karakis et al. (2021)	Cohort Israel	Urine	Asthma	No effects observed.
Kayembe-Kitenge et al. (2020)	Occupational DR Congo Cross-sectional	Urine	Pulmonary function	No uranium-specific analyses.
Kocher et al. (2016)	Occupational United States Cross-sectional	Occupational	Pneumoconiosis	No effects reported.
Zablotska et al. (2013)	Occupational Canada cohort	Occupational	Mortality from COPD and asthma	No associations observed.

COPD = chronic obstructive pulmonary disease.

D.14. URINARY EFFECTS

ATSDR Summary

ATSDR determined there was sufficient information from experimental studies to conclude that uranium is a kidney toxicant. ATSDR 2013 reviewed acute and subchronic exposure toxicity

studies that report increased incidence of histological effects and alterations in urinary markers of renal damage in rats, mice, dogs, and rabbits.

Newly Identified Human Studies

Twelve (n = 12) epidemiological studies meeting PECO criteria were identified in the IRIS literature search for metabolic outcomes (see Table D-18). Some studies observed an association between uranium exposure and kidney disease (Park and An, 2022); a deficit in some of the measured kidney filtration measures (Shelley et al., 2014); and a decrease in eGFR (estimated glomerular filtration rate) (Wu et al., 2018b). A number of studies had potential limitations, including selection bias and exposure assessment concerns.

Newly Identified Animal Studies

Eighteen animal toxicity studies (14 studies using rats and 4 studies using mice) were identified in the date-limited literature search. Outcomes considered in these studies include organ weights, macroscopic appearance, histopathology, and markers of renal disease. In SD rats, subchronic and chronic exposure to uranyl nitrate resulted in altered urinary flow and renal vascular resistance, kidney weight, and markers of renal disease (see Table D-19). The remaining studies report no effects on kidney weight, histopathology, macroscopic appearance, or markers of renal disease in exposed SD rats. However, most of the available studies exposed SD rats to uranium concentrations (40 mg/L) known to be non-toxic to the urinary system (Guéguen et al., 2007; Tissandié et al., 2007; Souidi et al., 2005). In C57BL/6J and Kunming mice uranium exposure did not affect markers of renal disease, and in ApoE null mice there were no treatment-related effects on macroscopic appearance of the kidney or markers of renal disease.

Conclusion

The available toxicological and epidemiological studies identified in the literature search update provide further support of the studies and evidence considered by ATSDR 2013. Based on these findings, EPA will evaluate the available evidence (studies identified in the IRIS literature search and studies cited in ATSDR 2013) for dose-response analysis on uranium-induced urinary effects.

Units of Analysis

Humans: Kidney disease, markers of kidney function.

Animals: Urinary and serum markers of renal disease/function, organ weights, organ morphology/histopathology.

Table D-18. Studies of urinary endpoints in humans identified 2011–2022

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Nanayakkara et al. (2019)	Sri Lanka Case-control	Urine, hair, drinking water	Chronic kidney disease	No effects reported.
Okaneku et al. (2015)	U.S. (NHANES) Cross-sectional	Urine	Renal function markers	No effects reported.
Park and An (2022)	U.S. (NHANES) Cross-sectional	Urine	Kidney disease	Significant association.
Rango et al. (2015)	Sri Lanka Cross-sectional	Urine	Chronic kidney disease	No effects reported.
Shelley et al. (2014)	Occupational Cross-sectional	Urine	Kidney function markers	Significant negative association.
Weaver et al. (2014)	Mexico Cross-sectional	Urine	eGFR measures	No significant findings.
Wu et al. (2018b)	China Cross-sectional	Urine	eGFR measures	Significant negative association.
Oruc et al. (2022)	Turkey Case-control	Blood	Trace element status in hemodialysis patients	No effects observed.
Butler-Dawson et al. (2021)	Occupational Guatemala cohort	Urine	Increase in creatinine as a marker of kidney injury	No effects observed.
Samson et al. (2016)	Occupational France Cohort	Occupational	Renal disease mortality	Significant deficits in deaths.

Reference	Study design	Exposure measurement	Endpoints	Author-reported findings
Yang et al. (2019)	China Cross-sectional	Urine, blood	eGFR	No effects reported.
Zablotska et al. (2013)	Occupational Canada cohort	Occupational	Mortality from nephritis and nephrosis	No effects reported.

eGFR = estimated glomerular filtration rate.

Table D-19. Summary of toxicological studies reporting on uranium-induced urinary effects

Reference	Experimental design	Author-reported findings
Rat studies		
Rouas et al. (2011)	Male SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo	No effects on histopathology or histological markers of renal disease
Wade-Gueye et al. (2012)		Decreased serum creatinine, no effect on other markers of renal disease.
Grison et al. (2013)		Increased relative (but not absolute) kidney weight, plasma creatinine, and urinary potassium and sodium.
Grison et al. (2019)		No effects on plasma or urine markers of renal damage
Dublineau et al. (2014)	Male SD rats exposed to uranyl nitrate (0.009, 0.09, 0.23, 0.45, 0.9, 1.8, 5.4 mg/kg-d in drinking water) for 9 mo	No macroscopic or organ weight changes, or effects on markers of renal disease.
Grison et al. (2016)	Male and female SD rats exposed to uranyl nitrate (0, 0.015, 0. 15, 1.5, 40 mg/L in drinking water) for 9 mo	Decreased kidney weight and urine volume. Decreased urine calcium concentration, protein levels, and urea concentration.
Poisson et al. (2014a)	Male SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 90 d	No effects on plasma markers of renal disease.
Legendre et al. (2016)	Male SD rats exposed to uranyl nitrate (0, 40, 120 mg/L in drinking water) from GD 1 to PND 168	No effects on kidney weight or plasma markers of renal disease.
Souidi et al. (2018)	Male SD rats exposed to natural uranium (0, 40, 120 mg/L in drinking water) for 9 mo	Decreased serum urea at low dose and decreased creatinine at high dose.
Grison et al. (2018)	Male and female F0 generation SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 9 mo	F0 and F1 generation: no effects on kidney weight or markers of renal disease.

Reference	Experimental design	Author-reported findings
		F2 generation: decreased kidney weight in males. No effect on markers of renal disease
Lu et al. (2021)	Male SD rats exposed to depleted uranium (0, 3, 30, 300 mg/kg in food) for 6 or 12 mo	No effects on kidney weights or plasma markers of renal disease.
Vicente-Vicente et al. (2013)	Male SD rats exposed to uranyl nitrate (0, 5.4 g/L in drinking water) for 11 or 21 wk	11 wk: decreased urinary flow. No change in plasma creatinine, plasma urea, proteinuria, in glucosuria. 21 wk: decreased urinary flow and increased renal vascular resistance. No change in renal blood flow, plasma.
Gueguen et al. (2014)	Male SD rats exposed to uranyl nitrate (0, 40 mg/L in drinking water) for 1–18 mo	No effects on plasma markers of renal disease, organ weights, or histopathology.
	Male SD rats exposed to uranyl nitrate (0, 0, 0.2, 2, 5, 10, 20, 40, 120 mg/L in drinking water) for 9 mo	
Poisson et al. (2014b)	Male SD rats exposed to uranyl nitrate (0, 40, 120, 400 mg/L in drinking water) for 3 mo	No effects on kidney histopathology or urinary or plasma markers of renal disease.
	Male SD rats exposed to uranyl nitrate (0, 40, 120, 600 mg/L in drinking water) for 9 mo	
Mouse studies		
Bolt et al. (2019)	Male & female C57BL/6J mice exposed to uranyl acetate (0, 5, 50 mg/L in drinking water) for 60 d	No effects on plasma markers of renal disease.
Hao et al. (2013b)	Male Kunming mice exposed to uranyl nitrate (0, 0.4, 4, 40 mg/kg-d in food) for 4 mo	No effects on plasma markers of renal disease.
Lestaevel et al. (2014)	Male ApoE null mice exposed to uranyl nitrate (0, 20 mg/L) for 14 wk	No effect on plasma markers of renal disease
Souidi et al. (2012)	Male ApoE null mice exposed to uranyl nitrate (0, 20 mg/L in drinking water) for 3 mo	No effect on macroscopic appearance or plasma markers of renal disease.

D.15. OTHER EFFECTS

EPA also evaluated other outcomes not captured in ATSDR 2013 that were identified in the IRIS literature search.

Newly Identified Human Studies

Kim et al. (2019) measured oxidative stress; Shiue (2013) examined vision, hearing, and balance; Baj et al. (2022) examined optic chiasm; Strand et al. (2014) examined all-cause mortality; Shiue (2015) measured self-rated health; Bouet et al. (2018) examined all causes of death (cancer and noncancer); and Lewicka et al. (2019) examined prepregnancy BMI.

Newly Identified Animal Studies

The were no new animal toxicity studies that evaluated outcomes not already considered in ATSDR 2013.