A Review of the Scientific Literature As It Pertains to Gulf War Illnesses

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RAND

Depleted Uranium

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A Review of the Scientific Literature As It Pertains to Gulf War Illnesses

VOLUME 7

DEPLETED URANIUM

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This literature review, one of eight commissioned by the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses, summarizes the existing scientific literature on the health effects of depleted uranium that may have affected service members who served in Operations Desert Shield and Desert Storm and recommends additional areas of research where appropriate. The eight RAND reviews are intended to complement efforts by the Defense Department and other federal agencies as they attempt to understand the full range of health implications of service in that conflict.

While many veterans have reported an array of physical and mental health complaints since the war, it is not yet clear the extent to which veterans are experiencing either higher-than-expected rates of identifiable illnesses with known etiologies or any other illnesses from as yet unidentified origins.

The other seven RAND literature reviews deal with chemical and biological warfare agents, oil well fires, pesticides, pyridostigmine bromide, immunizations, infectious diseases, and stress. The topics of these reviews all represent plausible causes of some of the illnesses Gulf War veterans have reported.

The reviews are intended principally to summarize the scientific literature on the known health effects of given exposures to these risk factors. Where available evidence permits, the reviews also summarize what is known about the range of actual exposures in the Gulf and assess the plausibility of the risk factor at-hand as a cause of illnesses. Statements related to the Gulf War experience should be regarded as suggestive rather than definitive, for much more research both on health effects and exposures remains to be completed before definitive statements are made.

These reviews are limited to literature published or accepted for publication in peer-reviewed journals, books, government publications, and conference proceedings. Unpublished information was occasionally used, but only to develop hypotheses.

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Uranium is a naturally occurring heavy metal that is both radioactive and ubiquitous. Small amounts are present in rocks, soil, and materials made from them. It is also present in air, water, and food, and thus people come into contact with or consume tiny amounts of it daily. Uranium is best known in its enriched form, which is used for nuclear power plants and nuclear weapons. Uranium is enriched by increasing the proportion of the more radioactive isotopes. The by-product of this process, which depletes uranium of its most radioactive isotopes, is called depleted uranium (DU). It is about 40 percent less radioactive than natural uranium and has a variety of commercial and military applications. The latter include improved armor and antiarmor rounds with increased penetrating power, both of which take advantage of the metal's density and metallurgical properties.

Very little literature directly addresses the health effects of DU. However, a wide body of literature deals with the health effects of natural and enriched uranium, and a review of that literature is relevant. The toxicological effects of natural uranium are identical to those of DU; while the radiological effects of DU are always less pronounced because DU is less radioactive than natural uranium. In general, heavy-metal toxicity is regarded as posing a more serious health risk than its radiation. This is because DU produces a low level of radiation per unit mass. The most abundant isotope in natural uranium, ^{238}U, has a very long half-life (4.5 billion years), which means that it decays slowly and thus produces fewer disintegrations per mass than an isotope that decays rapidly, such as ^{234}U (half-life of 245,000 years). As mentioned, DU is less radioactive than natural uranium and, indeed, is classified in the lowest hazard class of all radioactive materials.

In addition to being very dense (almost twice as dense as lead), DU, like any uranium, is pyrophoric, that is, in fine particles it can ignite easily. When a DU penetrator strikes armor or burns, it produces uranium dusts or aerosol particles, which can be inhaled. Once internalized, a fraction of the particles dissolve and enter the bloodstream, where most uranium is excreted from the

body through the kidneys. These inhaled fine particulates or dusts of oxidized uranium metal, uranium oxides, are presently thought in the published literature to be the primary compounds of interest.

REGULATION STANDARDS

Several different U.S. government agencies regulate and make recommendations about exposure to uranium. This report provides the present radiological standards for both occupational and population exposure. Both standards are important because military personnel are not classified as radiation workers unless their jobs specifically qualify as such. This report also provides the chemical toxicity guidelines and recommended kidney concentration standard of 3 μg/g of kidney.

HEALTH EFFECTS

The health effects of DU depend on several factors. The first is whether the exposure is internal or external. Internal effects can be caused by either chemical or radiological toxicity. Health effects related to external exposure are limited to ionizing radiation emitted by uranium and its immediate decay products.

INTERNAL EXPOSURES

The main routes of natural uranium into the human body are by inhalation and ingestion. A very small percentage of the inhaled uranium is retained by the lymph nodes for a long time, and another small fraction is solubilized and goes to the blood, where most is subsequently excreted. A fraction of the blood content is deposited in the kidneys, liver, other organs, and the skeleton. In the military environment, additional routes of exposure exist. When a DU weapon impacts a target, the fragments can penetrate the body or any dusts produced can be inhaled, ingested, or be deposited on wounds.

Chemical Effects of Inhaled Uranium

Extensive information is available about the occupational exposure of workers in the uranium industry. No increase in overall deaths has been observed as a result of exposure to uranium in several epidemiological studies of workers exposed to uranium. One animal study designed to establish exposure end points induced mortality in rats when they were exposed to extraordinary concentrations of uranium oxides much higher than in occupational settings.

Evidence about hepatic effects from exposure to uranium oxides is more equivocal. Hematological effects have been observed in one study of miners exposed to uranium for up to 20 years. However, most animal studies found no hematological effects. Immune system effects have not been associated with inhaled uranium oxide exposure in uranium industry workers, and no evidence exists showing an association between uranium inhalation exposure and adverse effects on the nervous system.

The kidney is the target organ for uranium, and, as such, would be expected to experience the most dramatic health effects if sufficient uranium were present. A study of uranium mill workers occupationally exposed to "yellowcake," a soluble uranium compound, reported findings of reduced proximal renal tubular reabsorption of amino acids and of low molecular weight proteins. Another study of workers exposed to insoluble uranium dust reported no renal injury. Animal studies show that the solubility of the inhaled uranium compound dramatically affects renal outcomes. Although soluble uranium compounds have caused renal damage, insoluble uranium oxides appear to be far less toxic to kidneys. When exposure is less than American Conference of Governmental Industrial Hygienists (ACGIH) recommended amounts, the scientific literature does not indicate negative health effects.

Radiological Effects of Inhaled Uranium

Negative effects from the exposure to the ionizing radiation from depleted or natural uranium have not been observed in humans. Some epidemiological studies show evidence of lung cancer in miners, but this is associated with the exposure to airborne short-lived decay products of radon and cigarette smoking. Some animal studies have examined pulmonary damage from exposure to uranium oxides. Exposures over three years to 5.1 mg UO_2/m^3 in air did not result in lung damage but did cause minimal fibrosis, suggesting radiation injury, in the lymph nodes of dogs and monkeys and the lungs of monkeys.

Cancer rates in almost 19,000 highly exposed uranium industry workers who worked at Oak Ridge between 1943 and 1947 have been examined, and no excess cancers were observed through 1974. Other epidemiological studies of lung cancer in uranium mill and metal processing plant workers (environments without radon) have either found no excess cancers or attributed them to known carcinogens other than uranium, such as radon.

Human studies have examined bone cancers, and no associations between them and internal or external radiation exposure from natural uranium were reported. A variety of cancers developed when rats were exposed to enriched uranium; however, because DU is orders of magnitude less radioactive than enriched uranium, these data have little relevance to the possible health effects

of DU. High exposures may also be nephrotoxic; however, there is no evidence that either natural or depleted uranium can induce this effect. Gastrointestinal effects produced from inhalation of high levels of radioactive material have been reported in both human and animal studies. There is no conclusive evidence of reproductive effects.

In sum, cancer is the only radiation-associated disease that has been shown to be related to inhalation of radioactive particulates in humans, but there is no evidence documented in the literature of cancer or any other adverse health effect related to the radiation received from exposure even to natural uranium, which is more radioactive than DU.

Chemical Effects of Ingested Uranium

Chemical toxicity of ingested uranium is determined largely by the water solubility of the compound and, therefore, ease of uptake from the gastrointestinal (GI) tract. Compared with industrial compounds, uranium oxides are generally thought to be less soluble or insoluble and, therefore, of very low toxicity.

No studies report human deaths or other health effects from oral exposures to uranium oxides. Mortality, usually from renal failure, can be induced in animals at very high oral intake levels. No human studies were found in the peer-reviewed published literature that showed respiratory, cardiovascular, hematological, musculoskeletal, hepatic, endocrine, dermal, ocular, body weight, or other system effects in humans exposed to uranium compounds. No epidemiological studies were located that examined neurological effects following uranium ingestion.

While the possible toxic effects of uranium on other organ systems have not been rigorously excluded, extensive work points to the kidney as the major target organ. A recent study described analyses of renal function following a lifetime of drinking water with uranium levels in the range 2-781 μg/day. The exposed group excreted more glucose in urine than did the control group, but the only valid measure of glomerular dysfunction tested (proteinuria) remained unchanged.

Respiratory effects have not been observed in animals following ingestion of uranium oxides. Hepatic effects have been observed in animals dosed with very high levels of insoluble uranium. No harmful effects on body weight were seen in intermediate-duration oral studies of dogs given up to 10 g UO_2/kg/day for a year.

Thus, only limited evidence suggests that even chronic exposure to natural uranium in food or water, except presumably at extraordinary concentrations,

is associated with morbidity in man or animals. This conclusion makes it unlikely that DU would have any such effects.

Radiological Effects of Ingested Uranium

No human or animal studies associate adverse health effects with ingested DU. No evidence has been found to associate human exposure to ingested uranium compounds and carcinogenesis. Likewise, no oral animal studies report evidence of cancer induction.

Chemical and Radiological Effects of Embedded Uranium

What is known about the health effects of embedded uranium results primarily from the clinical follow-up of the wounded veterans of the Gulf War. Thirty-three individuals are being followed by Department of Veterans Affairs (VA) researchers, and about half of these have been identified as having embedded DU fragments. To date, although these individuals have an array of health problems related to traumatic injuries, no manifestations of kidney disease attributable to the chemical toxicity of DU have been found. Neither do they appear to have any manifestations attributable to radiation effects. These patients continue to be followed. AFRRI is also conducting important studies of the effect of embedded DU pellets on rats.

EXTERNAL EXPOSURES

Radiation rather than chemical toxicity poses the external health hazard.

DU exposes the skin to alpha, beta, and gamma radiation. In the case of short-term radiation from particulates deposited on skin, more than 95 percent of the radiation present is in the form of alpha radiation, which has a very short range and will not penetrate the dead outer layer of the skin and thus poses no documented health risk. Beta and gamma radiation from ^{238}U decay products can irradiate cells in the deeper skin layers. Sufficient mass of DU to create radiation sufficient to be of concern can occur with intact munitions and armor. However, DU munitions are shielded to limit emitted radiation, and thus people working with intact munitions or armor usually face little risk. The measured exposure to gamma and beta radiation from bare penetrator or armor is well below recommended occupational levels (CHPPM, 1998).

Studies of workers occupationally exposed to uranium show no skin cancers resulting from this exposure. No animal studies have found skin cancers with this cause. As a point of perspective, to reach the occupational radiation dose

limit for beta and gamma radiation, a soldier would have to hold an unshielded DU penetrator for more than 250 hours.

CLINICAL DISCUSSION

The clinical discussion section outlines possible health effects from a clinical perspective. After discussing common diagnostic procedures, including a 24-hour urine analysis, the section details symptoms and the relation, if any, of diseases of various body systems to exposure to DU. Areas discussed include lung cancer, kidney disease, liver disease, osteosarcoma, and reproductive and developmental conditions.

CONCLUSIONS

From the scientific literature, the review reaches the following insights and conclusions:

- Although any increase in radiation to the human body can be calculated to be harmful from extrapolation from higher levels, there are no peer-reviewed published reports of detectable increases of cancer or other negative health effects from radiation exposure to inhaled or ingested natural uranium at levels far exceeding those likely in the Gulf. This is mainly because the body is very effective at eliminating ingested and inhaled natural uranium and because the low radioactivity per unit mass of natural and depleted uranium means that the mass of uranium needed for significant internal exposure is virtually impossible to obtain.

- External radiation takes the primary form of alpha radiation, but amounts of beta and gamma radiation also exist. Alpha radiation is not capable of penetrating cloth or skin and would therefore have no negative health effect. Beta and gamma radiation, which can have negative health effects, have been measured at levels below those expected to be of concern.

- Large variations in exposure to natural uranium in the normal environment have not been associated with negative health effects.

- Radiation-related effects from embedded fragments will depend on the size of the fragment and its proximity to vital organs.

- Exposure to uranium and other heavy metals in large doses can cause changes in renal function and at very high levels result in renal failure.

- In spite of these findings, no increased morbidity or frequency of end-stage renal disease has been observed in relatively large occupational popula-

tions chronically exposed to natural uranium at concentrations above normal ambient ones.

- The cohort of individuals, about half of whom have embedded fragments, who are being followed at the Baltimore VA Medical Center as part of the DU Follow-Up Program, represents a group of Gulf War veterans who received the highest levels of exposure to DU during the Gulf War. Although many of these veterans have health problems related to their injuries in the Gulf War and those with embedded fragments have elevated urine uranium levels, researchers to date report neither adverse renal effects attributable to chemical toxicity of DU nor any adverse health effects they relate to DU radiation (McDiarmid, 1998b). They do, however, note several biochemical perturbations in neuroendocrine parameters related to urinary uranium concentrations and in some subtle neuropsychological test findings; the clinical significance of these is unclear.

Finally, the report encourages continued research because the use of DU is likely to expand in the future.

ACKNOWLEDGMENTS

ACGIH	American Conference of Governmental Industrial Hygienists
AED	Aerodynamic Equivalent Diameter
AEPI	U.S. Army Environmental Policy Institute
AFRRI	Armed Forces Radiobiology Research Institute
ALARA	As low as reasonably achievable
ATSDR	Agency for Toxic Substances and Disease Registry
BEIR	Biological Effects of Ionizing Radiation
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHPPM	Center for Health Promotion and Preventive Medicine (formerly Army Environmental Hygiene Agency)
CNS	Central nervous system
DoD	Department of Defense
EDTA	Edetic acid
EPA	Environmental Protection Agency
ERAMS	Environmental Radiation Ambient Monitoring Program
FR	*Federal Register*
GAO	General Accounting Office
GI	Gastrointestinal
HHS	Department of Health and Human Services
ICRP	International Commission on Radiological Protection
MPC	Maximum permissible concentration
NCRP	National Council on Radiation Protection and Measurements
NIOSH	National Institute for Occupational Safety and Health
NRC	Nuclear Regulatory Commission
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSAGWI	Office of the Special Assistant (to the Secretary of Defense) for Gulf War Illnesses
OSHA	Occupational Safety and Health Administration
PHS	Public Health Service
TLV®	Threshold Limit Value

UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
VA	Department of Veterans Affairs
WHO	World Health Organization

SYMBOLS

α	alpha
ß	beta
δ	delta
γ	gamma
$\mu Ci/g$	microcuries per gram
μg	microgram
$\mu g/L$	microgram per liter
μm	micrometer
μR	microroentgen
<	less than
>	greater than
^{234}U	uranium 234
^{235}U	uranium 235
^{236}U	uranium 236
^{238}U	uranium 238
Ac	actinium
Am	americium
Bq	becquerel (1 disintegration per second)
Ci	curie
cm	centimeter
Cs	cesium
dpm	disintegrations per minute
DU	depleted uranium
Depleted U_3O_8	depleted triuranium octaoxide
Depleted UO_2	depleted uranium dioxide
Depleted UO_3	depleted uranium trioxide
g	gram
g/m^3	gram per cubic meter
Gy	Gray absorbed energy or dose (1 Gy = 100 rad)
hr	hour
kg	kilogram
L	liter

m	meter
MeV	million electron volts
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mrad	millirad (absorbed energy or dose (100 ergs/gram))
ng	nanogram
nm	nanometer
pCi	picocuries
pCi/g	picocuries per gram
pg	picogram
pH	relative acidity of a fluid
Po	polonium
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
R	roentgen
Ra	radium
rem	roentgen-equivalent man (absorbed energy or dose (100 ergs/gram) corrected by a quality factor that accounts for differences in radiation type (alpha, beta, gamma))
Rn	radon
sec	second
Sv	Sievert (absorbed energy dose (1 Sv = 100 rem)
Sr	strontium
Tc	technetium
Th	thorium
U	uranium
U(IV)	uranium with oxidation state 4
U(O)	uranium metal, uranium with zero oxidation state
U(VI)	uranium with oxidation state 6
U_3O_8	triuranium octaoxide
U^o	elemental uranium
UO_2	uranium dioxide (uraninite)
UO_2^{2+}	uranyl ion
UO_3	uranium trioxide

INTRODUCTION

Uranium is a silver-colored heavy metal in its pure form that is natural, ubiquitous, and radioactive. Small amounts are commonly present in all rock, soil, and materials made from earth's natural substances. Found in air, water, and food, small amounts are consumed and inhaled by all people on the planet every day.

Uranium is produced and used widely in commercial and military applications. U.S. uranium production peaked in 1980 at 21,852 short tons of U_3O_8 and from that point decreased to 1,534 short tons in 1993 (HHS, 1997b). In 1994, the production again increased, to 1,700 short tons. Uranium is mined from the earth where natural deposits are in concentrations ranging from 0.05 percent to tens of percent by mass. These deposits, called uranium ore, are typically found in sandstone formations. Historically, nearly all U.S. uranium has come from mines in New Mexico, Colorado, Wyoming, Utah, and Arizona.

Uranium is perhaps most recognized in the form of enriched uranium, which is used for nuclear power and nuclear weapons. However, depleted uranium (DU), a by-product of the enrichment process, is used commercially in medicine (radiation shields), aviation (counterweights), space (satellite ballast), and petroleum exploration (drilling equipment). DU has also been used for military purposes. It offers improved defense when used as armor shielding and enhanced power when used in armor penetrating munitions. The United States is not alone in using DU for military purposes. The United Kingdom, Russia, Turkey, Saudi Arabia, Pakistan, Thailand, Israel, and France are developing or already possess weapon systems that contain DU in their inventories (AEPI, 1994).

Two major health concerns are related to the use of DU in military applications: heavy-metal toxicity effects and radiation effects. Heavy metals, such as uranium, lead, tungsten, and others, in sufficient amounts, are toxic to humans and animals. Although much less radioactive than naturally occurring uranium, DU is radioactive and poses a potential health risk from internal and ex-

ternal radiation exposure. DU's toxicity is generally considered to be the greater of the two potential health threats.

For both health issues, many factors will determine whether a health effect may result. Among others, these factors include the toxicological dose (how much and how long), route and magnitude of exposure, and location of embedded fragments. In addition, other factors including age, sex, diet, family history, health status, and lifestyle may affect the overall health consequences of exposure.

Although published health literature dealing directly with DU is scarce, much can be learned from the literature that deals with natural and enriched uranium, which have been studied extensively. This is because both enriched and natural uranium are much more radioactive than DU and, therefore, would have a greater radiation effect than would DU. The chemical toxic effects of natural and enriched uranium are identical to those of DU.

RADIOLOGICAL CONSIDERATIONS

DU is less radioactive than naturally occurring uranium because it has fewer of the more radioactive isotopes per unit weight than does natural uranium. Naturally occurring uranium contains a mixture of three different isotopes:[1] ^{234}U, ^{235}U, and ^{238}U. Uranium-238, ^{235}U, and ^{234}U constitute 99.2745 percent, 0.7200 percent, and 0.0055 percent, respectively, of the weight of naturally occurring uranium.

All of the isotopes of uranium are radioactive and decay into thorium, radium, etc., isotopes of lead (progeny or decay products) until a stable nonradioactive isotope of lead is produced (the complete radioactive decay series for ^{235}U and ^{238}U are shown in Appendixes A and B). This process of radioactive decay also emits ionizing radiation (alpha particles, beta particles, or gamma rays) with each nuclear transformation. U-238, which constitutes more than 99 percent of the mass of natural uranium, is the least radioactive per unit weight. In contrast, ^{235}U exhibits approximately seven times and ^{234}U approximately 18,000 times the radioactivity of ^{238}U per unit weight. The three isotopes of naturally occurring uranium—^{238}U, ^{235}U, and ^{234}U—possess half-lives of 4.5 x 10^9, 7.1 x 10^8, and 2.5 x 10^5 years, respectively. The very long half-life of ^{238}U (4.5 billion years), the most abundant isotope, yields a very low decay rate per unit mass of

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[1]Isotopes of an element have the same number of electrons and protons but have different numbers of neutrons, which give the isotopes different elemental weights.

uranium.[2] Because of the high percentage of ^{238}U and its slow decay rate, naturally occurring uranium is, in fact, one of the least radioactive substances among unstable isotopes on the planet. DU can be up to 50 percent less radioactive than naturally occurring uranium depending on the degree of depletion. The material generally used by the U.S. Department of Defense (DoD) is 40 percent less radioactive than natural uranium. The radioactivity of each uranium isotope in 1 μg of either natural or depleted uranium is shown in Table 1.1.

Depleted uranium has a different isotopic mix from natural uranium. This is because DU is the by-product of fuel- and weapons-grade uranium refining. Nuclear power production and nuclear weapons usually require a greater concentration of ^{235}U, ranging from 2 percent to 90 percent ^{235}U by weight, rather than the 0.72 percent of ^{235}U found in nature (see Table 1.1). To achieve this increased concentration of ^{235}U, naturally occurring uranium is subjected to an

Table 1.1

Radiological Characteristics of Natural and Depleted Uranium

Isotope	Half-Life (years)	Alpha Particle Energy MeV (percent)	Isotopic (percent)	Activity (mBq/ μgU)	Activity Ratio ^{234}U/^{238}U	Activity ^{235}U/^{238}U
NATURAL					1.00	0.048
^{238}U	4.468 x 10^9	4.147 (23) 4.196 (77)	99.2745	12.40		
^{234}U	2.450 x 10^5	4.724 (28) 4.776 (72)	0.0055	12.40		
^{235}U	7.037 x 10^8	4.364 (11) 4.395 (55)	0.7200	0.60		
Total				25.40		
DEPLETED					0.18	0.013
^{238}U	4.468 x 10^9	4.147 (23) 4.196 (77)	99.8000	12.40		
^{234}U	2.454 x 10^5	4.724 (28) 4.776 (72)	0.0010	2.26		
^{235}U	7.037 x 10^8	4.364 (11) 4.395 (55)	0.2000	0.16		
Total				14.80		

SOURCE: Browne et al., 1986.

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[2]The radioactive decay rate of any radionuclide is the product of the decay constant, λ (λ = Ln2/half-life in seconds), and the number of atoms, N, present. Decay rate (disintegrations per second) = λN.

enrichment process. The enrichment process increases the percentage of ^{235}U in fuel- and weapons-grade uranium, resulting in enriched uranium. Depleted uranium, which is "depleted" of both ^{235}U and ^{234}U (the relatively more radioactive isotopes), is a residual of the enrichment process.

The Nuclear Regulatory Commission (NRC) defines depleted uranium as uranium in which the percentage of the ^{235}U isotope by weight is less than 0.711 percent (10 CFR 40.4). The military specifications designate that the DU used by DoD contain less than 0.3 percent ^{235}U (AEPI, 1995). In actuality, DoD uses only DU that contains approximately 0.2 percent ^{235}U (AEPI, 1995).

Radioactivity is measured in nuclear transformations (disintegrations) per second per unit mass (e.g., becquerels per gram (Bq/g), where a becquerel is equal to 1 disintegration per second). DU has a specific activity of 14.8 mBq/μg.[3] As such, DU's radioactivity is 40 percent less than that of naturally occurring uranium (25.4 mBq/μg) and orders of magnitude less than that of the enriched uranium used for nuclear power and weapons ($\approx$ 1,750 mBq/μg).

DU is classified as a low-level radioactive material. In comparison, several consumer products contain radioactive material that also emits ionizing radiation, such as present-day smoke detectors. In medicine, radioactive materials and other sources of ionizing radiation are widely used in the diagnosis and treatment of some diseases.

Uranium, in any form, is certainly not alone as a source of ionizing radiation. The world is bathed with low levels of radiation all the time. The sources of radiation dose include radon (55 percent of the total), cosmic rays (8 percent), rock and soil (8 percent), internal exposures from food and water consumed daily in the diet (11 percent), and man-made sources, such as X rays, nuclear medicinal exposure, consumer products, and other sources (HHS, 1997a) (see Figure 1.1).

The hazard of ionizing radiation is derived from the energy it transfers to the matter, including biological matter, through which it travels. This energy is dissipated in the living tissue by diverse molecular interactions, including those with DNA (genetic material) that may result in genetic damage (HHS, 1997a).

All uranium isotopes are *primarily* alpha particle (α) emitters. These alpha particles will travel only about 30 μm in soft tissue and, therefore, are unable to penetrate paper, glass, or even the dead superficial layer of skin. Consequently, alpha particles present a hazard only if internalized and then only to critical cell structures within the range of the alpha particle from the site of deposition

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[3]The symbol m stands for milli (10^{-3}) and μ for micro (10^{-6}).

Commercial products 3%
Terrestrial 8%
Medicine 4%
Medical x-ray exams 11%
Natural internal 10%
Other less than 1%
Cosmic rays 8%
Radon 55%
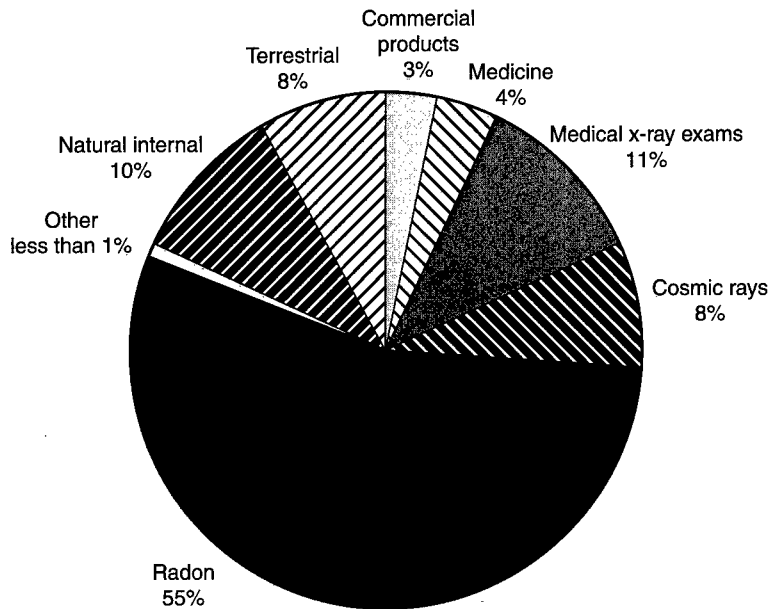
SOURCE: HHS 1997a (as adapted from NCRP 1987 Report #93).

Figure 1.1—Radiation Sources

(UNSCEAR, 1982, 1986, 1988). Beta particles (ß) have greater ability to penetrate the skin. In most circumstances, beta particles only present a hazard if internalized. In contrast, gamma rays (γ) are extremely penetrating. As such, gamma rays present a hazard both internally and externally.

Despite the fact that all uranium isotopes are primarily alpha emitters, other forms of radiation are present. This is because the uranium isotopes decay to other radioactive isotopes (decay products). The natural uranium series is in equilibrium (i.e., the radioactivity of each isotope is the same per unit weight of soil or ores.) When uranium is separated from the ore, the decay chain is broken. Thorium-234 (^{234}Th) and protactinium-234 (^{234}Pa) build up into equilibrium with the ^{238}U within several months. The remaining members of the chain following ^{234}U take thousands of years to reestablish equilibrium and can be considered trivial. Uranium-235 follows the same pattern, and only thorium-231 (^{231}Th) builds into equilibrium rapidly. Therefore, at any given time, some decay products of uranium are present. The decay products are responsible for the presence of beta and gamma forms of ionizing radiation. (See Appendix A for decay schemes of the uranium series.)

CHEMICAL CONSIDERATIONS

Uranium is a heavy metal similar to tungsten, lead, and cadmium. Unlike the radiological characteristics of an element, chemical characteristics of a heavy metal are independent of its isotopic form. All isotopes of uranium exhibit the same chemical behavior (reactivity) and possess identical physical characteristics, such as melting point, boiling point, and volatility. Because naturally occurring uranium, enriched uranium, and depleted uranium vary only in their isotopic mix, they are chemically identical and exert the same chemical effects on the body. Therefore, discussion of the chemical effects of DU will generally refer to "uranium" to cover the natural, enriched, and depleted forms of the metal.

DU possesses certain unique physical properties, such as its remarkable density (19 g/cm^3, 1.7 times the density of lead), pyrophoric nature (tendency of fine particles to spontaneously ignite in air), and ductility. Because of these unique characteristics, DU has attracted uses from both the civilian and military communities. To name a few, DU is used commercially in medicine, aviation, space, petroleum exploration, and by the military.

The pyrophoric nature of DU is of special relevance to the health effects resulting from DU's use in munitions and armor. Both the impact of a DU penetrator on a target and the burning of DU produce DU dusts or aerosol particles. In addition to resulting in aerosol particles, when DU burns, the high temperatures created act to oxidize uranium metal to a series of complex oxides, predominantly depleted triuranium octaoxide (U_3O_8), but also depleted uranium dioxide (UO_2), and depleted uranium trioxide (UO_3) (AEPI, 1995; CHPPM, 1998). Upon weathering, the nonoxidized small particles and surfaces of remaining uranium metal will also slowly oxidize to those three DU oxides over time (CHPPM, 1998).

Originally it was thought that up to 70 percent of the DU round may be aerosolized upon impact of a DU penetrator on its target or in fires in which DU burns (AEPI, 1995). However, based on more refined testing, the percentage of the original material to aerosolize is now known to range from 10 to 35 percent with a maximum of 70 percent (CHPPM, 1998). The percentage varies according to a number of factors, such as the hardness of the target, velocity and angle of impact, pathway through the target (i.e., what it impacts—engine, DU armor, etc.). If the round easily penetrates a target, as it does non-DU armor, less of it will aerosolize than it does when hitting a nonpenetrable target, such as laminated steel. In many cases of DU hits during the Gulf War, the DU penetrator went completely through (out the other side) the target armor.

Although other industrial compounds exist,[4] the uranium compounds of concern from the military use of DU are primarily limited to the uranium oxides. In the body, the oxides are mostly metabolized to the uranyl ion (UO_2^{++}). This discussion is limited to the uranium compounds present in a military environment, namely DU metal and its oxides: U_3O_8, UO_2, and UO_3.

The solubility of uranium varies greatly depending on the particular compound and the solvent. Body fluids can dissolve uranium oxides. Once solubilized, uranium may react with biological molecules and exert its toxic effects (Hursh and Spoor, 1973).

In many of its chemical properties, uranium is typical of the heavy metals. Heavy-metal compounds in solution are usually highly reactive and can exert broad cytotoxic effects. Heavy metals, including uranium, exhibit great affinity for biological molecules containing phosphate residues, such as glucose phosphate, phospholipids, and nucleic acids; or sulfhydryl groups, including cysteine, glutathione, and many proteins and oxyanions (oxygen-containing anions). Because of their high affinity for biological molecules, these heavy metals do not exist (except perhaps very transiently) as free ions in biological systems. The heavy metals are present, instead, as complexes with a great variety of molecules (ligands)(Hursh and Spoor, 1973).[5]

For uranium toxicity, the most important oxyanions in biological systems are the carbonate/bicarbonate compounds (Hursh and Spoor, 1973). It has been estimated, for instance, that 47 percent of U(VI) circulating in blood is contained in the inorganic fraction, primarily as $[UO_2(CO_3)_2]^2$ (Durbin, 1984). The compound is stable near neutral pH (the pH of blood) and in this form does not significantly react further with biological molecules. It readily decomposes, however, at more acid pH in urine, with liberation of the reactive uranyl ion.[6]

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[4]Uranyl salts such as uranyl nitrate, uranyl sulfate, or uranyl acetate and many other compounds of uranium, such as the uranates and halides, are all used in the uranium industry. Some, such as the uranyl salts, are common laboratory reagents. These nonoxide uranium compounds, however, are absent in the military environment (CHPPM, 1998).

[5]This was illustrated, for instance, for inorganic Cd, Hg, or Zn: when injected into the renal artery these metals are instantaneously sequestered by nondiffusible macromolecules, such as plasma proteins, and within fractions of a second become nonfilterable at the glomerulus (Foulkes, 1974). Low-molecular-weight ligands do not significantly contribute to metal binding under the conditions of those experiments, presumably because they are present in plasma in much lower molar concentrations than proteins. The binding of metals by proteins is prevented by higher concentrations of diffusible SH compounds.

[6]Dissolved uranium, similar to other heavy metals, reacts with diffusible chelating compounds, such as EDTA, to form relatively stable and inert complexes in which it can no longer react with other ligands in biological systems. The inert complexes are thereupon filtered and excreted in urine. Such chelating compounds have been therapeutically administered to experimental animals immediately following exposure to uranium. This is called chelation therapy and has proven useful in decreasing tissue levels and increasing excretion of uranium in mice (Domingo, 1990).

Once the uranium is solubilized in the blood, the kidney will efficiently excrete about 90 percent of it in urine over approximately three days. Renal excretion of uranium, like that of other heavy metals, is determined by such factors as the filterability of circulating complexes and on the ability of filtered complexes or their decomposition products to be reabsorbed or secreted in the tubule. In one study (Hursh and Spoor, 1973), more than two-thirds of uranium injected intravenously as uranyl nitrate into man was excreted in the urine within one day.[7] Because a major portion of uranium circulating in blood is excreted in urine, increased urinary uranium excretion can provide a sensitive quantitative measure of exposure, especially acute exposure.[8]

It also provides an indication of the amount of exposure over longer periods of time for insoluble uranium compounds, depending on the particular compound and the amount internalized. Embedded fragments present a chronic, steady-state exposure as the metal solubilizes. The background rate of urinary excretion of uranium from natural sources falls into the range of 50–500 ng/day (AEPI, 1995).

The remaining uranium not excreted mostly distributes to bone and soft tissue, including the kidney, liver, lung, fat, muscle, and then, to some extent, to all other organs. In spite of their nonspecific affinity for biological compounds, heavy metals are characterized by specific primary target organs in the body where a change in function is observed. Although uranium in the body distributes to all organs with the main reservoir being the skeleton, the target organ is the kidney, where functional change is observed. The acidification of urine leading to the decomposition of the uranyl-carbonate complexes in tubular urine could help explain the organ-specific reaction of uranium with the kidney (Hursh and Spoor, 1973).

REGULATORY STANDARDS

Several different U.S. government agencies regulate and make recommendations about exposure to uranium. Those agencies include the Nuclear Regulatory Commission (NRC), the Department of Energy (DOE), the Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease

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[7] The ICRP (1995, p. 220) uses a standard of 80 percent uranium urine excretion in 24 hours.

[8] The measurement of uranium is based on either fluorometric analysis for total uranium mass, radiochemical separation and counting using alpha spectrometry, neutron activation of the ^{235}U with fission track or delayed neutron counting, or inductively coupled plasma mass spectrometry (ICP-MS). The alpha spectrometric analysis permits the isotopic species to be determined in addition to mass. Many data are reported in mass units, typically micrograms, and thus are a measurement of only the ^{238}U, because the mass of uranium is almost exclusively ^{238}U. One μg of $^{238}U = 12.4$ mBq $= 0.33$ pCi.

Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), and the National Institute for Occupational Safety and Health (NIOSH). The International Commission on Radiological Protection (ICRP), and the National Council on Radiation Protection and Measurements (NCRP) also recommend standards for radiation protection. The EPA, NRC, DOE, and the states promulgate the regulations based on recommendations from the NCRP and ICRP, as well as ATSDR, CDC, NIOSH, WHO, and others.[9]

Radiation Protection Guidelines

The organizations that have promulgated basic radiation protection standards for more than 40 years are the NCRP and the ICRP. The dose limit guidelines for human exposure were reduced during this period by about a factor of two as the data on radiation carcinogenesis have developed, mainly from Japanese atomic bomb survivors.

The present guideline for occupational exposure used by NCRP and ICRP is 10 and 20 mSv per year (1 and 2 rem per year) effective dose, respectively. The objective of both organizations is to limit the lifetime radiation dose for maximally exposed persons to 0.7 Sv (70 rem) by NCRP and 1 Sv (100 rem) by ICRP. The NCRP recommends that the lifetime effective dose be limited in 10s of mSv to the value of his or her age (age x 10 mSv, not including medical or natural background exposure). The annual dose should also be limited to 50 mSv (5 rem).

The ICRP recommendation is stated to limit exposure to 100 mSv in five years with no more than 50 mSv in a single year. These lifetime dose figures limit the lifetime fatal cancer risk to less than 3 percent for maximally exposed occupational workers.

Population exposures are also considered because all persons can be exposed in various situations that produce some incremental radiation over what is considered average. Because populations are assumed to have a range of sensitivities, annual exposure is set at a factor of 10 below occupational limits. Thus, a maximum annual effective dose of 5 mSv (500 mrem) is recommended for infrequent exposure, and for continuous or frequent exposure it is recommended that the annual effective dose not exceed 1 mSv (100 mrem). Both these population limits are for exposure to man-made radiation sources other than medical and normal background (NCRP, 1993). The population exposure limits are intended to provide an annual level of carcinogenic risk comparable

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[9]Standards are presented below for completeness and for benchmarks against which to analyze exposure levels. Standards need to be constantly evaluated in light of new research and information. RAND is neither endorsing nor critically evaluating the standards presented.

with other sources, namely one per 10,000 to 1 per 1,000,000. Although this risk is minimal, exposure to radiation, no matter how small, is thought to carry some level of risk.

Military personnel are not classified as radiation workers unless their job specifically qualifies as such. Under battlefield conditions, this classification needs to be determined explicitly so that individuals with duties requiring known exposure to radioactivity, such as cleanup of contaminated equipment, can be monitored and exposure controlled appropriately (NAS, 1997).

Chemical Toxicity Guidelines for Uranium in Air

In 1944, an urgent need arose for toxicological guidance for the safety of those handling uranium in laboratories and plants for the Manhattan Project. Because this need had to be met before experimental work was available, it was decided to adapt as the maximum permissible level for uranium in air, the value for lead, namely 150 µg per m^3. This standard had been used in the lead industry since 1933. This decision was based on the assumption that the radiological toxicity was less important than the chemical toxicity and that lead would be a good surrogate.

Animal experiments with dogs, rats, rabbits, and guinea pigs performed at the University of Rochester are summarized in two reports, one dealing with soluble uranium (Hodge et al., 1949a) and the other with insoluble uranium (Hodge et al., 1949b). This was the most extensive toxicology study of any sort undertaken up to that time. The Rochester experiments were conducted on a scale probably unequaled in the history of toxicology (Hodge et al., 1973). The result was that uranium was classified as a chemical toxin affecting the kidney.

The air concentrations for soluble uranium were based on two established principles (Hodge et al., 1973):

- Under exposures at or near the maximum permissible concentration in air, the amount of uranium present in the lung or in the kidney or the amount deposited in bone will never, with natural uranium, constitute a radiological hazard.

- The known typical uranium injury to the kidney is an extremely reliable indicator of chemical toxicity, and an amount of soluble uranium compound in the atmosphere that fails to produce kidney injury is a physiologically safe concentration.

The calculations for human exposure based on these animal studies suggested that the permissible dust exposure concentration for natural uranium in soluble form be set at 50 µg/m^3 for an industrial exposure of eight hours per day for a

working lifetime. This guideline was used at all of the U.S. government uranium-processing facilities, and extensive replacement of industrial equipment was initiated to comply with this air concentration and to permit high production rates (Christofano and Harris, 1960).

The Rochester recommendation for insoluble uranium compounds in air was calculated on the basis of the then-standard occupational limit for an organ of 15 rem/year (0.15 Sv/yr) and a limit of 100 µg/m³ was proposed. However, the limit of 250 µg/m³ was proposed by the same authors for insoluble compounds based on chemical toxicity (Voegtlin and Hodge, 1953). The authors stated that "the chemical toxicity limit of 250 µg/m³ offered a reasonable margin of safety, and the radiological limit of 100 µg/m³ also offered a reasonable margin of safety." The proposal of two different limits from the same data inevitably caused confusion (Hodge et al., 1973).

The American Conference of Governmental Industrial Hygienists (ACGIH) adopted the maximum permissible concentration of 200 µg/m³ for soluble uranium along with a permissible concentration of 200 µg/m³ for insoluble natural uranium (ACGIH, 1993).

Recommended Kidney Concentration

The selection of 3 µg/g of kidney as a de facto permissible standard is based on the radiological limit calculated by ICRP (ICRP, 1959). The ICRP (1959) limit is stated as a whole body content. First the permissible radiation dose to the kidney is calculated and then divided by the fraction of the whole body content in the kidney to obtain the whole body content. The ICRP (1959) value for the whole body content was 0.005 µCi (185 Bq), and the fraction, at that time assumed to be in the 300 gram of kidney, was 0.065. Thus $0.005/0.33 \times 10^{-6} \times 0.065/300 = 3.2$ µg/g of kidney.

If this calculation were redone based on today's ICRP annual dose limits of 20 mSv (2 rem) versus the historic limit of 150 mSv (15 rem), and the now well-established fraction of uranium in the kidney, 0.0036 (see Figure 2.5), the permissible body burden would increase by a factor of 2.5.

Current federal and state regulations limit radiation workers' doses to a total effective equivalent dose of 50 mSv/year (5 rem/year) and a committed equivalent dose to any organ of 500 mSv/year (50 rem/year) (10 CFR 20; 10 CFR 835). The EPA has issued regulations for the nuclear fuel cycle that limit the total body dose of members of the public to 15 mrem per year (.15 mSv) and a single organ (except the thyroid) dose to 50 mrem per year (.50 mSv) (40 CFR 190). Currently the NRC cleanup rule specifies 25 mrem per year (.25 mSv) for public exposure.

OSHA, ACGIH, and NRC recommend a limit of 250 µg/m³ for insoluble uranium and 50 µg/m³ for soluble uranium (time-weighted average) for chronic occupational exposure (40-hour work week over the course of a 40-year career) (29 CFR 1910.1000). The short-term exposure limit to natural uranium in the air was set at 600 µg/m³ by the same groups. Based on the Clean Water Act, EPA has proposed a drinking water standard for naturally occurring uranium of 20 µg/L (EPA, 1991). This standard is under review at the EPA (1998).

METHODS OF DETECTION AND ANALYSIS

In the research to be presented, a number of methods have been used to determine the amount and timing of exposure to uranium and DU. In the case of individuals who have been exposed by inhalation or ingestion, researchers use urinalysis. This could be in the form of a 24-hour urine collection or spot urinalysis. (See "Ingestion—Radiological Toxicity," p. 46, and "Diagnosis," p. 58, for a description of the results of urinalysis). Researchers have sometimes used radiological scans including whole body scans to detect exposure, particularly in the case of embedded fragments (See "Embedded Fragments and Wound Contamination," p. 49, and "Diagnosis," p. 58). Additionally, researchers have examined bone ash and tissue samples (usually as part of autopsy). This type of analysis has yielded a great deal of valuable information but obviously cannot be used as a medical tool for diagnosis and treatment of exposed patients. (See "Radiological Considerations," p. 2, "Inhalation—Radiological Toxicity," p. 34, and "Ingestion—Radiological Toxicity," p. 46, for results of this type of research.)

HEALTH EFFECTS

OVERVIEW

The search for acute and chronic health effects from uranium exposure dates to 1824 when Christian Gmelin reported on uranyl nitrate, chloride, and sulphate in dogs and rabbits (Hodge, 1973). Early studies of humans were conducted from about 1860 into the early 1900s, during which time uranium was administered as a therapeutic agent for diabetes because it had been shown to increase glucose excretion (Hodge, 1973). The Manhattan Project (1943–1953) and atomic energy program served to increase vastly the collective knowledge of the biological consequences of exposure to uranium and uranium compounds. However, during these incipient years of research, the work pertained to natural uranium and its compounds and, accordingly, dealt with the chemical toxicity of uranium (USAEC, 1958). This early period of research on the chemistry and toxicology of uranium produced extensive reviews (Hodge, 1973; Tannenbaum, 1951; Voegtlin and Hodge, 1949). The radiological toxicity of enriched uranium was studied much later (Leach, 1970, 1973; Filippova, 1978; Bair, 1970). Very little health-related research has been completed specifically on DU, but there has been extensive research on natural and enriched uranium, both of which pose a greater radiological hazard and an identical toxicological chemical hazard.

Health effects of DU are determined by many factors. One of the first factors to consider is whether the DU exposure was internal or external. Health effects related to internal exposure may result from either chemical or radiological toxicity but depend on the extent of exposure. Three main pathways exist by which internalization of uranium may occur: ingestion, inhalation, and embedded fragments or wound contamination. The characteristic physicochemical properties of uranium metal and each uranium compound influence its uptake and distribution in various pools or compartments in the body and, eventually, its elimination by the body and, therefore, the resulting chemical and radiological toxicity. In contrast to internal health effects, the possible health effects re-

lated to external exposure are limited to radiological exposure. The balance of the report is structured to deal with the health effects of internal and external exposure to DU in a military environment.

INTERNAL EXPOSURE

In nonmilitary situations the main routes of uranium uptake by the human body are inhalation and ingestion, as is the case with other heavy metals. In the military environment, additional routes of uranium exposure exist such as from embedded metal fragments slowly dissolving in the body and uranium-contaminated open wounds. All of these routes of internalization contribute to the total body burden of uranium.

Outside the military or industrial settings, the major portion of the natural body burden of uranium for typical civilians is derived from ingested and inhaled material. There is a limited amount of natural uranium in the air we breathe, the food we eat, and water we drink. The origin of the uranium may be natural, or it may have been contributed to the environment by man-made sources, such as application of uranium-containing superphosphate fertilizer to crop land or combustion of fossil fuel.

Once uranium enters the body, a portion will be soluble as determined by its chemical and physical characteristics. The more soluble a compound is, the quicker it will be absorbed from the lung into the blood and the more completely it will be absorbed from lung and gastrointestinal tract; fractional absorption of uranium compounds from the intestine is generally low. The most-soluble compounds will be absorbed from the lungs within hours or days (Type F for fast dissolution, formerly called Class D). Occupationally, workers processing uranium are usually exposed to its more soluble forms. These include uranyl fluoride, uranium tetrachloride, and other nonoxide compounds. The less-soluble compounds are more likely to require weeks to be solubilized and absorbed (Type M for medium dissolution, formerly called Class W). These compounds include UO_3 as well as nonoxide compounds. The relatively insoluble compounds are more likely to require years to be solubilized and absorbed (Type S for slow dissolution, formerly called Class Y). These compounds include UO_2 and U_3O_8 (ICRP, 1995). Even the metallic form slowly solubilizes in biological fluids. Natural environmental exposure includes both soluble and insoluble forms of uranium.

The solubility determines the ease of absorption and, therefore, the chemical dose delivered to the target organ and its chemical toxicity. In general, the soluble compounds, such as the halides and uranates, are far more toxic to the kidney because they promote a greater blood concentration, while insoluble

compounds, such as oxides are more toxic to the lung because their longer residence in the lung produces a larger radiation dose. (Domingo, 1987; Maynard and Hodge, 1949; Stokinger, 1981). As previously discussed, many of these compounds are laboratory reagents and industrial chemicals and are absent from the military environment. As such, they are not relevant to the discussion of health effects related to the military use of DU.

Uranium dissolved in blood circulates bound to erythrocytes, as a complex with transferrin and other plasma proteins, and as diffusible complexes with low molecular weight, ligands (Voegtlin and Hodge, 1949; Hursh and Spoor, 1973). Diffusibility implies also that these compounds are filtered in the glomerulus. The carbonate-bicarbonate complexes are of special importance, but it is likely that complexes with glutathione and other sulfhydryl compounds also exist (Voegtlin and Hodge, 1949; Hursh and Spoor, 1973).

The kidney (see Figure 2.1) is considered the target organ for uranium for chemical toxicity. The primary renal site of action of uranium is the proximal tubule where proton secretion degrades the bicarbonate complex of the uranyl ion, permitting the uranium to react with apical cell membranes of the tubular epithelium. This view is supported by the observation that alkalinization of urine increases urinary uranium excretion. It has not been established whether the reaction between uranyl ions and the cell membrane directly interferes with membrane function, as has been reported in yeast, or whether the primary target of the metal lies inside the renal cell.

Like mercury, cadmium, and other heavy-metal ions, excess uranyl ions depress glomerular function, tubular secretion of organic anions, and reabsorption of filtered glucose and amino acids in the proximal tubule, and the function of the more distal nephron segments (Bowman and Foulkes, 1970). The biological oxidation of uranium compounds to the divalent uranyl cation of hexavalent uranium has already been mentioned. The uranyl ion, in turn, forms a variety of salts and biological complexes, chief among which are the carbonate compounds.

Although there is no assurance that the toxicity of uranium is the same in various tissue compartments, the overall maximum permissible (renal) concentration (MPC) has frequently been suggested to be 3 µg uranium/g kidney (Voegtlin and Hodge, 1949; Hursh and Spoor, 1973) (See Chapter One, "Recommended Kidney Concentration," p. 11, for more information). The MPC is defined here as that metal concentration in the kidney associated with a significant increase of the frequency of kidney malfunction, such as proteinuria and glucosuria. However, limited confidence can be attributed to the
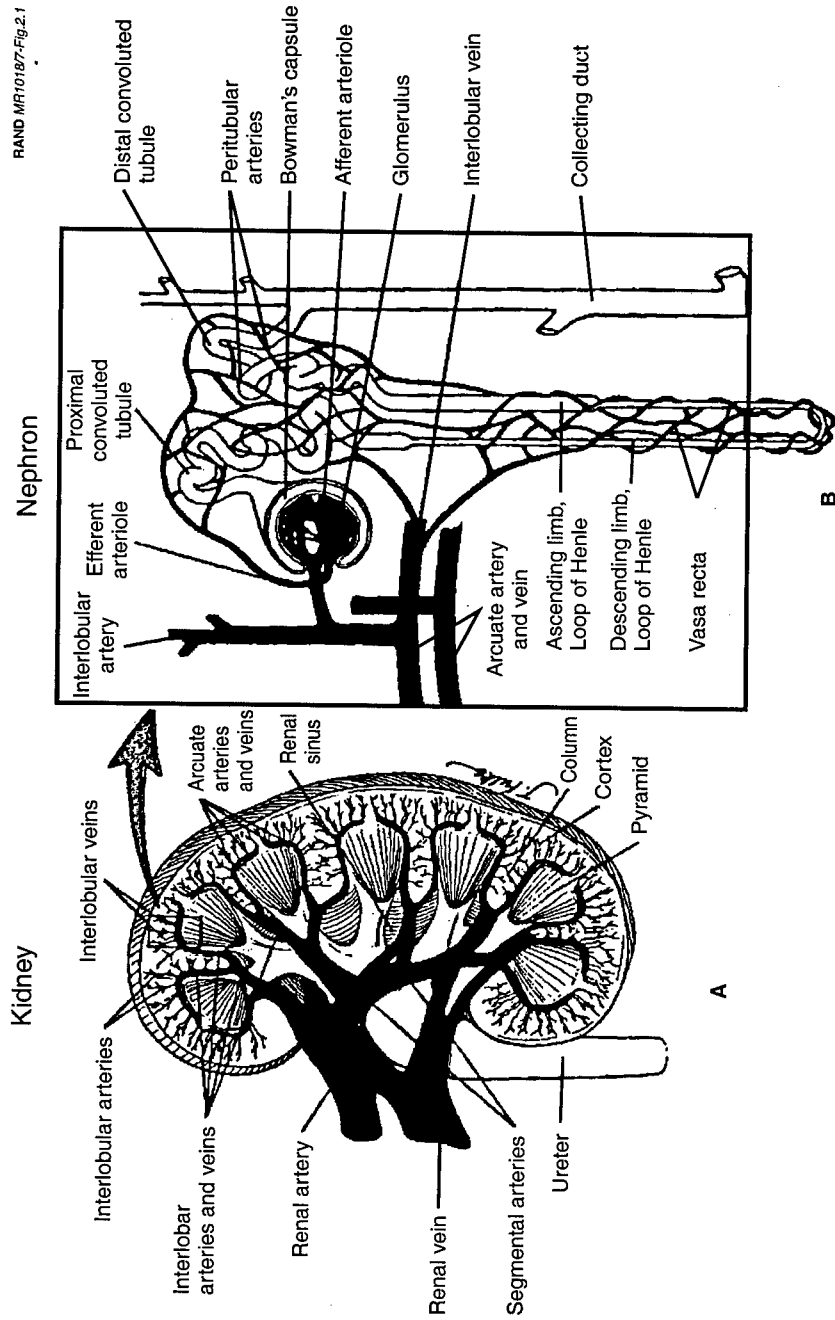
Figure 2.1—Human Kidney and Nephron

SOURCE: Seely et al., 1989.

significance of that figure for the general population for several reasons.[1] In fact, it is difficult to define a unique MPC of uranium in the kidney that will be valid for all types of exposure of differing populations. In spite of the incomplete justification for a unique MPC of uranium in the kidney, existing guidelines based on the figure of 3 µg per gram kidney have appeared to protect at-risk human populations adequately (see below, "Inhalation—Chemical Toxicity").

The schematic in Figure 2.2 depicts how uranium interacts with the body. Inhaled, ingested, or embedded fragments reach the blood after solubilizing either at the site of entry or at some other location in the body where they end up. For instance, some inhaled uranium enters the blood from the lungs, and some of the uranium originally in the lungs ends up in the gastrointestinal tract as a result of mucociliary clearance from the respiratory tract and subsequent swallowing. Uranium then accumulates to some degree in all organs. As discussed, the major portion of uranium in blood is excreted in the urine, with the remainder distributed mostly to bone and soft tissue.[2] There are few data to show the content and distribution of uranium in human tissue from inhalation and ingestion from natural sources. Fisenne et al. (1988, 1993) summarized all of the published data for uranium in human tissue and blood. The measurements are shown in Table 2.1. The normal range for the total mass of uranium in a human being is 2-62 µg (ERDA, 1975; USUR, 1984; Wrenn, 1985; Fisenne, 1986; Fisenne, 1994).

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[1] Reasons: The direct determination of MPC did not measure a steady-state concentration level, but was based on postmortem analyses, which summarized a range of studies on patients (Hursh and Spoor, 1973). The results may, therefore, bear little relationship to the concentration at which damage would first become overt in otherwise healthy individuals. It further ignores the likelihood that, as with other metals, the damaged kidney may lose uranium at an accelerated rate. Nor does the estimate recognize the fact that renal uranium appears to be present in more than one kinetic pool. The anatomical, morphological, and chemical definition of these uranium pools, or their toxicological significance, remain to be elucidated. Further, distribution of uranium between such pools may be affected by the rate and duration of exposure and other factors. Indeed, the distribution of some heavy metals in the body is known to be influenced by total dose and the rate and route of administration (Aungst, 1981). This presumably is due to the nonlinearity of the processes of metal absorption, distribution, and excretion. Possible changes in compartmentation of uranium in the body as a function of dose and rate, route of its administration, and the possible influence of compartmentation on toxicity have not systematically been explored. Finally, the suggested MPC of uranium ignores the possibility of repair and acquired tolerance. In work with experimental animals, renal change following exposure to uranium has frequently been observed at levels well below the guidance figure of 3 µg per gram (Foulkes, 1990). Present AFRRI studies are also finding acquired tolerance and no adverse renal effects in rats exposed to high levels of DU. The ACGIH today uses threshold limiting value (TLV) for the maximum permissible concentration for inhaled uranium (ACGIH, 1993).

[2] Deposition of the uranyl and other heavy-metal ions in bone is believed to involve competition with calcium for reaction with superficial phosphate groups. Some heavy-metal ions also replace calcium in the crystal structure of bone (Voegtlin and Hodge 1949; Hursh and Spoor, 1973).

RAND *MR1018/7-Fig. 2.2*
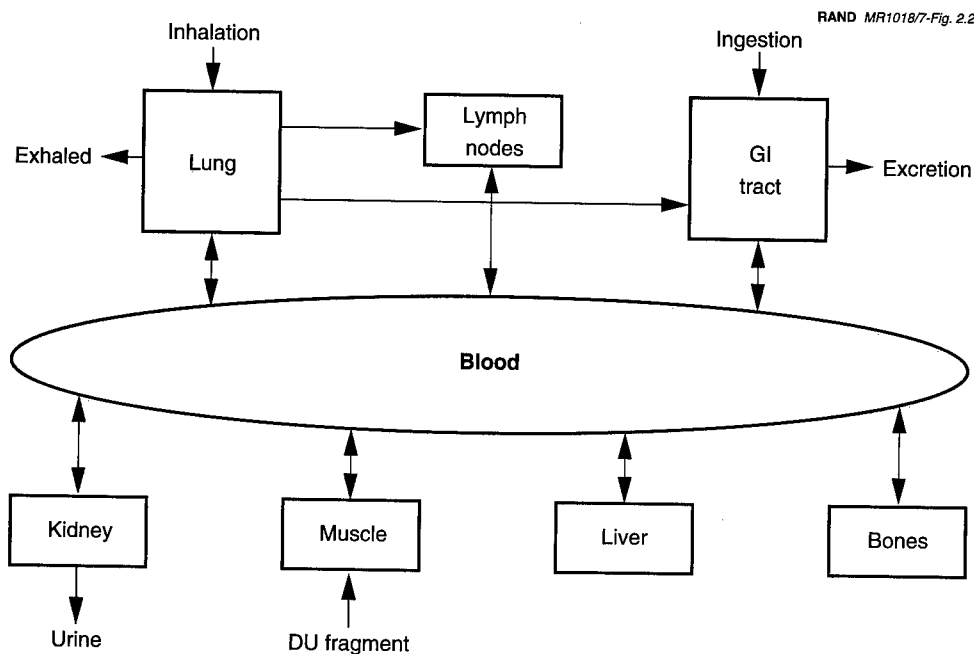
Figure 2.2—Compartmental Model for Internalization of Depleted Uranium

Bone ash data provide an insight into the amount of natural uranium inhaled and ingested in various countries because in a steady state (see Figure 2.2) the percentage going to bones is known. *In spite of large differences across countries, we do not observe known adverse health consequences as a result of these differences.* Because the radiological effects of DU are less than those of natural uranium and the chemical effects are identical, we can infer that exposure to DU at these levels would also have few health effects on a population.

The large variation in skeletal uranium content in the United States and other countries demonstrates the difference in daily uptake, mainly from drinking water. This suggests that baseline urinary excretion in the normal population varies widely, and excretion data for exposed persons should be interpreted against a suitable control group.

A plot of the data for uranium in bone ash for the 12 countries is shown in Figure 2.3. The bone ash data fit a log-normal distribution better than a normal distribution. The geometric mean is 7.3 μg/kg ash (88 mBq ^{238}U/kg ash), with a geometric standard deviation of 4.2, indicating a very skewed distribution. This spread is related to dietary habits and to the water concentration in particular. The arithmetic mean of bone ash data is 11 ± 11 μg/kg ash (130 mBq ^{238}U/kg

Table 2.1

Uranium Concentration in Human Tissues and Blood

Country/Locale	References	µg U per kg Wet Tissue or Blood					
		Lung	Liver	Kidney	Muscle	Fat	Blood
Australia: 5 cities	Fisenne et al., 1984						
Austria: Unknown	Hoffman, 1942			5			0.23±0.18
Brazil: Sao Paulo	Fisenne and Perry, 1980						
Canada: 5 cities	Fisenne and Perry, 1980						
England: London	Hamilton, 1972		0.25		0.19	0.6	0.69±0.45
India: Bombay	Ganguly, 1970; Parshad et al., 1980			2.2			1.3±0.3
Japan: Tokyo 4 cities Tokyo	Igarashi et al., 1985 Nozaki et al., 1970 Ikeda et al., 1977	170	0.24	0.34	0.43		0.64±0.65
Nepal: Katmandu	Fisenne et al., 1984						
Nigeria: Lagos	Fisenne and Perry, 1980						
USSR: Moscow Moscow Minsk	Fisenne et al., 1984 Drutman and Mordasheva, 1985 Malenchenko et al., 1972	 5.4±0.8 6.8±0.5	 11±1.5 5.8±0.6	 5.3±0.9 5.5±0.6	 6.5±1.0 7.7±1.1	 1.9	 1.1±0.02
United States: New York Illinois 5 regions Pennsylvania Utah Colorado Wisconsin	Fisenne and Welford, 1986 Fisenne and Perry, 1985 Lucas, 1983 Broadway, 1983 Singh et al., 1986 Singh et al., 1986 Singh et al., 1986 Fisenne and Perry, 1980	0.50±0.39 1.17 1.02 1.02	0.20±0.31 0.12 0.33 0.30	0.43±0.26 0.39 0.90 1.00			0.14±0.09 0.1
Yugoslavia: Unknown	Picer and Strohl, 1968						0.45
All: n=		7	8	9	4	2	8
Mean + SD		2.5±2.5	2.3±4.0	2.3±2.3	3.7±4.0	1.3±0.9	0.58±0.44
Range		0.50–6.8	0.12–11	0.34–5.5	0.19–7.7	0.6–1.9	0.1–1.3

Table 2.1—Continued

Country/Locale	Bone	Bone Type	Bone Ash (µg U/kg)	MM[b]	Ratio Bone/Blood	Ratio Liver/Kidney
Australia:						
5 cities	0.49±0.36	FRV (8)	3.5±2.6	3		
Austria:						
Unknown	0.53	F(1)	1.5	1	2.30	
Brazil:						
Sao Paulo	7.7±1.1	F(2)	22±3	3		
Canada:						
5 cities	2.5±2.0	V(10)	18±14	3		
England:						
London	3.5±0.9	6 types (61)	23±6	2	5.07	
India:						
Bombay	5.3	?(ng)	21	2	4.08	
Japan:						
Tokyo	0.75±0.29	FRS(17)	2.5±1.3	2		1.42
4 cities	2.2±0.4	RS1(46)	8.6±1.4	4		
Tokyo	2.7±1.9	FMRS(21)	8.8±9.1	2	4.22	
Nepal:						
Katmandu	2.2±1.0	V(9)	16±7	3		
Nigeria:						
Lagos	7.1±0.6	V(3)	51±4	3		
USSR:						
Moscow	2.7±0.1	5 types (2)	11±1	3		
Moscow	3.6±1.8	5 types (152)	15±5	1	3.27	0.48
Minsk	5.5±2.0	RS(30)	18±7	1		0.95
United States:						
New York	0.33±0.20	V(58)	2.4±1.4	1	2.36	2.15
Illinois	0.25±0.30	?(33)	1.7±2.0	2	2.50	
5 regions	0.82±0.60	V(10)	5.5±4.0	3		3.25
Pennsylvania	0.39	V(13)	2.6	3		
	0.67	R(13)	2.7	3		2.73
Utah	0.61	V(53)	4.0	3		
	1.7	R(53)	6.8	3		3.33
Colorado	0.92	V(19)	6.1	3		
	1.9	R(19)	7.7	3		
Wisconsin	1.2±0.3	Sk(6)	4.9±1.1	3		
Yugoslavia:						
Unknown	0.10	?(ng)	0.41	4	0.22	
All: n=	26		26			
Mean + SD	2.4±2.3		11±11			
Range	0.10–7.1		0.4–51			

[a]Bone type and number of measurements: F = femur, M = mandible, R = rib, S = skull, Sk = blended skeletons, St = sternum, V = vertebrae, ? = unspecified. The number of measurements is given in parentheses; ng = not given.

[b]MM = Measurement method: 1 = fluorimetry; 2 = fission track; 3 = alpha spectrometry; 4 = neutron activation analysis; 5 = gamma spectrometry. The percentage of dry ash used to convert values given in mass or activity per kg wet weight for the various bone types were sternum and vertebrae = 5%; rib = 25%; femur, mandible, and skull = 35%; unspecified = 25%. The standard deviations noted in the table were either given by the author(s) or calculated from the published data. In some cases only a mean value without a standard deviation is given.
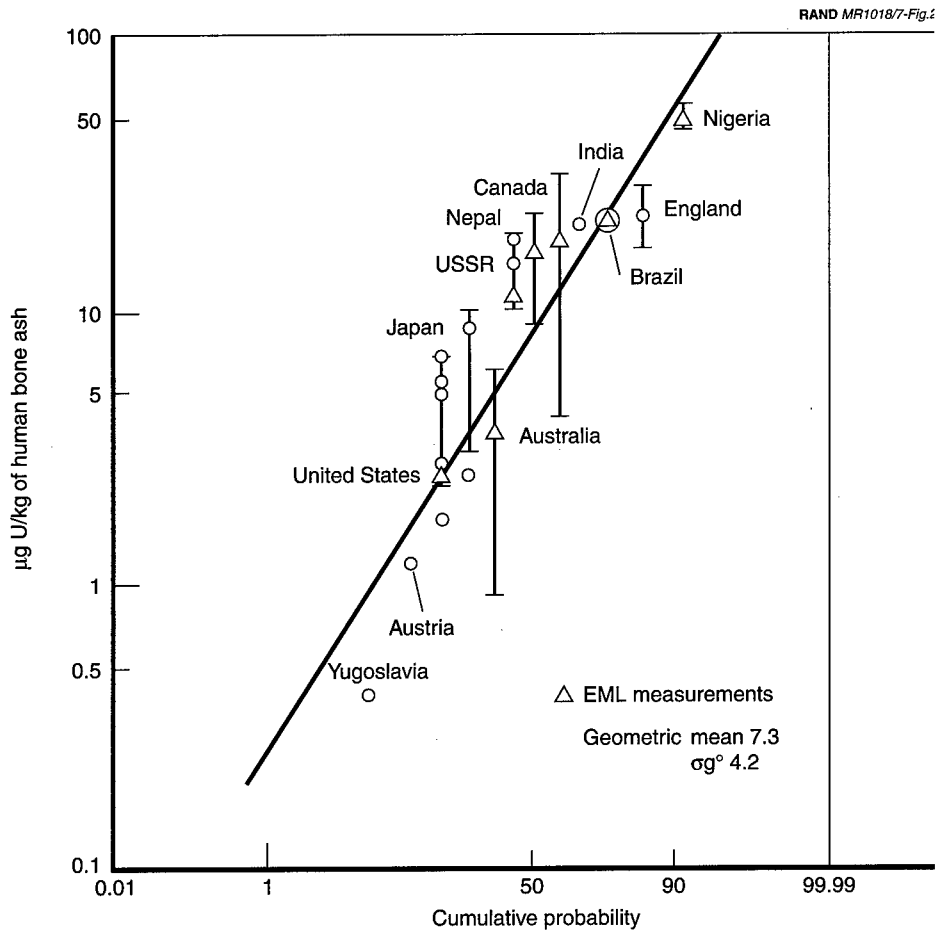
Figure 2.3—Cumulative Frequency Distribution of Natural Uranium in Bone Ash

ash) with a range of 0.4 to 51 µg/kg ash (5 to 610 mBq ^{238}U/kg ash). In short, bone ash data provide an insight into the amount of uranium that naturally distributes in the bone in various countries. We find a 100-fold difference across countries, with concentrations increasing with age. These data show that what is high in one area may be normal in another but that areas with higher rates do not have known resulting adverse health consequences. Given that depletion of uranium does not alter its chemical properties, and that radiation from DU is less than from natural uranium, exposure to DU at these levels would appear not to have known adverse health consequences.

Uranium was reported in tissue samples of lung, kidney, skeleton, and liver from an urban population in Bombay, India (Dang et al., 1995). The measurement was by neutron activation and gamma ray counting of the Neptunium-239 (^{239}Np) fission product. The arithmetic and geometric mean organ burdens reported are shown in Table 2.2. The reported concentration for 15 samples of skeleton tissue is 0.56 μg U/kg wet weight (7 mBq ^{238}U/kg wet weight), with a range of 0.1 to 1.6 μg U/kg wet weight (1 to 19 mBq ^{238}U/kg wet weight).

To compare the skeletal value with the data for Bombay in Table 2.2, the wet weight is about 2 μg U/kg ash weight (25 mBq ^{238}U/kg ash), or a factor of ten below the Bombay value reported earlier. The reason for this is not known. It suggests that given the skewed nature of uranium distribution in bone large numbers of samples are needed to provide a reliable estimate of the mean value. Clinically, uranium exists in small amounts in all organs, and no radiological or toxicological effect is observed. Note that the concentration here is far below the 3 μg U/g of kidney de facto standard.

Table 2.2

The Concentration of Uranium in Different Human Tissues in an Urban Population in Bombay, India, Compared with Literature Values (in μg U/kg wet weight)

Tissue	Literature Range[a]	Mean (Bombay)	SD (Bombay)	Geometric Mean (Bombay)	Geometric Standard Deviation (Bombay)
Lungs	0.34–3.60 (15)[b]	1.45	1.00	1.13	2.0
Kidneys	0.11–2.54 (15)	0.81	0.76	0.57	2.6
Skeleton	0.10–1.63 (15)	0.56	0.45	0.40	2.4
Liver	0.016–0.34 (15)	0.12	0.11	0.08	3.3
Heart	0.07–0.40 (12)	0.18	0.12	0.19	2.6
Muscle	0.003–0.22 (15)	0.09	0.07	0.06	2.7

SOURCE: Dang et al., 1995.
[a]Literature values from Fisenne, 1986; Igarashi, 1985; Hamilton, 1972; Wrenn, 1985.
[b]Number of samples is in parentheses.

A measurement of the uranium concentration of 83 μg U/kg bone ash (1,000 mBq ^{238}U/kg ash) from Beijing residents was reported by Lianquing (1988). This point, if added to the original published data in Table 2.1, would be the highest reported concentration in bone ash to date. The water in Beijing is also elevated in ^{238}U, with intake estimated at 110 mBq/day.[3]

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[3]The published data are reported in various units, particularly the skeletal values. The reported concentration units are in micrograms or mBq, per unit wet weight, per unit dry weight, per cubic centimeter of wet bone, per unit ash weight, or per gram of calcium. In some cases it is not stated whether the bone marrow was removed. It is of value to convert across the various units to compare data, and data for different bone types. It is necessary to convert to activity per unit wet bone when estimating radiation doses to cells on bone surfaces, the targets for carcinogenesis. The

One study was performed on tissue samples separated by age to investigate whether there is an age dependence of uranium in the available organs (Fisenne, 1986) (see Figure 2.4). There were 27 lung, 58 vertebra, 27 liver, and
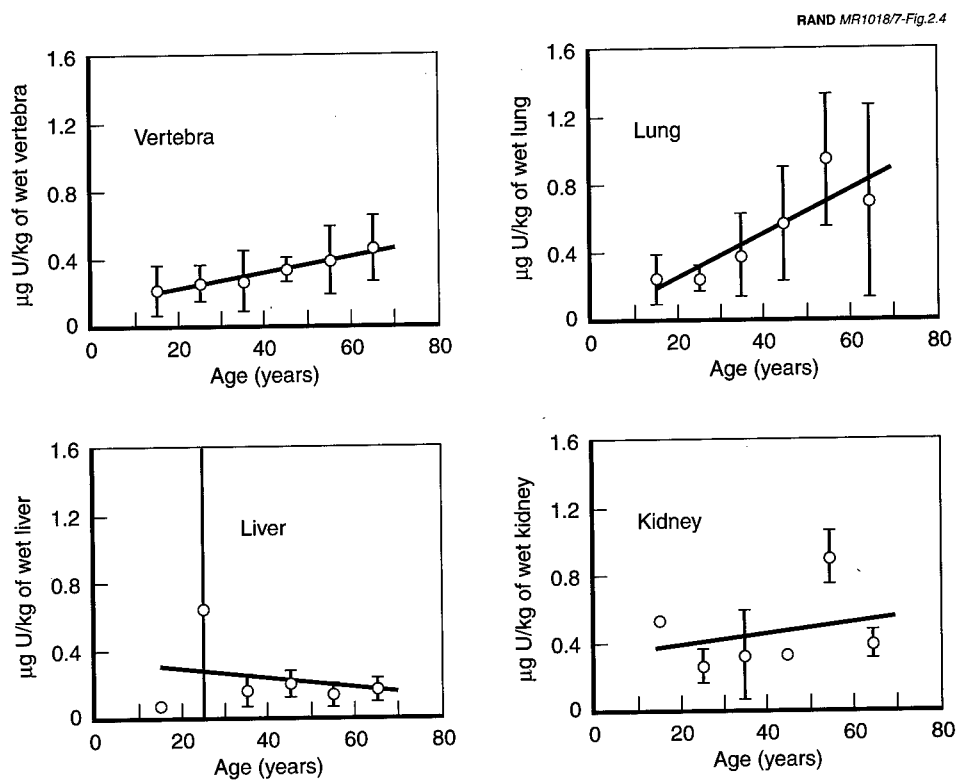
SOURCE: Fisenne, Welford, 1986.

Figure 2.4—Natural Uranium Concentrations as a Function of Age in Human Organs and Bones in New York City

following data apply for osseous tissue (i.e., bone with normal water content in hydroxyapatite plus the collagen matrix) (Fisenne et al., 1988).

F_a = calcium content of bone ash (0.37 g Ca/g ash measured, value for all bone types)

F_{ap} = Calcium in hydroxyapatite (0.40 g Ca/g hydroxyapatite ($Ca_{10}(OH)_2(PO_4)_6$)

F_{db} = Fraction of hydroxyapatite in dried (marrow-free) bone. Measured values include 0.57 for rib, vertebra; 0.70 for femoral shaft (Woodard, 1962)

F_w = Gram dry osseous tissue per gram wet osseous tissue (0.86 for rib, 0.88 for femur) (Gong et al., 1965)

F_d = Mass density of osseous tissue (1.92 g/cm³ for rib and vertebrae, 1.99 g/cm³ for femoral shaft) (Gong et al., 1965)

The adult male and female skeletons contain 5.0 and 4.0 kg of osseous tissue, respectively (ICRP, 1975).

12 kidney samples from New York City accident victims, ranging in age from 14 to 73 years. The data were combined into six age groups. The results are shown in Table 2.4. There was no statistically significant difference due to sex. The analysis of variance of the uranium concentration in lung and vertebrae showed an increase in the means with age at the 95 percent confidence level. There was a threefold increase in lung concentration and twofold increase in the vertebra concentration over the age range. The relatively large increase in lung concentration with age probably indicates that the inhalation intake is retained in the pulmonary lymph nodes for long periods (Fisenne, 1986). There is no statistically significant difference in uranium concentration among bone types (i.e., vertebra, rib, femur) (Harley, 1990).

Figure 2.5 shows the average distribution of ^{238}U in the body from chronic intake, calculated from Table 2.1 and standard organ weights (Fisenne, 1993). The organ contents in decreasing amount are skeleton (380 mBq), muscle (132 mBq), fat (110 mBq), blood (25 mBq), lungs (12 mBq), liver (5.4 mBq), and kidneys (2.4 mBq). The total body content is 670 mBq (56 μg).

Several authors note that the log normal distribution of uranium in bone seen in Figure 2.3, with a range of over a factor of ten, does not agree with the

SOURCE: Fisenne, 1993.
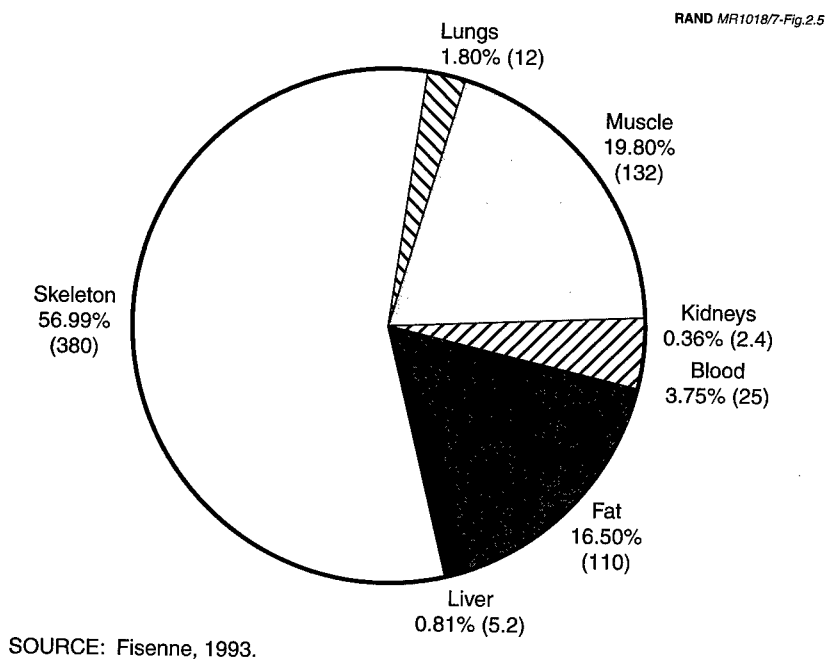
Figure 2.5—Distribution of Naturally Occurring ^{238}U in the Human Body (mBq)

reported range of dietary intake of only a factor of three. The reason for this is not known but probably represents the influence of water on the total uranium intake.

Following exposure to uranium and its distribution among various body compartments, or pools, uranium disappears from various tissues at different rates. The half-life in bone is approximately 300 days while in blood it is less than one-half day (Hursh and Spoor, 1973). In the lungs (Eidson, 1994), retention of uranium depends on the solubility of the various oxides to which the lung is initially exposed. Even within some tissues, the uranium is distributed between compartments and exhibits a range of half-lives. Renal uranium, for instance, is lost at rates reflecting its presence in at least two distinct kinetic pools, one with a relatively short half-life of around six days and a second one with an indeterminate half-life (Hursh and Spoor, 1973). This conclusion is complicated by the likelihood that, as with other metals, the onset of renal damage will decrease the retention time of uranium.

Inhalation

Uranium is present in limited concentrations in the air we breathe. The origin of this uranium may be natural, or it may result from such human activities as the combustion of fossil fuel. Background inhalation was estimated from measurements in filtered air samples in New York City (Fisenne, 1987).[4] Annual inhalation intake of natural uranium totaled about 14.7 mBq/year (Fisenne, 1987).[5] This agrees well with the average age-weighted annual intake of 14.2 mBq/year reported in UNSCEAR (UNSCEAR, 1993). (See Appendix F for UNSCEAR intake tables.)

Very little of the amount of natural uranium that is inhaled eventually reaches the kidney. This is because the body is amazingly efficient at clearing alien

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[4]The trend of uranium in air has been observed from 1978 to 1993 (Stevenson and Pan, 1996). The EPA has monitored total isotopic uranium in air in 25 U.S. cities in their Environmental Radiation Ambient Monitoring Program (ERAMS). It is interesting to note that there is a noticeable reduction in the ERAMS uranium air concentration measurements at six of these cities by a factor of four over the period from 1978 to 1993 (from 4 to 1 μBq/m^3). The reason for this is not known; however, the reduction may be associated with lower use of certain fuel types, such as coal. Some airborne uranium is of volcanic origin; eruptions such as Mount St. Helens threw enormous amounts of matter into the stratosphere. This component would be diminishing at the same rate as that observed for nuclear weapons fallout, or about a five- to six-year half-life in the stratosphere.

One of the ERAMS sites, Lynchburg, Virginia, showed a significant increase in the ^{234}U/^{238}U ratio as well as the total uranium activity (about 9 μBq/m^3 versus the normal 1 to 3 μBq/m^3). The addition of a maximum of 1 percent enriched uranium from a local nuclear fuel facility was postulated.

[5]Data calculations use data in Table 4 times 365 days. Total annual intake calculation: 14 mBq/year = [1.22 mBq/day from ^{238}U + 0.019 mBq/day from ^{234}U + 0.0007 mBq/day from ^{235}U] x 365 days/year.

substances through a variety of mechanisms. Of the natural uranium inhaled, 75 percent is exhaled and only 25 percent is retained in the lungs. Of the 25 percent uranium initially retained in the lungs, 80 percent is cleared by the bronchial mucociliary mechanism, which results in most of the natural uranium finding its way to the GI tract where most is excreted and only a fraction enters the bloodstream. Of the 20 percent deposited in the lungs that is not cleared by the mucociliary action, 15 percent ends up in the lymph nodes for a long period and 5 percent enters the blood (either directly from the lungs or from the GI tract or lymph system).[6] Then of the original 100 percent of natural uranium that entered the body via inhalation, less than 1 percent eventually makes its way to the kidney, where it might affect renal function (ICRP, 1995). Figure 2.2 shows a model of the basic features of distribution in the body following inhalation. Figure 2.6 below shows the percentage disposition of inhaled uranium.

In the military environment, DU inhalation exposure may contribute to the total uranium body burden and any health effects that may result from a sufficiently large body burden. When a DU penetrator strikes a hard target, it forms DU dust. From 10 to 35 percent of the original material is aerosolized and approximately 60 to 69 percent of the aerosolized fraction is respirable. From the heat of combustion as well as weathering, these small particles will eventually become oxidized, forming predominately depleted U_3O_8 but also small amounts of depleted UO_2 and depleted UO_3 (CHPPM, 1998). Most of the

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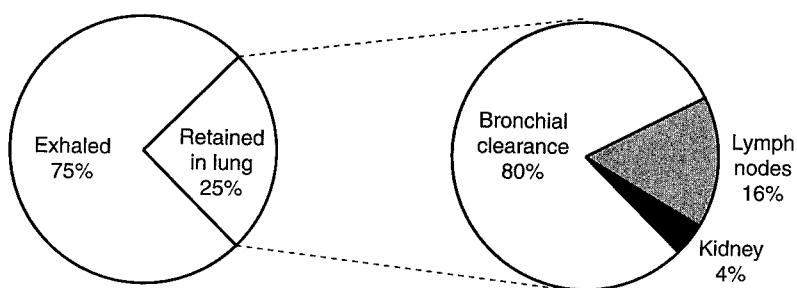
Figure 2.6—Distribution of Inhaled Uranium

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[6] About 10 percent of the amount inhaled is solubilized and goes to the blood where it is excreted or deposited in the kidney, liver, other organs, and the skeleton.

suspended aerosols will rapidly settle to the ground. Activity or surface winds may disturb the settled particles and resuspend and redistribute a fraction of them (see Appendix C).

As discussed, aerosolized particles from the impact are small enough to be inhaled. The primary hazard from inhaled uranium aerosols is related to the extent and rate of transfer of inhaled uranium to the blood and the presumed amounts reaching their primary targets in the kidney. Two factors will influence the degree of hazard: the site of deposition in the respiratory tract, dependent on the aerodynamic equivalent diameter (AED), and the fate in the lung, dependent on the physical and chemical characteristics of the particles, such as the solubility, exposed surface areas, and intercrystalline forces (Eidson, 1994). A radiation dose is delivered to the airways and lung while the uranium remains in the lung.

After inhalation, 95 percent of the larger (greater than 10 µm AED) particles are deposited in the upper respiratory tract (bronchioles, bronchi, trachea). The majority of these particles are cleared to the pharynx by the normal bronchial mucociliary clearance mechanism and swallowed or blown out of the nose. "As such, it is only the smaller respirable particles which represent a potential health hazard from inhaled (natural) uranium. As particle size decreases below 10 µm, deposition decreases in the extrathoracic and bronchial regions but increases in the bronchioles and alveoli (pulmonary regions) such that, at particle sizes below 0.5 µm, the alveoli represent the major site of deposition. Retention of particles in various lung compartments depends on the efficiency of the mucocillary clearance mechanism which decreases in the deeper portions of the lung, or by macrophage action and solubilization." (ICRP 1994.)

The percentage of DU aerosol particles that are respirable varies according to the circumstance by which it oxidizes. For particles generated by fire, the percentage smaller than 10 µm AED ranges from 0.1 to 33, while particles generated from impact of a hard target are virtually all smaller than 10 µm AED (CHPPM, 1998). It is the respirable particles that present a potential health hazard from uranium inhalation.

Respirable DU particles, i.e., particulate DU that reach the alveoli, may be cleared from the lungs by macrophage action or by solution and transfer into the blood. The alveolar epithelium is generally more permeable to dissolved heavy metals than is the intestinal epithelium. This may be related to various factors, such as greater leakiness of the gap junctions between cells, fluidity of cell membranes, relatively long contact time with alveolar tissue, and low concentrations of binding compounds in the alveolar fluids that would make the metal unavailable for absorption (see review by Foulkes, 1994).

Inhalation—Chemical Toxicity. Extensive information is available on the occupational exposure of workers in the uranium industry. These include workers in both uranium mines and in contractor facilities, where uranium was separated from the ore and uranium metal was produced for the enrichment process for nuclear weapons and nuclear fuel. Workers' exposure to uranium during the peak operational era was high in some cases. There were occupational guidelines and standards at the time; however, in many cases these standards were exceeded. Poldenak et al. (1982) report exposures of up to 9,000–10,000 µg natural U/m^3 at the Y-12 plant in Oak Ridge and at the Mallinckrodt plant (outside of St. Louis). No adverse health effects appeared in the uranium millers who worked with uranium and were exposed to levels of natural uranium far in excess of present standards.

There is, however, convincing evidence of excess lung cancer in underground uranium miners. It is well established that the carcinogenic agent in the mines is not the uranium ore but the gaseous decay products of radon-222. Radon has two alpha-emitting short-lived decay products that form in the air and deposit efficiently on the bronchial surfaces. Two publications showed that the lung dose from inhaled uranium ore was too low to be of significance relative to the bronchial dose from radon decay products (Harley et al. 1981, 1984).

Considerable effort has been devoted to the follow-up of 11 underground mining cohorts. The risk of lung cancer from ^{222}Rn exposure is now well quantified and provides the data that form the basis for the existing guidelines for indoor radon-222 (NCRP, 1984a, 1984b; NIH, 1994; NRC, 1988; NRC, 1998).

The mines also had other airborne substances, such as ore dust, blast fumes, and diesel fumes (in later years only). The literature indicates that the relationship of lung cancer risk across a broad spectrum of other air contaminants was similar only to exposure to radon-222; no other substance could be implicated (NRC, 1988). Smoking enhanced lung cancer risk in a submultiplicative manner such that for the same radon exposure, the risk of getting cancer among individuals who had ever smoked was twice as high as that of those who never had.

Data relating actual air concentration of uranium and urinary excretion are scant. One large study was conducted by the USAEC Health and Safety Laboratory in a uranium refinery in 1950 and 1951 (Lippman, 1964). Air and urine samples were taken in two plants. In Plant 1, UO$_2$ was hydrofluorinated to UF$_4$ and in Plant 2 the UF$_4$ was fluorinated to UF$_6$. The exposure in Plant 1 was mainly to UO$_2$ and UF$_4$, while in Plant 2 the exposure was to UF$_6$ and its hydrolysis product UO$_2$F$_2$.

Both plants operated 24 hours a day with four shifts of personnel. A urine-sampling program was initiated in 1950, with spot samples taken in pairs, one

at the end of the work week and one 48 hours later, just before the men returned to work. The urine-sampling program continued until late 1951 when both plants were permanently closed.

A comprehensive air-sampling program began in 1949 and continued until plant closure. For 1950 and 1951, there are air and urine data for the same group of men. Both general air and breathing zone samples were taken so that time-weighted average air dust exposures could be calculated for each man in the plants. During this period approximately 3,000 air samples and 1,000 urine samples were collected from the operating personnel (Lippman, 1959). The data were analyzed by Lippman (1964) and are shown in Figures 2.7 and 2.8 for both *soluble* and *insoluble* uranium.

RAND *MR1018/7-Fig.2.7*
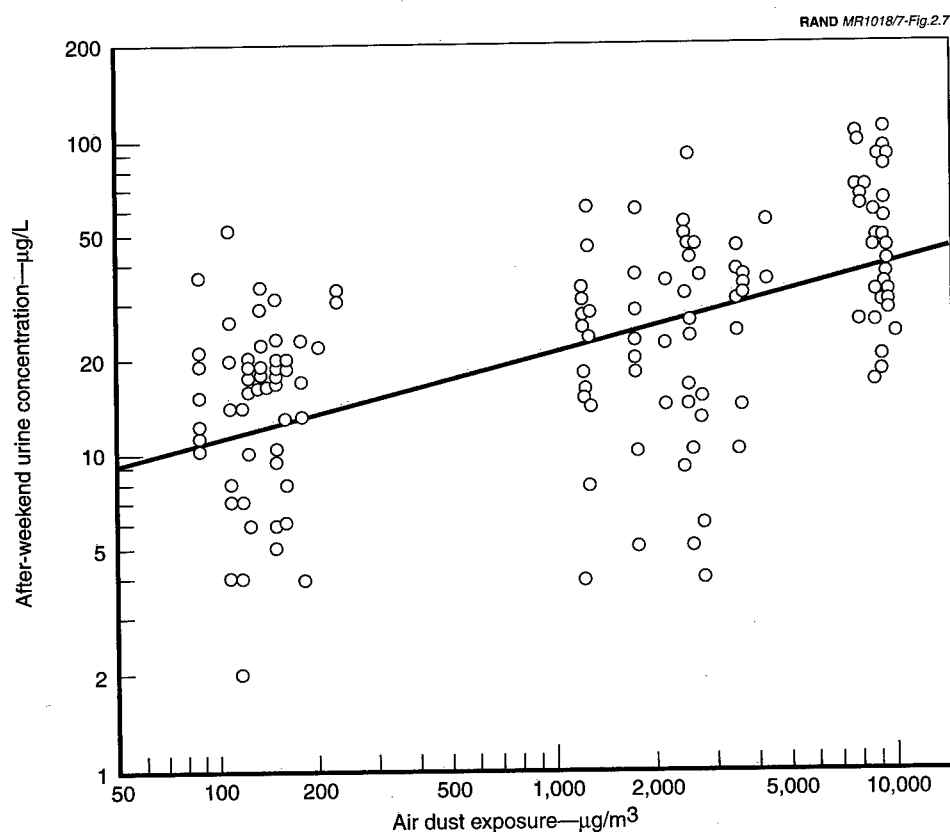
SOURCE: Lippman, 1964.

Figure 2.7—Exposure to *Insoluble* Uranium: Air Dust Exposure Versus After-Weekend Urine Concentration
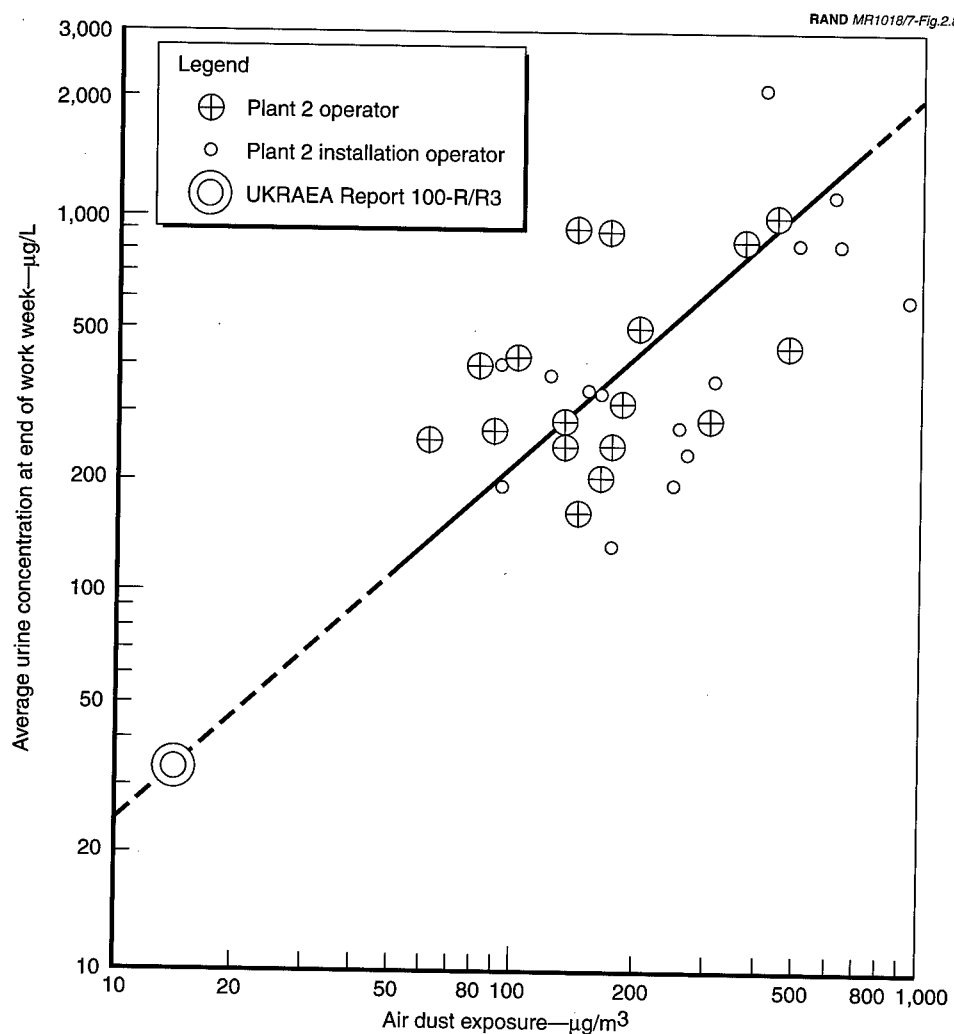
SOURCE: Lippman, 1964.

Figure 2.8—Exposure to *Soluble* Uranium Compounds: Air Dust Exposure Versus
Average of Before-Weekend Urine Samples

An excellent review of the uranium excretion data collected by the Health and
Safety Laboratory of the USAEC in contractor facilities was prepared by
Lippmann et al. (1964). They developed a generalized expression for urinary
excretion for any uranium compound as a function of time. The following ex-
pression described excretion well:

Excretion rate $y = At^B$,

where y = the excretion rate, t = time, and A and B are constants.

No increase in overall deaths has been observed as a result of exposure to uranium in several epidemiological studies of workers exposed to uranium in mills and metal processing plants (Archer, 1973a; Brown, 1987; Checkoway, 1988; Hadjimichael, 1983; Poldenak, 1981; Waxweiler, 1983). In one animal inhalation study examining the effects of UO_2, no increased mortality was observed at concentrations of 5 mg UO_2/m^3 for 5 years (Leach et al. 1970). However, exposure to extraordinarily elevated concentrations of uranium oxides much higher than occupational exposures has been found to induce mortality in animals (Rothstein, 1949; Leach et al., 1984). Rothstein observed increased mortality in a variety of animals exposed to 19 mg UO_3/m^3 for six hours a day, 5.5 days a week, for four weeks. Leach observed 50 percent mortality when rats were exposed to 8,114 mg U/m^3 for 10 minutes. The cause of death, in most cases, was chemically induced renal failure (Leach et al., 1984; HHS, 1998). These exposures are 50 to more than 100,000 times higher than the current maximum permissible concentrations for inhalation exposure to soluble and insoluble uranium compounds, set by the American Conference of Governmental Industrial Hygienists (ACGIH, 1993).

Equivocal evidence was found that associates uranium oxide exposure with hepatic effects. One study examining toxic effects in a variety of animals exposed to concentrations of 19 mg UO_3/m^3 for four weeks reported moderately fatty livers in some of the rabbits and rats tested, while other animals in the study exhibited no such effect (Rothstein, 1949). In another animal study, animals exposed to 22 mg UO_2/m^3 for 30 days showed no hepatic effects (Rothstein, 1949). Dygert (1949) found no hepatic effect in animals exposed to concentrations of up to 17 mg U_3O_8/m^3 for 26 days. Likewise, no hepatic effects were observed in animals exposed to 10 mg UO_2/m^3 for one to two years (Stokinger, 1953).

Hematological effects have been observed in uranium miners exposed to uranium for up to 20 years (ambient uranium concentrations were not noted). Vich and Kriklava (1970) observed small, but statistically significant, differences in hemoglobin concentration, hematocrit values, mean corpuscular volumes, and red blood cell counts. All values were still within normal limits, however, and no damage to red blood cell formation was observed. In another human study, there were no changes in hematological parameters associated with uranium dust (including UO_2) at concentrations ranging from 0.5 to 2.5 mg/m^3, and for short periods approaching 10 mg/m^3, for five years (Eisenbud and Quigley, 1956).

In another study, researchers found that rats exposed to a weighted mean of 19 mg UO_3/m^3 for four weeks (with short periods approaching 30 to 40 mg

UO_3/m^3) exhibited significant differences in myeloid and lymphoid cells of the bone marrow but found no significant hematological change. No causal association with uranium was inferred (Rothstein, 1949). Several other animal inhalation studies also found no hematological effects. Exposures as high as 22 mg UO_2/m^3 for 30 days or 17 mg U_3O_8/m^3 for up to 40 days in a variety of animal models found no adverse effects on the blood (Dygert, 1949; Rothstein, 1949; Leach, 1970, 1973).

Immune system effects have not been associated with inhaled uranium oxide exposure in uranium industry workers (Cragle, 1988). In corresponding animal studies, animals exposed to UO_2 dusts at a concentration of 5 mg U/m^3 for one to five years did not exhibit any pathologic changes in their spleens (Leach, 1970, 1973). Tracheobronchial lymph node fibrosis has been observed and is discussed in the next section, radiation toxicity.

No evidence was found showing an association between uranium inhalation and adverse effects on the nervous system (Kathren, 1986; USNRC, 1986; Zhao, 1990; Brown, 1987; Carpenter, 1988; Cragle, 1988; Poldenak, 1981; Reyes, 1984). There is no information on GI, musculoskeletal, cardiovascular, endocrine, or dermal toxicological effects of uranium oxides (HHS, 1997b). No significant adverse effects on body weight were observed in several animal inhalation studies (Dygert, 1949, Rothstein, 1949; Leach, 1970, 1973).

The issue of possible reproductive and developmental effects from natural uranium and DU is discussed in detail below (see "Reproductive Effects of DU," p. 63).

Uranium has been identified as a nephrotoxic metal in animals, similar to other heavy metals, such as cadmium, lead, and mercury (Goodman, 1995). Indeed, even though a large fraction of the total body burden of uranium following oral uptake may accumulate in the skeleton, the kidney is a major target organ for the metal, and renal shutdown is routinely observed following ingestion or injection of high doses of soluble uranium compounds, such as uranyl salts or ammonium diuranate. Lungs and tracheobronchial lymph nodes have been reported as containing the highest concentrations of uranium following prolonged inhalation exposure to natural uranium dust (mean concentration 5 mg natural UO_2/m^3, 1 μm mass median particle diameter). Dogs, monkeys, and rats thus exposed for as long as five years showed little evidence of serious injury (Leach et al., 1970). The uranium concentration in the lymph nodes exceeded that in kidneys by several orders of magnitude. Following a two- to six-year post-exposure period, dogs and monkeys showed no evidence of uranium toxicity evidenced in body weight, mortality, or renal histology (Leach et al., 1973). Renal malfunction following uranium inhalation, as further discussed below, has only been observed following much higher exposures.

Because the kidney is the target organ for the chemical effects of uranium, the most dramatic health effects are expected to be associated with the kidneys. Uranium has been identified as a nephrotoxic metal, although less so than cadmium, lead, and mercury (Goodman, 1985). In the nephron, uranium exerts its toxic effect mostly in the proximal tubules but also in the glomerulus and other areas of the tubules (Voegtlin and Hodge, 1949; Hursh and Spoor, 1973). In 1995, the Health Physics Society, on behalf of the American National Standards Institute, issued a *Bioassay Program for Uranium*. This report (HPS N 13.22-1995) suggests that 40 and 8 mg inhalation intakes of soluble uranium would be expected to behave as threshold intakes for inducing permanent and transient renal injury, respectively. However, many assumptions go into this estimate, e.g., lung deposition based on a default particle size of 1 μ AMAD and 50 percent absorption from the lungs (Health Physics Society, 1995). Therefore, values need to be adjusted to suit actual exposure scenarios.

The solubility of the uranium compound to which exposure has occurred affects the intake required to cause kidney damage. Uranium oxides (U_3O_8 and UO_2) are relatively insoluble compounds (Types M and S). As discussed, these uranium compounds are retained longer in the lungs and cause lower toxicity to distal organs such as the kidney than that observed with more soluble industrial compounds. Uranium trioxide is considered between Type F and M (Morrow et al., 1972).

Uranium mill workers occupationally exposed to elevated levels of "yellowcake" have also been studied. Yellowcake can be either ammonium or magnesium diuranate with a mixture of compounds with formal composition that ranges from $(NH_4)_2UO_4$ to $(NH_4)_2U_8O_{252}$ with approximate composition for ammonium diuranate of $(NH_4)_2U_2O_7$ (*Encyclopedia of Chemical Technology*, 1983). The study reported findings that indicate reduced proximal renal tubular reabsorption of amino acids and low molecular weight proteins. Concentration data were not obtained. This finding, including mild proteinuria, aminoaciduria, and a dose-related increase in clearance of ß-2 microglobulin relative to that of creatinine, correlated with the duration of uranium exposure (Thun, 1985).

In another study, renal injury was not observed in workers exposed to 0.5 to 2.5 mg/m³ of insoluble uranium dust, including UO_2, for about five years (Eisenbud and Quigley, 1956). The authors noted, "The negative findings relative to renal injury among workers exposed to insoluble compounds are particularly significant in view of the high levels of exposure reported."

In animal studies, solubility of the inhaled uranium compound dramatically affects renal outcomes. Although soluble uranium compounds, such as uranium halides, have caused renal damage, insoluble uranium oxides appear far

less toxic to the kidneys. A variety of animals exposed to UO_2 at a concentration of about 5 mg U/m^3 for up to five years did not experience renal damage (Leach et al., 1970, 1973).

Other animal studies did observe nephrotoxic effects. Minimal renal pathology was observed in animals exposed to 10 mg UO_2/m^3 for up to two years (Stokinger, 1953). Dygert (1949) observed evidence of renal damage as indicated by a moderate degree of regenerative tubular changes in some animals exposed to 17 mg U_3O_8/m^3 for 26 days. In earlier studies examining the toxic effects of uranium trioxide inhalation in a variety of animals, evidence for renal injury was observed only in rabbits at a concentration of 19 mg UO_3/m^3 for four weeks, or a concentration of 22 mg UO_2/m^3 for 30 days (Rothstein, 1949).

Human case studies from accidental and chronic exposure as well as animals studied demonstrate regeneration of the damaged tubular epithelium when exposure is discontinued and sometimes, in animals, despite continuation of exposure (Bentley, 1985; Dygert, 1949; Maynard, 1949; Stokinger, 1953, 1981; Rothstein, 1949; Kathren, 1986; Eisenbud and Quigley, 1956). It is not known whether this phenomenon is related to the acquisition of increased tolerance to uranium. The hypothesis that resistance to uranium may be provided by the induction of the metal-binding protein metallothionein, which has been implicated in increased resistance to some other heavy metals, has not been critically tested and supported.

The toxicological significance of results from work on the pulmonary route of uptake of particulate uranium is difficult to evaluate unless the amount of the inhaled material that finds its way into the GI tract can be estimated. The conclusion is justified, however, that relatively short-term exposure to uranium oxide particles at concentrations up to 10 mg per cubic meter of inspired air does not cause renal lesions.

The U.S. Transuranium Registry (Kathren, 1995; Kathren and Ehrhart, 1998) is conducting a study to obtain tissue at autopsy from workers exposed in facilities processing uranium. To date no long-term renal changes have been observed. Their publications provide an abundance of human tissue data.

Inhalation—Radiological Toxicity. Negative health effects resulting from the radiation effects of depleted or natural uranium have not been observed in humans. (See Appendix D for a discussion of single-particle lung dosimetry.) There is evidence of lung cancer in miners from epidemiological studies, but this is related to exposure to a combination of airborne short-lived decay products of radon and other air toxicants, such as silica dust, diesel fumes, and cigarette smoke (NCRP, 1978; NIH, 1994; NRC, 1988). Uranium mill workers have not shown excess lung cancer or other disease despite their increased ex-

posure to uranium and radon progeny. A population of workers was exposed to insoluble uranium dust (including UO_2) at levels of 0.5–2.5 mg U/m^3 with some exposed up to an estimated 10 mg U/m^3 for about five years. None of these workers were exposed to other potential irritants. They did not exhibit respiratory disease (Eisenbud and Quigley, 1956).

Lung damage resulting from inhalation of uranium oxides is usually noncancerous alveolar epithelium damage of type II cells. The responses to chronic injury are hyperplasia, hypertrophy, and metaplasia (HHS, 1997b). In animal studies, lung and tracheobronchial lymph node fibrosis was reported in animals exposed by inhalation to 5.1 mg UO_2/m^3 (3.4 nCi/m^3) for three years (Leach et al., 1970).

Animal studies have also examined pulmonary damage from exposure to uranium oxides. Exposure to 5 mg UO_2/m^3 for more than three years did not result in damage to the lungs, but minimal fibrosis, suggestive of radiation injury, was occasionally observed in the tracheobronchial lymph nodes of dogs and monkeys and lungs of monkeys (Leach et al., 1970, 1973). Alpha radiation doses were estimated to have been greater than 500 rads in the lungs and greater than 7,000 rads in tracheobronchial lymph nodes. Lung fibrosis is consistent with relatively short-term high exposure rate in animal experiments.

Stokinger (1953), on the other hand, found that exposure to concentrations up to 10 mg UO_2/m^3 for up to one year was tolerated by dogs. Likewise, Dygert (1949) observed no evidence of injury to the lung resulting from exposure to 17 mg U_3O_8/m^3 for 26 days. Only very slight pulmonary change was observed in dogs and rats exposed to 19 mg UO_3/m^3 for four weeks.

Cancer rates in populations of highly exposed uranium industry workers have been examined. The rate of lung and skin cancer in these highly exposed populations was investigated in a follow-up study of mortality. Among 18,869 white males employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge, Tennessee, no excess cancers were observed through 1974 (Poldenak, 1981). This study, carried out at Oak Ridge National Laboratories, continues. Several other published epidemiological studies of uranium mills and metal processing plant workers have either found no excess cancer or documented that excess lung cancer was attributable to other known carcinogens (radon and its progeny and cigarette smoke) rather than uranium (Poldenak, 1981, 1982; Cragle, 1988; Reyes, 1984; Saccomanno, 1982; Hadjimichael, 1983; Carpenter, 1988). Although not statistically significant, a dose-response relationship between lung cancer and cumulative gamma radiation in a nuclear materials fabrication plant was noted by Checkoway (1998). (See Appendix E for a discussion of risks associated with radon exposure.)

Osteosarcoma (bone cancer) has been examined in the human studies. No association between osteosarcoma and uranium exposure was reported (Archer, 1973a; Cragle, 1988; Poldenak, 1981, 1982; Reyes, 1984; Saccomanno, 1976; Hadjimichael, 1983). Two studies link lymphatic malignancies to uranium exposure in uranium millers, but the authors suggest that 230Th (thorium-230), rather than the uranium, was the causative agent (Waxweiler et al., 1983; Archer, 1973b). Cragle (1988) observed an excess in leukemia deaths but was unable to determine if there was an association with radiation. A variety of cancers, including leukemia and carcinoma of the lungs and kidney, developed when rats were exposed to enriched uranium (92.8 percent ^{235}U). However, because DU is orders of magnitude less radioactive than enriched uranium, these data are of little relevance to possible radiation-related health effects of DU exposure.

High exposure to radiation may also be nephrotoxic (Goodman, 1985). Evidence in the mouse and dog suggests that combined alpha irradiation from enriched uranium and metallotoxicity may produce a greater nephrotoxicity than doses of either separately (Wrenn et al., 1987). Likewise, some evidence suggests that enriched uranium may affect the immune system (Morris et al., 1992). However, there is no evidence that natural or depleted uranium has the capacity to induce this toxicity.

GI effects resulting from high levels of inhalation have been reported. In a case study, a male worker at a uranium-enrichment plant was accidentally exposed in a closed room to inhalation of a high concentration of UF4 (estimated radioactivity of 187 nCi/m^3) for about five minutes. Six days after the accident, the patient reported dizziness, nausea, and loss of appetite. On the ninth day after the accident, the clinical findings were loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool. By the thirtieth day after the accident and at follow-up seven years later, all clinical findings had returned to normal (Zhao and Zhao, 1990). The clinical findings were undoubtedly due to the chemical effects of UF$_4$. In corresponding animal studies, exposure to enriched uranium damaged elements of the GI tract.

The issue of reproductive effects of inhaled uranium is discussed below (see "Reproductive Effects of DU" p. 63).

To summarize, cancer is the only radiation-associated disease that has been shown to be related to inhalation of radioactive particulates. For external gamma ray radiation, such as to atomic bomb survivors, there is a linear relationship with increasing dose yielding increased cancer risk. The best estimates are that a whole body effective dose of 1,000 mSv yields a cancer risk of about 4 percent. However, no evidence is documented in the literature of cancer or any other negative health effect related to the radiation received from exposure to

natural uranium, whether inhaled or ingested, even at very high doses. The biological properties of uranium in the body and its absorption from the GI tract are reasonably well known from occupational exposures, studies of normal environmental intake, and animal studies.

The radiation dose can be calculated for any body organ given the amount in the organ. Based on the distribution in the body and the known body organ content, no health effects from radiation would be expected even for high occupational exposures. This results mainly because of the low radioactivity of natural uranium and the inability to get enough into the body to deliver a radiation dose that could be significant in causing cancer. The same would be true for DU.

Natural uranium is inhaled daily in very small amounts by all persons. Estimates made from measurements of air concentrations in New York City show that about 1 μg of uranium is inhaled each year by each person. The source of this uranium is mostly resuspended soil particles of very small diameter.

It is important to note that 99 percent of the mass or weight of natural uranium or DU is always associated with the ^{238}U isotope and not the other isotopes of uranium (^{234}U, ^{235}U). Its low radioactivity per unit weight results from the much longer half-life of ^{238}U compared with that for the other two isotopes. Thus, in order to inhale a significant quantity of radioactivity, the air concentration must have large enough mass to be visible.

Any atmosphere considered dusty contains at least a few milligrams of mass per cubic meter (mg/m^3 equals 1,000 $μg/m^3$), and the particles can usually be seen. Occupational uranium exposures of this kind have occurred, for example, when uranium metal was handled by a worker and exploded on contact with air. These extraordinary exposures resulted in inhalation of tens of milligrams of uranium. The uranium in these cases was rapidly excreted in urine, with more than 99 percent excreted in less than one week, and no subsequent health effects or cancer have ever been seen (see Figure 2.9).

A great deal can be learned about radiation dose and organ and tissue retention from the natural uranium content of the body. This uranium is obtained normally throughout life both from daily inhalation intake and through ingestion of food. These data show quantitatively the steady-state tissue concentrations from continuous intake from sources that cannot be avoided.

For example, the inhalation intake from breathing New York City air was measured as about 1 μg per year, and the uranium is known to be in an insoluble form (see Figure 2.4). Figure 2.4 shows the uranium lung tissue concentration in the lungs as a function of age. Over a 40-year period, the lung content

RAND *MR1018/7-Fig.2.9*
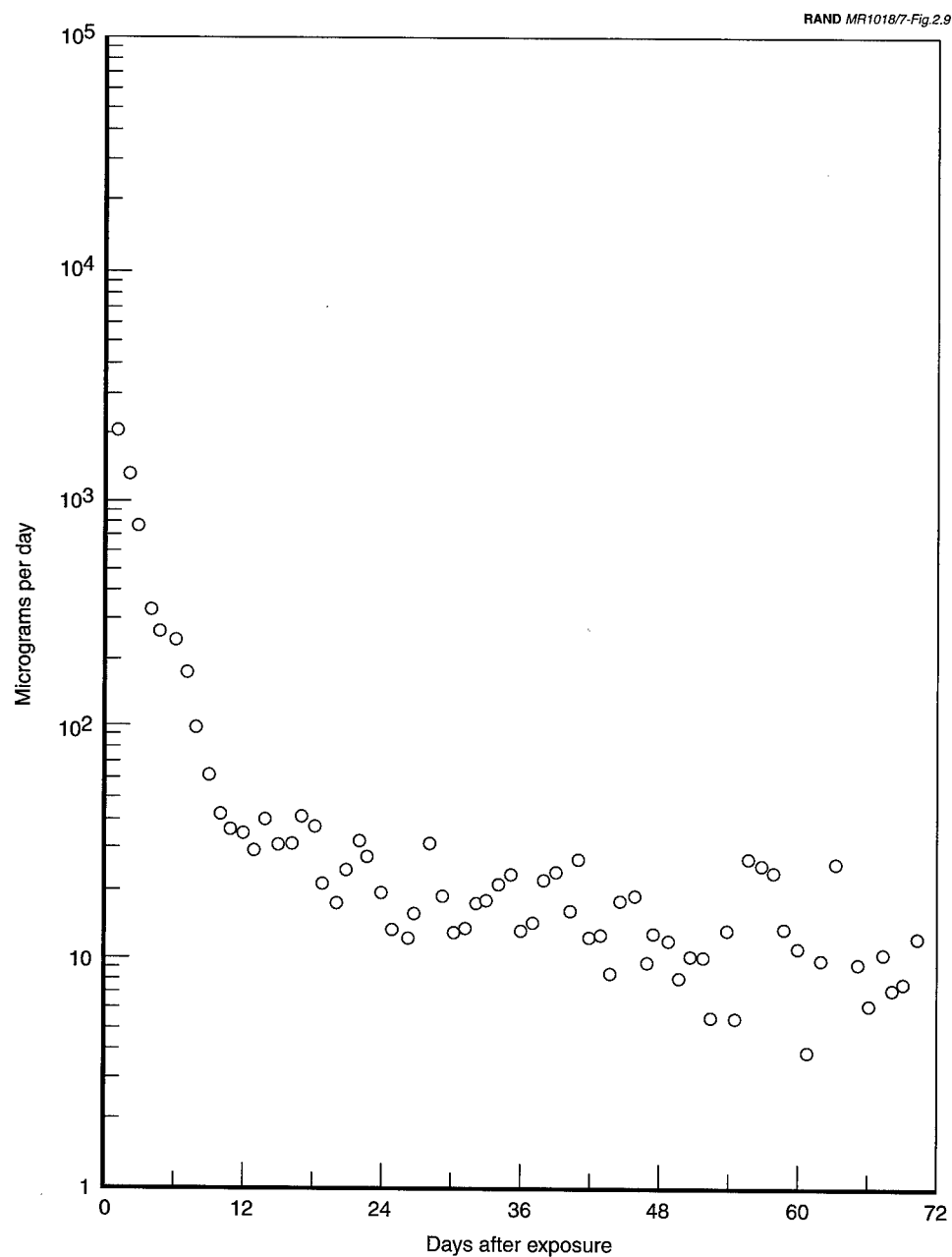
SOURCE: Eisenbud and Quigley, 1956.

Figure 2.9—Daily Excretion of Uranium by a Person Subjected to a Single Massive Exposure

increased from 0.4 µg by about 0.4 µg to a final value of 0.8 µg. The amount of uranium actually inhaled during 40 years, is 40 years x 1 µg per year or 40 µg. The increase of 0.4 µg in the lung suggests a retention of 1 percent, indicating the very efficient removal of inhaled uranium by the body.

The radiation dose factor (effective dose) for the lung from natural uranium is 0.001 mSv (0.1 mrem) per year per µg U per kg of lung. For New York City inhabitants, this translates to a radiation dose of 0.0005 mSv (0.05 mrem) per year and can be compared with an effective dose to the lung of 2 mSv (200 mrem) per year from other sources of inhaled natural radioactivity.

Thus, an unreasonable amount (2,000 µg) of DU would need to be inhaled to approach the existing dose from other natural exposures. An effective dose of less than 0.01 mSv (1 mrem) per year is considered a negligible exposure by the radiation guidance committees of NCRP and ICRP.

It is unlikely that any munitions explosion involving DU could have sustained air concentrations of DU in the mg/m³ range (1,000 µg/m³) for any length of time. Outside of struck vehicles dispersion of airborne material by normal wind speeds and ground deposition (fallout) dilute any clouds of material rapidly. (See OSAGWI, 1998, and CHPPM, 1998, for discussions of exposure).

Thus, based on the general literature, exposure to uranium of a large enough dose to be of radiological significance seems unlikely in the Gulf War; however, other groups such as the Office of the Special Assistant to the Secretary of Defense for Gulf War Illnesses (OSAGWI) (1998) and CHPPM (1998) are evaluating the level of exposure to DU in the Gulf War. Inhaled uranium is excreted efficiently, and long-term effects are unlikely because the radiation dose to organs is very small, i.e., much less than normal background radiation.

Even very small quantities of uranium, including background exposure, can be detected in a 24-hour urine analysis. As the body reaches a steady state (see the compartmental model in Figure 2.2) and as these steady-state values are known, if one knows normal background levels of excreted uranium, one can estimate industrial or battlefield exposure.[7] For this reason it is always important to obtain samples for both biological and environmental background levels so that quantitative estimates of exposure can be made without ambiguity. Urine samples can be used to predict total exposure and environmental soil samples show ground deposition, which can be used to determine the inventory of material dispersed.

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[7]In autopsy results, excess uranium in organs of highly exposed occupational workers (inhaling 40 to 50 mg of uranium) has been measured as long as 38 years after exposure (Kathren and Moore, 1986).

Ingestion

Another major pathway for human exposure to uranium is through ingestion. The major portion of the body burden of uranium in the general public is derived from ingestion of food and drinking water. Depending on where one lives and on one's diet, exposure to natural uranium varies and continues over an entire lifetime.

In addition to uranium intake from food and water, some uranium ingestion may also follow hand-to-mouth contact in presence of uranium-containing dusts. As discussed in the inhalation section, uranium particles deposited in the upper airways are cleared from the lungs by mucociliary action, swallowed, and eventually reach the GI tract.

Uranium is not efficiently absorbed from the intestinal lumen, as is the case with other heavy metals (Spencer et al., 1990). For instance, fractional uptake of cadmium from the adult intestine is much lower (1 to 5 percent) than that from the alveoli (Friberg, 1985);[8] however, the immature gut is generally much more permeable to cadmium than the mature organ (Foulkes, 1993). The actual uptake of heavy metals from the intestine is determined by the interplay of many factors besides age. They include the chemical species of the metal present in the lumen; the composition of the intestinal contents and the presence of metal chelators and nondigestible metal-binding polymers, nutrition, and such physiological variables as pregnancy and lactation; and others (Foulkes, 1994).

The generally very low fractional absorption of ingested uranium in the mature human is consonant with the observation that fecal excretion approximately equals oral intake (Voegtlin and Hodge, 1949; Hursh and Spoor, 1973; Spencer et al., 1990). This finding also excludes the occurrence of significant hepatic or enteric excretion of the metal under normal conditions. More than 90 percent of uranium taken up by the GI tract to blood is rapidly excreted in urine (Wrenn et al., 1985). At steady state (i.e., continuous intake), the urine-to-diet ratio equals the fractional uptake of uranium.

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[8]In spite of extensive work on the mechanism of intestinal absorption of heavy metals, no consensus has been reached in this field. The problem was recently reviewed by Foulkes (1995). No adequate evidence has been adduced for the participation of specific and saturable carrier systems in the process, and a possible role for carriers responsible for absorption of physiologically important metals, such as zinc or calcium, in the uptake also of nonessential and toxic heavy metals remains under discussion. A plausible model has been formulated for the whole process: It consists first of the electrostatic binding of the metal to the brush border membrane, followed by its internalization across the membrane at a rate determined by membrane fluidity. The role of membrane fluidity accounts for the temperature dependence of the process, while apparent saturability reflects neutralization of anionic membrane charges. This model satisfactorily accounts for the absorption of cadmium, but its applicability to uranium has not been explored.

There is some controversy concerning the relative uptake from water and food. The daily intake of uranium in food is estimated to be from 1 to 2 µg/day (Hamilton, 1972; Welford, 1967; Fisenne et al., 1987). In a few places, the intake of uranium from drinking water may exceed that from food (Cothern, 1983).

Uptake measurements from food and water separately were made in the only controlled dietary study in the metabolic research ward in the VA Hospital at Hines, Illinois (Spencer et al., 1990). Four patients, diagnosed for psychoneurosis, received a standard diet for weeks or months prior to uranium measurements. The uranium measurements on diet and excreta were made over a period of 24 to 54 days. In the Spencer et al study (1990), when total diet was used, the uptake to blood of ^{234}U and ^{238}U were 1.8 and 1.5 percent, respectively. However, the water consumed by the patients had a relatively high uranium concentration of 10.4 and 7.3 mBq/L of ^{234}U and ^{238}U, respectively, stemming from natural sources in the region.

The four patients' water intake varied from 0.9 to 3.6 liters per day. The linear regression of urinary output versus uranium intake in water was very good, with 5 percent and 4 percent uptake for ^{234}U and ^{238}U, respectively. Water was not given with food in this study because water could have an effect on solubility of uranium in food. The uptake is therefore from the water itself. It appears from this one controlled study that uptake of uranium from water is greater than that estimated from the total diet. This finding generally holds for heavy metals.

Fractional GI uptake for uranium is known to vary inversely with the amount ingested. The fractional GI uptake (blood/diet) in historical human experiments ranged from 0.005 to 0.05 (Hursh et al., 1969). The ICRP (1979) has used 0.05 for water-soluble inorganic compounds of uranium (hexavalent uranium). The most recent ICRP value for GI uptake of unspecified compounds of uranium is 0.02 (ICRP, 1997). In a study of ^{234}U and ^{238}U administered in a single 3,000 mBq dose in water, the uptake as measured by urinary excretion ranged from 0 to 2.5 percent for 12 subjects (Wrenn et al., 1988).

Relatively few measurements are available for the uranium concentration in food products. Data for uranium in the diet are commonly estimated in four ways: the concentration in individual items is measured and intake estimated; a collection of typical individual food items are analyzed as a group in the "market basket" technique; typical meals are prepared and composited over several days and analyzed as a single sample; or fecal excretion is measured and analyzed (Singh, 1990). Each method has its merits.

Early estimates were made of uranium in the composite diet of six countries: France, West Germany, USSR, United Kingdom, Japan, and the United States and were summarized by Harley (1988). These data are shown in Table 2.3.

Table 2.3

Daily Dietary Intake of ^{238}U in Various Countries

Country	Region	^{238}U (mBq/day)
France		12
West Germany		30
USSR	Moscow	45
United Kingdom		12
Japan	Sapporo	18
	Kyoto	18
	Okayama	11–60
United States	Chicago	17
	New York, 1963	16
	New York, 1978	15
	San Francisco	16

SOURCE: Harley, 1988.

Items from 19 individual food categories and tap water in New York City were analyzed for isotopic uranium (^{234}U, ^{235}U, ^{238}U) (Fisenne et al., 1987). Annual consumption of these 19 categories were estimated, and total uranium consumption was calculated for each isotope. The average daily intake in New York City was 18.3 ± 0.5, 0.74 ± 0.08, and 15.9 ± 0.4 mBq for ^{234}U, ^{235}U, and ^{238}U, respectively. The main contributors to the diet are shellfish, bakery products, and fresh vegetables. The average daily intake included inhalation intake, estimated from measurements in filtered air samples in New York City. The daily intake in the 19 categories and the water and inhalation intake are shown in Table 2.4.

The ^{238}U in the diet in 31 cities in Japan was measured. Each sample consisted of the total of the daily whole meals collected from five adult males in one sampling place. The average daily intake in the 31 cities was 0.71 ± 0.32 μg/day (8.5 ± 3.8 mBq/day). The data are shown in Table 2.5.

A market basket study of uranium in the diet in Mito, Ibaraki prefecture, Japan, found an average daily intake of 15.5 ± 0.8 mBq/day. The authors state that imported foods would increase this average by a factor of 1.6. The measurements were performed by ICP-MS and are considered normal levels. The committee on the Biological Effects of Ionizing Radiation reports that eating food or drinking water that has normal amounts of uranium will not likely cause cancer or other health problems in people (BEIR IV, 1988).

Ingestion—Chemical Toxicity. The chemical toxicity of ingested uranium is determined largely by the water solubility of the compound and therefore, ease of uptake from the GI tract. In general, compared with the industrial

Table 2.4

Intake of Natural Uranium Isotopes in Diet, Water, and Air in New York City

Food Type	Consumption (kg/yr)	^{238}U (mBq/yr)	^{234}U (mBq/yr)	^{235}U (mBq/yr)
Annual				
Fresh vegetables	48	1,142	1,128.0	58.0
Canned vegetables	22	92	99.0	2.6
Root vegetables	10	77	125.0	1.3
Potatoes	38	34	41.0	1.9
Dry beans	3	83	93.0	4.0
Fresh fruit	59	118	118.0	0.0
Canned fruit	11	11	29.0	0.2
Fruit juice	28	17	15.0	0.0
Bakery products	44	1,012	1,305.0	56.0
Flour	34	164	129.0	8.5
Whole grain products	11	187	277.0	11.0
Macaroni	3	11	11.0	0.3
Rice	3	9	7.5	0.5
Meat	79	184	145.0	1.3
Poultry	20	16	15.0	1.3
Eggs	15	28	15.0	0.5
Fresh fish	8	105	145.0	3.3
Shellfish	1	1,935	2,200.0	90.0
Dairy products	200	147	200.0	10.0
Daily				
Dietary intake (mBq)		14.700	16.800	0.6900
Water intake (mBq)		1.220	1.460	0.0490
Inhalation intake (mBq)		0.019	0.019	0.0007
Total intake (mBq)		15.900	18.300	0.7400

SOURCE: Fisenne, 1987.

compounds, the uranium oxides are considered to be less soluble or insoluble and, therefore, of very low toxicity (Tannenbaum, 1951; Maynard, 1949). Intravenous administration of uranyl salts in several animal species tested (for review see Bentley et al., 1985) produces signs of renal malfunction; the threshold dose is suggested to lie at 10 μg/kg body weight.

There are no studies that report human deaths from oral exposure to uranium oxides (HHS, 1997b). No mortality was observed in mice dosed at 0.02 to 20 mg UO_2/day/mouse for a year (Tannenbaum, 1951). Likewise, no mortality and no evidence of toxicity appeared in mice dosed 100 mg U_3O_8/day/mouse for a year (Tannenbaum, 1951). Maynard observed no toxicity in rats fed a diet up to 20 percent uranium by weight in the form of UO_2 or U_3O_8 or up to 0.5 percent uranium in the form of UO_3. Mortality can be induced in animals at very high oral intake levels. One hundred percent mortality was observed in a 30-day rat

Table 2.5

Daily Intake of ^{238}U in 31 Locations in Japan During 1981[a]

Location	^{238}U µg/day		Location	^{238}U µg/day	
	Summer	Winter		Summer	Winter
Sapporo	1.06	2.94	Osaka	0.40	0.91
Aomori	1.23	0.54	Hyoto	0.75	0.65
Miyagi	0.55	0.93	Wakayama	0.56	0.45
Akita	0.70	0.34	Tottori	0.45	0.37
Yamagata	0.74	0.79	Shimane	1.01	0.54
Fukushima	0.70	0.49	Okayama	0.95	0.69
Tokyo	1.24	1.50	Hiroshima	1.38	0.32
Kanagawa	0.89	1.11	Yamaguchi	0.40	0.42
Ibaraki	0.87	0.84	Ehime	0.73	0.36
Nagano	0.70	0.52	Kochi	0.32	0.24
Niigata	1.21	0.47	Fukuoka	1.20	0.30
Isihawa	0.76	0.90	Saga	0.89	0.45
Fukui	0.89	0.60	Nagasaki	0.52	0.26
Shizuoka	0.63	0.50	Kagoshima	0.32	0.32
Aichi	1.28	0.87	Okinawa	0.91	0.87
Kyoto	1.12	0.98			

SOURCE: BEIR IV, 1988.

[a]The mean for the areas tested was 0.72 ± 0.32.

study with a diet consisting of 2 percent uranium in the form of UO_3 (Maynard et al., 1953).

No human studies were located related to respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal endocrine, dermal, ocular, body weight, or other systemic effects in human exposure to uranium compounds through the oral route (HHS, 1997b).

Respiratory effects have not been observed in animals following ingestion of uranium oxides. In animals fed diets of 20 percent uranium in the form of UO_2 for 30 days, no adverse effects on the respiratory system were found (Maynard and Hodge, 1942; Maynard et al., 1953). Likewise, no adverse cardiovascular effects were observed in animal studies following oral exposure (Maynard and Hodge, 1942; Maynard et al., 1953).

The adverse effects on the GI tract were observed following a case study of a human volunteer (Butterworth, 1955). Following a single dose of uranyl nitrate (14.3 mg/kg), a compound considered far more toxic than an oxide, acute nausea, vomiting, and diarrhea occurred within a few hours. Within 24 hours, no clinical effects remained (Butterworth, 1955).

No studies were located that noted an association between uranium oxides and hematological parameters (HHS, 1997b). Immune system effects have not been attributed to uranium oxide exposure (Maynard et al., 1953). Although hepatic

effects have been observed in animals dosed with very high levels of insoluble uranium, dogs dosed with up to 10 g UO_2/kg/day for one year exhibited no hepatic effects (Maynard and Hodge, 1949).

No animal studies were located that examined effects of ingested uranium oxides on the endocrine system. No harmful effects on body weight were seen in intermediate-duration oral studies of dogs given up to 10 g UO_2/kg/day for one year (Maynard and Hodge, 1949; Maynard, 1953).

No epidemiological studies were located that examined neurological effects following uranium ingestion. And no animal studies examined the effect of uranium oxides on the neurological system (HHS, 1997b).

Reproductive, developmental, and genotoxic effects have also been investigated. No studies were located that reported reproductive effects in humans following oral exposure to uranium for any duration (HHS, 1997b).

Gene mutation and chromosomal aberrations following alpha radiation exposure emitted by uranium decay products might be a concern. However, no studies were located that reported genotoxic effects in humans or animals following oral exposure to uranium for any duration.

The possibility of teratological actions of ingested uranium was looked for in mice. Developmental effects, such as reduced fetal body weight and length, and external malformations have been observed with nonoxide uranium compounds (Domingo et al., 1989); a no-effect-level of below 5 mg uranyl acetate dihydrate per kg per day during pregnancy was suggested. No such studies have examined developmental effects associated with uranium oxide ingestion. Also, no studies were located that reported reproductive effects in humans following oral exposure to uranium for any duration.

While possible toxic effects of uranium on other organ systems have not been rigorously excluded, extensive work points to the kidney as the major target organ. The recent work of Zamora et al. (1998) is therefore of special interest. Zamora et al. described analyses on renal function after a lifetime of exposure to natural uranium of 20 control subjects consuming drinking water containing less than 1 μg U/L and 30 subjects exposed to higher uranium levels (range 2–781 μg/L). The higher-exposure group took in a total of 3–570 μg/day; intake by the control group amounted to 0.3–20 μg/day. The exposed group excreted significantly more glucose in the urine than did the control group. Excretion of alkaline phosphatase (a marker of cytotoxicity) and of ß2-microglobulin (a marker of proximal tubular function) were positively correlated with uranium intake. The only valid measure of glomerular malfunction tested (proteinuria) remained unchanged. No clearances were reported, and a constant urinary excretion of creatinine can, of course, throw no light on the glomerular filtration

rate. In the absence of information on the reversibility of the observed changes in tubular function, their clinical significance must remain in question. This is especially true because most of the functions measured remained within the reference (normal) limits.

A more general question then arises: when should a subclinical effect be labeled adverse? There is no consensus on this problem. Thus, would the decreased body weight looked for in the work of Maynard et al. (1953), as quoted above, have represented a harmful effect? The possibility of acquired partial tolerance to several heavy metals, including uranium, was demonstrated in animals upon preexposure to low levels. As already discussed above under the heading of tolerance to inhaled uranium, acquired resistance to, for instance, cadmium can be explained in terms of the induction of the metal-binding protein metallothionein; no such role of metallothionein has been demonstrated in uranium exposure.

No nephrotoxic effects were observed in dogs fed 1 g UO_2/kg/day for one year. Moderate to severe histological effects were observed in dogs fed 10 g UO_2/kg/day for one year (Maynard and Hodge, 1949). Regeneration of damaged tubular epithelium has been observed in animal studies after discontinuation of exposure (Bentley et al., 1985; Dygert, 1949; Maynard and Hodge, 1949; Rothstein, 1949; Stokinger et al., 1953). The regenerated epithelial cells appear different from normal.

In conclusion, there is only limited evidence to suggest that even chronic exposure to natural uranium in food or drinking water, except at very high concentrations, is associated with increased morbidity in humans or animals. This conclusion makes it unlikely that DU would have any such effects.

Ingestion—Radiological Toxicity. No human or animal studies associate adverse health effects with the radioactivity of ingested DU. No evidence has been found to associate human exposure to ingested uranium compounds and carcinogenesis. Likewise, no oral animal studies reported the evidence of cancer induction (Maynard and Hodge, 1949; Maynard et al., 1953; Tannenbaum and Silverstone, 1951, Kathren and Moore, 1986).[9] Note that much of this evidence and discussion was presented earlier in the report as considerations related to the radiological effects of inhaled and ingested uranium are similar.

The major pathway for entry of natural uranium into the body is through water and food. In a weapons explosion involving DU, ingestion of material could certainly result by directly swallowing airborne material or ingesting soil con-

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[9]Backup material that refers to natural uranium in tissue and diet is included in Tables 2.1, 2.4, and 2.5.

taminated with DU. Also, most inhaled uranium is cleared by the lung and swallowed, mimicking ingestion.

The radiation dose to the kidney in New York City residents, using the measured kidney concentration of 0.43 µg/kg (0.00043 µg/g), is 0.0004 mSv (.040 mrem) effective dose per year. Ingestion of DU in a munitions explosion or fire would likely be short-term with small fractional uptake and subsequent rapid excretion of absorbed uranium reaching the blood. The radiation dose to the kidney from the de facto standard of 3,000 µg/kg kidney would deliver an effective dose of 4 mSv (400 mrem) per year. This is less than the small group limit for infrequent exposure of 5 mSv (500 mrem) per year and the occupational limit of 10 mSv per year (See "Regulatory Standards," p. 8). Continuous uptake is unlikely, except in the case of embedded uranium in a wound. In a wound, the solubilized uranium presents a continuous daily input to blood and is equivalent to continuous intake from food or water. This is described later.

Today, quantitative estimates of exposure to detect even minute concentrations of uranium in bioassay (urine or tissue) samples can be made with high sensitivity and accuracy. Even in the case of single short-term exposure, it is sometimes possible to measure excretion concentrations long after exposure if the exposure is sufficiently large and base-line levels are known. Bioassay samples can sometimes be used in this way to estimate retrospectively the total exposure and radiation dose.

Urinary Excretion: The best body fluid in which to measure uranium is urine because soluble uranium, once absorbed, is rapidly eliminated from the body through the kidney (Lauwerys, 1993). Excretion basically occurs as a two-phase process with 70–86 percent being excreted in the first 24 hours, and the remainder excreted over the period of many months (Berlin, 1986).

As an example, a worker was exposed to massive amounts of uranium fumes by inhalation and ingestion following the sudden accidental explosion of powdered uranium metal. The rapid excretion of uranium by this worker is shown in Figure 2.9 (Eisenbud and Quigley, 1956). Figure 2.9 shows that in the first 10 days, levels dropped extremely rapidly from more than 20,000 to about 10 micrograms of uranium per liter of urine.

In unexposed individuals, almost all daily intake of uranium comes from drinking water and ingestion of such foods as vegetables, grains, and salt (Berlin, 1986; Fisenne, 1987). In the absence of an acute environmental exposure, inhalation of uranium accounts for less than 2 percent of the contribution from diet (Dang, 1992). Absorption from skin is also possible if uranium sources are water soluble. Water-insoluble compounds (e.g., metal armor) have not been detected (Berlin, 1986). From water and diet, the GI absorption factor itself (the percentage of ingested uranium actually absorbed) is about 2 to 5

percent. Studies of unexposed individuals have shown that urinary concentrations average 12.8 ng/L (Dang, 1992) with a daily excretion of 30.9 ± 19.6 ng/24 hours (Medley, 1994).

Following acute inhalation, little uranium reaches the lower lung, as was previously discussed. This is because particle size is such that most is captured by the respiratory tract (and ultimately swallowed). Estimates suggest that from 1 to 5 percent of uranium-containing dust will penetrate to the pulmonary parenchyma and ultimately be absorbed (Berlin, 1986).

Studies suggest that considerable amounts of uranium must be present in the circulation to cause significant renal damage. Studies in dogs suggest that 10 mg/kg intravenously produced acute renal failure. In nonlethal doses, renal injury presents with evidence of tubular damage (cellular and noncellular casts on urinalysis). After several days, the renal tubular epithelium begins to regenerate and is generally complete by two to three weeks (Berlin, 1986). While at first the regenerated tubular cells appear structurally different, they ultimately regain their normal appearance. However, function is restored within weeks of the start of epithelial regeneration.

Berlin and Rudell (1996) report that uranium concentrations in urine of up to 2.84 mg/L have been observed without clinical evidence of renal damage. This concentration exceeds 220,000 times more than has been reported in unexposed subjects (Dang, 1992). From the standpoint of occupational exposure, the United States Energy Research and Development Administration (1975) set a maximum safe limit at 250 µg/L, a concentration about 20,000 times the average background.

With the exception of individuals with embedded DU fragments, measuring urinary uranium in Gulf War veterans at this time would not be expected to provide useful information. Previously exposed individuals would now be expected to have urinary levels within the range of unexposed individuals, perhaps up to about 300 ng/L (Dang, 1992). In the absence of acute renal failure in the Persian Gulf, which would have been obvious shortly after exposure, medical and experimental evidence does not suggest that veterans are suffering from long-term renal uranium toxicity. Routine monitoring or evaluation of veterans for evidence of renal damage (e.g., serum creatinine, blood urea nitrogen, microalbuminurea) is not warranted.

If in the future the possibility of acute exposure to uranium is considered, urine should be collected in the first day following the event. Efforts should be made to collect a 24-hour specimen for analysis because studies have documented considerable variation in urinary uranium concentrations among those with nontoxic occupational exposures (Medley, 1994).

In summary, the databases developed for tissue concentrations of uranium acquired from normal dietary intake are of major importance. They permit a quantitative value for uranium organ content per unit intake from the natural uranium content of diet. Controlled studies of dietary intake of natural uranium showed that uranium in food is poorly absorbed by the gut compared with uranium in water. Uranium in water is in a more available form. Under natural conditions, i.e., intake of a few µg per day, the fractional uranium uptake from water to blood is about 5 percent (Spencer et al., 1990). With increasing mass of uranium, the gut is less able to absorb uranium and the fractional uptake to blood is less.

The dietary intake of uranium from food and water in New York City is about 1 µg per day. The steady-state uranium organ burdens associated with this intake are shown in Figure 2.4. This is a powerful relationship as the organ content for other continuous exposure situations can be calculated readily. For example, the kidney concentration in New York City residents is 0.4 µg/kg and, assuming this arises from water, means that for ingestion of 1 µg per day from water the kidney concentration would be 4 µg/kg. The de facto standard (MPC) for uranium in the kidney is 3,000 µg/kg of kidney. Again, it is unlikely that an ingestion exposure to DU would be as high as 1,000 µg per day, or enough to attain the guideline concentration for kidney. For short-term or single exposures, the radiation dose would be less than for the same amount given continuously. The dosimetry for specific individuals or case events should be derived for the known conditions of ingestion exposure.

Exposure to ingested, inhaled, or embedded uranium can be diagnosed by looking at the level of uranium in the urine through urinalysis. Urinary excretion is a positive, rapid, and unambiguous identification of exposure to ingested or inhaled uranium. Once in the body, any uranium compound will be soluble to some degree and cleared to the blood. When in the blood, any uranium is rapidly excreted in urine.

Embedded Fragments and Wound Contamination

Embedded DU fragments and wound contamination with DU dust is another pathway for exposure, seen almost exclusively in the military environment. In combat use, DU metal fragments from a penetrator or a vehicle's hull armor can scatter inside the vehicle, killing and injuring personnel, destroying equipment, and causing secondary explosions and fires. As the use of DU munitions is relatively recent, there is little published literature on exposure to embedded fragments.

As a result of "friendly fire" incidents during the Persian Gulf War, DoD has reported that DU munitions struck a number of Bradley Fighting Vehicles and

Abrams Tanks[10] (OSAGWI, 1998). The friendly fire incidents killed 13 soldiers and wounded many more (GAO, 1993). The total number of soldiers wounded by DU is not known; however, the Office of the Army Surgeon General identified 22 soldiers whose medical records indicate they have embedded fragments that might be DU. Another 13 soldiers were wounded and hospitalized but were not specifically identified as having fragment wounds. The remaining crew members of the DU-struck vehicles were either not wounded during the incident or had minor wounds that were treated in the field (Daxon, 1993; Kearsley, 1993).

Following the Gulf War, the Office of the Army Surgeon General requested the Armed Forces Radiobiology Research Institute (AFRRI) to "assess the health risks associated with implanted DU fragments in the body to provide medical guidance for current and future patients with these fragments, and provide recommendations for future research." (Daxon, 1993.) Following a review of the medical literature, AFRRI concluded that this situation is radiologically and toxicologically unique. Until recently, there was no human or animal literature evaluating the health effects of embedded DU fragments. As such, the federal government has since funded research at AFRRI and the Inhalation Toxicology Research Institute (ITRI), University of New Mexico, to understand the behavior, physiology, histology, and biokinetics, as well as the carcinogenic potential of embedded DU metal. The research continues.

In addition, since the exposure has not been studied, the AFRRI recommended long-term follow-up for the affected soldiers. However, no compelling evidence to change standard medical criteria for fragment removal was found (Daxon, 1993). In response to the AFRRI recommendation, physicians and scientists from DoD and the VA drafted the protocol to be used in the follow-up effort. The protocol, reviewed and revised by a panel of experts, was submitted to the Army on December 7, 1992, and implemented in late 1993 as the Depleted Uranium Follow-Up Program at the Baltimore VA Medical Center. Since late 1996, the program has been under the clinical leadership of Dr. Melissa McDiarmid.[11]

The DU Follow-Up Program at the Baltimore VA Medical Center provides ongoing clinical surveillance to Gulf War veterans with known or suspected embedded DU fragments, DU-contaminated wounds, or significant amounts of inhaled DU aerosols (Daxon, 1993).

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[10]In addition, three Abrams tanks were intentionally destroyed to avoid enemy capture.

[11]As of the date of this report, the findings of much of this important research conducted by the DU Follow-Up Program have not yet been published. The information provided here should therefore be considered preliminary. The information here comes primarily from briefings by Dr. McDiarmid, conference abstracts, and secondary sources.

"The DU Follow-Up Program at the Baltimore Veterans Administration Medical Center began a medical surveillance program to assess the health of approximately 35 soldiers" (exact number was 33 (Kane et al., 1998)) in 1993 who had been in vehicles "struck by DU munitions. . . . Early phases of the program focused on the exposure assessment of these troops by measuring the early biologic effects of both the radiologic and presumed chemical toxicity of DU." (McDiarmid et al., 1998a.) The original research protocols included very thorough questionnaires and a series of medical and laboratory tests. Among other issues, questionnaires were designed to gather medical, social, family, reproductive, and occupational exposure histories. Tests were conducted to study renal function including urinalysis, creatinine, and proximal tubular function tests (ß-2 microglobulin and retinol-binding protein). Other laboratory studies included blood chemistries, urinary uranium, and neuroendocrine measures. Among other tests and studies, patients also received detailed physical examinations, neuropsychological tests, and radiology tests (McDiarmid, 1998b).

The scope of the surveillance of the original patients was expanded in 1997, and this "more recent follow-up has attempted to identify the most sensitive and relevant biologic measures of uranium and have included uranium determinations in spot and 24-hour urines, seminal fluid and whole body radiation counting in both the DU exposure cohort and non-DU exposed Gulf War veteran controls. Early markers of proximal tubular effect and reproductive hormone values were also assessed." (McDiarmid et al., 1998a).

Currently, 33 participants are in the program. All were evaluated at the Baltimore VA Medical Center in 1993 and 1994, and 29 were reevaluated in 1997. Of those evaluated, about half have been identified radiographically as having retained metal fragments. In 1997, the majority of individuals identified radiographically as having retained DU fragments had elevated 24-hour urinary uranium levels (McDiarmid, 1998b). This suggests that DU is being oxidized in body fluids. Thus, these metal fragments are not entirely inert. Most individuals who did not have embedded fragments did not have elevated urinary uranium levels (McDiarmid, 1998b).

Twenty-six DU exposed participants in the DU Follow-Up Program at the Baltimore VA and 19 unexposed persons underwent whole body radiation counting (WBRC) (McPhaul et al., 1998). A summary statistic based on the WBRC result was derived for each participant, and this correlated highly with the 24-hour urinary uranium result (McDiarmid, 1998b).

Although these individuals have an array of health problems, many of which are related to their combat injuries, *to date no manifestations of kidney disease attributable to the chemical toxicity of DU have been found; neither do these individuals appear to have manifestations attributable to radiation effects*

(McDiarmid et al., 1998a; McDiarmid, 1998b), but several perturbations in biochemical and neuropsychological testing have been correlated with elevated urinary uranium, the clinical significance of which is unclear (McDiarmid, 1998b). These patients continue to be followed to be sure that this remains the case.

Laboratory tests also found DU in semen in samples from some but not all veterans exposed to DU. This is not altogether surprising as DU disperses throughout the body. It is not clear what effect if any this might have on reproduction of a couple, where one partner has an embedded DU fragment. To date, all births to couples in the DU Follow-Up Program have been normal (McDiarmid, 1998b). There have also been no studies to determine the level, if any, of uranium from dietary intake appearing in semen in individuals living in areas with high levels of natural uranium.

Participants in the DU Follow-Up Program at the Baltimore VA Medical Center also participated in a set of standard tests to measure neurocognitive function. "As a group these individuals performed normally on standard tests of attention, memory, and problem solving. However, there was a statistical relationship between elevated urine uranium and lowered efficiency and accuracy" (Kane et al., 1998) measured in a follow-up computerized test. Researchers have urged caution in looking at these results as "an analysis of individual cases suggested that the performance of a few patients might have been responsible for this relationship on this relatively small sample of patients with elevated uranium levels. There was no evidence of worsening performance over time." (Kane et al., 1998.)

A series of important studies assessing the effects of embedded uranium in rats is presently being conducted by the Armed Forces Radiobiology Research Institute (AFRRI).[12] AFRRI is looking into the redistribution and toxicity of embedded DU fragments; in a separate study, it is studying the effect of DU on reproduction and fetal development (McClain, 1998). Male and female Sprague-Dawley rats weighing 250–300 g had four to 32 DU or tantalum control pellets (1 mm diameter by 2 mm in length) implanted in their legs (Benson and Pellmar, 1998b). Comparisons of exposure levels between rats and humans are difficult, but researchers indicate that the rats with the smallest number of DU pellets had a higher urinary uranium level than Gulf War veterans with embedded fragments, who were among the most highly exposed Gulf War veterans. A number of studies "to assess kidney function, uranium distribution,

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[12]The AFRRI work is ongoing and the results presented here are preliminary. The preliminary information in this paper comes from an abstract and poster session at the Conference on Federally Sponsored Gulf War Veterans' Illness Research, July 17–19, 1998, or as part of briefings. A paper by Pellmar et al. has been accepted for publication by *Toxicological Sciences*.

reproductive capability, behavior, and electrophysiology" (Benson and Pellmar, 1998b) were conducted.

At a recent conference and in a forthcoming paper (Benson and Pellmar, 1998a,b; Pellmar et al., forthcoming), researchers reported on preliminary results of their studies. "Uranium levels were high and dose-dependent in the kidney, urine, and bone [in DU implanted rats]. Despite high uranium levels in the kidney, no renal toxicity was evident." (Benson and Pellmar 1998b.) Twenty-four-hour urinary uranium levels in rats 12 months after implantation with 0, 4, 10, or 20 DU pellets were 0, 2, 4, and 11 µg, respectively. Unexpectedly, uranium was also found in hippocampus of the brain of DU implanted rats, but no neurotoxicity was evident (Benson and Pellmar, 1998a). Benson and Pellmar (1998a) concluded that "these data suggest that renal toxicity may be less of a hazard than anticipated, but that cognitive deficits need to be considered."

AFRRI is also examining the effects of implanted DU pellets on reproduction in female rats, measuring various maternal and litter parameters, including pup weight and litter size (see "Reproductive Effects of DU," p. 63). Results from mother rats with high levels of uranium indicate the pups are normal. Preliminary results suggest there may be a decrease in litter size in female rats impregnated six months after implantation with the largest number of DU pellets used (32) (McClain, 1998).

Elsewhere, it has also been reported that 27 members of the 144th Service and Supply Company, Army National Guard, potentially exposed themselves when they worked on DU-contaminated vehicles for three weeks without protective gear (AEPI, 1995). The CHPPM was assigned by Office of the Army Surgeon General to obtain and perform radio-chemical analyses on voluntary urine samples from personnel of the 144th. Among the members of the 144th Service and Supply Company, Army National Guard, tested at the CHPPM facility in 1993, no measurable increase in uranium excretion was found (OSAGWI, 1998).

From a radiological perspective, particles embedded in skin can irradiate the cells in the basal layer, the target cells for skin cancer. (Note: this refers to fragments embedded in the skin and not to DU radiological exposure from outside the body). For example, if a 100 µm fragment of DU was embedded near the basement membrane, it could irradiate a target cell, causing genetic damage that might result in skin cancer. The decay rate (i.e., alpha particle emission rate) of DU is very low for micrometer-size particles. However, the decay rate of a large 100 µm DU particle at 0.15 Bq is sufficient to kill all cells within the alpha particle range. In the case of an embedded fragment, damage to tissue next to the fragment would be caused primarily by alpha radiation while in the case of

radiation external to the body, gamma and beta rays are the only rays that can penetrate the body and do damage.

EXTERNAL EXPOSURE

The primary external health hazard from DU is beta and gamma radiation generated by the radioactive decay of uranium decay products. The vast majority of DU radiation (more than 95 percent) is alpha radiation, which cannot penetrate paper or skin and has been shown not to cause adverse external health effects. Gamma and beta radiation from decay products can penetrate the skin and in sufficient amounts could pose a health risk. Intact munitions and armor have the potential for amassing sufficient DU to generate enough beta and gamma radiation to exceed occupational levels. However, all DU weapon systems are shielded to control gamma and beta radiation emitted from DU. As such, they present very little external exposure risk for personnel working with intact munitions and armor (AEPI, 1995; Danesi, 1990). Chemical toxicity does not pose a threat unless the metal is internalized.

The potential radiological health effects from external DU exposure, including bare penetrator, armor, and dust, are small (AEPI, 1994). The dose of radiation received depends on several factors, including the amount present, the type and configuration of the DU, the distance from the DU source, and the time exposed.

The obvious target for external radiation exposure from DU deposited on the body is the skin. The alpha decay of a single particle is very low, with the additional factor of an increased distance from the skin surface to the target cell. The skin surface is composed of a layer of dead cells collectively called the epidermis. New cells are generated from basal cells in the stratum basale, a layer close to the basement membrane. Overlying the basal cells in the stratum basale are three other layers of cells: the stratum granulosum, the stratum lucidum, and the stratum corneum. The cells in the layers above the basal layer are terminally differentiated and therefore not susceptible to damage that could produce a cancerous growth.

The International Commission on Radiological Protection (1974) measured epidermal thickness in males aged 26 to 30 years. The average thickness is about 50 μm, and the thinnest epidermis is 34 μm on the front of the forearm. The range of the ^{238}U alpha particle is 28 μm in tissue. Thus, most of the target cells are outside the range of particles deposited on the surface. The beta and gamma radiation from the decay products can irradiate cells in the basal layer.

Since alpha particles emitted by uranium will not penetrate the dead outer layer of the skin, the effects of acute dermal exposure to ionizing radiation, including

erythema (redness of the skin) and epilation (loss of hair), will not be observed (Upton, 1992). Studies of uranium miners, millers, and processors have not reported these effects.

Likewise, only the putative stem cells (basal cells) that are cycling and that regenerate the cells in the upper layers are targets for carcinogenesis. Once cells are terminally differentiated, skin cancer cannot be induced. Out of 11 underground uranium mining cohorts studied, skin cancer was observed only in Czechoslovak and Chinese miners (Sevcova et al., 1983). In those studies that observed skin cancer, airborne arsenic, a known carcinogen, was also present in the mines and is considered to be the relevant substance. In addition, workers near nuclear reactors are subjected to skin deposition of small particles of highly radioactive activation products (denoted "fleas"). These particles attain decay rates of beta radioactivity of many thousands of disintegrations per minute. However, no skin cancer has been observed from this source. Likewise, no animal studies examining dermal exposure to uranium observed cancer after any duration of exposure.

The Army monitors soldiers and support workers according to NRC occupational exposure standards (10 CFR 20.1201) for beta and gamma radiation. The current occupational exposure radiation dose limit (beta and gamma) for skin is 50,000 mrem/year (500 mSv/year). Holding a DU penetrator without shielding (spent DU penetrator) would deliver a skin dose of approximately 200 mrem/hour (AEPI, 1995). The NRC occupational exposure standard could only be exceeded if a piece of DU were carried for more than 250 hours (AEPI, 1995).

No dermal effects and no body weight changes were seen following a single application of 1 to 2 g UO_2 (mixed in lanolin) per rabbit to the shaved skin of rabbits (Orcutt, 1949). Using similar doses, no effects were observed for U_3O_8. However, mortality was observed following a single application of 1 to 2 g UO_3 mixed in lanolin per rabbit to the shaved skin of rabbits (Orcutt, 1949). Sixty-seven percent mortality of New Zealand rabbits was seen with a single application of either 344 mg UCl_5 per kg tissue or 666 mg UO_3 per kg tissue (Orcutt, 1949). Orcutt also suggested that the order of species susceptibility to acute uranium toxicity was—from the most susceptible to least susceptible—rabbit, rat, guinea pig, pig, and mouse (Orcutt, 1949). DeRey et al. (1983) found that 100 percent, 60 percent, and 100 percent mortality rates were induced in male rats dermally exposed to 237 mg uranyl nitrate hexahydrate, 1,965 mg uranyl acetate, or 1,928 mg ammonium diuranate per kg of tissue, respectively. Chemically induced renal failure was responsible for all deaths (HHS, 1998). There are no recommended maximum permissible concentrations for exposure of human skin to uranium. However, the levels that induced mortality from dermal exposure in animals are extremely high. No human has ever died from dermal exposure to natural uranium (HHS, 1998).

No studies examined neurological effects from uranium oxide compounds; however, no neurological signs were observed in animals exposed to uranyl nitrate hexahydrate (Orcutt, 1949). No studies were located regarding the neurological effects for humans exposed to external uranium. Also, studies located for humans and animals do not describe any other effects, including reproductive, developmental, or genotoxic effects, following dermal exposure to uranium for any duration.

Radiation measurements inside a M1A1AHA tank have been taken. The decay products of ^{238}U, ^{234}Th (t1/2, 24.1 days) and ^{234}Pa (t1/2, 1.17 min) build into equilibrium rapidly. The ^{234}Pa emits penetrating gamma rays, and the potential for external whole body dose is present. The M1A1AHA tank contains DU armor and may contain DU munitions. The external gamma ray dose rate is stated to be 0.01–0.02 mrem/hr to the commander, loader, and gunner, while the driver's head can receive 0.13 mrem/hr with DU ammunition overhead (AEPI, 1995). These dose rates are assumed to be in excess of normal background radiation, which averages 0.01 mrem/hr inside a tank. The measurements of external gamma ray radiation are summarized in CHPPM, 1998, from measurements performed in the 1980s by Parkhurst et al. (see CHPPM, 1998; Parkhurst, 1991). These are shown in Appendix G and are below occupational exposure norms.

Low-level whole body radiation is generally defined as less than 0.01 Sv (10 rem). No effects have ever been observed in populations of humans or animals exposed to low-level radiation. Researchers are trying to determine whether low-level radiation increases risks of cancer or whether a threshold level exists. This is an important research need.

CLINICAL DISCUSSION

This section discusses the possible health effects associated with DU based on the research data previously presented. This discussion may be helpful to the clinician when evaluating a patient with possible exposure to DU. The clinical conditions discussed in this section are common. It is important, therefore, not to attribute conditions uniformly to Gulf War service when a veteran presents to his or her physician with findings generally observed in an otherwise matched civilian or unexposed military cohort. For this reason, statistics on common clinical conditions that have at times been theorized to be associated with DU are presented in the following discussion.

DU is a low-level radioactive heavy metal. As such, exposure to it in large enough quantities and in certain circumstances has the potential to cause adverse health effects by either chemical or radiological mechanisms. There is very little information on the health effects of DU; however, natural and en-

riched forms of uranium have been studied for decades and are well understood. Because DU is chemically identical to natural and enriched uranium, the toxicological health effects observed from those studied forms can be directly applied to DU. Because DU is 40 percent less radioactive than natural uranium and orders of magnitude less than enriched uranium, radiological health effects from DU are much less than from the more radioactive and better-studied forms of uranium.

Many human epidemiology and animal studies have been reviewed. Epidemiology is the tool used to evaluate the determinants and distribution of disease and injury in human populations. Epidemiology evaluates but cannot prove which factors or agents may cause or contribute to good or bad health effects. It is from epidemiological studies that we understand some very important health information—that tobacco smoking causes lung cancer and a low-fat diet reduces the risk of heart attacks, for example. Therefore, when epidemiological studies exist, public health professionals rely primarily on their results to evaluate potential health effects.

In contrast, animal studies examine how chemicals are absorbed, distributed, and excreted. Although it is usually difficult to extrapolate data from animal studies and apply the results directly to humans, for obvious ethical considerations humans cannot be subjected to laboratory tests where no potential benefit can accrue. Therefore, medical science and our regulatory apparatus routinely use and refer to animal studies for indications of possible health outcomes for humans, such as cancer and birth defects.

As mentioned, uranium is well understood, and we are all exposed to it in varying amounts every day. Fortunately, there are several large epidemiological studies involving uranium for us to examine and interpret. The studied populations were exposed occupationally to elevated concentrations of natural and enriched uranium over very long periods, including whole working lifetimes. In addition, there are case studies of acutely exposed individuals from occupational accidents. These exposures are far greater than known DU exposures during the Gulf War.

No human epidemiological studies are published that document mortality or detrimental respiratory, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular effects, or any other systemic health effects from uranium oxides (HHS, 1997b). The authors attributed many of the effects observed in populations exposed to uranium compounds to other causative agents.

Veterans of the Gulf War without embedded DU fragments tested in the last few years (years after the cessation of the Gulf War) have shown no increased urinary uranium concentrations. In contrast, individuals with evidence of retained fragments have shown increased excretion of uranium.

Diagnosis

Once exposure is suspected or known, the first step in the clinical process is diagnosis. The process and tests laid out below are fairly standard, but although DoD and the VA have agreed on appropriate steps of a DU evaluation, no clinical practice guideline for the treatment of exposure to DU exists.[13] Furthermore, the diagnostic process is properly determined by a physician in consultation with the patient. Almost all patients differ and must be treated accordingly.

If, after a detailed patient history, the clinical decision is made to evaluate a possible recent exposure to DU, a 24-hour urinary bioassay is usually the best method of determining whether exposure has taken place and at what level. Urinary excretion clears almost the entire uranium content of blood each day (80 to 95 percent). The analytical measurement is performed easily, and therefore, the majority of patients receive a 24-hour urinary uranium test following a recent exposure. Obtaining blood samples for uranium, in contrast, is much less valuable because of the rapid clearance of uranium in the urine; furthermore, the analytical technique is complicated by the blood matrix.

A 24-hour urine sample is preferred to a random spot urine specimen because the fraction of the daily amount excreted in a spot sample varies widely. Excretion of uranium does not progress at a constant rate throughout the day, so reliance on a spot sample is likely to yield misleading results. Although it is being debated in the scientific literature, some people believe that urinary uranium normalized for creatinine should be used.

Criteria have been developed to monitor occupational exposure to uranium, and urinary uranium assays have been used to evaluate ongoing exposure. The occupational criteria for determining whether the guideline of 3 µg/g kidney had been exceeded was 30 µg/L of urine. This is a fairly rapid assessment that can be performed to determine whether workers should be removed from an operation.

Results from work by McDiarmid (1998a and 1998b) with veterans and by AFRRI (Benson and Pellmar, 1998a) with rats indicate that urinary uranium concentrations in 24-hour urine collections are usually elevated when embedded fragments are present. In the case of embedded fragments, sometimes additional information can be gleaned through the use of scans. In some cases, whole body scans may be appropriate.

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[13]Developing a clinical practice guideline for any condition is a lengthy and involved process and is beyond the scope of this study.

Whole body counting (sometimes called *in vivo* gamma spectrometry), however, is not a common diagnostic tool. Only a few institutions in the United States and abroad possess whole body counters. The most-sensitive instruments require massive shielding to lower the normal radioactive background.

The detection limit for measurement for natural uranium in a whole body counter is generally about 70–110 Bq (2–3 nCi) when the uranium body burden is distributed. This is equivalent to a body burden of approximately 10 milligrams. If a fragment is identified, localized counting at the body site is a more efficient method for the measurement, and somewhat less activity can be detected. The ability to detect DU depends on the detector used, the particle size, and the inherent shielding of the facility. Facility shielding is critical because DU radiation is so low that the background radiation would need to be exceedingly low to detect a difference.

While the testing described above is not usually medically indicated for Gulf War veterans who do not have embedded fragments, each patient must be individually evaluated by his or her physician, and the specific tests ordered will depend on symptoms and the findings that result from that evaluation.

Lung Cancer

Although uranium is radioactive, inhalation of uranium has not been demonstrated to pose a risk of cancer. However, many heavy metals are not radioactive and can cause cancer in humans. DU is an extremely weak radioactive material that has never been implicated in lung cancer in human populations. Individuals who inhaled DU that remains in the lungs (insoluble fraction) from exposures during Persian Gulf service should not be concerned that they harbor a serious threat to life. The literature suggests that there may be an increased risk of cancer among individuals exposed to enriched uranium, but that compound is orders of magnitude more radioactive than DU. Even exposure to natural uranium, with a radioactivity more than DU, is not considered to be a health threat. The lung cancer reported in uranium miners has been scientifically attributed to exposure to another airborne substance, namely radon (NCRP, 1984; NIH, 1994; NRC, 1998).

As a point of reference, lung cancer is the most common cancer in the United States today. The American Cancer Society estimates that there will be 171,500 new cases of lung cancer in 1998, accounting for 14 percent of cancer diagnoses. The incidence rate (annual) is declining in men, from a high of 87 per 100,000 in 1984 to 74 in 1994. Recently, the rate of increase among women has started to slow. In 1994, the incidence rate in women was 42 per 100,000.

Signs and symptoms of lung cancer include persistent cough, sputum streaked with blood, chest pain, and recurring pneumonia or bronchitis. Regarding risk factors, cigarette smoking is by far the most important in the development of lung cancer. Other risk factors include exposure to certain industrial substances, such as arsenic; some organic chemicals, radon, and asbestos, particularly for persons who smoke; radiation exposure from occupational, medical, and environmental sources; air pollution; tuberculosis; and environmental tobacco smoke in nonsmokers (American Cancer Society, 1998).

Kidney Disease

Nephrotoxicity is a chemically related risk associated with uranium exposure and has been documented in animal studies at high exposure levels. The kidney is the organ system responsible for excretion of wastes, such as urea, from the blood. In the kidney, more than a million nephrons filter the blood under pressure in the glomerulus and then reabsorb water and selected substances into the blood in the tubules. They also secrete certain solutes from the blood into urine. Water, nitrogenous wastes, and many other substances (excluding colloids, such as proteins that are too large to pass through a healthy glomerulus) pass into the renal tubule, the concentrating and diluting section of the kidney. In the renal tubule (proximal convoluted tubule, Henle's loop, distal convoluted tubule, and collecting duct), most of the substances are reabsorbed into the blood. Thus formed, the urine is conducted from the nephrons via the renal tubules into the ureter, which leads to the bladder.

Uranium internalized in high enough doses is toxic to the kidney (in milligram amounts), but even this exposure resulted in no long-term kidney change. It depresses glomerular function and tubular solute transport. Following inhalation and ingestion of uranium, one may experience no effect, acute but reversible damage to the glomeruli and tubules, or irreparable chronic renal damage, depending on the exposure level.

There are several signs of renal tubular dysfunction and glomerular damage. They include increases in urinary catalase, mild proteinuria, aminoaciduria, and increase in clearance of ß-2 microglobulin relative to that of creatinine and altered serum creatinine levels. Routine urine laboratory tests are available to detect these changes. To date, neither renal tubular dysfunction nor glomerular damage has been commonly observed among Gulf War veterans, even among veterans with embedded DU fragments.

There is evidence in humans and animals of repair of damaged tubular epithelial tissue. Acute exposures from accidents have caused acute renal damage, but all exposed persons have recovered with no observable long-term clinical signs or symptoms. The likelihood of developing delayed renal disease from

DU exposure if there has been no acute toxicity is not observed or supported by medical evidence. Furthermore, although no formal study has been conducted, evaluations of individuals who worked in DU testing sites across the United States have not shown increased rates of renal failure 15 to 20 years later (Oxenberg, 1998).

Many other conditions are associated with the kidneys but are not associated with nephrotoxicity from uranium exposure or other toxic substances. Examples include kidney stones (nephrolithiasis) and urinary tract infections (pyelonephritis).

Although chronic kidney disease has not been observed in human populations exposed to uranium, kidney disease is common in the United States. More than 20 million Americans suffer from diseases of the kidney and urinary tract. More than 90,000 die each year because of these diseases. About 200,000 Americans suffer from chronic kidney failure and need dialysis to stay alive. Diabetes is the leading cause of chronic kidney failure. It accounts for approximately one-third of new cases of chronic kidney failure in the United States each year. Uncontrolled or poorly controlled high blood pressure is the second leading cause of chronic kidney failure in the United States. It accounts for about 30 percent of all cases. Currently, some 1 million Americans are treated each year for kidney stones. The majority of these cases occur in people between 20 and 40 years of age. Kidney stones are more common in men, who account for about four out of five cases. Approximately 27 million American outpatient visits result from kidney and urinary tract problems (National Kidney Foundation, New York).

Liver Disease

The liver is the primary organ in the body responsible for metabolizing impurities and synthesizing proteins essential for life. The liver is also involved in sugar and fat metabolism. When individuals have liver damage, many normal body functions start to break down. Heavy metals have the potential to be toxic to the hepatocytes, the liver cells responsible for the majority of liver function. As these cells die, acute hepatic failure (with profound exposures) may ensue or scarring (cirrhosis) may occur with continued less severe exposures (e.g., chronic alcohol intake or hepatitis).

The liver is an incredibly resilient organ. Acute and chronic insult requires extremely high doses of most toxic substances, including uranium. Animal studies have suggested the possibility of hepatic injury as a result of high doses of uranium. However, liver toxicity has *not* been a finding among those exposed to DU. Liver toxicity has not been observed in workers at testing sites where individuals were exposed for considerably longer than those serving in the

Persian Gulf and not in other occupationally exposed individuals, such as mine workers. In addition, abnormal liver function tests have not been a common finding among individuals who served in the Gulf, making future hepatic disease not likely.[14]

Liver disease is common in the United States but higher-than-expected rates have not been observed in Gulf War veterans. Liver, bile duct, or gallbladder diseases afflict approximately 25 million Americans, or one in every ten. Liver and gallbladder disease is the seventh leading disease-related cause of death. Eliminating alcohol abuse alone could prevent 75–80 percent of the cases of cirrhosis.

Bone Cancer (Osteosarcoma)

Because bone retains uranium, the potential for an increased risk of bone cancer has been explored. As the bone concentration of uranium rises, the committee on the Biological Effects of Ionizing Radiation (NRC, 1988) reports, steadily eating food or drinking water that has uranium in it can be calculated to cause osteosarcoma in humans. The committee reports that the average daily diet of people contains 1 pCi of uranium. The upper limit to the number of bone sarcomas that is calculated to occur is one to two per every 1 million people based on the radiation dose. However, in real life even enriched uranium has not been shown to cause osteosarcomas in people or in animals.

Osteosarcoma is the most common of a number of different types of bone cancer. Bone contains osteoblasts responsible for forming bone matrix (connective tissue and mineral that gives bone its strength) and osteoclasts that prevent too much bone matrix from accumulating. Bone also contains bone marrow. Bone marrow contains fat cells and, most important, hematopoietic cells (the cells that produce blood).

Like osteoblasts of normal bone, the osteosarcomas produce bone matrix. However, the "malignant bone" tissue of an osteosarcoma is not as strong as normal bones. Further osteosarcomas can spread beyond the bone into nearby

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[14]The common blood tests for hepatocyte damage include elevated alanine aminotransferase (ACT or SGPT), aspartate aminotransferase (AST or SGOT), and bilirubin. Damage to the biliary system will produce elevated alkaline phosphatase and gamma glutamyltranspeptidase (GGT). With extensive liver damage, evidence of failure of the liver's synthetic capacity emerges with decreased production of albumin and other serum proteins. This results in ascites, decreased clotting factors resulting in bleeding tendencies, and decreased capacity to metabolize sugars, which in turn results in impaired glucose tolerance or diabetes.

tissues or through the bloodstream to the lungs, other bones, or other organs of the body.

There are about 900 new cases of osteosarcoma diagnosed in the United States every year. Teenagers are the most commonly affected age group. Osteosarcomas represent about 5 percent of all childhood cancers. In the adolescent years, only leukemias, brain tumors, and lymphomas occur more commonly than osteosarcoma. About 25 percent to 30 percent of patients diagnosed with localized high-grade osteosarcoma will die from the disease. Osteosarcoma is almost twice as common in males as in females. There appears to be a threshold level of radionuclides associated with induction of osteosarcoma. The large study of radium dial painters showed that no osteosarcomas were observed below a dose of about 1,000 rads (10 Gray) (Rowland et al., 1978).

Patients treated with radiation for another cancer have a higher risk of later developing postradiation osteosarcoma. Being treated at a younger age and/or being treated with higher doses of radiation both increase the risk of developing osteosarcoma. There is minimal if any danger of developing osteosarcoma from having diagnostic X rays.

The risk of osteosarcoma clearly increases with radiation dose. However, the amount of radiation emitted by DU is insufficient to raise the risk of osteosarcoma. This is particularly true in adults, whose risk is already quite low (osteosarcomas are more common when bones are growing rapidly, such as in adolescents). Continuous intake of natural dietary uranium (about 35 mBq or 1.4 µg/day) results in a skeletal alpha dose of 0.25 µGy/year (25 µrad/year) in the United States (Fisenne et al., 1988). Osteosarcoma has never been observed in humans at a skeletal dose less than about 10 Gy and has not been observed in populations exposed to any form of uranium, including enriched uranium.

Reproductive Effects of DU

Information also exists regarding the potential impact continued exposure to elevated uranium levels may have on reproductive health. As with other discussions in this report, consideration must be given to both the radioactive and heavy-metal toxicity associated with exposure. Reproductive health effects can be divided conceptually into structural effects (those damaging or destroying the reproductive system including the germ lines and supportive structures), genotoxic effects (those that alter genetic material that would be passed to offspring, leading either to fetal demise or birth defects), and developmental effects (those affecting the existing fetus, adversely impacting *in utero* development).

Studies that address human reproductive effects of uranium are limited, and most of the discussions concern exposure to high levels of high-specific-activity uranium, or natural uranium in combination with other sources with the potential to impact reproductive health (e.g., miners exposed to radon and tobacco products). Uranium is primarily an alpha-emitting source of radiation; there is therefore, the potential for DNA damage and fragmentation (ATSDR, 1997, Chapter 2). However, in a report prepared for the U.S. Public Health Service, the Research Triangle Institute was unable to unequivocally identify genetic effects in humans exposed to any radiation level. The study concludes, "because the specific activities of natural and depleted uranium are low, no radiological health hazard is expected from exposure to natural and depleted uranium." (ATSDR, 1997.)

Much effort has been expended in the continuous follow-up of Japanese atomic-bomb survivors, with particular emphasis on genetic and teratogenic effects. The average exposure to the follow-up population of 40,000 persons was 0.30 Sv (30 rem). No statistically significant effects of parental exposure have been found. The atomic-bomb study accounted for the genetically significant dose, the sample size, the sensitivity of the end points, i.e., untoward pregnancy outcomes, sex chromosomal anomalies, survival through the first 17 years of life, and the frequency of biochemical variants (UNSCEAR, 1986). Their conclusion, noting the absence of significant genetic effects in the Hiroshima and Nagasaki populations, is consistent with the expectations based on mouse data (UNSCEAR, 1986).

No genetic or teratogenic effects have been observed from natural background radiation. The genetically significant radiation dose to the gonads from DU in veterans, even with the highest exposure, is increased negligibly above the natural background. For Gulf War veterans, this increase is less than would be expected to occur naturally for individuals living in areas where uranium is more abundant in food and water sources (see Chapter Two). Therefore, no significant genetic effects due to radiation from DU would be expected in Gulf War veterans.

From a toxicological perspective, the uranyl ion, however, is reactive and complexes with organic and inorganic compounds to form chemical substances with the potential to damage DNA. Studies document the impact of mutagenic compounds on reproductive health. Information regarding the explicit impact uranium has on reproductive function in animals varies. Table 2.6 lists various studies and their reported results. Most studies do not demonstrate structural damage at the histologic level; however, some forms of uranium, particularly uranyl nitrate, have been shown to be genotoxic in *in vitro* settings (Lin, 1993).

Table 2.6

Reproduction Studies Examining the Effects of Uranium on Reproductive Health

Study	Study Design	Results
Domingo et al., 1989	Natural Uranyl acetate dihydrate Pregnant Mice Administration: Gavage Impact: Developmental	5, 10, 25, 50 mg/kg/day Material toxicity Decreased fetal body weight/length Malformations at 25 at 50 mg/kg/day Some fetotoxicity at 25 mg/kg/day No embryolethality
Hu et al., 1990	Enriched UO_2F_2 Male Mice Intraperitoneal Impact: Genotoxicity	2 mg UO_2F_2/kg 0.5–6.0 mg/kg (dosing study) Dose relationship DNA elution and UO_2F_2
Malenchenko, 1978	Natural $UO_2 (NO_3)6$–H_2O Rats Subcutaneous (acute) Oral (chronic) Impact: Structural	Acute: 0.1 mg/kg x 5 days (SQ) Chronic 0.1% uranyl nitrate in water x 4 month Autoimmune appearing thyroiditis and orchitis
Llobet, 1991	Natural Uranyl acetate dihydrate Male Mice Oral (in water) Impact: Structural	0, 10, 20, 40, 80 mg/kg/day x 64 days No signs of clinical toxicity Decreased sperm counts at all levels Body weights unchanged Histopathologic alterations in 80 mg group Focal tubular atrophy and interstitial cell alterations occur
Lin et al., 1993	Uranyl nitrate *In vitro* Chinese Hamster Ovaries Impact: Genotoxicity	0.01–0.30 mM concentration range Dose-related response 50% inhibition of viability at 0.049 mM Decreased cell cycle kinetics Increased micronuclei and chromosomal aberrations Uranyl nitrate is genotoxic and cytotoxic
Paternain, 1989	Uranyl acetate dihydrate Oral Mice Impact: Genotoxicity, Developmental	0, 5, 10, 25 mg/kg/day x 60 days (males) and through mating/breeding (females) No adverse effect on fertility Embryo lethality at 25 mg/kg/day levels Slow offspring growth
Benson and Pellmar, 1998	DU Pellets Embedded Rats Impact: No effect on structural, genotoxic, or developmental aspects of reproductive health	0 to 32 1 mm diameter, 2 mm long pellets Significant placental and fetal accumulation No effect on maternal or litter parameters
McClain, 1998	DU Pellets Embedded Female Rats Impact: Developmental	0 to 32 1 mm diameter, 2 mm long pellets Uranium accumulates in the placenta and fetus Decreased litter size with breeding at 6 months post-implantation
Brandom, 1978	Miners (men) Peripheral blood lymphocytes Impact: Genotoxicity	Increased chromosome aberrations
Dupree, 1987	Uranium processors (white men) Mortality Impact: Possibly Genotoxicity	Increased death from all causes, laryngeal carcinoma, circulatory and atherosclerosis, respiratory diseases, pneumonia

Preliminary results by AFRRI (McClain, 1998) suggest that, at least in animal models, there may be some effects on reproduction (litter size) when DU is implanted into female rats at high levels, particularly when breeding occurred several months after implantation (i.e., some delayed effect). Results suggest that litter size decreases when female rats have implanted with 32 DU pellets (1 mm diameter x 2 mm long). This effect was not noted in female rats implanted with from 4 to 20 pellets for litters right after implantation (Benson and Pellmar, 1998).

With respect to the studies shown in Table 2.6, the concentrations of uranium used to elicit any observed effects through ingestion or inhalation are orders of magnitude greater than the highest exposure that would occur in military or industrial settings (see Table 2.7). To attain the same concentration in blood as in the Swiss mice experiments (Paternain, 1989; Llobet, 1991), grams of uranium would have to be inhaled daily. This quantity was clearly not achievable in the Gulf War setting.

Table 2.7

Calculated Blood Uranium Concentrations in Animal Experiments with Mice Versus an Equivalent Human Inhalation During the Gulf War (mg/kg body weight/day)

MOUSE		
Ingested dose (mg/kg/day)	Ingested per day (mg)	Blood (dose x 0.05) (mg/kg/day)
5	0.15	0.25
10	0.30	0.50
25	0.75	1.25
HUMAN		
Inhaled dose (mg/kg/day)	Inhaled per day (mg)	Blood (dose x 0.01) mg/kg/day
25	1,750	0.25
50	3,500	0.50
125	8,750	1.25

NOTE: Calculations are based on a human male weighing 70 kg and a mouse weighing 0.03 kg. The mouse experiments described above were designed to understand reliable standards for drinking water for humans. Their conclusions were that no toxic effect of any kind could be detected in humans with a drinking water standard of 100 µg per liter. (Paternain, 1989; Llobet, 1991)

Similarly, for the AFRRI studies employing the use of embedded uranium pellets, the lowest dose to which rats were exposed is reported greater than the highest possible DU levels observed in Persian Gulf veterans with embedded DU fragments (McClain, 1998). Findings also demonstrate the presence of DU in the placenta and the fetus, although the concentration of DU in the fetus is about one order of magnitude less than in the placenta. This result suggests that, while the placenta-fetal barrier protects the developing fetus somewhat from DU, that protection is far less than absolute. No animal studies were found that studied the reproductive effect of uranium on male rats. However, the AFRRI is planning to perform such a study on male animals exposed to DU.

Studies are currently under way by McDiarmid and colleagues at the Baltimore VA Medical Center as part of the DU Follow-Up Program to further evaluate the 33 Gulf War veterans. About half of these 33 individuals have embedded DU fragments. Findings to date have failed to demonstrate clinically relevant abnormalities (beyond those associated with the specific injury). However, most of the veterans with embedded fragments, as previously discussed, continue to have elevations in urinary uranium excretion. VA researchers have also found DU in the semen of some of the veterans with embedded fragments. To date, approximately 17 children have been born to female partners of these 33 men. All of these offspring are without evidence of birth defects (McDiarmid, 1998b). Investigators are completing a follow-up of these individuals, comparing additional laboratory parameters (e.g., sperm morphology and activity, semen characteristics, and serum hormone levels) relative to a control group who did not have uranium exposure (McDiarmid and Keogh, 1998). To date, these investigators have observed normal sperm morphology and counts. Furthermore, examination for chromosomal aberrations and sister chromatid exchange were within the reference limits. Therefore, increased chromosomal aberrations that were reported among uranium miners (Brandom, 1978) have not been found to date among Persian Gulf veterans with embedded DU. There are too few offspring among the 33 veterans with possible embedded DU to draw any conclusions similar to those observed with respect to sex ratio differences in uranium miners' offspring (Müller, 1967).

In summary, to the extent that reproductive health issues related to uranium have been investigated to date, there have not been findings that would suggest a relationship between levels of exposures that could have occurred in the Persian Gulf and those that are associated with adverse outcomes in animal experiments. Further studies are currently under way, particularly with respect to evaluating the impact of uranium on male reproductive health.

CONCLUDING REMARKS AND FUTURE RESEARCH

After examining the chemical and physical nature of DU, this report has surveyed the literature related to the health effects of DU through both external and internal exposure. Potential health effects were divided into those associated with radiation and with heavy-metal toxicology.

Few studies to date in the literature have focused directly on DU. On the other hand, there is a wealth of literature related to natural and enriched uranium. This literature provides many relevant insights because the heavy-metal chemical toxicity of DU is the same as that of natural and enriched uranium. Further, both natural and enriched uranium are far more radioactive than DU. Therefore, if no adverse health effects to natural uranium are reported, one may reasonably conclude the same will be the case for DU.

RADIATION EFFECTS

The literature review examined the extensive published data on radiation that has looked at the relationship between exposure to uranium through various pathways—inhalation, ingestion, and external exposure—and possible health effects. Available information includes data on human exposure to natural uranium through the normal pathways of diet and inhalation, studies of miners and millers in the uranium industry, findings on animals, and some studies relating directly to Gulf War veterans.

From the scientific literature it is concluded that:

- Although any increase in radiation to the human body can be calculated to be harmful from extrapolation from higher levels, there are no peer-reviewed published reports of detectable increases of cancer or other negative health effects from radiation exposure to inhaled or ingested natural uranium at levels far exceeding those likely in the Gulf. This is mainly because the body is very effective at eliminating ingested and inhaled natural uranium and because the low radioactivity per unit mass of natural

uranium and DU means that the mass of uranium needed for significant internal exposure is virtually impossible to obtain.

- External radiation in the form of alpha radiation cannot penetrate cloth or skin and would therefore have no negative health effect. Beta and gamma radiation, which can have negative health effects, have been measured at levels below those expected to be of concern.

- Large variations in exposure to radioactivity from natural uranium in the normal environment have not been associated with negative health effects.

- Radiation-related effects from embedded fragments will depend on the size of the fragment and its proximity to vital organs.

- The cohort of individuals, about half of whom have embedded fragments, who are being followed at the Baltimore VA Medical Center as part of the DU Follow-Up Program, represents a group of Gulf War veterans who received the highest levels of exposure to DU during the Gulf War. Although many of these veterans have health problems related to their injuries in the Gulf War and those with embedded fragments have elevated urinary uranium levels, researchers to date do not find adverse health effects they relate to radiation from DU, but several perturbations in biochemical and neuropsychological testing have been correlated with elevated urinary uranium, the clinical significance of which is unclear (McDiarmid, 1998b).

HEAVY-METAL TOXICOLOGICAL EFFECTS

Uranium in the form of the isotopically depleted metal used for military purposes in the Gulf War presents primarily a potential chemical rather than radiological hazard. Like most heavy metals, uranium possesses a high chemical affinity for proteins and other biological molecules. It normally is taken up into the body through the lungs (via inhalation) or intestine (via ingestion) but in military settings may also penetrate the body as fragments. These slowly dissolve, posing a risk of chemical exposure.

The kidneys show special sensitivity to the chemical toxicity of uranium. While this does not exclude the possibility of the metal inflicting functional lesions in other organ systems, the first adverse chemical effects following high or prolonged exposure to uranium are found in the kidney. Proximal tubular function in particular is depressed, but lesions in other nephron segments have also been reported. In the case of high exposures, renal function can serve as a sensitive biomonitor.

The literature provides the following insights:

- Exposure to uranium and other heavy metals in large doses can cause changes in renal function and at very high levels result in renal failure.

- In spite of these findings, no increased morbidity or frequency of end-stage renal disease has been observed in relatively large occupational populations chronically exposed to natural uranium at concentrations above normal ambient ones.

- As indicated above, the individuals being followed as part of the DU Follow-Up Program at the Baltimore VA Medical Center who were exposed to aerosolized DU and in about half the cases to embedded fragments, represent a sample of individuals who received some of the highest exposure to DU in the Gulf War. Researchers report no adverse renal effects due to DU exposure, although most individuals with embedded fragment have elevated urinary uranium levels, but several perturbations in biochemical and neuropsychological testing have been correlated with elevated urinary uranium, the clinical significance of which is unclear (McDiarmid, 1998b).

RESEARCH

Although there is already a large body of literature on natural uranium, below we list some areas likely to prove fruitful in enhancing our knowledge of the health effects of DU. We encourage additional research into both the effects of exposure and long-term epidemiology studies to further our understanding of the health effects of DU. Among other research, the following areas of inquiry would be useful:

- It would be helpful to conduct further long-term epidemiological studies in veterans of the Gulf War to the degree that the availability of exposure information permits such research.

- Because risk assessment has advanced greatly since many of the standards for both occupational and population exposures were developed, reexamination of those standards and refined dose response end points by these organizations would be helpful.

- Research to better understand the mechanisms and dose response of exposure to DU on renal function would be helpful. Attempts should be made to correlate nephrotoxicity with renal uranium concentration following different modes and levels of exposure. Knowledge of cortical concentration would be more informative than total renal uranium levels. The U.S. Transuranium Registry is a continuing source of these data (Kathren and Ehrhart, 1998). It is also important to continue work to understand the mechanism by which natural and depleted uranium exert toxic effects on the body. This would include work to understand the nature and toxico-

logical significance of the separate uranium pools kinetically identified in the kidney. Modern techniques should permit analysis of distribution of the toxic metal in the kidney, and more-sophisticated dose-effect studies than those relying on total tissue concentration at one arbitrary time are appropriate.

- The work of the DU Follow-Up Program being conducted and expanded at the Baltimore VA Medical Center is important and needs to continue. The cohort and research present the best opportunity to study the effects of human exposure to DU over time that is now available.

- Although ionizing radiation from DU is in the form of alpha particles, the decay products emit gamma and beta radiation that could affect those in proximity to DU weapons. Although research to date has indicated that levels of exposure are significantly below occupational levels, ongoing efforts to study the levels of exposure from such radiation to soldiers in proximity to DU weapons or armor should continue, especially as weapons and weapon systems vary over time.

- A research protocol should be developed to study troops in the next situation in which they are likely to be exposed to DU. This would include urinalysis of a sample of individuals with oversampling of those likely to be exposed (e.g., troops in charge of damaged tank cleanup) before deployment, and tests immediately after significant exposure and for some time. Once exposure information is obtained, following health outcomes over time in well-designed epidemiology studies would provide needed information.

- In the meantime, although there is already a large body of literature on natural uranium, animal studies that simulate exposure to DU in a chemical form consistent with exposure from weapons and via various pathways (inhalation, ingestion, and embedded) at various levels to study health effects and various diagnostic techniques would enhance understanding of possible health effects if any, limits of exposure, and mechanisms of action.

In conclusion, the use of DU munitions and armor is likely to expand greatly over the coming years, both in the U.S. military and in other countries. It is therefore important to continue research to further our knowledge of any potential health risks that might result from different levels and pathways of exposure.

PRINCIPAL DECAY SCHEME OF THE URANIUM SERIES

RAND *MR1018/7-A.1*

^{238}U (UI)
4.5 x 10^9 years
4.2 MeV

^{234}U (UII)
2.5 x 10^5 years
4.7-4.8 MeV

^{234}Pa (UX$_2$)
1.2 minutes
2.3 MeV

^{234}Th (UX$_1$)
14 days
0.2, 0.1 MeV

^{230}Th (Io)
8.0 x 10^4 years
4.6-4.7 MeV

^{226}Ra
1,600 years
4.8 MeV

^{222}Rn
3.82 days
5.5 MeV

^{218}Po (RaA)
3.05 minutes
6.0 MeV

^{214}Po (RaC')
1.6 x 10^{-4} seconds
7.7 MeV

^{210}Po (RaF)
138 days
5.3 MeV

^{214}Bi (RaC)
19.7 minutes
0.4-3.3 MeV

^{210}Bi (RaE)
5.0 days
1.2 MeV

^{214}Pb (RaB)
26.8 minutes
0.7, 1.0 MeV

^{210}Pb (RaD)
22 years
< 0.1 MeV

^{206}Pb (RaG)
Stable

Beta Decay
Alpha Decay

Figure A.1—Principal Decay Scheme of the Uranium Series

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PRINCIPAL DECAY SCHEME OF THE ACTINIUM SERIES

RAND *MR1018/7-B.2*
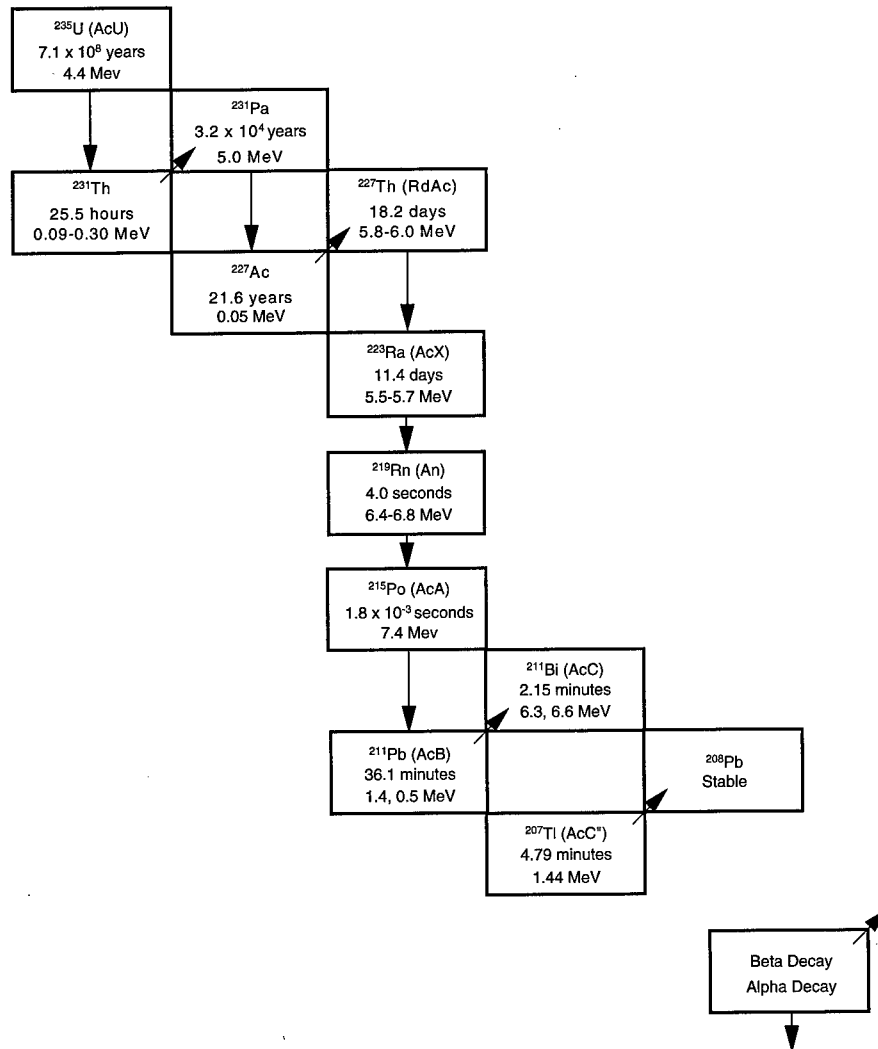
Figure B.1—Principal Decay Scheme of the Actinium Series

RESUSPENSION

One widely used method to determine the environmental transport of small aerosolized particles due to resuspension is utilized by the U.S. Department of Energy (DOE) computer code RESRAD. This code addresses the calculation of potential exposure due to material deposited on the ground at DOE sites formerly used in the production of nuclear weapons and fuel. The equation for the environmental transport factor (ETF) is:

$$ETF \text{ (g/yr)} = ASR \times FA \times FCD \times FO \times FI$$

where

ETF = environmental transport factor for dust inhalation (g/yr)

ASR = air/soil concentration ratio = average mass loading of airborne contaminated soil particles (2×10^{-4} g/m^3).

FA = area factor (dimensionless)

FCD = cover and depth factor (dimensionless)

FO = occupancy factor (dimensionless)

FI = annual breathing rate (8,400 m^3/yr)

The area factor, FA, is the fraction of airborne dust contaminated. It is calculated using a mixing model for estimating the dilution of contaminated dust that is resuspended on-site by uncontaminated dust blown in from off-site. In the particular case of DU, it would be the fraction of surface soil contaminated with DU. Isotopic analysis is necessary to separate DU from natural uranium. The factor, FA, is estimated in RESRAD from:

$$FA = \frac{\sqrt{A}}{\sqrt{A+DL}}$$

where

A = area of the contaminated zone (m^2)

DL = dilution length (3 m)

The dilution length, DL, depends on the wind speed, mixing height, resuspension rate, and thickness of the resuspendable dust layer (Gilbert et al., 1983). Estimates of the lower and upper bounds of DL are 0.03 and 250 m, respectively.

The cover and depth factor, FCD, is the fraction of resuspendable soil particles at the ground surface that are contaminated:

$$FCD = \frac{T(t)}{d_m}$$

where

T(t) = thickness of contaminated zone at time t

d_m = depth of soil mixing layer (0.15 m)

The occupancy factor, FO, depends on the time spent in the contaminated area. An upper limit is assumed to be a few percent, in zones where a DU puff occurred.

The total annual inhalation exposure (in grams of DU inhaled per year) is then estimated from the equation assuming average values and a credible range of values.

A complicating factor in the estimation of the environmental transport factor, ETF, is that natural uranium is present in all soil and resuspended airborne soil. The natural concentration averages 37 mBq/g. The EPA has measured uranium in air for many years. This includes measurements in 25 cities in the United States in their Environmental Radiation Ambient Monitoring Program (ERAMS). DU present must be evaluated in the presence of natural uranium, and isotopic values are requisite to provide sufficient information.

SINGLE-PARTICLE LUNG DOSIMETRY

Single-particle lung dosimetry is not applicable for inhaled aerosol particles of DU because of its very low specific activity. An aggregate of particles is necessary to confer a radiation dose.

As an example, a 1 μm particle in the lung would emit about five alpha particles per year, resulting in a negligible radiation dose, assuming the particle was resident for that long a time. As a frame of reference, lung cancer has been well documented in underground miners exposed to the short-lived alpha emitting decay products of ^{222}Rn gas (^{218}Po and ^{214}Po). The decay products are formed in air as atoms and rapidly attach to the ambient aerosol particles and, when inhaled, deposit on the bronchial airways. The bronchial airways are the site of the majority of lung cancers (Saccomanno et al., 1995). Lung cancer associated with the gas exchange or pulmonary region is rare.

The bronchial airways are lined with a thin layer of tissue called bronchial epithelium. The epithelium averages 30 to 40 μm in thickness and the target cells for lung cancer are in this area. The specific target cells are basal and secretory cells and lie at a depth of about 25 μm in the epithelium, within the range of all alpha particles emitted from decay products deposited on the bronchial airway surface. The function of the target or stem cells is to continually produce the cells that constitute the airway lining. These are fully differentiated cells and have a life span of a few months. Lung cancer can only arise in stem cells (i.e., cells capable of ongoing division).

The number of target cells in the bronchial epithelium required to be hit in order to develop a lung cancer can be calculated from the physical dosimetry of the inhaled decay products and the observed lung cancer risk in the miners. This calculation has been performed, and it is estimated that about 10^9 hits are necessary (Harley et al., 1996). Thus, although it requires perhaps only one very special or "particular hit" of a cell to develop a cancer, the "particular hit" must be exquisitely correct and the requirement is that a very large number of hits of the target cells is needed to provide that "particular hit."

An estimate of the amount and number of DU particles inhaled may be made with the stipulation that about 10^9 target cells must be hit to produce a cancer. If the aerosol particle size inhaled is assumed to be 1 μm, then about one gram must be inhaled per day (10^{11} particles/day) for several weeks, because of the requisite 10^9 target cells to be hit.

In the Colorado uranium mining cohort of 3,360 men, for example, there were on average 10^8 calculated target cells in bronchial epithelium hit per person because of their short-lived decay product exposure. Less than 10 percent of lung cancer is documented to date (NIH, 1994) with some of the lung cancer associated with smoking. In summary, lung cancer stemming from alpha particle irradiation is a very-low-probability event.

EXPOSURE TO RADON (^{222}RN) AND ITS DECAY PRODUCTS

Lung cancer is well documented in underground mines, where miners are exposed to the short-lived decay products of ^{222}Rn gas. The decay products are solids (^{218}Po, ^{214}Pb, and ^{214}Bi), and although they are formed as atoms, the majority rapidly attach to the ambient aerosol particles (0.1 to 0.2 μm diameter). These particles are inhaled, and a fraction deposit on the bronchial airway epithelium, a thin layer where the target cells for carcinogenesis are located. The decay products have a very short half-life, ranging from 3.05 to 26.8 minutes, and therefore the decay products have the opportunity to emit alpha particles before bronchial clearance removes them.

The most complete analysis of the health detriment to underground miners is published in the document "Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Miners Studies" (NIH, 1994). This work brought together the investigators from each of the 11 mining groups, and their data were analyzed jointly to provide the best information for estimating the lung cancer risk from exposure to ^{222}Rn and decay products. There were 2,701 lung cancer deaths among 68,000 miners accumulating about 1.2 million person-years of exposure.

In all of the 11 cohorts, the excess relative risk (ERR) of lung cancer (the fractional increase in lung cancer) was linearly related to the cumulative exposure estimated in working level months (WLM). Thus, although other carcinogens may be present in mine atmospheres, a clear relationship was associated with exposure to ^{222}Rn decay products.

One important aspect of the data is that the ERR at very high exposures tends to flatten out. This observation is erroneously called the inverse exposure effect. It is usually stated that the lung cancer risk per unit exposure increases for low exposures compared with high exposures. The flattening of the response curve is likely the result of cell killing due to multiple traversals of cell nuclei. Therefore, the effect is a reduced response at high exposure, not an increased response at low exposure.

This terminology has caused considerable confusion with the implication that domestic exposure can somehow be "more dangerous" than mine exposure. This is not true, and it has been demonstrated that no additional risk above the linearity showed in all cohorts is present in domestic exposures. In fact, no domestic study has yet shown a statistically significant excess of lung cancer.

The main features of the lung cancer risk model derived from the jointly analyzed data are as follows:

1. There is a reduction in risk subsequent to cessation of mining. This is called the time since exposure (TSE factor) effect.

2. There appears to be no clear age at start of exposure effect (i.e., the age at start of mining is not an obvious factor). However, the age attained after start of mining is a factor and there is decreased risk with older age (AGE factor).

3. Longer duration (DUR factor) or lower ^{222}Rn concentration (WL factor) gives rise to larger risk. As this is the way the model parameters are derived, it is the reason for the so called "inverse exposure effect."

The two models derived from the joint analysis are considered equally likely as a fit to the observations. A striking feature of the data is the time since exposure effect, with three time windows modeled for the joint analysis versus two time windows modeled in the BEIR IV report when four cohorts were available for analysis.

1. TSE/AGE/WL Model for Relative Risk (RR)

$$RR = 1 + \beta \times (w_{5-14} + \theta_2 w_{15-24} + \theta_3 w_{25+}) \times \phi_{age} \times \gamma_{WL}$$

w_{5-14}, w_{15-24} = the exposure in WLM 5 to 14 years prior to the end of mining, etc.

$\beta = 0.0611, \theta_2 = 0.81, \theta_3 = 0.40$

ϕ_{age} = 1 for age <55

= 0.65 for age from 55 to 64

= 0.38 for age from 65 to 74

= 0.22 for age 75 and greater

γ_{WL} = 1.0 for WL < 0.5

= 0.51 for WL from 0.5 to 0.9

= 0.32 for WL from 1.0 to 2.9

= 0.27 for WL from 3.0 to 4.9

= 0.13 for WL from 5.0 to 14.9

= 0.10 for WL 15 and greater.

2. TSE/AGE/DUR Model for Relative Risk (RR)

$$RR = 1 + ß \times (w_{5\text{-}14} + \theta_2 w_{15\text{-}24} + \theta_3 w_{25+}) \times \phi_{age} \times \gamma_{DUR}$$

$ß = 0.0611, \theta_2 = 0.81, \theta_3 = 0.40$

ϕ_{age} = 1 for age <55

= 0.57 for age from 55 to 64

= 0.34 for age from 65 to 74

= 0.28 for age 75 and greater

γ_{DUR} = 1.0 for DUR < 0.5

= 3.17 for DUR from 0.5 to 14.9

= 5.27 for DUR from 15.0 to 24.9

= 9.08 for DUR from 25.0 to 34.9

= 13.6 for DUR 35 and greater.

The nature of the short-lived decay products of ^{222}Rn provides an efficient means to irradiate target cells for cancer in the bronchial epithelium. They attach to very small ambient aerosol particles (about 0.1 to 0.2 µm diameter) and a few percent of these deposit on the airway surface on inhalation. The majority of the decay products actually deposit in the pulmonary region (about 25 percent), but the large area of the gas exchange region in the pulmonary compartment yields few alpha particle decays per unit area, yielding less dose. Thus the majority of lung cancer associated with ^{222}Rn decay products is bronchogenic, similar to that for tobacco-related lung cancer (Saccomanno, et al., 1996).

UNSCEAR TABLES

Table F.1

Conversion Coefficients from Air Kerma to Effective Dose for Terrestrial Gamma Rays

Radionuclides	Conversion Coefficient (Sv per Gy)		
	Adults	Children	Infants
K-40	0.74	0.81	0.95
Th-232 series	0.72	0.81	0.92
U-238 series	0.69	0.78	0.91
Overall	0.72	0.80	0.93

Table F.2

National Estimates of the Average Annual Effective Dose from Terrestrial Gamma Rays

Country	Effective Dose (mSv)
Bulgaria	0.45
Canada	0.23
China	0.55
Denmark	0.36
Finland	0.49
Germany	0.41
Japan	0.32
Norway	0.48
Spain	0.40
Sweden	0.65
United Kingdom	0.35
United States	0.28
USSR	0.32
Population-weighted world average	0.45

Table F.3

Reference Annual Intake of Food and Air

Intake	Food Consumption (kg per year)		
	Adults	Children	Infants
Milk products	105	110	120
Meat products	50	35	15
Grain products	140	90	45
Leafy vegetables	60	40	20
Roots and fruits	170	110	60
Fish products	25	10	5
Water and beverages	500	350	150
Intake	Breathing Rate (m^3 per year)		
	Adults	Children	Infants
Air	8,000	5,500	1,400

Table F.4

Reference Activity Concentrations of Natural Radionuclides in Food and Air

Intake	^{238}U–^{234}U	^{230}Th	^{226}Rn	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	^{228}Th	^{235}U
				Activity Concentration (mBq/kg)					
Milk products	1	0.5	5.0	40	60	0.30	5.0	0.30	0.05
Meat products	2	2.0	15.0	80	60	1.00	10.0	1.00	0.05
Grain products	20	10.0	30.0	100	100	3.00	60.0	3.00	1.00
Leafy vegetables	20	20.0	50.0	30	30	15.00	40.0	1.50	1.00
Roots and fruits	3	0.5	30.0	25	30	0.50	20.0	0.50	0.10
Fish products	30	NA	100.0	200	2,000	NA	NA	NA	NA
Water supplies	1	0.1	0.5	10	5	0.05	0.5	0.05	0.04

Intake	^{238}U–^{234}U	^{230}Th	^{226}Rn	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	^{228}Th	^{235}U
				Activity Concentration (μBq/m^3)					
Air	1	0.5	0.5	500	50	1	1	1	0.05

Table F.5

Committed Effective Dose per Unit Activity Intake of Natural Radionuclides for Adults

Radionuclide	Ingestion		Inhalation	
	Fractional Transfer in Blood	Dose Coefficient (µSv/Bq)	Class of Solubility	Dose Coefficient (µSv/Bq)
U-238	0.0500	0.025	Y	30
U-234	0.0500	0.030	Y	30
Th-230	0.0002	0.070	Y	50
Ra-226	0.2000	0.200	W	2
Pb-210	0.2000	1.000	D	2
Po-210	0.1000	0.200	D	1
Th-232	0.0002	0.400	Y	200
Ra-228	0.2000	0.300	W	1
Th-228	0.0002	0.070	Y	100
U-235	0.0500	0.030	Y	30
Pa-231	0.0010	2.000	W	200
Ac-227	0.0010	2.000	W	300

Table F.6

Average Age-Weighted Annual Intakes of Natural Radionuclides and Associated Effective Doses

Radionuclide	Ingestion		Inhalation	
	Intake (Bq)	Dose (µSv)	Intake (mBq)	Dose (µSv)
U-238	4.90	0.12	6.9	0.21
U-234	4.90	0.15	6.9	0.21
Th-230	2.50	0.18	3.5	0.18
Ra-226	19.00	3.80	3.5	0.01
Pb-210	32.00	32.00	3,500.0	7.00
Po-210	55.00	11.00	350.0	0.35
Th-232	1.30	0.52	6.9	1.40
Ra-228	13.00	3.90	6.9	0.01
Th-228	2.30	0.09	6.9	0.69
U-235	0.21	0.01	0.4	0.01
Total	146.60	52.00	3,291.9	10.00

MEASURED DEEP DOSE RATES FOR M60A3 AND M1 TANKS

Table G.1

Measured Deep Dose Rates for the M60A3 Tank

Dosimeter Location	Dose Rates (mrem/hr)
Crew Members	
Driver	
Head	0.15
Torso	0.18
Left leg	0.21
Average (incl. leg)	0.18
Loader	
Head	0.09
Torso	0.13
Groin	0.18
Average	0.04
Gunner	0.04
Commander	
Head	0.03
Chest	0.04
Groin	0.04
Average	0.04
Tank Structures	
Steering column	0.19
Ledge behind commander	0.05
Ammo stacked 3-high on floor	
Top	0.33
Front	0.14
Between unpackaged cartridges	1.99
Top hatch above driver	0.11
Back chassis below bustle	0.12

SOURCE: OSAGWI, 1998, Tables 17–18, p. 36.

Table G.2

Measured Deep Dose Rates for the M1 Tank

Dosimeter Location	Dose Rates (mrem/hr)
Crew Members	
Driver	
Head	0.15
Back	0.05
Groin	0.12
Average	0.11
Loader	
Head	0.01
Back	0.01
Average	0.01
Gunner	
Torso	0.01
Commander	
Head	0.01
Torso	0.01
Tank Structures	
Steering column	0.19
Ammo stacked 3-high on floor	0.47
Support between ready boxes	0.00
Top of bustle, penetrator end	0.30
Back end of bustle	0.09
Underside of bustle above driver	0.31
Running board	0.01

SOURCE: OSAGWI, 1998, Tables 17–18, p. 36.

Absorbed Dose, Radiation—The energy absorbed per unit mass. The special name is the Gray (Gy = 1 joule per kilogram). The historical unit is the rad (rad = 100 ergs/gram). The conversion is 100 rad = 1 Gy.

Absorbed Fraction—A term used in internal dosimetry. It is that fraction of the photon energy (emitted within a specified volume of material) that is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape, and composition of the volume.

Absorption—The process by which radiation imparts some or all of its energy to any material through which it passes.

Activity—The number of nuclear transformations occurring in a given quantity of material per unit time (see curie, becquerel).

Activity Median Aerodynamic Diameter (AMAD)—The diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire aerosol.

Acute Radiation Syndrome—The symptoms that, taken together, characterize a person suffering from the effects of intense radiation. The effects occur within hours or days.

Alpha particle—A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus, but of nuclear origin. It comprises two neutrons and two protons and has a mass number of 4 and an electrostatic charge of +2.

Alpha Track—The track of ionized atoms left in any matter by an alpha particle that has traveled through the matter.

Atom—The smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the *nucleus*, which contains *protons* and *neutrons* and an outer shell of *electrons*.

Atomic Mass (u)—The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1.6604×10^{-24} g.

Atomic Number—The number of protons in the nucleus of a neutral atom of a nuclide. The "effective atomic number" is calculated from the composition and atomic numbers of a compound or mixture. An element of this atomic number would interact with photons in the same way as the compound or mixture (Symbol: Z).

Atomic Mass Number—See Mass Number.

Atomic Weight—The weighted mean of the masses of the neutral atoms of an element expressed in atomic mass units.

Background Radiation—The amount of radiation to which a member of the general population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body.

Becquerel (Bq)—International System of Units unit of activity and equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (1 Bq = 1 disintegration per second = 2.7×10^{-11} Ci).

Beta Particle—Charged particle emitted from the nucleus of an atom. A beta particle has a mass and charge equal in magnitude to that of the electron. The charge may be either +1 or –1.

Biological Half-Time—The time required for a biological system, such as that of a human, to eliminate by natural process half of the amount of a substance (such as a chemical substance or radioactive material) that has entered it.

Body burden, Chemical—The total amount of a substance found in a biological system, such as that of a human.

Body burden, Radioactivity—The amount of radioactive material present in the total body.

Bone Seeker—Any compound or ion that migrates in the body and preferentially deposits into bone.

Carcinogen—A chemical capable of inducing cancer.

Carcinoma—Malignant neoplasm composed of epithelial cells, regardless of their derivation.

Charged Particle—An ion. An elementary particle carrying a positive or negative charge.

Collective dose—The sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation.

Committed Effective Dose (S)—Following an intake into the body of a radioactive material there is a period during which the material gives rise to an effective dose. The committed effective dose is the time integral of the effective dose rate. If the time interval is not specified it is implied that the value is 50 years for the adult.

Committed Equivalent Dose $H_t(t)$—Following an intake into the body of a radioactive material there is a period of time during which the material gives rise to an equivalent dose. The committed equivalent dose is the time integral of the equivalent dose rate. If the time interval is not specified it is implied that the value is 50 years for the adult.

Contamination, Radioactive—Deposition of radioactive material in any place where it is not desired.

Cosmic Rays—High-energy particulate and electromagnetic radiation, which originate outside the earth's atmosphere.

Curie (Ci)—A unit of radioactivity. One curie equals that quantity of radioactive material in which there are 3.7×10^{10} nuclear transformations per second (1 Ci = 3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq). The activity of 1 gram of radium is approximately 1 Ci.

Daughter Products—See Progeny.

Decay, Radioactive—Transformation of the nucleus of an unstable nuclide by spontaneous emission of charged particles and/or photons (see Disintegration).

Decay Chain or Decay Series—A sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny. Sometimes, to distinguish the sequence, the daughter of the first daughter is called the granddaughter, etc.

Decay Constant (λ)—The fraction of the number of atoms of a radioactive nuclide that decay in unit time (see Disintegration Constant).

Decay Product, Daughter Product—A new isotope formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a

radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product (daughter product) may be either radioactive or stable.

Depleted uranium—Uranium having a percentage of ^{235}U smaller than the 0.7 percent found in natural uranium. It is obtained as a by-product from uranium isotope separation (see Enrichment).

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Disintegration Constant—The fraction of the number of atoms of a radioactive nuclide which decay in unit time; λ is the symbol for the decay constant in the equation $N = N_0 e^{-\lambda t}$, where N_0 is the initial number of atoms present, and N is the number of atoms present after some time (t) (see Decay Constant).

Disintegration, Nuclear—A spontaneous nuclear transformation (radioactivity) characterized by the emission of energy and/or mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see Transformation, Nuclear).

Dose Assessment—An estimate of the radiation dose to an individual or a population group usually by means of predictive modeling techniques, sometimes supplemented by the results of measurement.

Dose, Effective—The effective dose is the equivalent dose (H_t) multiplied by a tissue-weighting factor, w_t, with the special name Sievert (Sv). The tissue-weighting factor represents the contribution of the organ or tissue to the total detriment due to the effect resulting from uniform irradiation of the body. $E = (w_r)(w_t)(D)$

The sum of the weighted equivalent doses in all the tissues and organs in the body. It is given by $E = \Sigma W_t H_t$ where W_t is the weighting factor for tissue T.

Dose, Equivalent (H_t)—The equivalent dose is absorbed dose D multiplied by a radiation-weighting factor W_r to account for the different qualities of radiation (alpha, beta, and gamma) in terms of potential effect. The special name is the Sievert (Sv). The present weighting factors are as follows: alpha radiation is w_r = 20; beta and gamma radiation w_r = 1. The dose equivalent expresses all radiation on a common risk scale. (The unit of equivalent dose is the rem. In SI units, the equivalent dose is the sievert, which equals 100 rem.)

Dose, Pharmacological—A general term denoting the quantity (mass) of a substance introduced into the body. For special purposes it must be appropriately qualified.

Dose, Radiation Absorbed—The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad equals 100 ergs per gram. In SI Units, the absorbed dose is the gray, which is 1 J/kg (see Rad). Absorbed dose rate is the absorbed dose per unit time.

Dose, Radiation Cumulative—The total dose resulting from repeated or continuous exposures to radiation.

Dose Rate—Absorbed dose delivered per unit time.

Dosimetry—Quantification of radiation doses to individuals or populations resulting from specified exposures.

Electron—A stable elementary particle having an electric charge equal to $\pm 1.60210 \times 10^{-19}$ C (coulombs) and a rest mass equal to 9.1091×10^{-31} kg. A positron is a positively charged "electron" (see Positron).

Electron Volt—A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: keV for thousand or kilo electron volts, MeV for million or mega electron volts.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Enriched Material—(1) Material in which the relative amount of one or more isotopes of a constituent has been increased. (2) Uranium in which the abundance of the ^{235}U isotope is increased above normal.

Enrichment, Isotopic—An isotopic separation process by which the relative abundance of the isotopes of a given element is altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium is increased from 0.7 percent to >90 percent in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U).

Equilibrium, Radioactive—In a radioactive series, the state that prevails when the ratios between the activities of two or more successive members of the series remains constant.

> **Secular Equilibrium**—If a parent element has a very much longer half-life than the daughters (so there is not appreciable change in its amount in the time interval required for later products to attain equilibrium) then, after equilibrium is reached, equal numbers of atoms of all members of the series disintegrate in unit time. This condition is never exactly attained but is essentially established in such a case as radium and its series to ^{210}Pb. The half-life of radium is about 1,600 years, of radon, approximately 3.82 days, and of each of the subsequent members, a few minutes. After about a month, essentially the equilibrium amount of radon is present; then (and for a long time) all members of the series disintegrate the same number of atoms per unit time. At this time, the activity of the daughter equals the activity of the parent.

> **Transient Equilibrium**—If the half-life of the parent is short enough so the quantity present decreases appreciably during the period under consideration, but is still longer than that of successive members of the series, a stage of equilibrium will be reached after which all members of the series decrease in activity exponentially with the period of the parent. At this time, the ratio of the parent activity to the daughter activity is constant. An example of this is radon (half-life of approximately 3.82 days) and successive members of the series to ^{210}Pb.

Exposure (Chemical)—Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure (Radiation)—Being exposed to ionizing radiation or to a radioactive material.

Gamma Ray, Penetrating—Short-wavelength electromagnetic radiation of nuclear origin.

Genetic Effect of Radiation—Inheritable change, chiefly mutations, produced by the absorption of ionizing radiation by germ cells.

Gray (Gy)—SI Unit of absorbed dose, J/kg (1 Gy = 1 J/kg = 100 rad).

Half-Life, Radioactive—Time required for a radioactive substance to lose 50 percent of its activity by decay. Each radionuclide has a unique half-life.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents, such as chemicals.

In vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In vivo—Occurring within the living organism.

Ion—Atomic particle, atom, or chemical radical bearing a net electrical charge, either negative or positive.

Ionization—The process by which a neutral atom or molecule acquires a positive or negative charge.

Ionization Path (Track)—The trail of ion pairs produced by ionizing radiation in its passage through matter.

Ionizing Radiation—Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions. Examples: alpha, beta, gamma, X rays, and neutrons. High doses of ionizing radiation may produce severe skin or tissue/organ damage.

Isobars—Nuclides having the same mass number but different atomic numbers.

Isotopes—Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons and therefore in the mass number. Almost identical chemical properties exist between isotopes of a particular element. The term should not be used as a synonym for nuclide.

> **Stable Isotope**—A nonradioactive isotope of an element.

Linear Energy Transfer (LET)—A measure of the ability of biological material to absorb energy from ionizing radiation; specifically, for charged particles traversing a medium, the energy lost per unit length of path. A similar quantity may be defined for photons.

> **Low-LET**—Energy transfer characteristic of light charged particles such as electrons produced by X- and gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

> **High-LET**—Energy transfer characteristic of heavy charged particles, such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.

Average LET—Is specified to even out the effect of a particle that is slowing down near the end of its path and to allow for the fact that secondary particles from photon or fast-neutron beams are not all of the same energy.

Lung Clearance Class (days, D; weeks, W; years, Y)—A classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract. Also used ICRP classes of F (fast), M (medium), and S (slow) clearance.

Mass Numbers (A)—The number of nucleons (protons and neutrons) in the nucleus of an atom.

Neutron—Elementary nuclear particle with no electric charge equal.

Nucleon—Common name for a constituent particle of the nucleus. Applied to a proton or neutron.

Nuclide—A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number A = (N+Z), and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Parent—A radionuclide that, on disintegration, yields a specified nuclide either directly or as a later member of a radioactive series.

Power, Stopping—A measure of the ability of a material to absorb energy from an ionizing particle passing through it; the greater the stopping power, the greater the energy absorbing ability (see Linear Energy Transfer).

Progeny—The decay product or products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton—Elementary nuclear particle with a positive electric charge equal numerically to the charge of the electron and a rest mass of 1.007277 mass units.

Rad (rad)—The unit of absorbed dose equal to 0.01 Gy or J/kg in any medium. (1 rad = 100 erg/g = 0.01 Gy) (see Absorbed Dose).

Radiation—The emission and propagation of energy through space or through a material medium in the form of waves (e.g., the emission and propagation of electromagnetic waves or of sound and elastic waves). The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation.

Such radiation commonly is classified according to frequency, as microwaves, infrared, visible (light), ultraviolet, and X and gamma rays (see Photon) and, by extension, corpuscular emission, such as alpha and beta radiation, neutrons, or rays of mixed or unknown type, such as cosmic radiation.

Radiation, Background—See Background Radiation.

Radiation, External—Radiation from a source outside the body.

Radiation, Internal—Radiation from a source within the body (as a result of deposition of radionuclides in body tissues).

Radiation, Ionizing—Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter (see Radiation).

Radioactivity—Spontaneous nuclear transformations that result in the formation of new elements. These transformations are accomplished by emission of alpha or beta particles from the nucleus or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by a gamma photon.

Radioactivity, Natural—The property of radioactivity exhibited by more than 50 naturally occurring radionuclides.

Radioisotopes—An unstable isotope of an element that decays or disintegrates spontaneously, emitting radiation. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radionuclide—A radioisotope or radioactive nuclide characterized by the constitution of its nucleus.

Reaction (Nuclear)—An induced nuclear disintegration (i.e., a process occurring when a nucleus interacts with a photon, an elementary particle, or another nucleus). In many cases the reaction can be represented by the symbolic equation: X+a→Y+b or, in abbreviated form, X(a,b) Y. X is the target nucleus, a is the incident particle or photon, b is an emitted particle or photon, and Y is the product nucleus.

Rem (rem)—A unit of equivalent dose. The equivalent dose in rem is numerically equal to the absorbed dose in rad multiplied by the quality factor (radiation-weighting factor) (1 rem = 0.01 sievert).

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior,

fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Roentgen—unit of x-radiation or gamma radiation equal to the amount of radiation that produces ionization of either sign equal to one electrostatic unit of charge in one cubic centimeter of dry air at 0 degrees and standard atmospheric pressure.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

SI Units—The International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/kilogram/second units, with special quantities for radiation including the becquerel, gray, and sievert.

Sickness, Acute Radiation (Syndrome)—The complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or large part) to ionizing radiation. Five Sv (500 rem) is fatal 50 percent of the time. The earliest of these symptoms are nausea, fatigue, vomiting, and diarrhea and may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high, death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

Sievert (Sv)—The SI unit of any of the quantities expressed as equivalent or effective dose. The equivalent dose in sieverts is equal to the absorbed dose, in grays, multiplied by the radiation-weighting factor (1 Sv = 100 rem). The effective dose is the equivalent dose multiplied by the tissue-weighting factor.

Specific-activity—Radioactivity per unit mass of a radionuclide.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Target Theory (Hit Theory)—A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion that subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Teratogen—Any chemical that causes birth defects.

Threshold Limit Value (TLV)—The maximum concentration of a substance to which most workers can be exposed without adverse effect. TLV is a term used exclusively by the American Conference of Governmental Industrial Hygienists (ACGIH). Other terms used to express the same concept are the MAC (maximum allowable concentration) and the OSHA equivalent PEL (permissible exposure limits).

Transformation, Nuclear—The process by which a nuclide is transformed into a different nuclide by absorbing or emitting a particle.

TWA—Time-weighted average.

X rays—Penetrating electromagnetic radiations whose wave lengths are very much shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. X rays (called characteristic X rays) are also produced when an orbital electron falls from a high energy level to a low energy level.

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