

## Exposure Pathways and Health Effects Associated with Chemical and Radiological Toxicity of Natural Uranium: A Review

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### ABSTRACT

Natural uranium exposure derives from the mining, milling, and processing of uranium ore, as well as from ingestion of groundwater that is naturally contaminated with uranium. Ingestion and inhalation are the primary routes of entry into the body. Absorption of uranium from the lungs or digestive track is typically low but can vary depending on compound specific solubility. From the blood, two-thirds of the uranium is excreted in urine over the first 24 hours and up to 80% to 90% of uranium deposited in the bone leaves the body within 1.5 years. The primary health outcomes of concern documented with respect to uranium are renal, developmental, reproductive, diminished bone growth, and DNA damage. The reported health effects derive from experimental animal studies and human epidemiology. The Lowest Observed Adverse Effect Level (LOAEL) derived from animal studies is  $50 \mu\text{g}/\text{m}^3$  for inhalation and  $60 \mu\text{g}/\text{kg}$  body weight/day for ingestion. The current respiratory standard of the Occupational Safety and Health Administration (OSHA),  $50 \mu\text{g}/\text{m}^3$ , affords no margin of safety. Considering the safety factors for species and individual variation, the ingestion LOAEL corresponds to the daily consumption set by the World Health Organization Drinking Water Standard at  $2 \mu\text{g}/\text{L}$ . Based

on economic considerations, the United States Environmental Protection Agency maximum contaminant level is  $30 \mu\text{g}/\text{L}$ . Further research is needed, with particular attention on the impact of uranium on indigenous populations, on routes of exposure in communities near uranium sites, on the combined exposures present at many uranium sites, on human developmental defects, and on health effects at or below established exposure standards.

### KEYWORDS

uranium, exposure, toxicity, mining, milling, health effects

### INTRODUCTION

Uranium is a metal having the highest atomic weight of any naturally occurring element on Earth. Uranium is present in trace amounts in soil and rock. When rock exists with a uranium concentration greater than  $1000 \text{ mg}/\text{kg}$ , uranium ore can be mined, concentrated, and processed. Natural uranium contains 99.274% U-238, 0.72% U-235, and 0.0057% U-234 by weight. The radioactive decay series for uranium 238, 234, and uranium 235 are presented in Fig. 1. The uranium decay series releases primarily alpha radiation, along with some gamma radiation. The metal has a very low specific activity and, accordingly, an extremely long half-life of 4.5 billion years.

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	Uranium-238 Series, includes <sup>234</sup> U Series					Uranium-235 Series				
Np										
U	<sup>238</sup> U 4.5E9		<sup>234</sup> U 2.5E5y			<sup>235</sup> U 7.1E8 y				
Pa		<sup>234</sup> Pa 1.2m					<sup>231</sup> Pa 3.3E4 y			
Th	<sup>234</sup> Th 24 d		<sup>230</sup> Th 8E4y			<sup>231</sup> Th 25.5 h		<sup>227</sup> Th 18.7 d		
Ac							<sup>227</sup> Ac 21.8 y			
Ra			<sup>226</sup> Ra 1600 y					<sup>223</sup> Ra 11.4 d		
Fr							<sup>223</sup> Fr 21.8 m			
Rn			<sup>222</sup> Rn 3.82 d					<sup>219</sup> Rn 4.0 s		
At				<sup>218</sup> At 2s					<sup>215</sup> At 1E-4s	
Po			<sup>218</sup> Po 3.05 m		<sup>214</sup> Po 1.6E-4s	<sup>210</sup> Po 138 d		<sup>215</sup> Po 1.8E-5		<sup>211</sup> Po 0.5 s
Bi				<sup>214</sup> Bi 19.7 m		<sup>210</sup> Bi 5.0 d			<sup>211</sup> Bi 2.15 m	
Pb			<sup>214</sup> Pb 26.8 m		<sup>210</sup> Pb 22.3y	<sup>206</sup> Pb stable		<sup>211</sup> Pb 36.1 m		<sup>207</sup> Pb stable
Tl				<sup>210</sup> Tl 1.3 m		<sup>206</sup> Tl 4.2 m			<sup>207</sup> Tl 4.79 m	

• ↓ alpha decay; ↗ beta decay; half life (d = days; m = minutes; s = seconds; y = years)

Fig. 1: Uranium Isotope Decay Series for uranium-238, uranium 234 and uranium 235 (redrawn from ATSDR, 1999).

Although depleted uranium has garnered much interest in recent years /1-3/, natural uranium can be a greater exposure risk for many people /4-5/. Although depleted and natural uranium are expected to have very similar toxicity, the modes of exposure and populations at risk differ greatly. Although reviews of uranium toxicity have been published /4-9/, the most recent being that of Craft et al. /10/, the

present review adds three distinct foci: First, the review explores in depth exposure to natural uranium, a topic treated lightly in most reviews on toxicity.

Second, it is much more succinct than the Agency for Toxic Substances and Disease Registry (ATSDR) and BEIR reviews. Third, it adds a discussion of possible policy implications.

### NATURALLY OCCURRING URANIUM

Uranium exists naturally in the earth's crusts from magmatic emplacement or hydrothermal deposition. Uranium minerals can result from primary or secondary deposition and exist most commonly as uraninite (a uranium-oxide), coffinite (a uranium-silicate), pitchblende (a form of uraninite), and carnotite (a uranium-vanadate). Uranium-phosphates, uranium-arsenates, uranium-vanadates, and uranium-carbonates are common secondary minerals, with uranium-sulfates, uranium-molybdates, uranium-tellurites, and uranium-selenites being less common. Compared with the gray-black-brown color of the more massive primary ore minerals, the secondary uranium minerals tend to be brighter in color (yellows, greens, oranges) and form as crusts, coatings, and films. Carnotite, for example, a bright yellow hydrated uranium vanadate, was initially mined in the Colorado Plateau Region. Transformation from primary to secondary minerals is governed largely by groundwater migration and geochemistry, atmospheric exposure, and topography. Many of these minerals are relatively insoluble and can remain in a fixed state, providing a source for mining uranium. Uranium carbonate ores can form soluble complex minerals with carbonate ions, however, which can result in groundwater contamination /11/.

### URANIUM MINING AND PROCESSING

The principal uranium mines and mills in the United States (U.S.), now closed, were located in the Colorado Plateau region that includes parts of New Mexico, Arizona, Colorado, and Utah. Many of these mines were operated on Native American land /12-13/. Most U.S. mills have been remediated under the Uranium Mill Tailings Radiation Control Act of 1978 (UMTRCA) [Pub. L. 95-604, Nov. 8, 1978, 92 Stat. 3021 (Title 42, Sec. 7901 et seq.)]. Yet, thousands of U.S. mines have just begun to be addressed /14-15/. Importantly, active

mining and processing of uranium continues outside of the U.S., with many uranium mines active or in development in all corners of the globe (<http://www.antenna.nl/wise/uranium/uproj.html>).

Uranium has been extracted from both underground and open-pit mines. The metal is also removed from the earth via *in situ* leaching. In the course of mining, the ore is hauled away from mine sites, and the waste rock and soil, called 'tailings', are left behind, often in large piles. The tailings have too little uranium to be of use but are still radioactive and may contain toxic heavy metals. The ore is transported to mills for processing into a more concentrated form of uranium known as 'yellow-cake', which is 90% uranium trioxide, with the remainder being ammonia, water, and impurities. Thus, uranium mill workers are exposed to uranium in a purer form than the ore to which miners are exposed. /4, 12, 16/.

The next step in the nuclear fuel process is to produce 'enriched' uranium, which has a U-235 concentration > 20%. Enrichment requires the conversion of yellowcake to uranium hexafluoride (UF<sub>6</sub>) through a multi-step chemical reaction beginning with dissolution in nitric acid, solvent extraction to remove impurities, precipitation with ammonium hydroxide, followed by hydrofluorination and fluorination. The final product, UF<sub>6</sub>, is a gas that can be processed so that the products are enriched uranium and depleted uranium.

A byproduct of the yellowcake enrichment process is an acidic waste referred to as *raffinate*. The raffinate stream contains trace amounts of toxic heavy metals as well as uranium, radium, and thorium and their decay products. When not disposed of properly, this waste can leach into the groundwater from settling ponds or runoff to contaminate soils and surface water.

### ROUTES OF EXPOSURE TO URANIUM

Currently, the U.S. Environmental Protection Agency (U.S. EPA) lists 23 National Priorities List (NPL) sites where uranium is a contaminant of

concern /17/. Twelve sites are regulated by the U.S. Department of Energy (U.S. DOE). Uranium, however, is explicitly excluded from the scoring system that is used to place sites on the NPL, precluding most abandoned mines from being listed. Mill sites are regulated and decommissioned under the U.S. DOE through UMTRCA or other mechanisms /18/.

Because uranium is a naturally occurring element in the human environment, trace levels can be found in water resources, air, soil, and food-stuffs. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates an average worldwide uranium concentration of 2.8 mg/kg in surface soil, 0.1 ng/m<sup>3</sup> in ambient air, and 3.0 µg/L in seawater /19/. The uranium concentration in groundwater tends to vary significantly, ranging from 0.1 to 10,000 µg/L /20/. The average total daily uranium intake by a 70-kg adult in Canada is estimated to be 2.6 µg, of which 77% is attributed to food consumption (2.0 µg) and the remainder to drinking water /21/.

#### Air

The intake of uranium from air is generally considered much less than that from food or water. Nevertheless, one must keep in mind that this route of exposure applies to average populations exposed to background levels averaging 0.1 ng/m<sup>3</sup> /19/. Not surprisingly, uranium concentrations in the air at or near a mine, mill, or enrichment plant have been documented as significantly higher than natural background levels. A 1979 unpublished report /22/ found that airborne levels of uranium were 10 times higher than background levels near the Jackpile uranium mine at Laguna Pueblo, New Mexico. Mean airborne uranium concentrations of 20 ng/m<sup>3</sup> have been detected at locations within 2 km of a Canadian uranium refinery, a concentration 200 times higher than background in that area /23/. Pettersson and Koperski /24/ of the Ranger Uranium Mines in Australia looked at the spread of

radiation from this active mining operation. Uranium and thorium were measured from dust that stuck to special collectors, as well as from the surface soil. The authors found that elevated levels of uranium and thorium could be measured at distances up to approximately 8 miles (~12.87 km) from the mine. The results of that study point to the potential for uranium to be spread over considerable distances in windblown dust.

Uranium from ore can become airborne through a variety of processes. During active mining operations, heavy machinery, blasting, and other activities generate dust that contains uranium particulate matter. Dirt containing uranium can also enter the home on clothing and shoes. In the past, this form of exposure was due largely to workers returning home with uranium-soiled clothing. One survey of Navajo uranium workers found that historically, virtually all workers laundered their dirty clothing in the home /25/. This practice may have exposed members of their families to uranium ore, but the magnitude of this route of exposure is unknown. Today, in the U.S. children and adults would be more likely to be exposed to uranium while engaging in recreational activities, such as playing on a tailings pile. Finally, some houses near mines have been built with tailing waste rocks /12, 26/.

Sources of uranium in the air other than those produced by mining can be found. Conversion plants used yellow cake as feedstock and made uranium hexoflouride, a gas that is easily released into the atmosphere, most notably during the major industrial accident at Sequoyah Fuels Corporation at Gore, Oklahoma in 1986 /27--28/. In contrast to solid uranium, which eventually settles out of the atmosphere, uranium hexoflouride is removed from air through dissolution in water.

#### Food

The U.S. EPA and the National Council on Radiation Protection and Measurements (NCRP) estimates that the daily dietary intake of uranium

from the ingestion of typical foods ranges from 1.0 to 1.4  $\mu\text{g}$  /29–30/. Recent data from Canada /21/ suggests a daily intake of 2.0  $\mu\text{g}$ , and persons living in close proximity to uranium mills or mines are expected to have significantly greater daily dietary intake, due to the presence of contaminated soil, groundwater, or air.

Levels of uranium in various foods have been measured and the U.S. EPA and NCRP have summarized the results. The highest concentrations were measured in onion, potato, parsley, and beef products. Fisenne et al. /31/ determined the concentration of uranium in various foodstuffs in New York City. Shellfish, fresh vegetables, and bakery products contained the highest levels of uranium. The International Commission of Radiological Protection (ICRP), based on data from seven geographic regions, estimates that milk products, cereals, fresh fruits, and vegetables comprise the majority of the daily dietary intake /32/. Starchy root vegetables and meat also make up a significant portion of the daily dietary intake. With this knowledge, the daily intake of uranium can be estimated. Dietary intake can vary appreciably, however, according to region and socioeconomic status. Caution should be taken to examine intake on a site-specific basis for an accurate risk evaluation.

For example, Thomas and Gates /33/ looked specifically at the effects of uranium mining on the lichen-caribou-human food chain in Northern Saskatchewan, Canada. Lichens efficiently accumulate atmospheric radionuclides, due to their lack of roots, large surface area, and durability. Northern Saskatchewan is home to several operating uranium mines, as well as to aboriginal communities that depend on caribou. Uranium was detectable in the feces, blood, and liver of caribou. Of the uranium present in dry lichens, 1% to 3% was transferred to caribou muscle, and 5% to 11% of the uranium found in the rumen contents of the caribou was transferred to caribou muscle.

Lapham and Millard /34/ investigated cattle raised near uranium mining and milling plants in

New Mexico. The uranium concentration in the vegetation in the control site was measured to be 0.004 pCi/g dry weight, whereas vegetation in the exposed area was found to have a uranium concentration of 0.3 pCi/g dry weight. Although the uranium concentration in the muscle tissue of unexposed control and exposed cattle were indistinguishable, livers and kidneys of exposed cattle had approximately 4 times more uranium than the control, and femurs contained 13 times more uranium than the control. More research is needed in this area, especially with regard to Native American populations whose members live in close proximity to milling and mining areas and consume food that they raise, hunt, and gather, in the vicinity /35/.

### Soil

UNSCEAR estimates a world average of 2.8 mg/kg uranium in surface soil. This amount varies significantly depending upon the area where the measurement is taken, due to the variations in bedrock composition from which the soil is derived. Uranium transport in the subsurface is a function of soil geochemistry. Uranium (VI) is thermodynamically stable in oxygenated groundwater and interacts strongly with solid phases, suggesting that U(VI)-soil particle interactions will govern the fate and transport of uranium in soil /36/. In addition to the oxidation state of uranium, adsorption and mobility is also governed by pH, carbonate, /37/ and interactions with pure iron mineral phases /36/. Once reduced to its tetravalent state, uranium is not as mobile in the subsurface.

Contaminated soil can become airborne and contribute to the ambient air concentration or exchange uranium with the aqueous phase. Soil can also be inadvertently ingested when persons have contaminated soil on their hands and then have contact with their mouths. Some children will also eat soil, which could greatly increase their

exposure to uranium. Hand-to-mouth contact is established as a significant route of exposure to lead for children living in homes with lead paint /38/. We do not know the level of importance of hand-to-mouth contact for populations living near uranium wastes.

### Water

Of the 23 uranium-contaminated hazardous waste sites listed on the final NPL in 2004, uranium was detected in surface water of 5 and in groundwater of 15. The uranium mill in Shiprock, New Mexico failed to manage waste both during and after milling. Site remediation was completed in 1986, with the consolidation of tailings in a disposal cell that is about 76 acres in area. Nevertheless, groundwater contamination and leakage into the adjacent San Juan River continues to be addressed /39/.

Uranium also occurs naturally as a contaminant in private water supplies. Orloff et al. /40/ investigated the high uranium content of private, residential wells in Greenville, South Carolina. The mean uranium concentration in such wells was reported at 620  $\mu\text{g/L}$ , which is approximately 20 times the current uranium maximum contaminant level (MCL). A recent Finish study reported finding uranium in drilled drinking water wells at concentrations ranging from 0.001 to 1920  $\mu\text{g/L}$  /41/.

Historically, Navajos working in uranium mines reported drinking the water that flowed from the walls of the underground mines /26/. The concentration of uranium in runoff from mine tailing piles can be very high. The U.S. EPA has measured uranium concentrations as high as 31,500  $\mu\text{g/L}$  in mine-discharge water /29/. Currently, the areas of the U.S. known to have elevated levels of naturally occurring uranium in groundwater are the Colorado Plateau, Pacific Mountain Range, Basin and Range, and the Eastern U.S. /40/.

The World Health Organization (WHO) has proposed a provisional health based guideline of 2  $\mu\text{g/L}$  of uranium in drinking water based on a

lowest observed adverse effect level (LOAEL) of 60  $\mu\text{g/L}$  (or a tolerable daily intake of 0.6  $\mu\text{g/kg/d}$ ) /42/. In December of 2003, the U.S. EPA adopted an MCL of 30  $\mu\text{g/L}$  for uranium in drinking water. The initial proposed standard was 20  $\mu\text{g/L}$ , but a cost benefit analysis of a 20  $\mu\text{g/L}$  MCL suggested that the benefits did not justify the costs. The 2003 ruling applies only to community water systems (CWS) and estimates that approximately 500 CWS will have to mitigate for uranium. The U.S. EPA reference dose (RfD) for daily oral exposure to uranium is 3  $\mu\text{g/L}$ , 10 times lower than the established MCL, and agrees with the health based WHO guideline.

## ROUTES OF ENTRY INTO THE BODY

### Absorption from Digestive Tract

If inhaled material containing uranium is swallowed or if contaminated foodstuffs or water is directly consumed, then uranium can enter the gastrointestinal (GI) tract. Large, insoluble particulate matter will typically pass through the GI tract more slowly than smaller particles ingested in solution. Once in the GI tract, the insoluble particles can be phagocytized (ingested) into lymph through Peyer's patches, aggregates of lymphoid tissue on the intestinal mucosa. Absorption can also occur via persorption, when epithelial cells slough off the tip of the villus and create a temporary gap in the membrane, allowing the entry of impermeable material /43/.

Leggett and Harrison /7/ reviewed studies of uranium uptake and clearance of ingested uranium. Body burden due to uranium ingestion is determined by the combined effect of absorption from the gut and excretion in the urine. Leggett and Harrison draw the conclusion that 1% to 1.5% of ingested uranium is absorbed. This amount is small when compared with certain heavy metals like lead, where up to 80% is absorbed into the blood

after ingestion /44/. Clearance studies in experimental animals indicated that two-thirds of the uranium in blood is excreted in urine over the first 24 hours, another 10% over the next 5 days, and a total of 85% to 90% over the first month /7/.

The uranium absorption rates for persons who are exposed to uranium in their drinking water or food, including those living in mining or milling communities have also been estimated. The estimate was achieved by measuring the uranium concentration in water and food, tracking the amount of each food ingested, and measuring how much passes through into the urine and feces. Absorption estimates varied by the analytical method used (for example, fluorometric, alpha spectrometry) and ranged from 0.3% to 3.2% /7/.

Animal studies have been useful in showing that the uptake of uranium is substantially more rapid in animals that have fasted compared with those that have been fed. Bhattacharyya et al. /45/ demonstrated that absorption in baboons that had been fed was 0.5%, compared with an uptake of 4.5% in fasting animals. In addition, both fed and fasted baboons absorbed seven times the amount of uranium as fed or fasted mice, suggesting species variation in absorption quantity.

Animal studies have also allowed researchers to test a variety of different chemical forms of uranium. In general, absorption from the intestines to the blood decreases as the solubility of uranium in water decreases. For example, uranium tetrafluoride is insoluble and is absorbed at 0.3% the rate of uranyl nitrate hexahydrate, a compound of uranium that is very soluble /7/.

The results of animal studies also suggest that very young animals can absorb greater quantities of uranium. Whereas one-day-old rats absorbed only 1% to 7% of ingested uranium, one-day old pigs retained 30% of ingested uranium in their bones. The intestines of most young animals and human babies are more permeable than that of adults because infants must absorb immunity factors, such as antibodies, from the mother's milk. No direct data are available for young humans. Data

for older children, however, suggest no appreciable variation in absorption rate over 5 years of age /7/.

### **Deposition, Clearance, Absorption from Lungs**

The fate of uranium-containing particles in the respiratory system depends on a number of factors: Particle size and shape, particle density, solubility of the uranium aerosol, lung structure, and respiratory characteristics /43/. Particles smaller than 1-5  $\mu\text{m}$  deposit in the alveoli, whereas larger particles are more easily expelled from the lung. During the first few hours after deposition, particles that are deposited can be phagocytized by pulmonary alveolar macrophages. Another possibility is that particulates can enter the alveolar interstitium directly by pinocytosis /43/.

Dang et al. /46/ calculated that class Y uranium was cleared from the chest (as a surrogate for the lungs) with a biological half-life of about 2,700 days (for example, the pulmonary region retains uranium for a half-time retention greater than 100 days /32/). Russell and Kathren /47/ measured uranium in the soft tissue of a worker (post mortem) who had been occupationally exposed to radioactive material. The quantity of uranium found in the tissue 20 years after retirement reflects a highly insoluble lung burden and emphasizes the importance of particulate solubility.

### **Dermal Absorption**

Dermal exposure to such soluble uranium compounds as uranyl nitrate, uranyl fluoride, and ammonium dirurate can result in poisoning and death because these compounds can be absorbed directly through the skin /3/. Petitot et al. /48/ investigated the effects of uranyl nitrate on intact or excoriated skin of rats and pigs and found a rapid uptake of uranium through excoriated skin and the residence of bioavailable uranium in superficial wounds.

### DISTRIBUTION OF URANIUM IN ORGANS

In 1978, the United States Transuranium and Uranium Registries (U.S.TUR) were created to provide answers to the many questions regarding uranium toxicity in the human body. This registry obtains tissue or whole bodies at the time of death from volunteer donors who have been exposed to uranium /47/. The first whole-body case donated to the U.S.TUR was an 83 year old man who worked for 28 years in an occupational setting where he handled radioactive materials. The uranium concentration was greatest in lung tissue, suggesting inhalation of insoluble particles. The skeleton possessed the second highest uranium concentration, consistent with known systemic models for uranium /47/. Dissimilar to most human models, the concentration of uranium in the spleen was appreciable. The author attributes this anomaly to red blood cell membrane-bound uranium being cleared through the reticuloendothelial system and then deposited and stored in the spleen. The lowest concentrations of uranium were detected in the liver and kidney, which is also consistent with additional registry cases and values reported in the literature /47/.

Dang et al. /49/ examined individuals living in Bombay who were exposed only to background levels of uranium. The concentration of uranium in their bodies was found to be highest in the bones. The total amount of uranium by organ was, from highest to lowest, bone>muscle>soft tissue>lung >kidney>liver>heart.

#### Retention of Uranium in Bones

Uranium can persist in the human body for varying lengths of time, depending on the affected organs and various exposure routes. Uranium that is deposited in the skeleton does so in a manner similar to calcium and alkaline earth metals, depositing especially in areas of active growth and remodeling /9/.

Taylor and Taylor /9/ reported that 80% to 90% of the uranium in bones is lost in about 1.5 years /9/. Some uranium leaves the bones quickly with a half-life of months, whereas a smaller amount can take years. Uranium also appears to distribute unevenly in the bones at first but becomes more evenly spread throughout bone volume over time /6/. In addition, one study found that when exchangeable bone mass was increased, usually a result of Paget's disease or osteomalacia, the amount of uranium excreted through the urine decreased /9/.

### BIOLOGICAL MONITORING

Human exposure to uranium can be measured by analysis of hair, urine, and feces or by whole body counting. Determining how much uranium the person was exposed to, when the exposure occurred, or how high concentrations were a month ago is not possible from a urine test. Urine tests are most useful for people who are currently exposed to uranium, such as workers in the uranium processing plant or community members drinking water contaminated with uranium. A whole-body counter measures the radioactive material in the body of human beings and animals using a device such as a high purity germanium detector. Heavy shielding is used to prevent contamination from naturally existing background radiation ([www.nrc.gov](http://www.nrc.gov)).

No federal standards exist for uranium in the urine, but Reif et al. /50/ recommend 1.5  $\mu\text{g/L}$  of uranium in urine as an action level, which if measured, would trigger intervention to reduce future exposures. The recommendation of 1.5  $\mu\text{g/L}$  uranium in urine would restrict radiation exposures below 50 mrem (annual effective dose equivalent). This calculation considers only radioactive effects of uranium and its decay products and does not take into account the chemical toxicity of uranium. The calculation is based on the model for uranium flow through the body developed by the ICRP.

Dang et al. /49/ also found that workers with a high amount of uranium in their lungs also had a high uranium concentration in their urine. For a population exposed only to background uranium, the authors observed urine levels of 0.12  $\mu\text{g/L}$  and blood levels of 0.013  $\mu\text{g/L}$ . Yu and Sherwood /51/ looked at occupational airborne and hand exposures to uranium and the resulting urinary excretion rates for workers in a uranium plant in England. The investigators found that air exposures below 10  $\mu\text{g/m}^3$  raised urinary excretion levels above the 1.5  $\mu\text{g/L}$  recommended by Reif et al. in their 1992 study. Not surprisingly, Yu and Sherwood found that concentrations of uranium in urine increased with increasing airborne exposure levels. They also observed that workers' hands soiled with uranium particulate contributed to the amount of uranium eliminated in urine.

## HEALTH EFFECTS OF URANIUM EXPOSURE

### Lethal Dose

The  $\text{LD}_{50}$  for rats and mice via the oral administration of uranyl acetate is similar for both animals, at 204 and 242 mg/g, respectively. The  $\text{LD}_{50}$  is significantly lower when the compound is administered subcutaneously, at 8.3 mg/g for the rat, and 20.4 mg/g for the mouse. The death of the animals was suggested to result from severe kidney failure /52/. Doses of this magnitude are highly unlikely in humans unless deliberate poisoning using purified uranium is involved.

Acute exposure through ingestion and skin absorption does occur, but is not typical. In one case, a man deliberately ingested 15 g of uranium acetate. Other cases involved a man who was exposed to approximately 0.09 g of uranium tetrafluoride ( $\text{UF}_4$ ) powder through ingestion and dermal exposure, and a man who was burned by a solution of uranyl nitrate and uranium oxide. All three suffered from kidney function impairment, but only

the patient who ingested 15g of uranium acetate failed to fully regain kidney function /53--54/.

### Renal Effects

Uranium can damage the kidneys by any route of exposure as long as the uranium enters the blood. In the U.S., The Agency for Toxic Substances and Disease Registry (ATSDR) /5/ lists the lowest airborne concentration at which adverse effects (LOAEL) on the kidney are seen in animals as 50  $\mu\text{g/m}^3$ . This value is the same as the Occupational Safety and Health Administration's (OSHA) airborne exposure limit for soluble uranium, affording no safety margin for extrapolation to humans. Table 1 presents selected uranium exposure standards recommended by various agencies.

Pinney et al. /55/ investigated the health of community residents living in the area surrounding a U.S. DOE uranium processing plant in Fernald, Ohio. During the period of operation from 1951 to 1958, an estimated 310,000 kg of airborne uranium was released, and 99,000 kg was released to surface water. Statistically significant elevations of urinary system diseases were encountered, including bladder and kidney disease, kidney stones, and chronic nephritis.

Rather than the glomerulus, the proximal tubule of the kidney has been shown to be at most risk for damage resulting from chronic uranium ingestion /56/. Whether this effect can lead to later kidney failure is unclear, increased susceptibility to osteoporosis could result as calcium leaking into the urine can cause a negative calcium balance /41/. Kidney injury was reported to progress up to 5 days after uranium exposure. Studies in animals have shown that regeneration of the tubules can take up to 8 weeks /54/. Accidental exposure to high amounts of uranium have led researchers to suggest a maximum safe uranium burden in the kidney of 0.26  $\mu\text{g/g}$ , equivalent to a total kidney content of approximately 80  $\mu\text{g}$  /53/.

**TABLE 1**  
Selected exposure standards for uranium

Agency	Type of Standard	Value
<b>GENERAL</b>		
International Commission on Radiation Protection	Radiation	
	a. Whole body, occupational	5,000 rem/year
	b. Individual, short term	500 mrem/year
	c. Individual, long term	100 mrem/year
Environmental Protection Agency	Chronic oral exposure to soluble uranium salts. RfD	3.0 µg/kg/day
Agency for Toxic Substances and Disease Registry	Intermediate duration ingestion	2.0 µg/kg/day
World Health Organization	Tolerable daily intake	0.6 µg/kg/day
US Nuclear Regulatory Commission	Occupational annual intake (natural uranium)	14.8 g/year
<b>INHALATION</b>		
Occupational Safety and Health Administration	Airborne uranium, occupational 8 hour working day	
	a. Insoluble	250 µg/m <sup>3</sup>
	b. Soluble	50 µg/m <sup>3</sup>
Environmental Protection Agency	Maximum dose to an individual of uranium in air	10 mrem
American Conference of Governmental Industrial Hygienists	Airborne uranium, occupational Soluble and insoluble	
	a. medium term exposure	200 µg/m <sup>3</sup>
	b. long term exposure	600 µg/m <sup>3</sup>
National Institute of Occupational Safety and Health	Airborne uranium, occupational	
	a. Insoluble, chronic	200 µg/m <sup>3</sup>
	b. Soluble, chronic	500 µg/m <sup>3</sup>
	c. Insoluble, short term	600 µg/m <sup>3</sup>
	d. Soluble, short term	10,000 µg/m <sup>3</sup>
Agency for Toxic Substances and Disease Registry	Minimal Risk Level for inhalation exposure	
	a. Insoluble intermediate duration	8.0 µg/m <sup>3</sup>
	b. Soluble intermediate duration	0.4 µg/m <sup>3</sup>
	c. Soluble chronic	0.3 µg/m <sup>3</sup>
<b>DRINKING WATER</b>		
Environmental Protection Agency	Drinking Water	30 µg/L
World Health Organization	Chemical Provisional Guideline	2 µg/L

Note: Data compiled (WHO, 2001)

### Developmental and Reproductive Effects

Domingo et al. /57/ administered uranyl acetate dihydrate by injection or by ingestion to pregnant mice. The resulting litters were seen to have birth defects, including cleft palate and skeletal defects. The exposure also resulted in reduced body size of both the mother and the fetuses. Oral exposure /58/ reduced the pregnancy rate, and an oral dose of 25 mg/kg caused the death of a number of fetuses. The lowest dose by oral exposure that produced an effect was 5 mg/kg. Whether uranium causes such effects in human populations is not known.

Llobet et al. /59/ evaluated the reproductive and developmental toxicity of uranium in male Swiss mice treated with doses of uranyl acetate dihydrate ranging from 0–80 mg/kg/day for 64 days. Mating male mice with untreated females to assess male fertility demonstrated a decreased pregnancy rate that was not dose dependent. No adverse effect on spermatogenesis or testicular function was noted in male mice.

Shields et al. /60/ investigated birth defects in Navajo uranium-mining communities. The authors compared their results to radiation exposure in fathers who were miners and to proximity of the home to mines and waste. They found a weak association between mothers living near uranium tailing or mine dumps and birth defects in their children. One should keep in mind that proximity to mine waste might not accurately reflect actual exposures. We must note that the analysis focused on radioactivity and did not consider the chemical developmental toxicity described here.

### Effect on DNA

Recent research has begun to look at the possibility that exposure to uranium can induce DNA repair deficiency in somatic cells. Au et al. /61–62/ conducted their studies by looking at non-smokers who resided near uranium mining or milling sites in Texas but had not worked in the

uranium industry. The authors found that residents living near the uranium mining and milling sites had higher frequencies of aberrant cells and elevated frequencies of chromosome deletions. The findings were not statistically significant in comparison with a non-exposed population.

A study of open-pit uranium miners (all non smokers) in Namibia /63/ revealed a statistically significant increase in chromosomal aberrations in lymphocytes in the miner group. The control group, however, consisted of both smokers and non-smokers. In a follow-up study that excluded smokers among the control group, Zaire et al. /64/ also found an increased frequency of chromosomal aberrations in whole blood cells. Prabhavathi et al. /65/ studied 160 nonsmoking workers employed in a nuclear fuel facility. Workers were occupationally exposed to such uranyl compounds as uranium dioxide, uranium trioxide, uranyl fluoride, and uranyl nitrate. The results indicated a significant increase in the incidence of chromosomal aberrations, attributed to a cumulative effect of the chemical toxicity and radiotoxicity of uranyl compounds.

### Respiratory Effects

Of the many cohort studies of cancer risks in uranium miners and processors /2, 66–71/, that the primary cause of respiratory damage and cancers are a result of exposure to radon progeny is widely accepted, and the cause of their pneumoconiosis is believed to be silica dust /13, 72/. Mines contain multiple respiratory hazards including radon, uranium ore dust, silica dust, diesel exhaust, and blasting smoke. Radon /73/ and diesel exhaust /74/ have been associated with lung cancer, independent of uranium mining. Because several hazardous materials exist in mines simultaneously, delineating risk based solely on exposure to uranium dust is difficult.

Reviews like the 1990 and 1999 ATSDR toxicological profiles /4-5/, as well as 1988 BEIR IV Review on Radon /6/, summarize findings from

older studies of animal exposure to uranyl compounds. The animal studies demonstrated inflammatory reactions to uranium aerosols, development of malignant lung tumors from uranyl nitrate exposure, and fibrosis resulting from the inhalation of uranium dioxide dust. Pulmonary edema and hemorrhage resulted only from chronic, high-dose exposures to uranium hexafluoride gas. It is essential to note that radiotoxicity, in addition to chemical toxicity, can play a significant role in respiratory damage, as insoluble uranium aerosols may remain in the lungs for years.

### Effects on Bone

Sylvester et al. /75/ implanted insoluble uranium dioxide subcutaneously in 20 female Wistar rats to evaluate the deleterious effect of an insoluble form of uranium on bone tissue and bone growth. Significant differences between experimental and control groups were noted in histology, body weight, bone histomorphometry, and bone growth. The difference in body weight was statistically significant, with treated animals showing less weight gain. A histologic study of tibia sections revealed that the trabeculae were shorter and thinner and had greater separation in treated animals. In treated rats, bone volume values and morphometry parameters, such as length and height, were statistically lower. The differences seen in the bones of treated animals are attributed to the residence of uranium dioxide in the subcutaneous tissue, providing a constant source of uranium metal.

Bigi et al. /76/ also used Wistar rats to investigate the effect of uranyl nitrate on tooth eruption and development. The animals received a single oral dose of uranyl nitrate, which resulted in statistically significant diminishing effects on bone formation, on bone resorption, and on tooth eruption and development. These findings are significant in that ingestion of uranium-contaminated water and fertilizers are an increasing exposure route. These studies were not executed in a manner such that an

LOAEL or NOAEL could be calculated.

### Gastrointestinal Effects

In a human experiment, a subject ingested 1g of uranyl nitrate, which resulted in acute nausea, vomiting, and diarrhea for the first few hours after ingestion but returned to normal within 24 hours. A person accidentally exposed to ~0.09 g of UF<sub>4</sub> experienced abdominal pain, vomiting, and loss of appetite for the first 9 days after exposure but then returned to normal /53/. Additionally, paralytic ileus (non-mechanical bowel obstruction) was seen in a patient who deliberately ingested 15 g of uranium acetate /54/. Because uranium in the GI tract produces symptoms such as vomiting and diarrhea, intestinal absorption is low, suggesting a low likelihood of acute uranium poisoning through this pathway /3/.

### Effect on the Heart

Few studies have looked at the effect of uranium on cardiovascular health /5/. Those studies that have looked at the association between uranium and cardiovascular disease have generally found no increase in mortality associated with the cardiovascular system. Nevertheless, Depree et al. /77/ noted an increase in cardiovascular disease among workers in a uranium processing plant. That study looked retrospectively at those who were working in the plant during World War II. In addition, the patient mentioned in the previous section who deliberately ingested 15 g of uranium nitrate suffered from myocarditis that resolved itself within 6 months /54/.

### Effects on Skin, Blood, Liver, Nervous System

Uranium-induced dermatitis can occur from exposure to a variety of uranium compounds and can result in irritation, redness, blistering, thickening, or hyperpigmentation of the skin ([www.osha-slc.gov](http://www.osha-slc.gov)). Consistent with this observation,

former miners have reported rashes that they associate with uranium mining /26/.

The 2003 summary on community health effects near the Fernald uranium processing plant reported statistically significant increases in serum creatine, white blood cells, and hemoglobin, as well as a decrease in mean corpuscular volume in persons living less than 2 miles from the plant /55/.

Animal studies have demonstrated liver damage due to uranium, but whether this damage is a direct result of the exposure or rather a result of kidney damage is unclear /9/. Effects on the liver were studied in uranium-enrichment workers and no increase in mortality was seen /5/. Ninety-one days of exposure of white rabbits to uranyl nitrate produced mild hepatic effects, including hepatocellular anisokaryosis (variation in cell nuclei size) and accentuation of architectural zonation /78/.

Little historical research has been done to assess the effects of uranium on the central nervous system (CNS), and current work has focused solely on the mobility and effects of depleted uranium on the CNS (largely in response to health effects in Gulf War veterans) /79–81/. Because depleted and natural uranium are expected to have similar toxicity, CNS effects from exposure to natural uranium may warrant future study.

#### SIGNIFICANCE TO PUBLIC HEALTH AND RESEARCH NEEDS

Negative health consequences are clearly associated with exposure to natural uranium and no health benefits are known. Many of the effects of uranium have been demonstrated most clearly in animals, but a growing body of human evidence has emerged from epidemiologic studies. At this time, the primary effects include kidney damage, developmental defects, genetic damage, and diminished bone growth. Other health consequences of uranium exposure are less well documented. Extrapolation to humans from existing animals studies should be based on conservative assumptions, but

this is not always the case.

For example, the U.S. federal occupational respiratory standard of  $50 \mu\text{g}/\text{m}^3$  appears to have no margin for safety. The standard is based on the LOAEL from animal studies /5/ and does not build in the standard 100-fold reduction for individual and species variation /82/. Worse, evidence from urinary excretion levels indicates that an exposure as low as  $10 \mu\text{g}/\text{m}^3$  can pose a health risk in humans /51/. Indeed, a number of states have set ambient air limits for uranium that are substantially lower than the occupational airborne limits set by federal agencies. Based on the scientific uncertainty and variation in established exposure limits, limiting exposures to below the strictest regulatory limits for respiratory exposure would be advisable.

Background levels of uranium in urine ( $0.12 \mu\text{g}/\text{L}$ ) and blood ( $0.013 \mu\text{g}/\text{L}$ ) were reported earlier in this paper. Considering levels several times background to be indicators of exposure might also be advisable. This would be more protective than the Department of Energy urine standard of  $1.5 \mu\text{g}/\text{L}$  for workers—a level based on radiological toxicity rather than on chemical toxicity.

The LOAEL from animal ingestion studies was reported at  $60 \mu\text{g}/\text{kg}/\text{d}$ . An uncertainty value of 100 is factored into the LOAEL (for both intraspecies and interspecies variation), an assumption is made that an adult drinks approximately 2 L of water per day, and assuming that water is only a fractional source of uranium, one arrives at the WHO standard of  $2 \mu\text{g}/\text{L}$  and the U.S. EPA reference dose of  $3 \mu\text{g}/\text{L}$ , whereas, the U.S. EPA MCL is  $30 \mu\text{g}/\text{L}$ , based on economic feasibility. For areas of the country that have groundwater naturally elevated in uranium, a target of  $2 \mu\text{g}/\text{L}$  may not be feasible for municipalities or private well owners due to limitations of available treatment technologies. Because state governments may adopt guidelines lower than the federal MCL, it is critical that each state assess its water supply individually, determining a standard not only protective of community water supplies but also one that would prompt homeowners and businesses

with private wells to seek treatment for exceeding these limits.

The growing epidemiologic evidence of various health effects in populations living near sites that released uranium into the environment is cause to be concerned that community exposures are substantial enough to cause adverse health effects. Protecting public and worker health from the toxic effects of uranium requires identifying pathways of exposure. Many such pathways are associated with abandoned mines, waste from uranium mills, wastes leaching from uranium processing plants, and consumption of drinking water contaminated with naturally occurring uranium.

A particularly important aspect of uranium toxicity is that exposure to natural uranium almost always involves concurrent multiple exposures to other toxic materials. Uranium mine tailings, and to a lesser extent yellow cake, contains other radionuclides in the uranium decay series and toxic, non-radioactive heavy metals. Mills and plants use solvents and acids as well. Natural groundwater similarly contains other heavy metals that can be found with uranium. No animal study has looked at such complex mixtures and human epidemiologic studies cannot distinguish which agent(s) out of the mix is causative. Possibly, synergistic risks require further investigation. In any case, that the combined effect will be greater than that of any single substance is almost certain. In addition, a LOAEL or NOAEL should be developed to reflect the variation in health effects resulting from exposure to specific uranium compounds and their solubility rather than lumping various compounds into one category.

We should keep in mind that the risks from uranium exposure are still being discovered. Indeed, the teratogenic effects of uranium were first reported in the late 1980s. We cannot assume that we know all the hazards of uranium. Accordingly, ongoing study of the health effects of uranium is needed. Particular attention must be directed to the impact of uranium on indigenous populations living closer to the land, to routes of exposure in

communities near uranium release sites, to human epidemiology for developmental defects, and to health effects at or below the established exposure standards.

Nevertheless, the need for further study must not hold us back from addressing populations that are currently exposed to doses substantially above background. There is more than enough convincing evidence that uranium is hazardous to human health. In our opinion, the most stringent exposure standards should be applied as evidence continues to accumulate.

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