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## Uranium, soluble salts (no CASRN)

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Reference Dose for Chronic Oral Exposure (RfD) ▼

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**0421**

### Uranium, soluble salts; no CASRN

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Uranium, soluble salts

**File First On-Line 10/01/1989**

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	10/01/1989
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	no data	

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Uranium, soluble salts

CASRN —

Last Revised — 10/01/1989

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of

deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### **\_\_I.A.1. Oral RfD Summary**

<b>Critical Effect</b>	<b>Experimental Doses*</b>	<b>UF</b>	<b>MF</b>	<b>RfD</b>
		1000	1	3E-3 mg/kg/day
Initial body weight loss; moderate nephrotoxicity	NOAEL: None			
30-Day Oral Rabbit Bioassay (diet)	LOAEL: 0.02 ppm uranyl nitrate hexahydrate in food (converted to 2.8 mg uranium/kg/day)			
Maynard and Hodge, 1949				

\*Conversion Factors: Test compound is 47% uranium by weight (molecular weight ratio 238/502). 1 ppm = 0.03 mg/kg/day (assumed rabbit food consumption).

### **\_\_I.A.2. Principal and Supporting Studies (Oral RfD)**

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

Rabbits, rats and dogs were administered uranium compounds in the diet for 30 days. Studies of rats and dogs were continued for longer periods with serial sacrifices up to 1 year (rats and dogs) or 2 years (rats only) of exposure. Rabbits showed greater sensitivity to the toxic effects of uranium. Rabbits (6/group; strain and sex not reported) were fed dietary levels of uranyl nitrate hexahydrate of 0, 0.02, 0.1, or 0.5% for 30 days (equivalent to doses of 2.8, 14, and 71 mg U/kg/day). Animals were examined daily, body weights were recorded weekly and kidneys were examined histologically at the termination of the experiment. Mortality was observed at the two highest doses (6 of 6 fed 71 mg U/kg/day, 4 of 6 fed 14 mg U/kg/day). During the first week of exposure, body weight losses were observed at all doses. After 30 days exposure, body weights of rabbits receiving 2.8 mg U/kg/day were similar to controls. Renal damage was judged to be moderate at the two lower doses and moderately severe at the highest dose. Based on this study, the lowest dose tested in rabbits (2.8 mg U/kg/day) was judged to be the LOAEL.

The toxicity of uranium compounds was less severe to rats and dogs, although water soluble uranium compounds (UO<sub>2</sub>F<sub>2</sub>, UO<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>, UCl<sub>4</sub>) were more toxic than insoluble compounds (Maynard and Hodge, 1949). LOAELs for these compounds were 39, 120, and 160 mg U/kg/day for rats, and 7.7, 9.5, and 132 mg U/kg/day for dogs, respectively. In most cases, LOAELs could be identified within the first 30 days of exposure.

Uranium is a classical nephrotoxic. The toxicity of this chemical to humans has been of interest since the 1800's when uranium was used as a homeopathic cure for diabetes mellitus (Hodge,

1973). These early reports demonstrate the susceptibility of humans to the nephrotoxicity of ingested uranium, but provide inadequate basis for estimating the threshold dose for toxic effects.

Hursh et al. (1969) administered single oral doses of uranyl nitrate (10.8 mg U/ 65 to 170 ug U/kg) to four hospital patients. Urinary levels of uranium and protein were determined. Urinary protein was not elevated in any of the patients.

Humans have been exposed to uranium compounds by intravenous injection in controlled experiments on uranium excretion and toxicity (Hursh and Spoor, 1973; Lussenhop et al., 1958). Single doses of 120 ug U/kg and higher administered to terminal brain tumor patients were associated with elevations in urinary excretion of catalase, albumin and non-protein nitrogen, and casts in the urine (Lussenhop et al., 1958). Hursh and Spoor (1973) describe a study in which seven patients were injected with uranyl nitrate (6.3, 6.3, 16, 30, 42, 55, or 71 ug U/kg). Renal function tests were performed including urinary catalase, protein, nitrogen, glomerular filtration rate, maximum tubular excretory capacity and urea clearance. Trace changes in urinary catalase were noted in patients receiving 55 or 71 ug U/kg.

Novikov and Yudina (1970) administered female rabbits (6 to 8/group) oral doses of uranyl nitrate of 0, 0.02, 0.2, and 1 mg U/kg/day for 12 months. No differences were noted compared with controls with respect to serum urea, creatinine or chlorides. Further experiments on enzyme levels in tissue homogenates were equivocal; enzyme activities were only expressed relative to the wet weight of the tissue from which the homogenate was prepared.

Limited data are available on the reproductive toxicity of uranium. Maynard and Hodge (1949) conducted a 2-year study of the reproductive effects of uranium. Administration of dietary levels of uranyl nitrate of 2% (equivalent to a dose of approximately 470 mg U kg/day) resulted in decreased food consumption, and declines in weight gain. Decreases in the number of litters born, litter size, were consistent with the decline in nutritional status of the animals.

In a second study by Maynard and Hodge (1949), rats (50/sex) were exposed to dietary levels of uranyl nitrate of 2% (about 460 mg/kg) for one day. Males and females were then paired, over a period of 7 months. Declines in total number of pups born (1959 vs. 1725; 12% decrease) and litter size (8.6 vs. 7.6; 7% decrease) were observed with treatment, but the actual number of litter bearing females increased from 43/50 to 44/50 with treatment.

### **\_\_\_I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — The UF of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of the chemical in lieu of specific data, and 10 for use with a LOAEL from an animal study. The uncertainty factor does not include an extra factor of 10 for less-than-lifetime exposure since experiments of acute/subacute duration have been shown to be adequately sensitive for determining doses which cause chronic nephrotoxicity. Rabbits inhaling uranyl nitrate dust (0.25 mg/cu.m) for 10 days showed similar, nephrotoxic effects (interstitial nephritis, tubular regeneration) compared with rabbits exposed to these levels for 6.5 months (Stokinger et al., 1949). Similarly, rats and dogs ingesting uranium compounds displayed similar NOAELs/LOAELs after 30 days exposure compared with exposures of 1 or 2 years (Maynard and Hodge, 1949).

MF — None

### **\_\_\_I.A.4. Additional Studies/Comments (Oral RfD)**

Pharmacokinetic models were considered in developing the RfD. Although parameters for

absorption, distribution, and accumulation in the kidney are uncertain, reasonable risks can be estimated for these parameters. However, data are inadequate for determining a threshold for uranium levels in the kidney which cause nephrotoxicity and it is questionable whether total uranium levels in the kidney are a good measure of the potential for toxicity. Because of these uncertainties, modeling approaches were not used to determine the RfD.

#### **\_\_\_I.A.5. Confidence in the Oral RfD**

Study — Medium  
Database — Medium  
RfD — Medium

The critical study is well designed, but used a small number of experimental animals; it rates medium confidence. The database is given a medium level of confidence since there are adequate studies on the effects of U in various species. Medium confidence in the RfD follows.

#### **\_\_\_I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — U.S. EPA, 1985

Other EPA Documentation — None

Agency Work Group Review — 01/19/1989

Verification Date — 01/19/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Uranium, soluble salts, conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

#### **\_\_\_I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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#### **\_\_\_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Uranium, soluble salts  
CASRN —

Not available at this time.

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### **\_\_II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Uranium, soluble salts  
CASRN —

This substance/agent has not undergone a complete evaluation and determination under US EPA's

IRIS program for evidence of human carcinogenic potential.

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## **\_VI. Bibliography**

Substance Name — Uranium, soluble salts

CASRN —

Last Revised — 10/01/1989

### **\_VI.A. Oral RfD References**

Hodge, H. 1973. A History of Uranium Poisoning 1824-1942. In: Uranium, Plutonium, Transplutonic Elements, H.C. Hodge, J.N. Stannard and J.B. Hursh, Ed. Springer-Verlag, New York. p. 1-68.

Hursh, J.B. and N.L. Spoor. 1973. Data on Man. In: Uranium, Plutonium, Transplutonium Elements, H.C. Hodge, J.N. Stannard and J.B. Hursh, Ed. Springer-Verlag, Berlin. p. 197-239.

Hursh, J.B., W.R. Neuman, T. Toribara, H. Wilson and C. Waterhouse. 1969. Oral ingestion of uranium by man. Health Phys. 17: 619-621.

Lussenhop, A.J., J.C. Gallimore, W.H. Sweet, E.G. Struxness and J. Robinson. 1958. The toxicity in man of hexavalent uranium following intravenous administration. Am. J. Roent. 79(1): 83-100.

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

Novikov, Y.V. and T.V. Yudina. 1970. Data on the biological effect of small amounts of natural uranium in water. Hyg. Sanit. 35: 225-261.

Stokinger, H.E., R.C. Baxter, H.P. Dygert, C.W. LaBelle, S. Lasin, et al. 1949. Toxicity following inhalation for 1 and 2 years. In: The Pharmacology and Toxicology of Uranium Compounds. Nations Nuclear Energy Service. Division VI, Vol. I, C. Voegtlin and H.C. Hodge, Ed. McGraw Hill, New York, NY. p. 1370-1778.

U.S. EPA. 1985. Drinking Water Criteria Document for Uranium. Office of Drinking Water, Washington, DC. (Draft)

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### **\_VI.B. Inhalation RfC References**

None

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### **\_VI.C. Carcinogenicity Assessment References**

None

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## **\_VII. Revision History**

Substance Name — Uranium, soluble salts

CASRN —

Date	Section	Description
10/01/1989	I.A.	Oral RfD summary on-line
10/01/1989	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory Action section on-line
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

## **\_VIII. Synonyms**

Substance Name — Uranium, soluble salts

CASRN —

Last Revised — 10/01/1989

- Uranium (soluble salts)

### **IRIS Home**

#### **Chronic Health Hazards for Non-Carcinogenic Effects**

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- Additional Studies/Comments
- Confidence in the Oral RfD
- EPA Documentation and Review

#### **Reference Concentration for Chronic Inhalation Exposure (RfC)**

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- Confidence in the Inhalation RfC
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##### **Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

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##### **Bibliography**

##### **Revision History**

##### **Synonyms**