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**THE POTENTIAL HUMAN HEALTH EFFECT(S) OF THE METAL
URANIUM IN THE ENVIRONMENT**

**Report on the known human health effects associated
with the exposure to the metal uranium**

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Introduction

Concern over the levels of the metal uranium in the environment as a result of industrial activities has been expressed by several Federal and State agencies (the term uranium metal as used in this report refers to all ionized forms of uranium). This concern is associated with potential human health effects of this metal on kidney function and bone formation. Although limits for the metal uranium in the environment remain to be set, the Environmental Protection Agency (EPA) is currently in the process of establishing guidance limits for this metal in water and soil. These limits will be established for both the metal and the associated radioactivity. The suggested limits currently being considered for water (including, drinking water, ground water and surface water) and soil are, 20 pCi/liter and 10 pCi/gram wet weight, respectively. For naturally occurring uranium EPA assumes that 1 ug of uranium metal equals 0.67 pCi at equilibrium (i.e. at equilibrium the mass ratio of ^{234}U to ^{238}U is small but their activities are equal). Thus the limits for water and soil on weight basis for the uranium metal would be 30 ug/liter and 15 ug/gram wet weight, respectively. We note that wastewater limits are currently under discussion by EPA and they estimate a decision in 12 months.

These limits are being established based on the potential increase in cancer death in populations that exceed this limit. Since there does not appear to be a significant correlation between cancer deaths and uranium metal exposure (see discussion below), these limits will probably be established based on the known association between radionuclides exposure and cancer deaths. The exposure limits for other health effects such as, kidney damage and retardation in bone formation apparently are not being considered by EPA. Whether the current and soon to be proposed limits will be sufficient to reduce the risk of uranium metal on kidney and bone abnormalities remains to be established. This report discusses these limits in relationship to the known human and experimental effects of uranium metal.

Chemistry of the Metal Uranium

This report will focus on the potential human health effects of the uranium metal. However, to better understand these effects the chemistry and geology of the uranium metal will be briefly discussed.

Uranium is a soft silvery-white metal with an atomic number of 92 and atomic weight of 238. Natural uranium (U) is a mixture of three isotopes, ^{238}U , ^{235}U and ^{234}U . The atomic percentages of these isotopes are given as ^{238}U , 99.276; ^{235}U , 0.718; and ^{234}U , 0.0056. Other short lived isotopes have made by nuclear reactions. The ratio of ^{238}U to ^{234}U is constant and is equal to

the ratio of their respective half lives, because ^{238}U is the parent and from it ^{234}U is formed by alpha and beta decays. Uranium contains gamma, alpha and beta emitting particles. Most of the radioactivity of uranium ores comes from the escaping ^{222}Rn radon and its short lived decay products. The removal of ^{222}Rn radon from uranium ores (which is effectively accomplished when the ore is leached) reduces the gamma and alpha activity. However radon concentrations return to the equilibrium value and its daughters will reappear after about 10 half lives (i.e. 40 days). The beta activity is due primarily to ^{234}Pa protactinium which is also removed together with its precursor thorium during the leaching of the uranium ore. However, the ratios of both of these isotopes also return to their original value within a year.

Uranium metal may exist in several oxidation states including, 2+, 3+, 4+, 5+ and 6+. The metal will react with some 150 different elements. The pure metal is very reactive and will form uranium oxide when exposed to air. Most of the compounds of uranium are very insoluble in aqueous solution. However compounds with a uranium oxidation state of 4+ or more are fairly soluble in aqueous solution. An example would be uranyl nitrate and uranium tetrafluoride.

The element uranium was first discovered in 1789 in the pitchblend of Saxony by Professor M.H. Klaproth of Germany. Professor Klaproth observed that when pitchblend was added to nitric acid and then to potash a yellow precipitate could be isolated. When the precipitate was heated to a high temperature a metallic substance was observed, and Klaproth thought he had isolated the pure metal. He named the metal "uranit" after the planet Uranus. A year later he changed the name to uranium. However several years later a French chemist E.M. Peligot proved that Klaproth did not isolate the pure metal but the oxide form. In 1841 Peligot purified the metal and in 1856 he described some of the more properties of uranium. D.I. Mendeleev in 1869 determined the approximate atomic weight.

During the late 1800's and early 1900's interest in uranium was purely academic. However in 1898 when Becquerel discovered the presence of radium in uranium ores, interest in uranium increased because of the demand for radium. Until 1942 uranium was mined for the radium. With the discovery of nuclear fission (1938/1939) new interest in uranium evolved. After the second world war the physical properties (specifically thermal conductivity) of uranium for atomic energy were described at a conference in Geneva (1). Since 1955 great efforts have been made to mine and process the uranium ore for the nuclear industry, which has resulted in a increase in the environmental levels of uranium.

Geology of the Metal Uranium

Uranium is widely distributed in the earth's crust (about 0.0004%). It is never found in the elemental state, but always in the chemical combination with other elements (approximately 150). The uranium ores that are mined economically usually contain uranium up to 0.1%, and this is observed in high-silica, acid rocks such as granite. The uranium minerals are broadly divided on the bases of occurrence in two classes, primary and secondary (2). The primary minerals, with the exception of pitchblends, appear in pigmetites and secondary minerals in autunite, carnotite, and tucholite. Other primary ores of uranium include, uraninite, brannerite, davidite, coffinite, and uranophane.

Uranium is mined in France, Canada, Australia, South Africa, Congo, and the U.S.A. (Colorado and Utah). The primary uranium species/compound mined are uranium oxide (UO_2) and uranium octoxide (U_3O_8) (3). This suggests that these species may predominate in soil, air (dust particles) and water as a result of mining activities. Since uranium reacts readily with many metals and minerals it is difficult to predict the predominant species that would be observed in the environment.

Levels of the Metal Uranium in the Environment

Several investigators and investigations suggest that the levels of uranium in air, water and soil have increased as a result of mining for uranium, mill tailings (the result of biological leaching), processing of uranium ores, processing of phosphate deposits for fertilizer and industrial releases from coal and nuclear power plants. Uranium mining was first established in the late 40's and in the USA in the early 50's primarily in the Colorado Plateau and the southwest (4). Mining gave rise to an increase in the surface and air levels of uranium. This increase was further affected by the processing of the ore. Mining and processing of the uranium ore also affected the species/compounds of uranium released into the environment. The process of mining and processing uranium ores is described below to illustrate the various species of uranium generated during these activities.

Uranium ores are preconcentrated by grinding of the ore into a small size (5). After grinding the uranium ore it is concentrated by radiometric or gravimetric sorting. The uranium in the ore is leached with a solution of sulphuric acid, or sodium carbonate (bicarbonate solution). The leaching process assures the recovery of 90 to 93% of uranium. Thus mill tailings (the residue from the purification process) contain relatively small amount of uranium. After leaching the leachate is separated from the solids by filtration. Uranium is then extracted from solution by ion exchange. The absorbed uranium is eluted from the resin with a solution containing high concentrations of chloride or nitrate ions. The pure uranyl nitrate ($UO_2(NO_3)_2$) forms the starting material in the industrial

production of a number of important uranium compounds. The first step is the preparation of uranium trioxide (UO_3) from uranyl nitrate. The UO_3 is then converted in the presence of hydrofluoric acid (HF) to uranium hexafluoride (UF_6) (green salt). The green salt is then reduced with magnesium or calcium to uranium metal. Based on this description of the mining and processing of uranium it is possible to see that the primary compounds of uranium likely to be observed in the environment include, UO_2 , U_3O_8 , UO_3 , UF_6 , $\text{UO}_2(\text{NO}_3)_2$. To the extent possible this report will focus on the above compounds of uranium.

High levels of uranium in soil may be observed at mining sites, in mill tailings, and at coal and nuclear plants and facilities. Acceptable limits for soil uranium remain to be established by EPA. However EPA has established a tentative limit of 15 ug U/gram of soil wet weight (6).

Limits for the Human Intake of the Metal Uranium

Concern of uranium in soil is associated with contamination of various foodstuffs. Dietary items with the highest uranium concentrations are tubers (e.g. potatoes, and turnips), fruits and vegetables, shellfish, and certain cooking additives, such as salt, fat and oil (7,8,9,10 and 11). According to Hamilton (7) cereals, and grains, tubers, fruits and vegetables comprise 83% of the uranium ingested through the human diet. These investigators estimated that the normal dietary intake (excluding meat and milk) of uranium ranges from 1 to 1.4 ug/day. In a recent publication Rayno estimated the uranium intake from beef and milk to be in the range of 3 ng to 5 ug/day (12). EPA estimates the total intake from food to be 1.3 to 1.4 ug/day (13). These estimates do not consider the species of uranium in the contaminated foods. The species will affect the amount of uranium absorbed by the gastrointestinal tract because of the relative solubility in aqueous solution of the various species of uranium.

Uranium may be introduced into surface, ground and drinking water as result of ore and phosphate mining, leaching of mill tailings, the processing of the uranium ores and/or phosphate deposits, and through the release from coal and nuclear power plants. The average concentrations of uranium in surface, ground or drinking water are reported as 1.49, 4.47 and 3.0 ug/liters, respectively (13). EPA estimates that of the 64,000 public drinking water supplies 0.1 to 3% have uranium concentrations exceeding 15 ug/liter (14). In an early report EPA showed that 25 to 650 water supplies exceeded 30 ug/liter (15). Since EPA has established a health guidance limit of 30 ug/liter (soon to be revised to 20 ug/liter) for drinking water, those water supplies with levels of 30 ug/liter would be exceeding the guidance limit. However, again the species of uranium was not determined in the drinking water studies or considered in

establishing guidance limit. It is noted that the guidance limit set for drinking water also applies to surface and ground water.

The concentration of uranium in air has not been studied as extensively as the concentration in water and foods. However EPA reports that the concentration of uranium in the atmosphere is in the range of 0.3 ug/m³ (16). Thus the intake of uranium in air would be minor when compared to food and water (the intake of uranium from air would be considerably higher at mining sites and processing facilities). We estimate that the normal average intake of uranium from air, water and food would range from 7 to 35 ug per day (this assumes 2 liters of water intake). It is noted that uranium in drinking water would account for approximately 87% of uranium intake.

Health Effects of the Metal Uranium

The health effects of uranium are dependent on the dose, species to which exposure occurs, on the rate of absorption, and the cumulative organ concentration of uranium. The half life of uranium in the body is an additional factor. The compounds of uranium most frequently encountered in the environment and the workplace include, uranium octoxide, uranium dioxide, uranium trioxide, ammonium diuranate ((NH₄)₂U₂O₇), uranium nitrate, uranium hexafluoride and uranium tetrafluoride (UF₄). Humans may be exposed to these compounds through air (inhalation) and skin absorption, water and food ingestion. Thus pulmonary, gastrointestinal and skin absorption are the primary routes for the absorption of these compounds into the body. Many of these compounds are insoluble in water, which can effect the amount of uranium absorbed into the body. Several investigators have reported the solubility of these compounds in biological fluids (17,18,19 and 20). Cooke and Holt (17) observed the following solubility for the above uranium compounds in biological fluids at 37°C; (1) UF₄, UF₆, and UO₂(NO₃)₂ 80 to 100% soluble in 10 days, (2) ((NH₄)₂U₂O₇), UO₃ and UF₆, 20 to 40% soluble 10 to 100 days and (3) UO₂ and U₃O₈ 3 to 15% soluble after 100 days or more. Since the solubility of these compounds would in part determine the availability of these compounds for absorption, it would appear that relatively small amounts of UO₂ and U₃O₈ would be absorbed. Thus one may anticipate that UO₂ and U₃O₈ would be less toxic on exposure than the more soluble forms of uranium.

The intestinal, pulmonary and skin absorption rates for all of the seven compounds of uranium listed above are not known. However it is known that these compounds are absorbed via the three routes described above (22, 23, 24, 25, 26 and 27). The International Commission on Radiological Protection in 1979 established a maximum permissible uranium intake for humans of 40 mg/day (the present permissible intake limit of 35 ug/day is approximately 1000 times lower than the previously established limit). The Commission have furthermore determined that 2 to 5% of ingested uranium is absorbed into the body.

Many reports in the literature have described the health effects of uranium, and it is from these observations that one can determine the critical organs associated with uranium toxicity. In order to establish guideline limits for uranium in air, water and food, it is necessary to determine the following, (1) the absorption rate and the factors effecting this rate for the seven compounds listed above (i.e. through the intestinal tract, pulmonary tract and skin) and (2) the dose-response effects (toxic effects) for the compounds listed above. When effects are observed the organ concentration of uranium should be determined to establish the minimum organ level of uranium required to induce the observed toxic effect. The major human health effect reported for uranium metal include, cancer, kidney damage and bone abnormalities. Other minor effects reported following uranium exposure include, autoimmune orchitis and thyroiditis. The minor effects have not always been observed following uranium exposure.

a) Cancer

Men working in underground uranium mines in North America and Europe have experienced excess cancer of the lungs that cannot be attributed to excessive cigarette smoking (28,29,30,31 and 32). It is assumed that these workers are exposed to UO_2 and U_3O_8 . Although the cancer rates are elevated in miners, it appears that the increase is associated with irradiation of tracheobronchial epithelium by alpha particles emitted during the radioactive decay of radon and its daughter products (31). Thus there is no strong evidence showing a significant relationship between the exposure to the metal uranium and lung cancer. In fact, Leach et al. in 1970 exposed the monkey, dog and rat to UO_2 (dose $5mg\ U/m^3$) for 5 years and did not observe a significant increase in lung tumors (32). However these investigators observed marked increases in levels of uranium in lung tissue and the tracheobronchial lymph nodes. The lung and tracheobronchial lymph nodes levels of uranium observed after 2 years exposure were 3600 and 70,000 $\mu g\ U/gram$ wet weight tissue, respectively in the monkey. Similar levels were observed in the dog and rat. These exposure were 28 times the Maximum Permissible Concentration in Air of $178.6\ \mu g\ U/m^3$ established by the International Commission on Radiological Protection (33). These investigators did not observe marked kidney damage, which is hardly surprising when one looks at the levels of uranium remaining in the lungs and tracheobronchial lymph nodes. If this observation can be extrapolated to other insoluble compounds of uranium such as U_3O_8 , then marked kidney damage would not be anticipated at the dose level and exposure route used in this study. In contrast to the insoluble UO_2 the more soluble UF_6 is rapidly cleared from the lungs and excreted from the body via the urine (34). Although the exact exposure dose was not known, kidney damage was observed in humans exposed to UF_6 . These observations suggest that uranium compounds which are quickly

cleared from the lungs may increase the risk of kidney damage, while those compounds which are slowly cleared may give rise to lung tumors as a result of the associated radioactivity. Thus miners may be at risk of developing lung cancer because the species of uranium most frequently encountered at the workplace includes, the insoluble species UO_2 and U_3O_8 . In contrast, workers at the processing facility would be at risk of developing both lung cancer and kidney damage because they may be exposed to both the insoluble and soluble species of uranium.

b) Kidney damage

Kidney damage is the most recognized effect following the exposure to the metal uranium. Most of the observed effects have been reported following the administration of $UO_2(NO_3)_2$ (35). LeConte in 1854 was first to report on the nephrotoxic effects of uranium. Since the report of LeConte several other investigators have confirmed the nephrotoxic effect of uranium on the kidney. The observed effects reported by these investigators include, a decrease in the glomerular filtration rate, polyuria, albuminuria, glycosuria, oliguria, casts, pathological lesions of the glomerulus and proximal tubules and fibrosis (35, 36, 37, 38, 39, 40, and 41). These effects were observed at doses of $UO_2(NO_3)_2$ greater 0.1 mg/kg. Thus 0.1 mg/kg body weight appears to be the no observed effect level for one time only exposure in both humans and animals.

In two recent epidemiological studies the relationship of uranium exposure in the workplace to kidney abnormalities was examined by Dr. M. Single and Dr. M. Tune of NIOSH. These studies were performed at the Fernald Facility in Ohio (Dr. Single) and in Tennessee (Dr. Tune). Significant correlations between uranium exposure and kidney abnormalities were not observed in workers at the Fernald Facility. In contrast Dr. Tune of NIOSH observed an increase in kidney stones and urinary tract infections in workers exposed to uranium. Dr. Tune compared security guards to workers exposed to uranium. The observations made on about 80 employees were as follows; kidney stones, 18% of exposed workers and 7% of Guards; urinary tract infections, 29% of exposed workers and 12% of Guards. The difference between the workers and Guards was statistically significant. These results suggest a relationship between uranium exposure and kidney abnormalities. However Dr. Tune also observed an increase in kidney stones and urinary tract infections in non-exposed workers. For example, the percent of non-exposed workers with kidney stones and urinary tract infections were, 23 and 26%, respectively, which suggests that others factors in the workplace may be responsible the increase in the incidence of kidney stones and urinary tract infections. The results of Dr. Tune have not been published because the studies are still in progress. We note that the difference observed between these two facilities may be related to the species of uranium in the workplace.

c) Bone abnormalities

Bone abnormalities have also been observed in experimental animals exposed to $UO_2(NO_3)_2$. Uranium is a bone seeker and thus accumulates in this tissue. The observed effects include, inhibition in bone formation and a decrease in the density of bone (42 and 43).

Conclusions and Recommendations

It is clear that the metal uranium is toxic when ingested or inhaled. The major sites of toxicity include, the lung, kidney and bone. These sites of toxicity have been identified following the acute exposure to uranium. However chronic toxic effect of uranium on these organs remains to be establish. Kidney damage and bone abnormalities appear to be the predominant effects observed following uranium exposure. Although the no effect level for kidney damage following a single exposure to uranium has been established, this no effect level after continuous exposure remains to be established.

The normal intake of uranium from air water and food is estimated to be 35 ug/day. This estimate would be significantly higher in workers mining and/or processing uranium ores. Most studies on the effect of uranium in the workplace have focused on the relationship between uranium exposure and cancer, which is also the case in experimental inhalation studies. Thus the chronic effect of uranium exposure in the workplace on bone and kidney function remains to be determined. It would seem important that the chronic effect of uranium on bone and kidney function be determined before establishing intake limits. However EPA is presently in process of establishing limits for uranium intake (i.e. air and water only). These limits will be related to the cancer deaths associated with total uranium exposure. These limits may or may not be sufficient to cover the chronic effects of uranium on kidney and bone function. It is noted that the FDA does not have established limits for this metal in foods.

In conclusion, many studies have been performed to determine the toxic effects of uranium. However, few of these studies have provided the necessary information for establishing guidance intake limits for the effects of uranium on kidney and bone function. We thus would recommend that dose-response studies (i.e. both inhalation and ingestion studies) on the effects of uranium on kidney and bone function be performed before establishing intake limits for uranium. We would also recommend that the dose-response studies use the uranium species that are very soluble and those that are very insoluble in aqueous solution. As noted above uranium toxicity is in part related to the solubility of the various uranium species in aqueous solution.

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