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WYOMING MINING ASSOCIATION

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OFFICE OF SECRETARY
RULEMAKINGS AND
ADJUDICATIONS STAFF

Secretary
U.S. Nuclear Regulatory Commission,
Washington, DC 20555–0001
ATTN: Rulemakings and Adjudications Staff

Gentlemen:

Subject: **Wyoming Mining Association's (WMA's) Comments on the Petition for Rulemaking submitted by James Salsman dated Wednesday, June 15, 2005 Federal Register Vol. 70, No. 114 pages 34699 to 34700**

The Wyoming Mining Association (WMA) is an industry association comprised of mining companies, suppliers, vendors, contractors, consultants and others located in Wyoming. Among the Association's mining company members are several uranium recovery licensees including an operating in-situ uranium recovery licensee, an in-situ uranium recovery licensee in the process of final restoration, the last remaining conventional uranium mill in Wyoming, and several licensees engaged in final reclamation of their sites.

The petition for rulemaking files by James Salsman is of concern to the Association since it directly addresses the regulatory limits for uranium exposure. James Salsman states in his petition that *"the regulations were designed to address only the radiological hazard of uranium, and not the heavy metal toxicity, which is known to be about six orders of magnitude worse."* In addition he states that *"the explicit limit to 10 mg/day of soluble uranium compounds (or about half a gram per year) in 10 CFR 20.1201(e) seems likely to allow substantial kidney damage and certain reproductive toxicity"*. James Salsman requests *"that the NRC revise its regulations in 10 CFR part 20 that specify limits for ingestion and inhalation occupational values, effluent concentrations, and releases to sewers, for all heavy metal radionuclides with nonradiological chemical toxicity hazards exceeding that of their radiological hazards so that those limits properly reflect the hazards associated with reproductive toxicity, danger to organs, and all other known nonradiological aspects of heavy metal toxicity"*.

The Association requests that this Petition for Rulemaking be denied for the following reasons:

1. Current regulations are designed to adequately address both the radiological and heavy metal toxicity of uranium and specifically acknowledge that uranium toxicity to the kidney, as a heavy metal, is greater than its radiotoxicity. 10 CFR 20.1201 Occupational dose limits for adults states:

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Template = SECY-067

SECY-02

(e) In addition to the annual dose limits, the licensee shall limit the soluble uranium intake by an individual to 10 milligrams in a week in consideration of chemical toxicity (see footnote 3 of appendix B to part 20).

Clearly current regulations account for the chemical toxicity of uranium.

2. The National Institute of Occupational Safety and Health (NIOSH) recently concluded a study of uranium mill workers. The study entitled *Mortality among a cohort of uranium mill workers: an update* (accepted for publication on March 27, 2003 - Occup Environ Med 2004; 61:57–64) is included in Appendix 1. This study states:

   Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected.

   Clearly if the chemical toxicity of uranium was "a*bout six orders of magnitude worse"* than its radiotoxicity as James Salsman suggests, then increased mortality would have been evident among the cohort of uranium millers.

3. The petitioner also discusses reproductive effects in his Petition for Rulemaking stating:

   "...NRC revise its regulations in 10 CFR part 20 that specify limits for ingestion and inhalation occupational values, effluent concentrations, and releases to sewers, for all heavy metal radionuclides with nonradiological chemical toxicity hazards exceeding that of their radiological hazards so that those limits properly reflect the hazards associated with reproductive toxicity..."

   The petitioner cites in the following posting on the Internet:

   http://www.vanderbilt.edu/radsafe/0412/msg00270.html

   a paper entitled, *A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development* (Toxicology and Industrial Health 2001; 17: 180±191). This paper discusses reproductive effects from uranium exposure in rats and is included in Appendix 2. While this paper discusses the toxicological effects of exposure to uranyl nitrate hexahydrate on rats, it clearly states:

   Fifty male/female pairs were fed diets of Purina Fox Chow containing 2% uranyl nitrate hexahydrate [UO2 (NO3)2] for seven months and were then placed on control diets of Purina Fox Chow for an additional five months.

   A diet containing two- (2) percent uranyl nitrate represents a huge uranium intake. At this huge dose the paper concluded:

   It was concluded that under the given conditions, uranium exposure had an adverse effect on rat reproductive functions in the absence of inanition.

   This effect was only observed in a diet that consisted of two- (2) percent uranyl nitrate hexahydrate, which is far in excess of any dose allowed by current regulation. This paper in no way challenges the current uranium dose limits (radiological or chemical).

4. A paper entitled *Uranium Deposition and Retention in a USTUR Whole Body Case* is included in Appendix 3. This paper discusses the autopsy of *"a whole body donation from a person with a documented occupational intake of uranium"*. Specifically this individual was *"an adult male who died from an acute cerebellar infarct at the age of 83"*. The individual *"worked as a power operator, utility operator, and metal operator for 28 years in a facility that processed and handled radioactive materials"*. The individual *"submitted numerous urine samples for uranium, plutonium, and fission product analysis"*.

   The paper concludes by stating, *"The relative amount of uranium in the various organs of this case were lung > skeleton>spleen > liver> kidney, which is in agreement with other reported observations from the literature..."* It also states, *"Autopsy results disclosed findings not uncommon in the aged with no indication of pathology possibly attributable solely to exposure to uranium."* Clearly based upon this paper, uranium concentration in the reproductive organs is not a major issue. At best the reproductive organs would rank sixth and in fact the testis rank seventh in order of uranium concentration in Table 3 of the paper.

5. The Association also is including in Appendix 4 a discussion prepared by Dr. Nancy Standler MD, Ph.D. (a pathologist with a doctorate from the Department of Radiation Biology and Biophysics of the University of Rochester) in further support of its request to deny the Petition for Rulemaking.

The Association appreciates the opportunity to comment on this Petition for Rulemaking. If you have any questions please do not hesitate to contact me.

Sincerely yours,

Marion Loomis

Marion Loomis
Executive Director

cc: Katie Sweeney - National Mining Association (NMA)
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Appendix 1

ORIGINAL ARTICLE

Mortality among a cohort of uranium mill workers: an update

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Occup Environ Med 2004;61:57–64

See end of article for authors' affiliations

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Aims: To evaluate the mortality experience of 1484 men employed in seven uranium mills in the Colorado Plateau for at least one year on or after 1 January 1940.
Methods: Vital status was updated through 1998, and life table analyses were conducted.
Results: Mortality from all causes and all cancers was less than expected based on US mortality rates. A statistically significant increase in non-malignant respiratory disease mortality and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease were observed. The excess in lymphatic and haematopoietic cancer mortality was due to an increase in mortality from lymphosarcoma and reticulosarcoma and Hodgkin's disease. Within the category of non-malignant respiratory disease, mortality from emphysema and pneumoconioses and other respiratory disease was increased. Mortality from lung cancer and emphysema was higher among workers hired prior to 1955 when exposures to uranium, silica, and vanadium were presumably higher. Mortality from these causes of death did not increase with employment duration.
Conclusions: Although the observed excesses were consistent with our a priori hypotheses, positive trends with employment duration were not observed. Limitations included the small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, the inability to estimate individual exposures, and the lack of smoking data. Because of these limitations, firm conclusions about the relation of the observed excesses in mortality and mill exposures are not possible.

In the United States, mining and milling of uranium ores to recover uranium for nuclear weapons began during World War II to support the Manhattan Project. Uranium bearing ores had been mined previously on a small scale, but mainly for the recovery of vanadium. Continued development and expansion of the industry after the war was promoted by a domestic uranium concentrate procurement programme that was established by the Atomic Energy Commission in 1947.[1] As early as 1949, health officials became concerned about the potential health risks associated with uranium mining and milling.[2]

The health risks associated with uranium mining have been extensively studied. Uranium miners have been found to have a substantially increased risk of death from lung cancer, which is associated with cumulative exposure to radon decay products.[3–5] Excess mortality from non-malignant respiratory diseases has also been found.[6] However, existing data concerning the health effects of uranium milling are limited. Waxweiler and colleagues reported a significantly increased risk of "other non-malignant respiratory disease" (standardised mortality ratio (SMR) = 2.50; observed (obs) = 39) among 2002 workers at seven uranium mills in the Colorado Plateau.[7] This category included emphysema, fibrosis, silicosis, and chronic obstructive pulmonary disease. Non-significant excesses were observed for lymphatic and haematopoietic malignancies other than leukaemia after 20 years latency (SMR = 2.3; obs = 6) and chronic renal disease (SMR = 1.67; obs = 6). In an earlier overlapping study of 662 uranium mill workers, Archer and colleagues observed an excess risk of mortality from lymphatic and haematopoietic malignancies other than leukaemia (SMR = 3.92; obs = 4).[8] Limited data from morbidity studies suggest that uranium millers may have an increased risk of pulmonary fibrosis[2] and renal tubular injury.[9]

The primary exposures of interest in uranium mills are uranium, silica, and vanadium containing dusts. Inhalation of uranium dust may pose an internal radiation hazard as well as the potential for chemical toxicity. High concentrations of radon and radon decay products, similar to the levels found in underground uranium mines, are not expected in the mills.

Because of continuing concern about the health effects of uranium milling, we extended the follow up of the cohort described by Waxweiler and colleagues.[7] The present report describes the mortality experience of the cohort through 21 additional years of observation. In addition, the risk of end stage renal disease was evaluated among the cohort.

Uranium milling process

The primary function of uranium mills is to extract and concentrate uranium from uranium containing ore to produce a semi-refined product known as yellowcake. Yellowcake is a chemically complex mixture of diuranates, basic uranyl sulphate, and hydrated uranium oxides that contains 80–96% uranium as U_3O_8, UO_3, and/or ammonium diuranate.[10] Yellowcake is used commercially to manufacture nuclear fuel for nuclear power and national defence purposes.

Conventional mills process uranium bearing ores from underground or open-pit mines. Until the mid-1970s, all yellowcake in the United States was produced at conventional uranium mills.[11] The main stages of the process in conventional mills involved: (1) ore handling and preparation; (2) extraction; (3) concentration and purification; and (4) precipitation, drying, and packaging. So-called "upgrader" facilities processed virgin ore that was initially too low in uranium content to process economically in a uranium mill. At an upgrader, a series of crushing, grinding, and chemical separation steps were employed to "upgrade" the percent

Main messages

- Potential exposures among uranium mill workers that may be associated with adverse health effects include uranium, silica, and vanadium containing dusts.
- We observed a statistically significant increase in mortality from non-malignant respiratory disease and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease. These findings were consistent with our a priori hypotheses.
- The SMRs for lung cancer and emphysema among men hired before 1955, when exposures to uranium, silica, and vanadium were presumably higher, were significantly increased and greater than the SMRs observed among men hired in 1955 or later. However, mortality for causes of death observed to be in excess did not increase with employment duration.
- Limitations include a lack of smoking data, small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, and the inability to estimate individual exposures to uranium, silica, and vanadium.

uranium contained in the final product, which was sent to a uranium mill for further processing. Unlike conventional uranium mills, upgrader facilities did not carry out concentration and purification of the uranium, and precipitation, drying, and packaging of yellowcake. In this paper, the term "mill" will be used in reference to both conventional uranium mills and upgrader facilities.

METHODS

Cohort description

The cohort was assembled from the personnel records obtained from the companies operating seven uranium mills (five conventional uranium mills and two upgraders). The original cohort described by Waxweiler and colleagues, which is referred to hereafter as the Waxweiler cohort, included 2002 men who had worked for at least one day after 1 January 1940, worked for at least one year in uranium mills, and never worked in underground uranium mines.[7] Because some of the work histories in the Waxweiler cohort were found to be coded inaccurately, we recoded all work histories. We also reviewed documentation from the original study to identify men who met the original cohort criteria, but had been omitted. Personnel records were obtained and work histories updated for cohort members who were still employed in 1971 when the personnel records were originally microfilmed. After re-coding the work histories, we limited the cohort to men who met the original cohort criteria, had never worked in an above-ground or underground uranium mine, and had worked for at least one year in the seven uranium mills before the personnel records were originally microfilmed in 1971 while the mills were operating to recover uranium and/or vanadium concentrates. The final cohort included 1485 men, 1438 (96.8%) of whom were in the Waxweiler cohort. Of the 564 workers not included in the current study, 103 (18.3%) worked in uranium mines, 318 (56.4%) never worked in one of the seven mills comprising the study, 141 (25.0%) worked for less than one year in the seven mills when they were operating, and one (0.2%) was excluded because the work history was incomplete. One woman whose gender was coded incorrectly in the Waxweiler cohort was also excluded.

Follow up

The vital status of all persons in the cohort was determined until 31 December 1998. Follow up included inquiry through the Social Security Administration, Internal Revenue Service, US Postal Service, National Death Index (NDI), and state bureaus of motor vehicles. Death certificates were obtained from state vital records offices for some deceased members of the cohort and coded by a trained nosologist according to the revision of the International Classification of Diseases in effect at the time of death. The causes of death for other deceased members of the cohort were obtained from the NDI.

To identify cohort members with treated end stage renal disease, the cohort was linked with the End Stage Renal Disease (ESRD) Program Management and Medical Information System (PMMIS) by name, social security number, and date of birth. The ESRD PMMIS is maintained by the Health Care Financing Administration (HCFA) and includes all individuals who received Medicare covered renal replacement therapy (dialysis or transplant) in 1977 or later. Approximately 93% of ESRD patients in the United States are included in the ESRD PMMIS.[12]

Analysis

The mortality experience of the cohort was analysed with the use of the National Institute for Occupational Safety and Health (NIOSH) modified life table analysis system (LTAS).[13 14] Each cohort member accumulated person-years at risk (PYAR) for each year of life after 1 January 1940 or completion of the one year eligibility period, whichever was later, until the date of death for deceased cohort members, the date last observed for persons lost to follow up, or the ending date of the study (31 December 1998) for cohort members known to be alive. Cohort members known to be alive after 1 January 1979 (the date that the NDI began) and not identified as deceased were assumed to be alive as of 31 December 1998. The PYAR were stratified into five year intervals by age and calendar time and were then multiplied by the appropriate US gender, race, and cause specific mortality rates to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause specific and total expected number of deaths. The ratio of observed to expected number of deaths was expressed as the standardised mortality ratio (SMR). Ninety five per cent confidence intervals (CI) were computed for the SMRs assuming a Poisson distribution for observed deaths. The mortality analysis was repeated using Colorado, New Mexico, Arizona, and Utah state mortality rates to generate expected numbers of deaths. In addition to analyses of underlying cause of death, all causes listed on the death certificate were analysed using multiple cause mortality methods described by Steenland and colleagues.[15] Multiple cause analyses are particularly important for diseases that may be prevalent at death but that are not the underlying cause of death.[15] In analyses using state or multiple cause mortality rates, person-years at risk started to accumulate on 1 January 1960, when the rates were first available, or completion of the one year eligibility period, whichever was later.

The end stage renal disease experience of the cohort was analysed using methods described by Calvert and colleagues.[16] Briefly, the modified life table analysis system was used to calculate PYAR, expected number of individuals developing ESRD, and standardised incidence ratios (SIRs) for ESRD. Since the ESRD PMMIS is considered incomplete prior to 1977, cohort members who died before this date were excluded from the ESRD analysis. PYAR for cohort members

who were alive on 1 January 1977 began to accumulate on this date. Cohort members accumulated PYAR until the first service date for those with ESRD, the date of death for deceased cohort members, the date last observed for those lost to follow up, or the ending date of the study for those known to be alive. The first service date for ESRD, which generally represents the date on which renal replacement therapy began, was used as a surrogate for the date of onset of ESRD. After the PYAR were stratified into five year intervals by age and calendar time, the PYAR were multiplied by the appropriate US ESRD incidence rates to calculate the expected number of cases for that stratum. The US incidence rates were developed by NIOSH from the HCFA PMMIS data and US census data as described elsewhere.[16] The expected number of treated ESRD cases in all strata were summed to yield the total expected number. The ratio of the observed to expected number of treated ESRD cases was expressed as the standardised incidence ratio (SIR). The SIR for four major categories of ESRD (systemic, non-systemic, other, and unknown) were also calculated.

We stratified SMRs and SIRs by duration of employment (1–2, 3–9, 10+ years), time since first employment (latency) (0–9, 10–19, 20+ years), and year of first employment (<1955, 1955+). In general, the cut points for duration of employment and time since first employment were retained from the original study; however, we lowered the cut point between the lowest and middle duration of employment categories so that the number of deaths in each category would be more similar. The cut point for year first employed was selected a priori based on the assumption that exposures in the earlier years (when there was little emphasis on dust control) would be higher than in later years. Duration of employment was based on employment in the seven cohort mills while they were operating to produce uranium and/or vanadium concentrates and included employment that occurred prior to the start of the follow up period. The analyses were repeated restricting the cohort to those who had worked in a conventional mill and to those who had worked in a conventional mill that produced both vanadium and uranium concentrates. Because of the potential impact of exposures encountered during other employment in the uranium industry, SMRs and SIRs were also conducted restricting the cohort to those without such employment. All analyses were done using the PC version of the LTAS[17] (http://www.cdc.gov/niosh/ltindex.html). Testing for heterogeneity and trend in the SMRs used the methods of Breslow and Day.[18]

Based on previous studies and the known toxic effects of uranium and silica, the a priori outcomes of interest in this study included non-malignant respiratory disease, chronic renal disease, lung cancer, and lymphatic and haematopoietic cancer other than leukaemia. Within the major category of non-malignant respiratory disease, the minor category "pneumoconiosis and other respiratory diseases" was of a priori interest.

RESULTS

A total of 1484 men contributing 49 925 person-years were included in the study. Table 1 presents the distribution of the cohort by vital status, plant type (conventional mill, upgrader), duration of employment, time since first employment, and first year of employment. Race was unknown for 642 (43.3%) members of the cohort. Because all workers of known race were white, workers of unknown race were classified as white in the analysis. In the total cohort, 656 (44.2%) men were alive, 810 (54.6%) were deceased, and 18 (1.2%) were lost to follow up. Causes of death were obtained from death certificates or the NDI for 794 (98.0%) of the individuals known to be deceased. Deaths with missing causes of death were included in the other and unknown causes category. The duration of employment of the cohort is relatively short with a median of 3.6 (range 1–36.3) years. Over half of the cohort was first employed prior to 1955. The median time since first employment, based on employment in the seven mills while they were operating, is 37 years.

Table 1 Characteristics of the study population

No. of workers	1485
Excluded from analysis*	1
Person-years at risk	49925
Mill type	
Conventional mill only	1412 (95.1%)
Upgrader only	44 (3.0%)
Both	28 (1.9%)
Vital status as of 31 Dec 1998	
Alive	656 (44.2%)
Dead	810 (54.6%)
Unknown	18 (1.2%)
Year of birth	1921 median
	1872–1951 range
Year of first employment†	
Prior to 1955	799 (53.8%)
1955 or later	685 (46.2%)
Duration of employment†	
1–2 years	634 (42.7%)
3–9 years	547 (36.9%)
10 + years	303 (20.4%)
Time since first employment†	
<10 years	76 (5.1%)
10–19 years	128 (8.6%)
20+ years	1280 (86.3%)

*Missing date of birth.
†Employment in the seven mills while operating to produce uranium and/or vanadium concentrates.

Almost all of the workers and person-years were from conventional uranium mills. Of the 1440 men who were employed at conventional mills, 1263 (87.7%) were employed at mills that recovered vanadium, 145 (10.1%) were employed at mills that did not recover vanadium, and 32 (2.2%) were employed both at mills that recovered vanadium and mills that did not recover vanadium. Among the entire cohort, 83 (5.6%) men had also been employed in other aspects of the uranium industry according to their employment application or other employment records.

Table 2 shows the results of the analysis for all causes of death. Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected. Among the outcomes of a priori interest, a statistically significant increase in mortality from non-malignant respiratory disease (SMR = 1.43; 95% CI 1.16 to 1.73; obs = 100) and non-significant increases in mortality from trachea, bronchus, and lung cancer (SMR = 1.13; 95% CI 0.89 to 1.41; obs = 78), lymphatic and haematopoietic malignancies other than leukaemia (SMR = 1.44; 95% CI 0.83 to 2.35; obs = 16), and chronic renal disease (SMR = 1.35; 95% CI 0.58 to 2.67; obs = 8) were observed. The excess in mortality from lymphatic and haematopoietic malignancies was due to an excess in mortality from lymphosarcoma and reticulosarcoma (SMR = 1.74; 95% CI 0.48 to 4.46; obs = 4) and Hodgkin's disease (SMR = 3.30; 95% CI 0.90 to 8.43; obs = 4). Within the major category of non-malignant respiratory disease, mortality from emphysema (SMR = 1.96; 95% CI 1.21 to 2.99; obs = 21) and pneumoconioses and other respiratory disease (SMR = 1.68; 95% CI 1.26 to 2.21; obs = 52) was significantly increased. Among outcomes other than those of a priori interest, non-significant increases in mortality from other and unspecified cancers (SMR = 1.59; 95% CI 0.98 to 2.43; obs = 21) and accidents (SMR = 1.26; 95% CI 0.93 to 1.68;

Table 2 Uranium mill workers' mortality (since 1940, US referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All causes	810	877.66	0.92‡	0.86 to 0.99
All cancers (140–208)	184	204.12	0.90	0.78 to 1.04
Buccal and pharyngeal CA (140–149)	2	5.06	0.40	0.05 to 1.43
All digestive CA (150–159)	33	53.18	0.62§	0.43 to 0.87
Oesophagus (150)	1	5.06	0.20	0.01 to 1.10
Colon (152–153)	12	18.96	0.63	0.33 to 1.11
Rectal (154)	2	4.77	0.42	0.05 to 1.51
Liver and biliary (155–156)	4	5.04	0.79	0.22 to 2.03
Pancreas (157)	6	10.30	0.58	0.21 to 1.27
All respiratory CA (160–165)	78	72.29	1.08	0.85 to 1.35
Trachea, bronchus, and lung (162)	78	68.93	1.13	0.89 to 1.41
Male genital CA (185–187)	15	19.67	0.76	0.43 to 1.26
All urinary CA (188–189)	5	11.03	0.45	0.15 to 1.06
Kidney (189.0–189.2)	4	4.96	0.81	0.22 to 2.06
Leukaemia/aleukaemia (204–208)	5	7.62	0.66	0.21 to 1.53
Lymphatic and haematopoietic CA other than leukaemia (200–203)	16	11.08	1.44	0.83 to 2.35
Lymphosarcoma and reticulosarcoma (200)	4	2.29	1.74	0.48 to 4.46
Hodgkin's disease (201)	4	1.21	3.30	0.90 to 8.43
Other lymphatic and haematopoietic CA (202–203)	8	7.57	1.06	0.46 to 2.08
Other/unspecified CA (194–199)	21	13.20	1.59	0.98 to 2.43
Tuberculosis (001–008)	2	3.88	0.52	0.06 to 1.86
Diabetes mellitus (250)	10	14.60	0.68	0.33 to 1.26
Heart disease (390–398, 402, 404, 410–414, 420–429)	293	349.10	0.84§	0.75 to 0.94
Ischemic heart disease (410–414)	236	280.07	0.84§	0.74 to 0.96
Other circulatory disease (401, 403, 405, 415–417, 430–459)	69	83.06	0.83	0.65 to 1.05
Non-malignant respiratory disease (460–519)	100	70.16	1.43§	1.16 to 1.73
Pneumonia (480–486)	25	23.76	1.05	0.68 to 1.55
Chronic and unspecified bronchitis (490–491)	2	2.20	0.91	0.11 to 3.28
Emphysema (492)	21	10.72	1.96§	1.21 to 2.99
Pneumoconioses and other respiratory disease (470–478, 494–519)	52	30.87	1.68§	1.26 to 2.21
Non-malignant digestive disease (520–579)	23	36.91	0.62‡	0.39 to 0.94
Non-malignant genitourinary disease (580–629)	13	13.03	1.00	0.53 to 1.71
Acute renal disease (580–581, 584)	1	1.16	0.86	0.02 to 4.79
Chronic renal disease (582–583, 585–587)	8	5.91	1.35	0.58 to 2.67
Ill defined conditions (780–796, 798–799)	4	8.01	0.50	0.14 to 1.28
Accidents (E800–E949)	47	37.23	1.26	0.93 to 1.68
Violence (E950–E978)	18	17.73	1.02	0.60 to 1.60
Suicide (E950–E959)	15	14.19	1.06	0.59 to 1.74
Homicide (E960–E978)	3	3.54	0.85	0.18 to 2.48
Other and unknown causes	27†	14.04	1.92§	1.27 to 2.80

*International Classification of Disease codes, 9th revision.
†Includes 16 observed deaths with missing death certificates.
‡95% confidence interval excludes the null value (1.0).
§99% confidence interval excludes the null value (1.0).

obs = 47) were observed. The observed other and unspecified cancers were metastatic cancers of unknown primary site. Mortality from all digestive cancers was significantly less than expected (SMR = 0.62; 95% CI 0.43 to 0.87; obs = 33).

An analysis was also conducted (not shown) using US rate files for 1960 to 1999 which have 99 causes of death instead of 92 because these rate files include more detailed categories of non-malignant respiratory disease and slightly different categories of malignancies of the lymphatic and haematopoietic system. Of the 1484 cohort members, 89 (6.0%) were not included in this analysis because they had either died or were lost to follow up before 1960. Only one death from silicosis (SMR = 5.93; 95% CI 0.15 to 32.94) and two deaths from pneumoconioses other than silicosis and asbestosis (SMR = 2.29; 95% CI 0.28 to 8.25) were observed. The remainder of the excess in non-malignant respiratory disease mortality was due to a significant excess in mortality from emphysema (SMR = 1.83; 95% CI 1.10 to 2.86) and other respiratory diseases (SMR = 1.62; 95% CI 1.19 to 2.15). Most of the observed deaths from other respiratory diseases were due to chronic obstructive lung disease. In the category of malignancies of the lymphatic and haematopoietic system other than leukaemia, mortality was significantly increased for Hodgkin's disease (SMR = 4.01; 95% CI 1.09 to 10.25, obs = 4) and non-significantly increased for non-Hodgkin's lymphoma (SMR = 1.25; 95% CI 0.54 to 2.46; obs = 8).

In order to evaluate whether regional variations in mortality rates could explain the findings, analyses were conducted using state rates as the comparison population (table 3). State rates are not available before 1960 so men who had either died or were lost to follow up before 1960 were also excluded from this analysis. The excess in mortality from cancer of the trachea, bronchus, and lung (SMR = 1.51; 95% CI 1.19 to 1.89) based on state rates was statistically significant and greater than the excess based on US rates since 1960 (SMR = 1.13; 95% CI 0.89 to 1.42). In contrast, the excess in mortality from emphysema (SMR = 1.25; 95% CI 0.75 to 1.95) and other respiratory diseases (SMR = 1.35; 95% CI 0.99 to 1.79) was less than the excess based on US rates. Mortality from chronic renal disease was not increased based on state rates (SMR = 1.02; 95% CI 0.33 to 2.39; obs = 5) and was similar to that based on US rates since 1960 (SMR = 1.00; 95% CI 0.32 to 2.35). This is in contrast to the excess in mortality from chronic renal disease observed based on US rates since 1940.

Tables 4 and 5 show mortality according to duration of employment and time since first employment for selected causes of death based on US rates. Overall mortality was highest among those with the shortest duration of employment and lowest among those with the longest duration of employment. Similar trends with duration of employment were observed for mortality from lung cancer, non-malignant

Table 3 Uranium mill workers' mortality (since 1960) from selected causes of death (state referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All respiratory CA (160–165)	75	51.98	1.44‡	1.13 to 1.81
Trachea, bronchus, and lung (162)	75	49.73	1.51‡	1.19 to 1.89
Leukaemia/aleukaemia (204–208)	5	6.51	0.77	0.25 to 1.80
Lymphatic and haematopoietic CA other than leukaemia (200–203)	15	9.58	1.57	0.88 to 2.58
Non-Hodgkin's lymphoma (200, 202)	8	5.71	1.40	0.60 to 2.76
Hodgkin's disease (201)	4	0.94	4.24†	1.15 to 10.84
Myeloma (203)	3	2.93	1.02	0.21 to 3.00
Other/unspecified CA (187, 194–199)	22	11.93	1.84‡	1.16 to 2.79
Non-malignant respiratory diseases (460–519)	94	79.32	1.19	0.96 to 1.45
Chronic and unspecified bronchitis (490–491)	1	2.74	0.36	0.01 to 2.03
Emphysema (492)	19	15.22	1.25	0.75 to 1.95
Asbestosis (501)	0	0.12	0.00	0.00 to 30.62
Silicosis (502)	1	0.45	2.22	0.06 to 12.36
Other pneumoconioses (500, 503, 505)	2	0.40	5.04	0.61 to 18.19
Other respiratory diseases (470–478, 494–499, 504, 506–519)	47	34.86	1.35	0.99 to 1.79
Non-malignant genitourinary disease (580–629)	10	10.51	0.95	0.46 to 1.75
Acute renal disease (580–581, 584)	1	0.79	1.26	0.03 to 6.99
Chronic renal disease (582–583, 585–587)	5	4.89	1.02	0.33 to 2.39

*International Classification of Disease codes, 9th revision.
†95% confidence interval excludes the null value (1.0).
‡99% confidence interval excludes the null value (1.0).

respiratory disease, and emphysema. A positive trend between mortality and duration of employment was not observed for any of the selected causes of death except other and unspecified cancers. The excess in mortality from Hodgkin's disease was confined to 20 years or more since first employment. Mortality from Hodgkin's disease was significantly increased over sevenfold among this group, but the confidence interval around the point estimate was wide (95% CI 1.96 to 18.40).

Mortality was also examined (not shown) by date of hire (pre-1955 versus 1955 or later). There appeared to be a relation between an earlier date of hire and increased mortality from trachea, bronchus, and lung cancer (prior to 1955: SMR = 1.34, 95% CI 1.02 to 1.74; 1955 or later: SMR = 0.79, 95% CI 0.49 to 1.21). Mortality from emphysema was also higher among men hired prior to 1955 (SMR = 2.22; 95% CI 1.29 to 3.56; obs = 17) than among men hired in 1955 or later (SMR = 1.30; 95% CI 0.36 to 3.33; obs = 4), but mortality from pneumoconiosis and other respiratory disease was similar among men hired prior to 1955 (SMR = 1.69; 95% CI 1.17 to 2.36) and men hired in 1955 or later (SMR = 1.68; 95% CI 0.99 to 2.65).

Analyses of multiple causes of death and end stage renal disease incidence were conducted to further evaluate the risk of renal disease among the cohort. The risk of chronic renal disease mortality was not increased (SMR = 1.05; 95% CI 0.69 to 1.54, obs = 26) in the multiple causes of death analysis. The risk of treated end stage renal disease was less than expected overall (SIR = 0.71; 95% CI 0.26 to 1.55, obs = 6). The risk of treated end stage renal disease of unknown aetiology was increased (SIR = 2.73; 95% CI 0.56 to 7.98, obs = 3). This finding was based on three observed cases and the confidence interval was wide. The primary cause of renal failure was missing in the ESRD PMMIS for two of the three observed cases, raising the possibility that these cases were misclassified. Death certificates were available for these cases; renal disease was mentioned on the death certificate for both, but not a specific type or aetiology of renal disease.

Similar results were obtained when the cohort was restricted to men who were employed in conventional mills and when the cohort was restricted to men who were employed in conventional mills that produced both uranium and vanadium concentrates. Results were also similar when

Table 4 Uranium mill workers' mortality (since 1940) from selected causes of death by duration of employment (US referent rates): update of cohort to 1998

Underlying cause of death	Duration of employment (years) 1–2 SMR (obs)	3–9 SMR (obs)	≥10 SMR (obs)	
All deaths	1.01 (352)	0.91 (295)	0.80 (163)†	‡
All cancers	0.94 (75)	0.91 (68)	0.83 (41)	
Trachea, bronchus, and lung CA	1.35 (36)	1.27 (32)	0.58 (10)	‡
Lymphatic and haematopoietic CA other than leukaemia	1.38 (6)	1.22 (5)	1.90 (5)	
Lymphosarcoma and reticulosarcoma	2.15 (2)	1.15 (1)	2.03 (1)	
Hodgkin's disease	1.91 (1)	4.25 (2)	4.57 (1)	
Other lymphatic and haematopoietic CA	1.03 (3)	0.73 (2)	1.56 (3)	
Other/unspecified CA	1.16 (6)	1.65 (8)	2.19 (7)	
Non-malignant respiratory disease	1.99 (53)†	1.12 (29)	1.02 (18)	‡
Emphysema	2.69 (11)†	1.79 (7)	1.11 (3)	
Pneumoconioses and other respiratory diseases	2.53 (29)†	1.07 (12)	1.35 (11)	
Chronic renal disease	1.27 (3)	1.33 (3)	1.53 (2)	

*95% confidence interval excludes the null value (1.0).
†99% confidence interval excludes the null value (1.0).
‡Test for trend p value <0.05.

Table 5 Uranium mill workers' mortality (since 1940) from selected causes of death by length of time since first employment (US referent rates): update of cohort to 1998

Underlying cause of death	Time since first employment (years) <10 SMR (obs)	10–19 SMR (obs)	≥20 SMR (obs)
All deaths	0.95 (68)	0.87 (125)	0.93 (617)
All cancers	0.62 (7)	0.88 (25)	0.92 (152)
Trachea, bronchus, and lung CA	0.36 (1)	1.45 (13)	1.12 (64)
Lymphatic and haematopoietic CA other than leukaemia	1.35 (1)	0.00 (0)	1.72 (15)
Lymphosarcoma and reticulosarcoma	3.33 (1)	0.00 (0)	2.24 (3)
Hodgkin's disease	0.00 (0)	0.00 (0)	7.19 (4)**
Other lymphatic and haematopoietic CA	0.00 (0)	0.00 (0)	1.18 (8)
Other/unspecified CA	0.00 (0)	1.21 (2)	1.76 (19)*
Non-malignant respiratory disease	1.32 (4)	1.48 (11)	1.42 (85)**
Emphysema	2.39 (1)	2.21 (4)	1.89 (16)*
Pneumoconioses and other respiratory diseases	3.73 (2)	2.24 (4)	1.61 (46)**
Chronic renal disease	3.95 (3)	1.23 (1)	0.92 (4)

*95% confidence interval excludes the null value (1.0).
**99% confidence interval excludes the null value (1.0).

the cohort was restricted to men without known employment in other aspects of the uranium industry.

DISCUSSION

Uranium exposure presents both chemical and radiological hazard potentials. Both the chemical and radiological toxicity are influenced by the biological solubility of a given uranium compound. Poorly soluble uranium compounds are cleared slowly from the lungs and pose a potential internal radiation hazard. More soluble compounds are absorbed rapidly from the lungs, decreasing the radiation hazard, but increasing the potential for renal toxicity.[19 20] In the ore handling and preparation areas of the mills, the uranium in ore dusts consists mostly of insoluble uranium oxides with a relatively small fraction of the more soluble uranium compounds. The potential for exposure to the long lived alpha emitters (uranium-238, uranium-234, thorium-230, radium-226, and lead-210) is greatest in these areas of the mill. In the yellowcake drying and packaging areas of the mill, the uranium in yellowcake consists of a complex mixture of uranium compounds of varying solubility. The composition and solubility of the yellowcake product depends on the drying temperature employed.[19 21] In mills that dry the product at relatively low temperatures (100–150°C), the yellowcake product is high in ammonium diuranate [$(NH_4)_2U_2O_7$] which is highly soluble in lung fluids; in mills that dry the product at relatively high temperatures (370–538°C), the yellowcake is high in uranium oxide (U_3O_8) which is mostly insoluble in lung fluids.[21 22] Based on available data on drying temperatures and drying equipment, four of the five conventional mills in this study used relatively high drying temperatures. The fifth mill did not prepare a dried yellowcake product; rather, it produced filter press cake or a uranium product liquor, depending on the year of operation. Accordingly, most mill workers in this study worked in mills that probably produced yellowcake of relatively low solubility.

Both human and animal data suggest that insoluble uranium compounds and thorium accumulate in the tracheobronchial lymph nodes.[23–26] Because of this, it has been suggested that studies of early uranium workers evaluate the effects on lymphatic tissues.[25] In the previous study of workers at the mills in this study, a significant increase in mortality from lymphatic and haematopoietic malignancies other than leukaemia was observed after 20 years latency, based on six deaths.[7] We also found an excess in mortality from lymphatic and haematopoietic malignancies other than leukaemia but the magnitude of the excess was less than the excess observed in the previous study. The observed excess was due to an excess in both Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality based on four observed deaths each. The ability to evaluate exposure response relations, using duration of employment as a surrogate of exposure, was limited by the small number of observed deaths from these cancers. Of the eight observed deaths due to Hodgkin's disease, lymphosarcoma, and reticulosarcoma in this study, three were observed in the previous study and one was observed in the study by Archer and colleagues.[8]

Hodgkin's disease and non-Hodgkin's lymphoma, a group of lymphomas which includes lymphosarcoma and reticulosarcoma, have not been clearly linked to radiation.[27 28] Data on the risk of death from Hodgkin's disease and non-Hodgkin's lymphoma among uranium or thorium workers are limited. An increased risk of Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality has been observed among uranium processing workers at the Fernald Feed Materials Production Center near Cincinnati, Ohio (SMR = 2.04, 95% CI 0.74 to 4.43, obs = 6; and SMR = 1.67, 95% CI 0.72 to 3.29, obs = 8, respectively)[29] and thorium processing workers (SMR = 1.64, 95% CI 0.33 to 4.79, obs = 3; and SMR = 1.14, 95% CI 0.23 to 3.34, obs = 3, respectively),[30] but not among uranium processing workers at the Y-12 plant at Oak Ridge, Tennessee[31] and Mallinckrodt Chemical Works in St Louis, Missouri[32] or among a combined cohort of uranium and other miners from 11 studies.[33] Hodgkin's disease mortality and incidence and non-Hodgkin's lymphoma incidence was associated with cumulative external radiation dose among workers at the Springsfield uranium production facility; the effects of internal exposures were not evaluated.[34] In general, these studies, like the current study, are limited by the small number of deaths from Hodgkin's disease and non-Hodgkin's lymphoma among exposed workers.

A new finding in this update not previously reported was a small increase in mortality from cancer of the trachea, bronchus, and lung, particularly relative to state rates. We also observed an increased risk of mortality from non-malignant respiratory disease. Mortality from lung cancer was higher based on state rates than US rates, whereas mortality from non-malignant respiratory disease was lower based on state rates than US rates. This is consistent with the relatively low smoking attributable mortality and relatively high chronic obstructive lung disease mortality in Arizona, Colorado, and New Mexico compared to other states.[35] The reason for the discrepancy in smoking-attributable mortality

and chronic obstructive lung disease mortality in many inland western states is unknown. However, the results suggest that regional differences in mortality may explain, in part, the observed excess in non-malignant respiratory disease mortality based on US rates.

The excess in both lung cancer mortality and emphysema mortality was greater among workers hired prior to 1955, when there was little emphasis on dust control and exposures to uranium and silica containing dusts were presumably higher. However, mortality from lung cancer and non-malignant respiratory disease was inversely related to duration of employment. We found no evidence that workers who were hired prior to 1955 were more likely to be short term workers. The inverse relation between lung cancer and emphysema mortality and duration of employment in this study may be a reflection of the healthy worker survivor effect, in which individuals who remain in the workforce over time tend to be healthier than those who leave.[36] Duration of employment may also be a poor surrogate of exposure in this study since exposures are thought to have varied considerably by mill area and over time.

Some data suggest that uranium workers other than miners may be at increased risk of lung cancer[29 31] and non-malignant respiratory disease.[37] Uranium ore dust has been shown to induce pulmonary lesions in animals[23 38 39] and lung cancer in rats.[40] Silica exposure has been reported to lead to the development of silicosis, emphysema, obstructive airways disease, and lymph node fibrosis.[41] Although the carcinogenicity of silica continues to be debated in the scientific community, several investigators have showed an increased risk of lung cancer among workers exposed to silica.[42-44] Vanadium containing compounds have known acute respiratory effects,[45] but it is less clear whether exposure to vanadium can lead to chronic non-malignant respiratory disease.[45 46] In this study, we only observed three deaths from silicosis and unspecified pneumoconioses. The majority of the excess in non-malignant respiratory disease mortality was due to mortality from emphysema and other respiratory disease.

Other potential explanations also exist for the observed excesses in mortality from lung cancer and non-malignant respiratory disease mortality. Smoking data are not available for this cohort, and differences in smoking habits between the cohort and the general population may partially explain the excesses observed. White men in the Colorado Plateau uranium miners cohort were heavy smokers,[6 47] but it is unknown whether the smoking habits of uranium mill workers who never worked underground in uranium mines would be similar to these miners. Even if the mill workers in this study were more likely to smoke than the general population, other investigators have shown that smoking is unlikely to account for SMRs above 1.3 for lung cancer and other smoking related diseases.[48] Other potential factors that may contribute to these excesses include unknown employment in underground uranium mines and employment in other mines with increased levels of radon and radon decay products. It is unlikely that the cohort included many mill workers who also worked as uranium miners. Mill workers who also worked in uranium mines were identified by reviewing the work history records and by matching the cohort to a NIOSH file of over 18 000 uranium miners. All identified uranium miners were excluded from the final cohort. However, members of the cohort may have been more likely to work in other types of mines than the general population.

We found a small non-significant excess in chronic renal disease when using US rates as a comparison; this excess was not apparent when only deaths between 1960 and 1998 were analysed (both underlying cause and multiple cause). Renal effects have been observed among silica exposed workers. Goldminers and industrial sand workers exposed to silica have been found to be at excess risk of death from renal disease and to have increased renal disease incidence.[16 49 50] Low level β_2 microglobulinuria and aminoaciduria has been observed among uranium mill workers exposed to soluble uranium compounds at a mill not in the current study,[9] but little data on chronic renal disease mortality among uranium workers exist. An increase in mortality from chronic nephritis (SMR = 1.88; 95% CI 0.75 to 3.81) was observed among uranium processing workers at Mallinckrodt, based on six observed deaths.[32] An excess in chronic renal disease mortality has been observed among uranium miners (SMR = 1.6; 95% CI 0.7 to 3.0, obs = 9), but the observed excess was not related to duration of employment.[6]

This study may have underestimated the risk of ESRD and renal disease mortality associated with uranium milling. We observed an excess in chronic renal disease mortality during the follow up period 1940–59, but not during the follow up period 1960–98. This suggests that the exclusion of cohort members who died or were lost to follow up prior to 1960 may have been a significant limitation in our ability to evaluate the risk of ESRD and chronic renal disease mortality using multiple cause of death data. Because the cohort is relatively old, approximately 22% of the cohort was excluded from the analysis of ESRD because they died or were lost to follow up before the ESRD PMMIS is first considered complete, which also reduced the statistical power of the ESRD analysis. In addition, the majority of the mill workers in this study were probably exposed to relatively insoluble forms of uranium. The risk of renal disease may be higher in mills using relatively low drying temperatures where the potential for exposure to soluble forms of uranium is greater. The study evaluated chronic renal disease mortality and ESRD and was not able to evaluate the risk of less severe renal effects.

In conclusion, we observed an excess in mortality from haematopoietic and lymphatic malignancies other than leukaemia, trachea, bronchus, and lung cancer, non-malignant respiratory disease, and chronic renal disease. Some of these excesses were based on a small number of deaths and the confidence intervals around the point estimates were wide. Limitations include the lack of smoking data, small cohort size and limited power to detect a moderately increased risk of some of the a priori outcomes of interest, and the inability to evaluate exposure-response relations using individual estimates of exposure to uranium, silica, and vanadium. Because of these limitations and the lack of a positive trend between the observed excesses and duration of employment, firm conclusions about the relation of the observed excesses and mill exposures are not possible.

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Appendix 2

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A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development†

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Depleted uranium (DU) is used in armor-penetrating munitions, military vehicle armor, and aircraft, ship and missile counterweighting/ballasting, as well as in a number of other military and commercial applications. Recent combat applications of DU alloy [i.e., Persian Gulf War (PGW) and Kosovo peacekeeping objective] resulted in human acute exposure to DU dust, vapor or aerosol, as well as chronic exposure from tissue embedding of DU shrapnel fragments. DU alloy is 99.8% ^{238}Uranium, and emits approximately 60% of the alpha, beta, and gamma radiation found in natural uranium (4.05×10^{-7} Ci/g DU alloy). DU is a heavy metal that is 160% more dense than lead and can remain within the body for many years and slowly solubilize. High levels of urinary uranium have been measured in PGW veterans 10 years after exposure to DU fragments and vapors. In rats, there is strong evidence of DU accumulation in tissues including testes, bone, kidneys, and brain. *In vitro* tests indicate that DU alloy may be both genotoxic and mutagenic, whereas a recent *in vivo* study suggests that tissue-embedded DU alloy may be carcinogenic in rats. There is limited available data for reproductive and teratological deficits from exposure to uranium *per se*, typically from oral, respiratory, or dermal exposure routes. Alternatively, there is no data available on the reproductive effects of DU embedded. This paper reviews published studies of reproductive toxicity in humans and animals from uranium or DU exposure, and discusses ongoing animal research to evaluate reproductive effects in male and female rats embedded with DU fragments, and possible consequences in F_1 and F_2 generations. *Toxicology and Industrial Health* 2001: 17, 180–191.

Key words: *depleted uranium and uranium; reproductive toxicology; teratogenesis; rodents; mechanisms of toxicity; review*

Introduction

The US Department of Defense (DoD) has utilized weapon systems containing depleted uranium (DU) alloy since the late 1970s. DU has multiple military applications because of its unique physical properties. DU has a high mass-to-volume ratio (1 cm^3=19 g), has a density 1.68 times greater than lead, and is highly combustible and ignites readily (e.g., pyrophoric) under certain conditions. Due to a high tensile strength, DU is used in helicopter blade rotor-tips, aircraft landing gear components, armor plating for military vehicles (Abrams Heavy Tanks), and as in munitions used to defeat armored and other "hard" targets such as concrete shelters and earthen bunkers. Because of this high mass-to-volume ratio, DU is also used as ballasting/counterweight material in aircraft, ships, missiles, and satellites. Commercially, DU is used in gamma-radiation shields of radiation therapy machines and linear accelerators and in containers for the transport of radioactive materials.

It is known that the United States Armed Forces used DU-containing munitions in both the Persian Gulf War (PGW) and Kosovo peacekeeping objective (Army Environmental Policy Institute [AEPI], 1995; Schoettler, 2001). Approximately 300 tons of DU was expended by US forces in the PGW (CHPPM, 2000; Fetter and von Hippel, 1999) and about 10 tons of DU was expended by US aircraft in the Kosovo air campaign (Schoettler, 2001). US contractors have produced at least 55 million small caliber (e.g., 25 and 30 mm) DU munitions and 1.6 million large caliber (e.g., 105 and 120 mm) DU munitions (AEPI, 1995). It is believed that other nations may possess DU-containing munitions, but this has not been confirmed.

The effects of DU exposure on human health and the environment have received increasing scrutiny by the general public, as well as by international governments and scientific organizations. Although there has been minimal scientific evaluation, exposure to DU has been associated in several reports with human health effects. Exposure to DU during the PGW, for example, was hypothesized as a causative factor in increased birth defects and cancers reported both by residents of the combat

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theater and by PGW veterans (Anonymous, 2001; Tashiro, 2000). Exposure to DU has been suggested as a possible cause of Persian Gulf War Illnesses (PGWI) (Domingo, 2001; Drozdiak, 2001; Durakovic, 2001). Use of DU munitions at the DoD training site on the island of Vieques has been proposed as a cause of an alleged 300% increase in cancer among the local population (Eglund, 2001). Similarly, exposure to DU munitions has been suggested as a cause of cancer among NATO troops returning from operations in Kosovo (Drozdiak, 2001; Ross 2001; Schoettler, 2001) and the "Balkan syndrome," a condition with ill-defined symptoms that are similar to PGWI.

Exposure to DU can occur by several different routes during military deployment. The impact of DU penetrators with solid objects results in the formation of DU dusts, vapors, and aerosols that can be inhaled or orally ingested. Although absorbance of DU through the intact dermis is unlikely, deposited DU particles can potentially penetrate dermal wounds. DU contamination of food, water supplies, and environmental surfaces (hand-to-mouth exposure) provides additional routes of human exposure. Penetration of the dermis by DU shards or fragments resulting from the impact of DU munitions or destruction of a DU-armored vehicle is also a possible route of exposure (McClain et al., 2001). Because DU shrapnel penetration may not always be medically identified, and sometimes cannot be removed surgically, the possibility exists for long-term human exposure to embedded DU fragments.

Expanding use of DU alloys in munitions and vehicle armor increases the likelihood of future incidents resulting in DU shrapnel wounds in male or female military and civilian personnel. Because it not always possible to remove embedded DU shrapnel, and it is known that tissue-embedded DU fragments slowly solubilize, the possibility exists for lifelong exposure to both DU radiation and heavy metal effects.

The known radiological and chemical properties of uranium or DU alloy suggest possible toxicity to rapidly dividing cell populations, such as that occurring in the gonads or developing fetus. There is limited scientific data for the effects of DU alloy exposure on reproduction and fetal development. Commonly, the more extensive data for exposure to uranium, *per se*, are assumed to be applicable to human risk analysis for DU. However, there is very little available data on the health effects associated with DU fragments embedded in muscle and other soft tissues. Studies of the reproductive and developmental toxicity of natural uranium compounds in rodents indicate that uranium is potentially toxic to reproductive tissues and teratogenic to the developing fetus as a result of high dose exposures (Domingo, 2001). Therefore, it would seem that DU alloy implanted in the soft tissues of rodents could potentially cause reproductive toxicity in adult rodents and embryotoxicity or possibly teratogenicity in their offspring. This paper explores several potential mechanisms for such reproductive and developmental effects of DU based on the known physical and chemical effects of uranium in biological systems.

Physical and chemical characteristics of uranium and DU

Uranium is a silver-white, lustrous, dense, and naturally occurring weakly radioactive element with an atomic number of 92 and an atomic weight of 238.0289 g/mol. Uranium is characterized as a heavy metal. Uranium occurs naturally in soil from 1 to 2 mg/kg, in crystal rocks at concentrations from 0.05 to 5 mg/kg, in water from 0.01 to 1500 μg/l, and in the air at levels from 0.02 to 0.30 ng/m^3 (ATSDR, 1999; US EPA, 1985). The average intake of environmental uranium by adults is estimated to be 460 μg/year from ingestion (foods, water) and 0.59 μg/year from inhalation, with an average of 90 μg U present in the adult body at any time point (66% skeletal; 16% in liver; 8% in kidneys; and 10% in other tissue compartments).

Uranium ores are mined, milled, and converted into metal and ceramics for nuclear reactors and nuclear weapons, which are the major uses of uranium (AEPI, 1995). Weapons and fuel grade uranium is extracted from uranium ore, converted to UF_6, and subsequently undergoes enrichment processing whereby the ^{235}U isotope in UF_6 is increased in concentration from 0.72% to 2–90% depending on the intended application (AEPI, 1995; Hartmann et al., 2000). Unprocessed DU, also referred to as DU hexafluoride (DUF_6), is a major by-product of the uranium enrichment process.

DU alloy used in DoD munitions and armored vehicles is not the same material that is formed in the uranium enrichment process. Unprocessed DU (DUF_6) is converted to uranium tetrafluoride (DUF_4), and then processed to DU metal. The DU metal is heat treated, and titanium steel is added to produce DU alloy (AEPI, 1995). DU used by DoD must contain less than 0.3% ^{235}U (10 CFR 40.4). DU alloy used by the DoD typically contains 0.2% ^{235}U by weight, with the isotopes ^{234}U, ^{236}U, and ^{238}U present at roughly 0.0006%, 0.0003%, and 99.8% by weight, respectively (AEPI, 1995). The specific radioactivity of DoD DU alloy is roughly 60% of the radioactivity of natural uranium (0.4 μCi/g versus 0.7 μCi/g) (AEPI, 1995). The half-lives for each of the three radioisotopes of uranium exceed 244,000 years.

Biological effects of DU alloy

The potential health hazards associated with exposure to DU alloy are both radiological and chemical, and both modes of toxicity would be expected to occur in cases where DU becomes internally deposited, such as in the retention of DU fragments in soft tissue, or the inhalation of DU aerosol. Toxicity through ingestion of DU particles is not a likely hazard based on the known pharmacokinetic

properties of uranium. About 2% of a dose of soluble uranium is absorbed through the gut, whereas 0.2% of a dose of insoluble uranium is absorbed (International Commission on Radiological Protection [ICRP], 1996; Leggett and Harrison, 1995). Greater than 90% of an oral dose of insoluble uranium is excreted in the feces within 72 hours (ICRP, 1995). Approximately 90% of all absorbed uranium is excreted in the urine within a few days (ICRP, 1996; 1995). Uranium is retained by the kidney and retention levels are correlated with increasing levels of nephrotoxicity in some species. This may be the result of uranium complexing with proximal tubule proteins (Wedeen, 1992). Several reviews and opinion papers have been recently published detailing the potential toxicity of DU exposure (Domingo, 2001; Durakovic, 1999; Hartmann et al., 2000; Hamilton, 2001). These reviews emphasize the existence of significant data gaps for evaluation of the toxicity of DU alloy, often substituting data for known effects from exposure to uranium *per se* (i.e., uranyl acetate dihydrate or uranyl fluoride).

The external radiological hazards of DU alloy are considered low (AEPI, 1995; Priest, 2001). Priest (2001) suggested that a worker completely surrounded by DU alloy for eight hours/day for a year would receive less than the permissible occupational exposure of 5,000 mrem/year. AEPI (1995) indicates that direct hand contact with a spent DU alloy kinetic energy penetrator (devoid of shielding) would deliver an estimated combined beta and gamma skin radiation dose of 200 mrem/hour and the only plausible way that a soldier could exceed the yearly radiation dose limit for skin (50,000 m/rem) would be if a piece of DU was from a penetrator was carried as a souvenir.

Internal exposure to uranium compounds has been identified as a potential radiological concern (Domingo, 2001; Hartmann et al., 2000; McClain et al., 2001). As mentioned previously, exposure to DU may occur by penetration of the dermis with DU fragments or particles, respiratory inhalation of DU vapor or insoluble particles (1–10 μm diameter range), or oral ingestion of soluble or insoluble DU forms. Ingested DU particles could be deposited in non-exchangeable bone, or other organ systems, whereas insoluble particles deposited in the lungs could remain chronically and result in increased risk for cancer (Hartmann et al., 2000). However, opinions continue to differ as to whether inhalation of uranium particles constitutes a causative agent for lung cancer (Priest, 2001).

The Priest (2001) has calculated that blood levels of more than 5 g of natural uranium are necessary to provide a radiation dose equivalent to the background dose of a person living in the United Kingdom for 50 years. Because DU alloy is less radioactive than natural uranium (AEPI, 1995), uptake of 60% more DU alloy (8 g) would be required to reach an equivalent background radiation dose of a person living in the United Kingdom for 50 years. The exact weight of DU fragments embedded in the soft tissues of the inoperable US military personnel struck with shrapnel during the PGW and Kosovo conflicts is generally unknown.

Results of several studies on the toxicity of DU alloy were reported by the Armed Forces Radiobiology Research Institute (AFRRI, Bethesda, MD). Study of the distribution of uranium in rats following implantation with 1 mm diameter × 2 mm long cylindrical DU alloy pellets (shrapnel simulants) indicated that uranium concentrations remained significantly elevated in several tissues at 18 months postimplantation (Pellmar et al., 1999a). Adult Sprague–Dawley rats were implanted with up to 20 DU alloy pellets in the gastrocnemius muscles. Controls were implanted with 20 tantalum pellets of equal size. DU-exposed rats (n=15) were implanted with 4, 10, or 20 DU pellets. Rats implanted with 4 DU pellets were also implanted with 6 tantalum pellets; rats implanted with 10 were implanted with 10 tantalum pellets. After implantation, the animals were sacrificed at one day, or 1, 6, 12 and 18 months postimplantation, and uranium concentrations measured in various tissue compartments. Uranium concentrations from DU-implanted rats were significantly elevated in the kidneys, liver, spleen, brain, serum, tibia, skull, and urine at most time points. The greatest concentrations of uranium were found in the kidneys and tibia at all time points measured. At 12 months postimplantation for the highest exposure condition, rats excreted an average of 1010±87 ng U/ml urine. Significantly higher uranium concentrations were also found in the testes, lymph nodes, teeth with lower jaw, heart, and lung tissues of DU- versus tantalum steel-implanted animals at 18 months postimplantation.

A second study of the effects of DU alloy on the kidneys indicated that implantation of as many as 32 DU alloy pellets had no effect on various measures of renal and general toxicity (Benson, 1998). Adult female rats were implanted with up to 16 DU alloy pellets in each biceps femoris muscle. Implantation of DU alloy pellets did not significantly impact mean body weight or urinary output as compared to controls when assessed at days 14, 28, 42, 56, 70, and 84 postimplantation. No signs or biomarkers of nephrotoxicity were detected in any of the DU-implanted rats at any of the study time points. Serum potassium, urea nitrogen, and glucose and creatinine clearance levels in DU-implanted rats were not significantly different from rats implanted with tantalum pellets only. Urinary levels of lactate dehydrogenase (LDH) and *N*-acetyl-beta-D-glucosaminidase (NAG) as well as urinary pH, osmolarity, and protein levels, were also not significantly different for DU-implanted rats. Uranium was, however, identified in the kidneys, liver, spleen, the cerebellum, femur, ovaries, and in muscle tissues proximal and distal to the implant site in DU-implanted rats sacrificed 84 days postimplantation.

Table 1. Neurobehavioral tests administered by Pellmar (1996) to Sprague–Dawley rats implanted with DU alloy versus tantalum steel pellets.

- Forelimb or hindlimb grip strength
- Conduction velocity of the sciatic nerve and duration of muscle action potentials
- Spontaneous locomotor activity (60 minutes during light phase of light/dark cycle)
- Learning and memory (trials to criterion, 72-hour recall of passive shock avoidance)
- Autonomic system function tests (lacrimation, salivation, palpebral closure, piloerection, defecation, urination)
- Sensorimotor function tests (tail pinch response, tactile response, auditory response, approach response)
- Neuromuscular function tests (gait analysis, three-minute spontaneous locomotor activity, rearing, level of alertness, foot splay, righting reflex, stereotypy, other unusual behaviors)
- CNS excitability (arousal, postural analysis, ease of removal from cage, ease of handling, convulsions)

Pellmar (1996) found that Sprague–Dawley rats implanted with DU alloy pellets exhibited minimal neurotoxicity as assessed by gross histopathology and by the battery of behavioral tests listed in Table 1. Rats were implanted with up to 20 DU alloy or tantalum steel pellets and examined at 30 days or 6 months after implantation. Gross examination of the brain tissue of DU-exposed rats indicated no obvious lesions. Mean body weights of rats embedded with 20 DU alloy pellets were, however, significantly lower than controls implanted with 20 tantalum pellets. No significant difference in neurobehavioral test scores was observed for rats implanted with 10 DU alloy/10 tantalum pellets or 20 DU alloy pellets when assessed at 30 days or six months postimplantation. The administered tests have been characterized as gross indicators of neurobehavioral effects (McClain et al., 2001).

Pellmar et al. (1999b) reported that hippocampus electrophysiology was altered among adult Sprague–Dawley rats implanted with DU alloy for 12 months. Hippocampal brain slice electrophysiology was compared between adult rats implanted with 4, 10, or 20 DU alloy pellets for 6 or 12 months. The hippocampus was selected because of its known role in learning, memory consolidation, and spatial orientation functions. Electrophysiological responses measured included: 1) evoked population spike (PS); 2) extracellularly recorded population synaptic potentials (pPSP); and 3) E/S coupling (e.g., measure of the ability of the pPSP to elicit the PS). Implantation with DU alloy for six months appeared to impair the capacity of the pPSP to support a normal PS in response to electrical input (e.g., E/S coupling). Evoked PS in hippocampal field CA1 were of significantly lower amplitude following stimulation among rats implanted with 20 DU pellets for six months as compared with controls implanted with 20 tantalum steel pellets for six months. No difference in pPSP was found between these two groups. Implantation of rats with 20 DU alloy pellets for 12 months was associated with a higher pPSP as compared with rats implanted with 20 tantalum steel pellets for 12 months. There was no significant difference in evoked PS between the hippocampal brain samples from DU- and tantalum-implanted rats. Implantation with 20 DU pellets for 12 months was associated with impairment of E/S coupling when compared with rats implanted with 20 tantalum steel pellets for 12 months.

Miller et al. (1998a) demonstrated that the urine from rats implanted with DU alloy pellets was mutagenic to *Salmonella typhimurium* strains TA98 and an equimolar mixture of strains TA7001 through TA7006. In this study, adult rats were implanted with up to 20 DU alloy or tantalum steel pellets and the mutagenicity of both urine and serum from the implanted animals was evaluated in the Ames assay at 0, 6, 12, and 18 months postimplantation. The number of revertant colonies was found to increase with increasing number of implanted DU alloy pellets and with longer DU implantation times. Serum from DU-implanted rats was not mutagenic in the Ames test at any of the study time points.

DU alloy has been shown to transform human osteoblast cells to a tumorigenic phenotype that resulted in the formation of tumors when implanted in athymic mice (Miller et al., 1998b). Exposure of human osteosarcoma (HOS) cells to increasing concentrations of DU-uranyl chloride (10–50 μM) resulted in a dose-dependent increase in transformed cells and greater number of athymic mice developing tumors when injected with a fixed number of DU-treated transformed cells. The incidence of sister chromatid exchanges (SCEs) among HOS cells at 24 hours following treatment with 10 μM DU-uranyl chloride was elevated 2-fold as compared to the SCE levels of untreated cells. The authors estimated that 0.0014% of all HOS cell nuclei were hit with alpha particles equaling a mean specific energy of 17 cGy, suggesting that alpha particle radiation played a negligible role in the transformation of HOS cells by DU-uranyl chloride.

Recent findings suggest that implanted DU alloy (0.75% titanium) is carcinogenic in rats (Hahn et al., 2002). Groups of male Wistar rats (n=50) were implanted with either four 1×2 mm cylindrical DU alloy pellets, four square 2.5×2.5×1.5 mm DU fragments, four square 5.0×5.0×1.5 mm DU fragments, four 5.0×5.0×1.5 mm tantalum steel fragments, or were given a 0.05-ml injection of Thorotrast, a 25% colloidal thorium dioxide radiographic contrast media. All materials were implanted in the biceps femoris muscle of each hind leg, two fragments per leg. Animals injected with Thorotrast received one 0.025 ml injection in the biceps femoris muscle in each hind leg. After implantation, the animals were housed and maintained for their life span. The median survival time for the various groups did not differ significantly and ranged from 576 to 620 days postimplantation. Body weight gain of treated versus sham surgery negative control animals did

not differ significantly at any time point. Tissue capsules surrounding the DU implantation sites were characterized histologically by severe fibrosis, inflammation, and tissue degeneration. Chronic inflammatory cells and particle-laden macrophages were frequently scattered throughout the capsule wall of DU implants. The fibrous capsules from tantalum-implanted rats were characterized by fibrosis with little inflammation and no degradation or mineralization. Radiographic profiles showed that Thorotrast injection sites were irregular and diffuse with no distinct boundaries and there was an accumulation of macrophages between muscle fibers. There was no evidence of fibrotic inflammation within the Thorotrast injection sites or surrounding tissues. Implantation site tumor incidence was found to be related to both the chemical composition and size of the implanted object (Table 2). The greatest number of tumors occurred in rats injected with Thorotrast. Tumor incidence for DU alloy fragments measuring 5.0 × 5.0 × 1.5 mm was significantly higher than those found in sham surgery control rats and also higher than the incidence for rats implanted with similar-sized tantalum fragments. The incidence of primary renal tumors was elevated (4%) for male rats with DU implants as compared with historical controls; however, the incidence was not statistically significant as compared with sham surgery controls. The incidence of renal tumors in DU-implanted rats was not correlated with renal uranium concentrations at the time of death. Tumor incidence associated with Thorotrast injection was correlated with the calculated effective alpha-particle radioactivity of the injected material. DU carcinogenicity correlated most closely with surface alpha radioactivity as compared with physical surface area suggesting that radioactive mechanisms may have played a role in DU tumorigenesis. On the other hand, the high levels of inflammation and fibrotic response associated with DU implantation does not rule out carcinogenesis related to a foreign body reaction which occurs frequently in rats implanted with solid materials.

Effects of DU exposure in PGW veterans

There are few studies available on the effects of uranium exposure on human reproduction and fetal development. As summarized by Domingo (2001), one study found that the frequency of female offspring among male uranium miners was significantly effected, suggesting alterations in sperm (Muller et al., 1967). A study by Zaire et al. (1997) found that 75 male uranium miners from Namibia, Africa, had higher levels of SCEs in white blood cells and decreased serum levels of testosterone as compared with 31 individuals with no occupational history in mining. Neither of these studies provides direct evidence of an effect on human reproduction in relation to uranium exposure, but suggests that further occupational studies should be conducted. Shields et al. (1992) reported a statistical association between maternal exposure to mine tailings or mine dumps and unfavorable birth outcomes among a population of Navajo Indians living in the Shiprock, NM uranium mining area.

Two recent publications reported the health status of US veterans exposed to DU during the PGW (McDiarmid et al., 2000; 2001). During Operation Desert Storm, 15 Bradley fighting vehicles and nine Abrams Heavy Tanks were hit with munitions containing DU penetrators, involving approximately 120 US male veterans (McDiarmid et al., 2000). Several of these soldiers were struck with fragments of DU in muscle and soft tissue that were not surgically removed (McDiarmid et al., 2001). This cohort was also potentially exposed to DU by inhalation of DU particles or vapors, and possibly by contamination of open wounds with DU particles. Thirty-three Gulf War veterans with exposure to DU were initially evaluated in 1993–94. At that time, it was discovered that veterans with retained metal fragments were excreting uranium in their urine at significantly higher levels than veterans without retained metal fragments (4.47 versus 0.03 μg/g creatinine) [(McDiarmid et al., 2000)]. However, there were no strong

Table 2. Tumor incidence among male Wistar rats implanted with DU or tantalum steel or injected with 25% colloidal thorium dioxide (Hahn et al., 2002).

	DU pellets (2 × 1 mm)	DU fragment (2.5 × 2.5 × 1.5 mm)	DU fragment (5.0 × 5.0 × 1.5 mm)	Tantalum fragment (5.0 × 5.0 × 1.1 mm)	Thorium dioxide	Sham controls
Volume (mm^3)[a]	1.6	9.4	37.5	27.5	50	–
Mass (mg)[a]	30	175	698	456	12.5	–
Surface area (mm^2)[a]	7.9	27.5	80	72	–	–
E alpha (Bq)[a]	6	20	59	–	115	
Benign tumors						
Fiborous histiocytoma	0		1	0	0	0
Fibroma	0		1	0	0	0
Granular cell myoblastoma	0			0	1	0
Malignant tumors						
Fibrous histiocytoma	0		7	2	13	0
Fibrosarcoma	0		2	0	10	0
Osteosarcoma	0		2	0	1	0

[a]Per pellet or fragment.

associations found between urinary uranium excretion levels and the occurrence of adverse health effects in DU-exposed veterans.

A 1997 follow-up evaluation of 29 of the 30 subjects assessed in 1993–94 found evidence of subtle perturbations in the reproductive and nervous system as compared with 38 non-exposed veterans (McDiarmid et al., 2000). In this evaluation, veterans underwent physical examination, clinical laboratory studies, neurocognitive/psychiatric assessment, urinary and semen uranium concentrations, whole-body radiation counting, reproductive health assessments (neuroendocrine concentrations, semen characteristics), and measures of the frequency of chromosomal aberrations and SCEs in peripheral blood lymphocytes. Among DU-exposed veterans, 24-hour urinary uranium concentrations were significantly elevated (0.01–30.74 μg/g creatinine) as compared with those of non-exposed veterans (0.01–0.047 μg/g creatinine). All veterans with retained metal fragments had 24-hour urinary uranium concentrations greater than 0.8 μg/g creatinine. Semen uranium concentrations were greater than the limit of detection (1.1 ng uranium/sample) for 5 of 17 DU-exposed veterans with elevated urinary uranium concentrations. Whole-body radiation counts showed that uranium levels were above the limit of detection for nine veterans; all of which were from the DU-exposed group. There was no apparent difference in semen characteristics (volume, count, concentration) and motility (percentage motile, progression, motion) among veterans with high (≥10 μg/g creatinine) versus low urinary uranium concentrations (<10 μg/g creatinine). Active medical problems were reported by 89% of DU-exposed veterans as opposed to 71.4% among controls, with problems of the nervous system being most frequently reported. Hematologic, renal, and neuroendocrine parameters were all within normal limits for all veterans. Veterans categorized as excreting high levels of uranium tended to have higher eosinophil counts and prolactin levels. No significant differences in chromosomal aberration or SCE levels occurred between veterans with high versus low urinary uranium concentrations. Neurocognitive tests showed a statistical relationship between urine uranium levels and lowered performance on computerized tests designed to assess performance efficiency. This result suggests that chronic DU exposure may impact neurocognitive function.

In 1999, a second assessment was conducted on 50 DU-exposed Gulf War veterans including 23 who had been evaluated in 1993 or 1997 (McDiarmid et al., 2001). Of the returning veterans, 17 had retained fragments or a history of retained fragments, and 6 had no history of retained fragments. Among the 27 first-time subjects, 6 had retained fragments or a history of retained fragments, whereas 23 had no history of fragment exposure. Urinary uranium concentrations for veterans with retained DU fragments ranged between 0.018 and 39.1 μg/g creatinine and 0.002 and 0.231 μg/g creatinine in DU-exposed veterans without retained metal fragments. A greater proportion of veterans reporting injuries was categorized as having high urinary uranium concentrations (≥0.10 μg/g creatinine). Veterans with high urinary uranium ($n=13$) had significantly higher mean neutrophil percentages, lower mean lymphocyte counts, and lower monocyte percentages. As a group, veterans with high urinary uranium had significantly elevated sperm counts, total progressive sperm, and total rapid progressive sperm as compared with veterans in the low urinary uranium group. Peripheral lymphocyte SCE frequency was significantly elevated among veterans with high urinary uranium concentrations and remained elevated after adjusting for smoking status. No significant differences were found for several renal function parameters or neurocognitive test scores between veterans with high versus low urinary uranium concentrations. However, a marginally significant association was found between urine uranium concentration (log transformed) and impairment after adjusting for intelligence and depression.

Animal studies of reproductive and developmental toxicity from exposure to uranium compounds

DU alloy To date, only one animal study has reported on the reproductive toxicity of DU alloy. Benson (1998) implanted adult female Sprague–Dawley rats with up to 12 DU alloy or tantalum steel pellets (1×2 mm) and mated them with male rats with no exposure to DU. All pregnant females were euthanized on gestation day 20 and the pups were delivered by cesarean section. There was no effect of DU implantation on maternal weight gain, food and water intake, time-to-pregnancy, or the percentage of litters carried to term as compared with controls implanted with tantalum steel only. Similarly, total number of pups per litter, litter sex ratio, and fetal weight were not affected by DU implantation in the mother. No signs of overt teratology were found in any of the litters.

However, a trend for increasing uranium concentration in maternal kidney tissue, placenta, and whole fetus tissue was found in relation to increasing number of implanted DU pellets (Benson and McBride, 1997).

Uranium and enriched uranium compounds Early experiments by Maynard and Hodge (1949) identified uranium as a possible reproductive toxicant in rats. Fifty male/female pairs were fed diets of Purina Fox Chow containing 2% uranyl nitrate hexahydrate [$UO_2(NO_3)_2$] for seven months and were then placed on control diets of Purina Fox Chow for an additional five months. A satellite control group of 50 male/female pairs was fed stock rations of Purina Fox Chow for the duration of the 12-month experiment. Both groups were allowed to breed continuously and the number of litters and average number of pups per litter were recorded. After the first seven months, average body weights of both male and female breeders were depressed

as compared with those of the satellite control group. At the end of seven months, the control breeder pairs had given birth to 249 litters as compared to 135 litters for uranium-exposed breeding pairs. The average number of young per litter was also lower with uranium-exposed pairs giving birth to 7.8, 7.8, and 7.5 pups per litter for the first, second, and third litters as compared to 7.9, 9.9, and 9.7 for these same litters born to control breeders. The average body weight of uranium-exposed breeders increased noticeably after their diets were shifted to the diet of satellite controls. However, body weights of uranium-exposed animals were still below those of controls at the end of the 12-month experiment with average female body weights of uranium-exposed breeders 25–40 g below those of satellite control females. The number of litters born to uranium-exposed breeder pairs remained lower as compared with satellite controls for the remainder of the experiment with satellite controls giving birth to 34, 15, and 2 litters in the 7th, 10th, and 12th month as compared with 18, 5, and 0 for uranium-exposed pairs at those same intervals. Irregular estrous cycles were identified in 13 uranium-exposed females as compared with 2 satellite control females over a three-month interval beginning with the fourth month of the experiment. Females in the uranium-exposed group that did not have litters over the first seven months of the experiment did not have any litters over the last five months of the experiment. It was concluded that the decrease in reproductive success in uranium-exposed animals may have been an indirect effect resulting from decreased food intake as evidenced by depressed body weights and irregular estrous cycles. However, it is possible that there was a direct chemical interaction on the reproductivity of uranium-exposed breeders given the fact that reproductivity continued to be poor once uranium was reduced to background levels in their diets.

A follow-up study by Maynard et al. (1953) found that the number of litters and number of offspring per litter were reduced in rat breeder pairs over a 10-month span immediately following exposure to 2% uranyl nitrate hexahydrate in their diets for 24 hours. In this experiment, 50 male/female breeder pairs were fed diets containing 2% uranyl nitrate hexahydrate for a single 24-hour period immediately following weaning (exact age not specified). A satellite control group of 50 breeder pairs was fed Purina Fox Chow ad libitum over the same 24-hour time period. Both uranium-exposed and satellite control pairs were then fed Purina Fox Chow ad libitum for 10 months. The male/female pairs were allowed to breed and produce litters with each litter being removed from the mother at birth. Body weight gain of uranium-fed rats over the 10-month observation period was comparable with control rats. By the end of the 10-month observation period, uranium-exposed breeder pairs had produced 233 litters as compared with 252 litters produced by control breeder pairs for a difference of 7%. Forty-four of 50 of the uranium-exposed females produced litters over the observation period as compared to 43 of 50 among control females. The number of offspring produced by uranium-exposed breeder pairs was reduced as compared to controls. Uranium-exposed breeders produced a total of 1725 pups as compared to the 1958 pups produced by control breeders for a difference of 12%. It was concluded that under the given conditions, uranium exposure had an adverse effect on rat reproductive functions in the absence of inanition.

Several studies have found evidence that uranium may be toxic to the male reproductive system at high dose levels (Llobet et al., 1991; Malenchenko et al., 1978; Maynard et al., 1953). Degenerative changes in the testes resulting in aspermia in the testes and epididymis were observed in male rats and were apparently a result of uranyl nitrate hexahydrate (0.1%, 0.5%, 1.0%, or 2.0%) being in their diet for two years (Maynard et al., 1953). Testicular atrophy was identified in rats fed 0.01–0.25% uranyl fluoride for two years (Maynard et al., 1953). However, testicular atrophy was also identified in a small percentage of control animals examined.

Malenchenko et al. (1978) presents evidence to suggest that uranium exposure causes morphologic changes in the rat testes possibly as the result of a uranium-induced autoimmune response. In this study, Wistar rats were either injected subcutaneously with uranyl nitrate at 0.01 mg/100 g body weight per day over five days or were given drinking water containing 0.1% uranyl nitrate for four months. Average testes weight was slightly decreased in animals injected with uranyl nitrate for five days as compared with controls (2.79Ł0.12 versus 2.48Ł0.38).

Average testes weight was significantly ($p<0.05$) decreased in rats exposed to uranyl nitrate for four months as compared to controls (3.14Ł0.09 versus 2.26Ł0.09). Titers of testicular autoantibodies were described as fairly high for rats with chronic exposure to uranium and the authors relate this finding to the possibility that the observed testicular changes are an autoimmune response to protein confirmation changes as a result of uranium–protein interactions. Four other references are cited by Malenchenko et al. (1978) as evidence of an interaction between uranium and the testes or thyroid but are not reviewed here.

Llobet et al. (1991) found no histological evidence that chronic uranium exposure had an adverse effect on testicular function or spermatogenesis in male Swiss mice exposed to dose levels equivalent to 10, 20, 40, and 80 mg/kg per day in their drinking water for 64 days. However, interstitial alterations and vacuolization of the Leydig cells was common in mice given dose levels equivalent to 80 mg/kg per day. The number of female mice impregnated successfully was significantly reduced at all levels of uranium exposure as compared with negative controls, but the number of implantations, resorptions, and

viable fetuses did not differ significantly between treated and negative control pregnancies. The average weights of the testes and epididymis also did not differ significantly among the treated and control groups when compared on a percentage body weight basis. Sperm motility, morphology, and spermatid counts were also not affected by uranium exposure, but the amount of spermatozoa was consistently and significantly lower for treated versus negative control animals when compared on a per gram of epididymis basis. Testicular injection with 2–6 mg/kg uranyl fluoride ($^{235}UO_2F_2$) containing enriched uranium resulted in a dose-dependent increase in chromosomal aberrations (i.e., DNA breakage, SCEs) in spermatogonia, primary spermatocytes, and mature sperm of adult mice (Hu and Zhu 1990; Zhu et al., 1994). It was concluded that the chromosomal aberrations were the result of both chemical and radiological interactions.

Exposure of the pregnant rodent dam to uranium either by oral gavage or subcutaneous injection produces maternal toxicity, as well as fetotoxicity and developmental defects (Bosque et al., 1992; 1993a; Domingo et al., 1989b; Paternain et al., 1989). Exposure of both male and female adult Swiss mice to uranyl acetate dihydrate by oral gavage at 5–25 mg/kg per day before mating and through gestation did not have an apparent affect on the ability to reproduce (Paternain et al., 1989). However, the total number of absorptions and dead fetuses were increased and the number of live-born fetuses was decreased among litters from parents exposed to a dose level of 25 mg U/kg per day. Pup body weight and length were also significantly reduced as compared with controls when measured at birth and on postnatal days 4 or 21 indicating that uranium retarded growth in uranium-exposed litters.

Fetal growth was reduced and a higher incidence of cleft palate and dorsal and facial hematomas was found among litters from pregnant Swiss–Webster mice dosed with uranyl acetate dihydrate at 5–50 mg/kg per day by gavage on gestational days 6–15 (Domingo et al., 1989a). The number of implantation sites per dam, resorptions per litter, and dead fetuses per litter were not significantly different as compared with controls. However, there was a dose-related decrease in average pup body weight and body length and a dose-related increase in the number of stunted fetuses per litter. A dose-related increase in the number of fetuses with cleft palate was also apparent. The number of dorsal and facial hematomas was significantly increased among pups from dams exposed to 5 and 50 mg/kg per day and increased among pups born to mothers dosed with 10 or 25 mg U/kg per day. Bipartite and misaligned sternebrae as well as poor ossification of the 13th and 14th rib, skull, and forelimb bones occurred at significantly higher levels among pups from uranium-exposed dams as compared with controls. Maternal toxicity was apparent at a dose level of 5 mg/kg per day indicated by decreased body weights as compared with controls, suggesting that the observed developmental variations may have resulted from a maternal toxic response. However, it was concluded that some of the fetal effects were independent of maternal toxicity (Domingo, 2001).

Domingo et al. (1989b) found that the combination of gestational and lactational exposure to uranyl acetate dehydrate had a significant effect on survival of pups through postnatal day 21. Pregnant Swiss mice were exposed to uranyl acetate dehydrate by oral gavage at dose levels equivalent to 0.05, 0.5, or 50 mg/kg per day beginning day 13 of gestation through postnatal day 21. Mean litter size, pup sex ratio, viability, and pup body weight and length were not significantly affected by the mother's exposure to uranium at 0.05, 0.5, or 5 mg/kg per day when evaluated at 0, 4, or 21 days of lactation. Mean litter size, viability, and the ratio of pups retained between lactation days 21 and 4 were significantly reduced for litters born to mothers exposed to 50 mg/kg per day. Development was not delayed among litters from all exposure groups as indicated by no differences in the number of days postbirth for pinna detachment, incisor eruption, and eye opening. A dose-related increase in liver weight was found among pups with increasing maternal dose levels of uranyl acetate dehydrate. Brain, heart, lung, kidney, and spleen weights of pups with exposure to uranium during gestation and lactation were not significantly different from the weights of these organs from control animals.

Administration of 1/40, 1/20, and 1/10 of the subcutaneous injection LD_{50} for uranyl acetate dihydrate on gestational days 6–15 resulted in both maternal toxicity and embryotoxicity at all dose levels (0.5, 1.0, and 2.0 mg/kg per day) (Bosque et al., 1993a). Fetotoxicity characterized by significant decreases in fetal weight and incomplete bone ossification at several sites was observed in offspring born to dams exposed to 1 or 2 mg/kg per day. Bosque et al. (1992) found that the number of dead and reabsorbed fetuses and percentage of postimplantation loss was greatest on day 10 of gestation following single subcutaneous injections of uranyl acetate dihydrate (4 mg/kg) on gestation days 9–12. Also, fetal weight was significantly reduced and a higher incidence of skeletal variations occurred among surviving offspring as compared with negative controls.

Administration of the uranium chelating agent Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) at dose levels of 500, 1000, or 1500 mg/kg per day, before injection of pregnant mice with 4 mg/kg uranyl acetate, reduced maternal mortality, but not the incidence of embryolethality among litters from exposed dams (Bosque et al., 1993b). Administration of Tiron at 1500 mg/kg per day reduced expected fetal growth retardation of uranium-exposed offspring, possibly due to a reduction in the amount of circulating uranium (Domingo, 2001).

Potential mechanisms for effects of uranium or DU on reproduction and fetal development

Modes of action Based on a review of the pertinent literature, there are several lines of evidence to suggest that DU exposure could potentially affect reproductive function and development in rodents. At this time, information on the reproductive and developmental effects of DU alloy in rodents is limited. However, existing data indicate that implanted DU translocates to the rodent testes and ovary, the placenta, and fetus (Benson, 1998; Pellmar et al., 1999a). DU has been shown to be genotoxic in *in vitro* cell model systems (Miller et al., 1998b) and possibly carcinogenic in rats (Hahn et al., 2002) suggesting that DU alloy could potentially disrupt or damage rapidly dividing cell populations in the fetus and adult rat.

Studies of the effects of natural uranium provide additional evidence that DU could have an adverse effect on rodent reproduction and development. Dosing of rodents with uranium has shown to cause testicular toxicity, maternal toxicity, fetotoxicity, increased developmental variations, and growth retardation independent of maternal toxic response (Domingo, 2001). Intratesticular injection of enriched uranium compounds increased the incidence of cytogenic damage in developing mouse sperm (Hu and Zhu, 1990). *In vitro* studies showed that uranium is both cytotoxic and genotoxic to Chinese hamster ovary (CHO) cells (Lin et al., 1993) and reduces cell number in developing mouse embryos in culture (Kundt et al., 2000).

Mechanisms of pathogenesis There are several mechanisms by which a toxicant may potentially affect rodent reproduction and fetal development (Table 3). Potential mechanisms of toxic action of DU alloy include mutagenicity and genotoxicity, disturbances in cell division, changes or inhibition of protein or steroid synthesis, disturbance or inhibition of enzyme systems, and disruption of behavioral patterns involved in normal reproduction. The end product of these mechanisms may be: 1) increased or decreased cell death; 2) disturbed cell-to-cell contact; 3) reduced biosynthesis; 4) increased morphogenetic pattern formation; or 5) disruption of tissue structure that may lead to abnormal pathogenesis in the reproductive system or developing fetus (Peters and Garbls-Berkvens, 1996). If repair processes inherent to fetal tissue become overwhelmed, dysmorphogenesis of the developing fetus may occur resulting in too few cells or cell products being formed to affect structure and functional maturation of the developing individual (Peters and Gerbis-Berkvens, 1996; Schardein, 2000; Wilson, 1973). Disruption of embryogenesis by vasoconstriction or other indirect pathways is also a possibility (Schardein, 2000).

Table 3. Potential mechanisms of reproductive toxicants[a].

1) Mutations
2) Chromosomal aberrations
3) Disturbances in cell division
4) Changes in nucleic acid composition and protein synthesis
5) Reduction in the amount of essential constituents for biosynthesis
6) Reduction of energy supply for embryonic and fetal development
7) Disturbance of enzyme systems
8) Disturbances in the regulation of water and electrolyte balances
9) Changes in membrane characteristics

[a]Adapted from Peters and Gerbls-Berkvens (1996) and Wilson (1973).

Mutations and chromosomal aberrations Both natural uranium and DU have been shown to be genotoxic to mammalian cells *in vitro* (Lin et al., 1993; Miller et al., 1998a; 1998b). Increased frequencies of SCEs have been reported for PGW veterans exposed to DU alloy (McDiarmid et al., 2001) and for uranium miners (Zaire et al., 1997). Because of its genotoxic potential, DU alloy could potentially interact with the genetic components of germ lines and somatic cells in adult rodents and in rodent fetus, respectively. Several other metals, including lead, chromium, cadmium, are genotoxic and can induce reproductive or developmental toxicity (Hoey 1966; Schardein, 2000; Thomas, 1995).

Disturbances in cell division Studies by Lin et al. (1993) indicated that uranium can produce decreased viability, depressed cell cycle kinetics, and an increase in several genotoxic endpoints in CHO cells. Uranium, delivered as uranyl nitrate, delayed development of mouse embryos in culture and was associated with lower embryo cell numbers through the hatched blastocyst stage, suggesting that uranium exposure resulted in severe alterations in DNA synthesis (Kundt et al., 2000). Several other metals arrest cell division under certain conditions, including chromium (VI) (Zhang et al., 2001), iron (Philpott et al., 1998), nickel (II) (Shiao et al., 1998), lithium (Mao et al., 2001), and beryllium (Lehnert et al., 2001). To date, there have been no studies conducted evaluating the capacity of DU alloy to produce disturbances in cell division.

Changes in protein or steroid synthesis There is some evidence that DU alloy may alter protein synthesis in mammalian cells. Northern blot analysis gave evidence that Rb tumor suppressor protein was underexpressed in DU-uranyl chloride-treated HOS cells (Miller et al., 1998b). Cells transformed to the tumorigenic phenotype by DU exposure were found to express high levels of the k-*ras* oncogene. Prolactin levels were elevated in DU-exposed Gulf War veterans (McDiarmid et al., 2000), although there was no apparent impact on sexual function or reproductive success of these individuals (McDiarmid et al., 2001).

Heavy metals can inhibit steroidogenesis in rodents. Lead has been shown to reduce steroidogenesis in rodent adrenal and Leydig cells (Liu et al., 2001; Ng and Liu, 1990;

Thoreux-Manlay et al., 1995). Mercuric chloride has shown to inhibit testicular steroidogenesis in rats (Chowdhury et al., 1985). Currently, there is no published evidence that uranium inhibits steroidogenesis in rodents.

Disturbance of enzyme systems Enzymes play a vital role in reproduction and fetal development. Several metals inhibit or interfere with liver cytochrome P-450 activity, including uranium (Pasanen et al., 1995), cadmium (Dudley et al., 1985), and arsenic (Falkner et al., 1993). Mercury ions may also inhibit gonadotropin synthesis in the hamster (Lamperti and Printz, 1973), possibly by the inhibition of enzyme systems.

Effect on parental libido and pup rearing behaviors Exposure to certain chemicals alters sexual behavior in adult rodents, including lead (Sant'Ana et al., 2001), chromium (Bataineh et al., 1997), di(2-ethylhexyl) phthalate (Moore et al., 2001), and polychlorinated biphenyls (PCBs) (Chung et al., 2001). Male rat sexual behavior was suppressed after the ingestion of manganese sulfate, aluminum chloride, lead acetate, and copper chloride in the drinking water at a concentration of 1000 ppm for 12 weeks (Bataineh et al., 1998). Llobet et al. (1991) notes that decreased pregnancy rates in male Swiss mice may have been the result of lowered libido related to chronic exposure to uranyl acetate.

Exposure of pregnant Swiss mice to 5, 10, 20, and 30 mg/kg body weight of bis(tri-$_n$-butyltin) oxide (TBTO) on days 6–15 of gestation produced an adverse, dose-related effect on the postnatal care provided by mothers to their offspring (Baroncelli et al., 1995).

The impact of DU implantation on sexual or parental care behaviors has not been specifically studied. Implantation of DU alloy has been shown to alter hippocampus electrophysiology in rats (Pellmar et al., 1999a; 1999b). However, further study is needed to determine the impact of these changes on rodent behavior.

Summary and ongoing research

At this time, the multigenerational effects of DU exposure on rodent reproduction and development are not known. Implanted DU alloy translocates to the gonads and developing fetus, and DU alloy is potentially genotoxic and possibly carcinogenic. A number of studies have shown that natural uranium is a reproductive toxicant in rodents and may be toxic and teratogenic to the developing rodent fetus. Collectively, these findings justify conducting studies on the reproductive toxicity and developmental effects of DU alloy in rodents in a multigenerational study. Format at this time, the effect of embedded DU alloy fragments on rat reproduction and development of P1 adults and successive generations (F_1, F_2) is currently being evaluated at the Naval Health Research Center Detachment Toxicology Laboratory, WPAFB, OH. Current information on DU and natural uranium from the scientific literature indicate that DU alloy may potentially impact rodent reproduction and development by direct or indirect chemical or radiological modes of action. Potential mechanisms of toxic action of DU alloy on these endpoints may include mutagenicity and genotoxicity, disturbances in cell division, changes or inhibition of protein or steroid synthesis, disturbance or inhibition of enzyme systems. Exposure to DU alloy may also impact rodent reproductive success by causing changes in sexual libido or by altering the quality of postnatal care administered by the parents. Alternatively, exposure to DU alloy may have no adverse impact on rodent reproductive success or fetal development.

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Appendix 3

Paper

URANIUM DEPOSITION AND RETENTION IN A USTUR WHOLE BODY CASE

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Abstract—This report describes a whole body donation from a person with a documented occupational intake of uranium. USTUR Case 1002 was an adult male who died from an acute cerebellar infarct at the age of 83. He worked as a power operator, utility operator, and metal operator for 28 years in a facility that processed and handled radioactive materials. Although he suffered a number of burns from hot metal and acids, cuts, abrasions, and puncture wounds during his many years of work, there were no corresponding health physics or medical records to indicate that these occurrences needed or required excision or decontamination due to the suspicion of the deposition of radioactive material. Over the course of his employment, USTUR Case 1002 submitted numerous urine samples for uranium, plutonium, and fission product analysis. The highest single uranium value measured during this time period was ~30 $\mu g\ L^{-1}$ recorded during the second year of his employment. A urinary bioassay sample taken before termination of employment measured 4.3 $\mu g\ L^{-1}$. The mean urinary uranium concentration per liter per year calculated from the employee's bioassay records covering the first eleven years of monitoring averaged less than 3 $\mu g\ L^{-1}$. The ratio of $^{234}U/^{238}U$ activity in the lung tissue was about 1, the same as that found in natural uranium. The highest concentration of uranium was found in a tracheobronchial lymph node. The uranium content in the various tissues of the body followed a rank order lung > skeleton > liver > kidney. Concentration of uranium in the kidney tissue was ~1.98 ng g^{-1}, about 3 orders of magnitude less than the generally accepted threshold level for permanent kidney damage of 3 $\mu g\ U\ g^{-1}$ and roughly equal to the 1.4 ng g^{-1} reported for Reference Man. The autopsy disclosed findings not uncommon in the aged: severe atherosclerosis, areas of sclerotic kidney glomeruli with stromal fibrous scarring, and moderate to severe arterionephrosclerosis. Lung sections contained parenchymal areas of acute vascular congestion and a mild degree of anthracosis.
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Key words: uranium; skeleton; kidneys; Reference Man

INTRODUCTION

In 1789, German chemist Martin Heinrich Klaproth reported the results of his research with pitchblende to the Berlin Academy, identifying a new metallic element, which he named uranium after the planet Uranus, which had only recently been discovered by William Herschel. Toxicity studies of uranium date back to as early as 1824, carried out as part of a larger study of all 18 then-known metals by Christian Gottlieb Gmelin, who observed that uranium was at best a weak poison if taken by mouth, but that injection of the nitrate or chloride into the jugular vein of a dog was sufficient to bring about death within a minute. Gmelin observed that the injected uranium salts produced large blood clots in the heart and great vessels, an effect also produced by the injected salts of palladium and barium (Hodge 1973).

Since the initial studies of Gmelin, there have been numerous experimental studies of the toxicity of uranium whose radioactive properties were discovered in 1896 by Henri Becquerel. These studies generally confirmed the feeble toxicity of ingested or inhaled uranium and indicated that, in dogs at least, damage to the proximal tubules of the kidney could result from uranium intake, and that uranium promoted excretion of sugar via the urine. This latter observation led to its use therapeutically as a treatment for diabetes early in the twentieth century.

Despite this long association and numerous toxicity studies with uranium over the years, there are still many unanswered important questions regarding the biokinetics and toxicology of uranium in humans. To provide answers to these questions, the U.S. Uranium Registry, now a part of the U.S. Transuranium and Uranium Registries (USTUR), was created in 1978. The basic plan of the Registry is to obtain tissue, or in some cases the whole body, at the time of death from volunteer donors with a known exposure to uranium, and to analyze these tissues for their radioactivity content. In this fashion, information could be gained regarding the distribution, dose, translocation, and fate of uranium in the body, which could be combined with autopsy results and personal exposure and medical histories to better understand the possible health implications of uranium in humans and to assure the adequacy of safety standards for workers and the general public. This paper reports on

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the first whole body donation to the USTUR from a person with a known occupational intake of uranium.

MATERIALS AND METHODS

USTUR Case 1002 was a Caucasian male who died at age 83, approximately 20 y after his retirement. Employment records state that he worked as a power operator, utility operator, and metal operator for 28 years in a facility that processed and handled radioactive materials. His duties brought him into areas of the facility where potential existed for exposure to various radioactive materials including thorium, uranium, plutonium, and americium and other transplutonics. Although he suffered a number of burns from hot metal and acids as well as cuts, abrasions, and puncture wounds during the course of his employment, there are no corresponding health physics or medical records to indicate that these occurrences required excision or decontamination from actual or suspected deposition of radioactive material. Moreover, examination of his health physics records did not disclose any acute accidental inhalation intakes of uranium or other radioactive materials.

Over the first 11 y of his employment, a total of 82 urine samples were collected and analyzed for uranium, plutonium, and fission products. Measurable levels of uranium were found in his urine; these data are summarized in Table 1. However, no plutonium or fission products were detected. With the exception of a single sample collected at the time of his retirement, no urine samples were collected or analyzed after his initial 11 y of employment. Present day health physics personnel at the work site state that reassignment of radiation material workers and others to new job duties that might or might not have involved working with uranium or other radioactive materials was common practice at that time. However, mandatory periodic urinary bioassay sampling of all workers handling or working with radioactive materials was required at the time. Thus it is likely that this worker incurred his uranium body burden from chronic low-level exposure to airborne uranium in the workplace during the first decade of his 28 y of employment, or 38–48 y prior to his death. This conclusion is consistent with his film badge results, which indicated a total lifetime whole body exposure of 11.42 rem of non-penetrating radiation and 4.33 rem of penetrating exposure, mostly during his early years of employment. The ratio of non-penetrating to penetrating dose is consistent with work with uranium since the external radiation field associated with uranium metal is primarily beta radiation (Kathren 1975). Case 1002 was removed from bioassay sampling 11 y after starting employment, indicative that his work no longer involved the potential internal exposure after this time.

Table 1. Urinary excretion of uranium in USTUR Case 1002.

Years of employment	Number of samples	Mean conc. ($\mu g\ L^{-1}$) $\pm \sigma^a$	Range ($\mu g\ L^{-1}$)	Estimated annual excretion (mg)[b]
1	5	2.0 ± 4.1	0.0–10.2	1.0
2	13	6.9 ± 8.5	0.0–30.1	3.5
3	10	7.6 ± 7.9	0.0–29.5	3.9
4	8	0.7 ± 1.9	0.0–5.7	0.4
5	5	4.5 ± 4.2	0.0–6.3	2.3
6	8	1.0 ± 1.8	0.0–4.2	0.5
7	11	0.9 ± 2.7	0.0–9.5	0.5
8	11	0 ± 0	0	0
9	6	0.7 ± 1.5	0–4.1	0.4
10	3	0 ± 0	0	0
11	2	3.5 ± 1.9	1.6–5.4	1.8
12–24	0	—	—	Not exposed
25	1	4.3	—	—
Total (years 1–11)		2.53 ± 3.14		14.3
All Years excluding zero values and value at termination		3.09 ± 3.83		

[a] Results below detection limit assumed to be zero.
[b] Estimated annual excretion of uranium = mean concentration × volume of urine excreted per day (1.4 L) × 365 d y^{-1}.

After completion of the autopsy, the bones were defleshed in accordance with the established USTUR protocol, and soft tissue and individual bone wet weights were obtained. The tissues were analyzed at Los Alamos National Laboratory for uranium by kinetic phosphorescence analysis (KPA) according to the method of Bushaw (1984). Selected tissue samples were also analyzed for isotopic uranium by alpha spectrometry after ashing and chemical separation of the uranium in accordance with the methods of Gonzales and Willis (1987) and Boyd and Eutsler (1987). Results of the tissue analysis for uranium are summarized in Tables 2 and 3 and given in detail in Appendix Tables A1 and A2 for soft tissue and bone, respectively. In addition, the Appendix tables also contain the wet weight values of the divided bone samples. Uranium content is reported in mass units, and represents the total uranium present in the sample as determined by KPA, which does not provide an isotopic measurement. Results of the isotopic measurements in selected samples are given in Table 4. Table 5 provides a comparison of the uranium content of selected tissues of USTUR Case 1002 with cases previously reported by the USTUR, data on New York City residents (Fisenne and Welford 1986), and data on Reference Man (ICRP 1975).

RESULTS AND DISCUSSION

Tissue content of uranium

Measurable levels of uranium were found in urine and these data are summarized in Table 1. The mean

Table 2. Comparison of calculated organ content of uranium in selected tissues.

	Uranium content, μg					
Organ	USTUR 1002	USTUR 1042	USTUR 0242	USTUR 0213	Reference Man (ICRP 1975)	New York City residents Fisenne and Welford (1986)
Spleen	12.50	—	0.13	0.09	—	—
Liver	2.92	216	0.20	0.20	0.45	0.36 ± 0.56
Lung	249.60	1,550	1.78	1.02	1.00	0.5 ± 0.39
Kidney (2)	0.39	77	0.29	0.63	7.00	0.13 ± 0.08
Skeleton[a]	43.70	4,917	42.60	35.90	59.00	6.6 ± 3.8
TBLN[b]	8.70	—	0.19	0.09	—	—

Case 1002
Total systemic 62.11,[c] μg.
Total in body 364.11[c] μg.
[a] Average concentration in bones assayed × 10^4 g of bone.
[b] Tracheobronchial lymph node.
[c] Includes total fat, skin, and muscle content calculated from Reference Man values.

Table 3. USTUR Case 1002. Systemic soft tissue uranium concentrations.

Tissue/Organ	ng/g
Spleen	102.8
Bladder	23.4
Blood	12.2
Thyroid	9.8
Eyes	7.5
Hair	6.5
Testis, peritesticular	5.4
Liver	2.5
Kidney	2.0
Brain	0.6
Remaining tissue (excluding respiratory tract)	<1.0

annual urinary concentration of uranium during this period was calculated as 2.53 ± 2.60 μg L^{-1}, with the highest single value, ~30 μg L^{-1}, recorded during his second year of work with uranium. Based on the urinary excretion data, the total uranium excreted via the urine during this period is estimated as 14.3 mg, corresponding to a urinary excretion of a few mg annually and an intake of perhaps on the order of a few tens of mg per year based on generally accepted models (ICRP 1994). Analysis of the single urine sample collected at the time of his retirement revealed an elevated uranium concentration of 4.3 μg L^{-1}, which, although appearing to be anomalously high in consideration of his likely exposure history and previous urine results, could be interpreted as suggestive of a long-term deposition of uranium in the body. The result of a single in vivo chest count made at the time of his retirement was less than the lower limit of detectability of <1 mg based on ^{235}U and natural uranium, suggestive, perhaps, that any long term deposition was at least in part not in the respiratory tract, and indicative of an inhalation intake of perhaps a few tens of mg over the 11-y exposure period some four decades or more prior to his death based on various biokinetic models (ICRP 1977, 1979, 1988, 1995a and b; Fisher et al. 1991; Wrenn et al. 1985, 1989).

Not unexpectedly considering the likely mode of exposure, the highest soft tissue concentrations of uranium were found in the respiratory tract, and in particular in the associated lymph nodes (Table 2). The inordinately high value of uranium in the lungs decades after intake is a reflection of a highly insoluble organ burden. Both mechanical and particle dissolution processes influence the clearance rate of uranium from the lung. Likewise, the very high concentration of uranium found in the tracheobronchial lymph nodes (TBLN) reflects the transportable fraction of uranium that was initially either physically entrapped or deposited in the lung parenchyma that subsequently cleared. The amount of uranium found in the respiratory tract is entirely consistent with the failure to detect a lung burden by in vivo counting, being a factor of 4 lower than the lower limit of detectability for the in vivo counting system.

Uranium is typical of many heavy metals in that it exhibits a strong affinity for biological molecules such as those containing phosphate groups, i.e., glucose phosphate and phospholipids; sulfhydryl groups, i.e., glutathione; and proteins and anions containing oxygen, i.e., carbonate and bicarbonate. Thus, free ions of heavy metals do not exist in the blood stream as such except in some transient sense, but they do exist as complexes with such biological molecules as those described. Inhaled particulate material makes first contact with lung epithelial lining fluid, which contains a variety of proteins, antioxidants, and surfactant lipids, which in the case of uranium forms a variety of complexes with the uranium particles, some of which are subsequently phagocytized. Although uranium does not form colloids in blood, aggregations of two or more uranium particles have been seen in macrophages following inhalation intake. The exact nature of how particle laden alveolar macrophages

Table 4. Summary of uranium content and concentration in bone. USTUR Case 1002.

	Weight (g) wet	Weight (g) ash	ng U	ng U/g wet	ng U/g ash
Skull	540	280	3,667	6.79	13
Vertebrae	846	186	2,743	3.24	15
Pelvis	528	128	917	1.74	7
Ribs	433	135	1,438	3.32	11
Sternum	78	11	85	1.09	8
Humerus	272	97	987	3.63	10
Radius	88	32	783	8.87	25
Ulna	103	43	613	5.95	14
Hand	140	37	2,167	15.48	59
Clavicle	56	18	273	4.89	15
Scapula	157	48	371	2.36	8
Femur	808	260	2,773	3.43	11
Patella	31	9	127	4.07	14
Fibula	110	40	582	5.29	15
Tibia	524	156	1,991	3.8	13
Foot	361	84	3,178	8.79	38
Sacrum + coccyx	243	43	544	2.24	13
Costal cartilage	24	0.4	127	5.3	318
Total for skeletal samples analyzed	5,342	1,607	23,366		

Table 5. Isotopic concentration of uranium in selected tissues of USTUR Case 1002.

Sample ID	Wet wt. LANL	ng U sample	± SD	^{238}U mBq per Sample	± SD	^{235}U mBq per sample	± SD	^{234}U mBq per sample	± SD
Liver	1,178	2,924	340	4.9	0.001	1.80	0.001	7.8	0.002
R-lung	548	132,745	10.735	1,207	0.068	40	0.008	1,202	0.068
Kid-R	91	240	19.8	3.1	0.001	0.15	0.015	3.5	0.001
Femur MS	147	783	54.8	10.5	0.002	1.30	0.001	15.7	0.002

migrate to the pulmonary and tracheobronchial lymph nodes via the lymphatics or migrate to the bronchioles to be transported by mucociliary action to the gastrointestinal tract is not completely understood.

Table 2 also provides a comparison of the uranium content of selected tissues of USTUR Case 1002 with those from USTUR Case 1042, another occupationally exposed case (Kathren et al. 1989); two whole body background cases previously reported by the USTUR (Kathren 1997); data on New York City residents reported by Fisenne and Welford (1986), and Reference Man (ICRP 1975). The relative content of uranium in the kidneys in the USTUR and NYC cases was low, on the order of 1–2% of the amount in the skeleton, as compared with 12% for Reference Man. Moreover, the kidney content of uranium in the two USTUR background cases and NYC residents was in all cases less than 1 μg, averaging 0.13 ± 0.08 in the latter and 0.46 ± 0.24 in the former, about an order of magnitude or more lower than the 7 μg reported for Reference Man (Table 2). Clearly, the Reference Man value for uranium in kidney is too high and should be reduced by at least a factor of 10.

Most systemic (i.e., rest of the body) soft tissues had mean uranium concentrations of <1 ng g^{-1} wet weight (Table 3), approximately the same level seen in two background or unexposed whole body cases previously reported by the USTUR (Kathren 1997). A number of soft tissues showed clearly elevated concentrations, most notably the spleen, which, with a concentration of 102.8 ng g^{-1} was two orders of magnitude greater than most of the soft tissues. Other tissues with significantly (i.e., order of magnitude) higher than average concentrations of uranium were the urinary bladder (23.4 ng g^{-1} wet weight), blood (12.2 ng g^{-1} wet weight), and thyroid (9.8 ng g^{-1} wet weight), followed by eyes (7.5) and testis and peritesticular tissue (4.5). The concentration of uranium in hair was 6.5 ng g^{-1}, at the upper end of the range of concentration values for the general public reported in the literature, i.e., a few tenths of ng to several ng g^{-1} (Byrne and Benedik 1991). Concentration in kidney and liver were lower still, but still about two to three fold greater than the average systemic soft tissue concentration, while concentration in fat was an order of magnitude lower than that in most of the tissues.

The elevated concentration of uranium in the spleen is most likely due to uranium bound to red blood cell membranes. One function of splenic macrophages is to remove fragments of abnormal red blood cells (RBC's)

and whole damaged RBC's from the circulation and store the iron as ferritin; some iron is attached to the protein transferrin and released back into the bloodstream. Thus, any uranium bound to such RBC's would be internalized (phagocytized) along with the damaged red blood cells/fragments and retained in situ. This observation is consistent with that of Hedaya et al. (1997) who observed high concentrations of uranium in the spleen of rats following intraperitoneal injection. In addition, uranium dissolved in blood circulates bound not only to erythrocytes but also to transferrin, plasma proteins, and a variety of diffusible ligands (Voegtlin and Hodge 1949).

The reason for the apparently elevated thyroid concentration of uranium in USTUR 1002 is unknown but is consistent with what was observed in one of the two USTUR background cases, and the modest concentration in the hair might be explained by the fact that uranium is a heavy metal, and heavy metals are normally excreted in the hair and nails, although the concentration in the nails in this case were not significantly higher than the soft tissue average. However, this value may be suspect as hair samples are easily contaminated by shampoos and hair dyes, many of which contain trace metals, which in turn can cause analytical interferences.

The uranium content of the skeleton is summarized in Table 4. The results of each specific bone sample analysis are given in Appendix A2. Following established USTUR procedures (McInroy et al. 1985), approximately half the skeleton was analyzed for uranium content in order to calculate the total skeleton burden outlined in Table 4. All vertebrae except C-1 were separated into the vertebral body, which is mostly cancellous bone with a large surface to volume ratio and the arch, which is mostly compact bone. The total wet weight (including red and yellow bone marrow) of skeletal samples analyzed for uranium was 5,342.14 g, slightly more than half of Reference Man skeleton weight of 10,000 g, and contained 23,366 ng U. This corresponds to an average uranium concentration of approximately 4.4 ng U g^{-1} of bone (wet weight) or 14.5 ng U g^{-1} ash.

The highest uranium concentration in a single skeletal sample was found in the costal cartilage (318 ng U g^{-1} ash); the lowest concentration was in the third thoracic vertebrae body and the third lumbar vertebrae body (4.7 ng U g^{-1} ash). Elevated concentrations of uranium were also found in the bones of the hand and foot (59.30 and 37.94 ng U g^{-1} ash, respectively) and in some vertebral arches and bodies. Among the bones of the hand and feet, the higher concentrations of uranium were found in some of the smaller generally odd shaped bones primarily from the phalanges with low ash weights. Elevated concentrations of uranium were also seen in the phalanges of USTUR 0213 and 0242, so-called "background" cases (Kathren 1997). This same observation has also been reported before for americium retention in at least one other USTUR whole body case, USTUR 0102 (McInroy et al. 1985), and possibly in other cases for plutonium and americium.

In the long bones, the highest concentration of uranium was found in the radius (24.50 ng U g^{-1} ash); the lowest concentration of uranium in the humerus (10.20 ng U g^{-1} ash). With few exceptions, the concentration of uranium, a volume seeker, in the more highly trabecularized ends of the various long bones was not greatly different from that of the shaft or compact bone areas. This contrasts somewhat with the long bone retention pattern generally seen with plutonium, a surface seeker, in which the long bone ends that have more trabecular bone (more surface area) also have greater cellular activity, i.e., bone remodeling and bone turnover rate retains a greater concentration of plutonium than compact bone. The concentration of uranium in the ends of long bones ranged from 7.6 to 113.9 ng U g^{-1} ash in the proximal end of the femur and the proximal end of the radius, respectively. By comparison, the concentration of uranium in the shafts of long bones ranged from 7.7 to 18.3 ng U g^{-1} ash in the distal shaft of the humerus and the proximal shaft of the radius, respectively.

The concentration of uranium activity in the 11 vertebrae that were divided and analyzed for uranium was inconsistent, ranging over an order of magnitude and with no apparent or obvious pattern. The uranium concentrations in the vertebral arches ranged from 4.7 to 58.4 ng U g^{-1} ash. Intravertebral concentrations were likewise inconsistent; the highest concentration in the arches was observed in C5, and significantly elevated concentrations were also noted in the arches of T1 and T5. Elevated concentrations of uranium in vertebral bodies were observed in T5 and T7, which had the greatest concentrations, and to a much lesser extent in T9 and L1.

Table 5 shows the results of isotopic measurements in selected tissues. The ratio of $^{234/238}$U in the lung tissue is about 1, same as that found in natural uranium. Although the $^{234/238}$U ratios for the liver and bone are somewhat elevated (i.e., greater than unity), the difference is not significantly different at the 95% confidence level, indicating that the chronic exposure suffered by USTUR 1002 during his early years of employment was likely to natural uranium.

Lack of knowledge of the exposure characteristics specific to this case limits application of the data from USTUR 1002 to biokinetic modeling. Additionally, the fact that the postmortem tissue concentration data for this

case are temporally many years after the intake(s) occurred obviates evaluation of the biokinetics at relatively short times after intake. It is of interest, however, to note that the long term systemic distribution of uranium in the soft tissues of this single occupationally exposed individual differs from the initial or short term pattern of tissue deposition observed in the so-called Boston injection cases who died relatively soon after their intake of uranium (Bernard and Struxness 1957; Luessenhop et al. 1958; Struxness et al. 1956), agreeing somewhat better but still not completely with the pattern of deposition observed in these cases after time.

In consonance with various systemic models for uranium (ICRP 1977, 1979, 1988, 1995a and b; Fisher et al. 1991; Wrenn et al. 1985, 1989; Durbin 1984), the skeleton contained the largest amount of uranium, about three-fourths of the systemic content, an observation in good agreement with post mortem tissue measurements (Fisenne and Welford 1986; Gonzales and McInroy 1991; Kathren 1997; Kathren et al. 1989) and with what would be predicted by the current ICRP model for a person of this age many years after intake (Leggett 1994). The ratio of uranium content in the skeleton to that in liver was approximately 15, albeit a factor of two smaller than the ratio of 30 that would be predicted by the ICRP Publication 69 model (ICRP 1995a and b) but clearly within the expected range of variability for a single case. However, contrary to most human models, an appreciable amount of uranium was also found in the spleen, suggestive as discussed above of RBC-membrane bound uranium clearance by the reticuloendothelial system with deposition or storage in the spleen. Even more striking than the total splenic content of uranium is the concentration (Table 3), which, at 102.8 ng g^{-1} of tissue was about an order of magnitude greater than the concentration in blood, and certainly consistent with preferential uranium clearance, retention, and/or deposition in the spleen. In any case, in consideration of refinements to the widely accepted and applied ICRP model, it would seem important to consider the spleen as a potential depot for inhaled uranium in insoluble form. Elevated levels of uranium were also found in the thyroid and urinary bladder of USTUR 1002. USTUR Case 0242, one of the two whole bodies whose tissues were analyzed for uranium by the USTUR, was an individual not known to have incurred an occupational or other exposure to uranium, and also exhibited an elevated concentration of uranium in the thyroid (Kathren 1997). In the second case assayed, USTUR 0213, the uranium concentration in the thyroid was typical of soft tissue concentrations generally. There is no obvious cause or explanation for the observed elevated thyroid concentrations in USTUR Cases 0242 and 1002, and the significance is unclear from a toxicological standpoint. However, the observed elevated thyroid concentrations relative to other soft tissue concentrations in two of the three USTUR whole body cases bears additional investigation with an eye towards factoring this into future biokinetic models.

Both kidney content and concentration were small, and the ratio of skeletal content to kidney content is in excellent agreement with the age dependent model put forth by the ICRP (ICRP 1995a; Leggett 1994) for an individual 25 y or so after uranium intake as a young adult. This observation also argues against the existence of a long term kidney compartment, although it is not inconsistent with a small kidney compartment with what might be termed an intermediate residence half time of 1,000 to 1,500 d as put forth in some models (Fisher et al. 1991; ICRP 1979; Wrenn et al. 1985, 1989) as well as in agreement with Durbin (1984) and other models that do not postulate a long term kidney retention compartment (ICRP 1995a; Leggett 1994; Leggett and Harrison 1995). The apparent equivocal long term retention of uranium in the kidney is indicative of both the complexity of uranium biokinetics in humans and of the dangers of extrapolation from a single case, and has been succinctly characterized by Leggett (1989) who wrote "Retention of uranium in the kidneys cannot be accurately characterized without consideration of the continual but diminishing inflow of uranium released from the bone and other tissues."

The relatively large retention in the lung is consistent with various models (ICRP 1995b) and recent work by Bertelli et al. (1998a and b), but inasmuch as the characteristics of exposing aerosol are unknown (e.g., particle size distribution, chemical form, time of exposure), it does not seem productive to speculate about respiratory tract biokinetics. The presence of uranium in the respiratory tract this long after exposure is clearly indicative that some unknown fraction of the inhalation intake was to highly insoluble material.

Taken as a whole, the systemic distribution of uranium in the soft tissues of USTUR 1002 is in good agreement with current models, as exemplified by the widely accepted and utilized model put forth in ICRP Publication 69 (ICRP 1995a; Leggett 1994). However, the observations of elevated concentrations in the thyroid and spleen pose interesting questions and hint at potential refinements to this model, which is primarily concerned with deposition in bone, liver and kidney, and are suggestive of a need to consider potential long term toxicological ramifications and perhaps include more specificity with respect to these tissues in future models.

The autopsy disclosed severe atherosclerosis involving the coronary vessels, the aorta, and the vessels at the base of the brain (Circle of Willis). An acute cerebellar infarct was present and was the immediate cause of death. Microscopic examination of H and E stained paraffin sections disclosed specific calcific atherosclerosis with high-grade stenosis of the coronary artery. In addition, sections of the myocardium showed small areas of fibrous scar tissue with moderate intimal thickening. The kidneys displayed areas of sclerotic glomeruli, with parenchymal vessels showing intimal thickening. The kidney also displayed areas of stromal fibrous scarring with some lymphocytic infiltration with moderate to severe arterionephrosclerosis. Lung sections with parenchymal areas of acute vascular congestion and a mild degree of anthracosis were also noted. Sections of the basal ganglia demonstrated slight gliotic scarification, consistent with old areas of cerebral infarction. Sections of occipital cortex with an area of cyst formation, gliosis, and deposition of pigment-laden histocytes consistent with an old cerebral cortical infarct were also observed.

CONCLUSION

Analysis of all the tissues from a whole body donor with a known occupational history of exposure to uranium showed elevated concentrations of uranium in the respiratory tract and spleen that are consistent with inhalation of natural uranium in a somewhat insoluble form. The low kidney concentrations in this case, other Registry cases, and other cases reported in the literature suggest that the Reference Man data on background quantities of uranium on the kidney are high by about an order of magnitude. The relative amount of uranium in the various organs of this case were lung > skeleton > spleen > liver > kidney, which is in agreement with other reported observations from the literature but not with Reference Man, which indicates that the amount of uranium in kidney is greater than that in liver. Autopsy results disclosed findings not uncommon in the aged with no indication of pathology possibly attributable solely to exposure to uranium.

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APPENDIX

Table A1. Uranium content in soft tissue of USTUR Case 1002.

Sample ID	Wet weight (g)	ng U	± SD	Concentration (ng U/g wet weight)
Liver	1,178	2,924	340.0	2.48
Lung-R	548	132,745	10,735.0	242.24
Lung-L	436	116,840	9,440.0	267.98
Larynx	126	232	20.0	1.84
Trachea	60	22,600	1,850.0	375.48
LN (Aortic)	5	4,438	358.0	840.53
TBLN	8	8,684	700.0	1,133.83
Kid-R	91	240	19.8	2.64
Kid-L	107	152	12.8	1.42
Adrenal	77	50	5.0	0.65
Heart	415	265	22.0	0.64
Pericardium	352	908	75.0	2.58
Periaortic scrap	108	1,552	124.0	14.33
Aortic Arch	124	503	42.0	4.04
Des-aorta(part)	56	77	6.9	1.38
Blood	9	109	9.3	12.20
Pancreas	121	74	6.5	0.61
Spleen	121	12,480	1,020.0	102.80
Esophagus	45	32	2.9	0.71
Diaphragm	66	161	13.0	2.48
Stomach	161	81	8.1	0.50
Small intestine	729	1,088	89.0	1.49
Large intestine	1,221	878	72.0	0.72
Omentum	463	279	24.0	0.60
Mesentary	589	188	16.0	0.32
Fat—abdominal	180	11	1.1	0.06
Epidura	71	39	3.9	0.55
Bladder	220	5,141	417.0	23.37
Prostate	37	58	5.0	1.57
Testis-R	6	37	3.5	5.92
Testis-L	12	42	3.7	3.43
Peritesticular tissue	5	28	2.7	5.37
Penis	67	25	2.5	0.37
Scrotum	102	32	3.2	0.31
Cerebrum	1,156	647	58.0	0.56
Cerebellum	78	79	8.8	1.01
Eyes	5	40	3.6	7.50
Thyroid	7	68	6.8	9.81
Hair—head	9	57	5.1	6.48
Skin				
Head	626	361	36.1	0.58
Up R arm	740	69	6.9	0.09
R forearm	290	143	14.3	0.49
R hand	176	59	5.3	0.34
R-foot	249	11	1.1	0.04
Salivary gland	13	7	0.7	0.52
Ear-R	18	9	0.9	0.49
RF-1	286	42	4.6	0.15
RF-2	398	13	1.6	0.23
RF-3	727	22	2.2	0.31
RF-4	324	4	1.2	0.01
RB-1	351	29	3.2	0.08
RB-2	315	16	1.8	0.05
RB-3	455	22	2.2	0.31
RB-4	546	31	3.1	0.06
Thigh-R1	648	84	8.4	0.13
Thigh-R2	928	806	80.6	0.87
Calf-R1	274	44	4.8	0.16
Calf-R2	233	31	3.5	0.13
Muscle				
Head	696	108	9.2	0.16
Tongue	68	10	1.0	0.15
R up arm	526	65	5.8	0.12
R forearm	1,098	115	11.5	0.10
R hand	143	100	8.6	0.70
Abdominal	1,909	1,640	132.0	0.86
R foot	292	25	2.3	0.09
R psoas	333	36	3.2	0.11
RF-1	740	210	21.0	0.28
RF-2	321	41	4.1	0.13
RF-3	675	36	3.6	0.05
RF-4	458	38	3.9	0.08
RB-1	826	37	3.7	0.04
RB-2	471	2,976	208.3	6.32
RB-3	688	26	2.6	0.04
RB-4	1,416	330	33.0	0.23
Thigh-R1	1,826	108	10.8	0.06
Thigh-R2	1,285	36	3.6	0.03
Calf-R1	592	30	3.3	0.05

Table A2. Uranium content in skeleton of USTUR Case 1002.[a]

Sample	Wet weight (g)	Ash weight (g)	ng U	± SD	ng U/g wet	ng U/g ash
Skull						
Frontal-1	33	19.7	282	24.1	8.5	14.3
Frontal-2	15	8.9	113	9.7	7.5	12.6
Frontal-3	15	8.6	113	9.6	7.4	13.2
Parietal-1	79	46.4	513	43.8	6.5	11.0
Parietal-2	92	53.6	615	52.4	6.7	11.5
Occipital	84	46.6	648	55.3	7.7	13.9
Temporal-1	23	13.8	155	13.2	6.7	11.2
Temporal-2	67	31.6	183	15.7	2.7	5.8
Temporal-3	6	2.3	110	9.4	20.0	47.8
Maxilla	79	24.9	398	34.0	5.0	16.0
Mandible	47	23.3	537	45.8	11.5	23.0
Vertebrae						
C-1	30	9.7	72	7.9	2.4	7.4
C-3a	24	5.4	30	3.4	1.2	5.6
C-3b	34	9.2	50	5.5	1.5	5.4
C-5a	16	3.4	252	38.0	16.0	74.1
C-5b	24	6.1	30	3.3	1.2	4.9
T-1a	22	6.3	128	11.2	5.8	20.3
T-1b	18	3.0	23	2.5	1.3	7.7
T-3a	21	6.1	70	6.3	3.3	11.5
T-3b	21	3.0	14	2.9	0.7	4.7
T-5a	22	6.7	220	44.0	9.9	32.8
T-5b	25	3.9	178	28.4	7.0	45.6
T-7a	25	7.8	90	10.0	3.6	11.5
T-7b	36	5.5	324	29.2	8.9	58.9
T-9a	32	9.3	92	10.1	2.9	9.9
T-9b	42	6.5	124	19.4	2.9	19.1
T-11a	33	10.1	95	10.5	2.9	9.4
T-11b	61	8.4	112	10.0	1.8	13.3
L-1a	44	12.6	182	15.6	4.2	14.4
L-1b	71	8.7	178	17.4	2.5	20.5
L-3a	46	13.9	181	16.3	3.9	13.0
L-3b	80	13.8	65	7.2	0.8	4.7
L-5a	49	13.5	132	11.9	2.7	9.8
L-5b	69	13.1	99	10.9	1.4	7.6
Pelvis						
Ilium crest	81	19.4	140	12.6	1.7	7.2
Ilium body	192	42.9	318	28.6	1.7	7.4
Ischium	254	65.8	459	36.8	1.8	7.0
Sacrum	241	42.9	515	41.2	2.1	12.0
Coccyx	2	0.2	29	3.2	15.3	145.0
Spinal cord	19	0.2	4	1.2	0.2	20.0
Ribs						
Rib ends	18	20.4	52	5.2	2.9	2.5
Rib#1	29	7.0	360	32.4	12.5	51.4
Rib#2	34	7.4	64	6.4	1.9	8.6
Rib#3	39	9.5	95	8.5	2.4	10.0
Rib#4	35	10.6	95	8.6	2.7	9.0
Rib#5	42	12.8	135	12.1	3.2	10.5
Rib#6	47	14.4	124	11.8	2.6	8.6
Rib#7	56	14.8	105	9.5	1.9	7.1
Rib#8	39	11.7	114	10.3	2.9	9.7
Rib#9	41	11.1	102	9.2	2.5	9.2
Rib#10	29	8.6	82	8.2	2.8	9.5
Rib#11	19	5.8	84	7.6	4.3	14.5
Rib#12	4	1.1	26	2.6	5.8	23.6
Costal cartilage-R	24	0.4	127	12.7	5.3	317.5
Sternum	78	11.4	85	8.5	1.1	7.5
Arm Bones						
Humerus PE	100	17.0	171	14.5	1.7	10.1
Humerus PS	82	27.9	243	21.9	3.0	8.7
Humerus DS	33	34.9	270	24.3	8.3	7.7
Humerus DE	57	17.0	303	24.9	5.3	17.8
Radius PE	9	2.0	228	19.8	26.5	114.0
Radius PS	34	14.1	258	24.0	7.7	18.3
Radius DS	27	11.9	170	14.8	6.2	14.3

Table A2. Continued.

Sample	Wet weight (g)	Ash weight (g)	ng U	± SD	ng U/g wet	ng U/g ash
Radius DE	19	3.9	127	11.0	6.8	32.6
Ulna PE	37	12.9	231	20.8	6.2	17.9
Ulna PS	32	15.8	216	21.6	6.8	13.7
Ulna DS	27	12.5	140	14.0	5.1	11.2
Ulna DE	6	1.4	26	2.6	4.0	18.6
Hand Bones						
Scaphoid	6	1.6	45	3.6	7.3	28.1
Lunate	5	1.2	312	74.0	63.7	260.0
Triangilar	3	0.9	72	7.4	21.2	80.0
Pisiform	2	0.5	55	6.2	23.9	110.0
Hamate	6	1.3	95	20.4	15.1	73.1
Capitate	7	1.6	50	12.6	7.1	31.2
Trapezoide	3	0.8	70	7.0	22.6	87.5
Trapezium	5	0.9	42	3.0	9.1	46.7
Metacarp-1	11	2.7	28	3.1	2.6	10.4
Metacarp-2	14	3.9	112	10.2	8.2	28.7
Metacarp-3	13	3.8	122	10.4	9.5	32.1
Metacarp-4	8	2.1	121	11.7	15.9	57.6
Metacarp-5	7	1.8	35	0.0	5.1	19.4
P-1	8	1.8	160	0.1	21.3	88.9
P-2	6	1.9	18	2.7	2.8	9.5
P-3	8	2.3	76	6.8	9.9	33.0
P-4	6	1.7	173	16.2	30.3	101.8
P-5	4	1.1	85	7.8	23.6	77.3
M-2	3	0.8	21	3.0	7.8	26.2
M-3	4	1.1	97	9.4	24.8	88.2
M-4	3	0.9	108	10.8	36.0	120.0
M-5	1	0.4	106	10.4	75.7	265.0
D-1	2	0.5	12	1.2	5.2	24.0
D-2	1	0.2	79	8.8	60.8	395.0
D-3	1	0.3	0	0.0	0.0	0.0
D-4	1	0.3	30	3.3	25.0	100.0
D-5	1	0.2	38	3.0	54.3	190.0
Fingernail	1	0.02	5	1.3	3.6	250.0
Clavicle, sternal	14	3.0	61	6.1	4.3	20.3
Clavical shaft	23	9.6	159	16.0	7.0	16.6
Clavical acromion	19	5.1	53	5.3	2.8	10.4
Scapula, proximal	35	9.0	107	9.6	3.0	11.9
Scapula, spine	50	14.9	112	10.5	2.3	7.5
Scapula, distal end	73	23.9	152	15.2	2.1	6.4
Leg Bones						
Femur PE	220	55.2	419	33.5	1.9	7.6
Femur PS	101	50.5	487	48.7	4.8	9.6
Femur MS	147	71.7	783	54.8	5.3	10.9
Femur DS	104	35.1	345	34.5	3.3	9.8
Femur DE	235	47.8	739	51.7	3.1	15.5
Patella-R	31	8.8	127	11.4	4.1	14.4
Patella-L	30	8.3	108	9.8	3.6	13.0
Fibula PE	16	2.7	118	11.2	7.5	43.7
Fibula PS	41	17.3	273	23.2	6.7	15.8
Fibula DS	37	15.6	147	13.2	4.0	9.4
Fibula DE	17	3.8	44	4.4	2.6	11.6
Tibia PE	162	25.9	289	26.0	1.8	11.2
Tibia PS	186	68.4	830	70.0	4.4	12.1
Tibia DS	109	46.6	544	48.0	5.0	11.7
Tibia DE	66	14.6	328	28.8	5.0	22.5
Foot Bones						
Talus	69	17.0	272	24.0	3.9	16.0
Calcaneus	106	22.7	445	37.9	4.2	19.6
Cuboid	21	4.1	173	14.7	8.0	42.2
Navicular	22	5.6	236	34.0	10.6	42.1
M cuneiform	17	3.9	72	7.2	4.2	18.5
I cuneiform	8	2.1	97	8.6	12.1	46.2
L cuneiform	10	2.3	46	4.0	4.6	20.0
Metatarsal 1	24	5.9	210	18.2	8.6	35.6
Metatarsal 2	15	4.1	117	18.0	8.0	28.5
Metatarsal 3	12	3.3	99	9.0	8.1	30.0
Metatarsal 4	12	3.4	194	19.2	15.5	57.1

Table A2. Continued.

Sample	Wet weight (g)	Ash weight (g)	ng U	± SD	ng U/g wet	ng U/g ash
Metatarsal 5	12	3.7	131	12.0	10.9	35.4
P-1	9	2.0	86	8.0	10.0	43.0
P-2	3	0.7	114	9.0	34.5	162.9
P-3	3	0.6	136	11.6	50.4	226.7
P-4	2	0.4	70	7.8	35.0	175.0
P-5	2	0.3	87	8.6	51.2	290.0
M-2	1	0.2	129	12.2	107.5	645.0
M-3	1	0.2	109	18.9	108.7	545.0
M-4	1	0.1	89	8.0	111.2	890.0
M-5	1	0.1	73	12.0	146.0	730.0
D-1	5	0.6	63	6.0	12.6	105.0
D-2	1	0.1	81	6.8	115.7	810.0
D-3	1	0.1	—	—	—	—
D-4	1	0.1	41	3.2	82.0	410.0
D-5	1	0.1	4	1.2	8.0	40.0
Toenails	2	0.03	4	1.3	2.2	133.3

[a] Notes: P = proximal; M = medial; and D = distal.

Appendix 4

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August 15, 2005

Secretary
U.S. Nuclear Regulatory Commission,
Washington, DC 20555–0001
ATTN: Rulemakings and Adjudications Staff

Dear NRC Secretary and Rule Making Staff,

Mr. Oscar Paulson of Kennecott thought that it might be of help to your committee to have a physician's input on the question of human uranium toxicity. If I were on your committee, I would like to have a feel for who was writing the letters I was reading, so I am taking the liberty to offer you a little information about myself before I make my comments. I am a practicing board certified pathologist with MD and residency training from the University of Pittsburgh. Prior to entering medical school, I did a PhD in biophysics from what was then the Department of Radiation Biology and Biophysics (now the Department of Biophysics) at the University of Rochester. As part of my coursework at the University of Rochester, I took virtually all of the available coursework on radiation biology in the department. I have written two textbooks of pathology for medical students, and have also been heavily involved with the commercial Kaplan Medical course that many medical students use to study for their board examinations. As part of that work, I have written roughly 5000 clinical scenario questions (3000 pages of text), or about half of the entire Internet question bank for that course, that over 70,000 medical students have used in the last 8 years to prepare for the required national examination taken after the second year of medical school.

I became involved with the specific problem of uranium toxicity about 2½ years ago

when Mr. Paulson contacted me because I was apparently the only person of whom he or any of his many contacts in the uranium industry were aware that had both a PhD with training about radiation biology and an MD degree. At the time, New Mexico was considering altering ground water standards for uranium, and Mr. Paulson asked me to look critically at the uranium toxicology literature. Since then I have also been involved in discussions about ground water uranium standards in Wyoming.

Let me stress, if I may, that while I was contacted to review material by Mr. Paulson, I am not now, never have been, and never will be an employee of the uranium industry. I make enough money as a working pathologist that I will not take any money in any form for work I do on these topics. I do them as a public service because I think we need good law, that balances medical and economic needs realistically. I have stressed in all of my contacts with the broader uranium community that I will write the truth as best I understand it, and that if I think we really do have a problem with uranium, I will say so publicly. But I also recognize the danger of producing bad law that is based on a panicky reaction to something that is perceived as a problem but in reality is not.

The study that I personally find most helpful in placing the risks of uranium in an appropriate context is a NIOSH study (I.E. Pinkerton, T.F. Bloom, M.J. Hein, and E.M. Ward: *Mortality among a cohort of uranium mill workers: an update,* Occup. Environ. Med. 1004; 61:57-64) that looked at the causes of death in people who had worked in uranium mills. The study 1484 men, and compared the numbers of deaths in a variety of medical categories to what would be expected from national and Colorado mortality statistics. Many of the people whose deaths were studied had been old enough to have been working in the early period of the uranium industry, before we had learned to be very careful with uranium. They thus are thought to have had much higher chronic exposures to uranium, possibly by one or two orders of magnitude, than what we presently allow people to have.

In the context of this setting, I feel confident that (despite the withholding of judgment expected of scientists) the study authors of the NIOSH study were expecting to "prove" that the uranium mill workers had died disproportionately of causes that could be linked to uranium toxicity. Instead, what they found was that one of the very few statistically significant results in the study was that uranium mill workers had a *lower* overall mortality rate than would have been predicted by either Colorado or national mortality norms. I have discussed this surprising result with people in the uranium industry. What we think may have happened is that once it was recognized that smoking acted synergistically with many different types of stone dust (coal, asbestos, silica) to cause lung disease, the uranium industry as a whole made a very serious effort to enforce no smoking bans in work sites with uranium exposure, and also made a very serious effort to discourage workers from smoking while not at work. We postulate that these efforts to discourage smoking were successful enough to completely swamp any effect of uranium toxicity on mortality. Additionally, employee health may have been improved by the fact that the uranium mills were worried about worker health and made an effort to provide medical insurance and encourage preventive medicine. But, whatever the reason, the fact remains that in this population who might reasonably have been expected to have

significant medical problems related to uranium toxicity, the death rate was lower rather than higher than that of the general population. To me, this is a very reassuring fact.

In the detailed analysis of the causes of death in this NIOSH study, the only causes which had a statistically significant increased incidence of death over what was expected was in deaths from Hodgkin's lymphoma and deaths from non-malignant respiratory diseases, such as emphysema. The respiratory deaths were mostly seen in men hired before 1955 and the rate of death did not increase with increasing employment duration. This suggests that these respiratory deaths may have been related to factors such as smoking or inhalation of dusts, without being a specific uranium effect.

With respect to the Hodgkin's deaths, only four deaths were involved, so we are talking about a very small number of individuals. This may be an incidental clustering rather than a true uranium caused problem, because Hodgkin's disease is not one of the forms of leukemia or lymphoma that have ever been previously linked to radiation exposure. The etiology of Hodgkin's disease has been extensively studied and instead is thought to be often related to exposure to the Epstein Barr virus, whose presence can be detected in many cases of Hodgkin's disease. It would make sense that a virally-linked cancer might produce clusters of cases, and this might be what happened in this study.

Of the specifics of the many causes of death looked at in the NIOSH study of the uranium mill workers, two additional features are of note. The first feature is that no other cancer was occurring in this population at a significantly increased rate. This means that, contrary to expectation, even at the significantly increased uranium doses seen in this population, increased cancer rate was only a theoretical rather than a real risk. This suggests that our current exposure standards have a considerable margin of safety with respect to cancer risk built into them.

The second feature to specifically note in these mortality statistics is that there was no statistically significant increase in the deaths due to renal failure. This is important because we do know that extremely severe acute exposures to uranium can cause life threatening acute renal failure, that may lead to either death, or in survivors, a usually complete resolution of renal problems with time (e.g. months to years). Further, several studies (M. Limson Zamora et al: *Chronic ingestion of uranium in drinking water: A study of kidney bioeffects in humans*, Toxicological Sciences 1998, 43:68-77; M.A. Moss: *Chronic low level uranium exposure via drinking water*, Canadian thesis from Dalhousie University, Halifax, Nova Scotia, 1985; Mao, Yang et al: *Inorganic components of drinking water and microalbuminuria*, Environmental Research 1995, 71:135-140) have suggested that mild renal disease characterized by asymptomatic [with no clinical symptoms], very mild, microproteinuria [leakage of tiny amounts of protein from serum into the urine] can develop with chronic uranium exposure, and there was concern in the uranium community at large that this renal disease might tend to progress to chronic renal failure. The fact that there were no excess deaths due to renal failure in the uranium mill workers suggests that our current much lower exposure standards also have a considerable margin of safety with respect to uranium chemical toxicity for clinically significant renal disease as well.

Mr. Salsman, in both his letters to you and in his writings published in the RAD-SAF internet message chains, expresses concern about uranium related reproductive effects. He apparently is very personally concerned with these issues, and appears on the Internet to be a military member who was exposed to depleted uranium munitions and who worries whether the exposure is affecting his life and family. He raises some interesting questions, and he is correct that there is very little human literature about the topic. Most of the papers he cites are either rodent studies or review articles based at least in part on rodent studies.

Before going forward, may I offer some comments about my impression of Mr. Salsman as he appears in the discussions he has been involved with on the Internet. Mr. Salsman appears to be an intelligent man with little specific training in uranium or medical toxicity in general who has conscientiously tried to develop a knowledge base pertinent to the toxicity of uranium, particularly depleted uranium in munitions. Generally this type of background suggests that, since Mr. Salsman has clearly tried to be diligent, he might find articles that are not widely known by other people, and are thus a potentially useful contribution to discussions of uranium toxicity. However, the same background means that Mr. Salsman probably has a limited general knowledge of both medicine and medical toxicity, and the conclusions he draws from the articles he has found need to be examined with care, since he is likely to be vulnerable to mistakes in interpretation that appear to be basic to others with more experience in these fields.

Let me try to sort through what I think we do know about the reproductive issues Mr. Salsman raises, with the understanding that that he may very well have identified an area in which better human studies would be helpful.

Mr. Salsman expresses concern about the accumulation of uranium in testes. In some of his Internet comments, he mentions a testicular accumulation of 5.4 ng/g. In these references, he usually just sort of throws the number around, without indicating any of the specifics on which it was based. By so doing, he implies a general significance to the number that I was not sure was warranted, particularly since he was giving no information about the context in which it had been obtained. Because of my concern about the basis for his "fact", I found his original reference to the number, and looked it up.

The original reference is a paper called "Uranium deposition and retention in a USTUR whole body case", by J. J. Russell and R. L. Kathren, that was published in March, 2004 in Health Physics 86(3), pp 273-284. The paper is well written and represents a significant contribution to the human uranium toxicity literature. It is based on the detailed analysis of the body of a single person who died at age 83 of a stroke and donated his body for research to the U.S. Transuranium and Uranium Registries (USTUR), which had been created in 1978 to obtain tissues for analysis from volunteer donors with a known exposure to uranium. This person was apparently the first with known occupational uranium exposures to have a complete analysis of the uranium content of different body sites based on tissues taken at autopsy.

The man had had a 28 year work history as a power operator, utility operator, and metal operator in a facility that handled radioactive materials, and was known to have had significant uranium exposures. He had then been retired for approximately 20 years before his death of a cerebellar stroke. Considerable information about his work history was available, and it was thought that he had had most of his uranium exposure in aerosol form during the first 11 years of his employment, 38 to 48 years prior to his death. Based on his film badge results while employed, the paper authors estimate that he had a total lifetime whole body exposure of 11.42 rem of non-penetrating radiation and 4.33 rem of penetrating exposure. Urine had been collected periodically throughout his employment and analyzed for uranium content; based on this information the paper authors estimated that he had excreted into urine a total of 14.3 milligrams (14 thousandths of a gram) of uranium during his employment.

For those readers who are not used to thinking in grams, a gram of water has 1 milliliter volume, or about 1/5 of a teaspoon. So we are talking about this man absorbing into his body an amount of uranium over the entire course of a year what would be equivalent in volume to a few drops of water. And he is being studied because he had a potentially much higher uranium exposure than would be expected if he had not worked in the uranium industry. The paper authors point out that this suggests that he was excreting a few milligrams (thousandths of a gram) per year of uranium during this period, and that based on generally accepted uranium models for urinary excretion, that this suggests that he took into his body a few tens of milligrams of uranium every year during the first part of his employment.

At the time of the man's death, his total body load of uranium (all of the uranium in his body) was estimated to be 364.11 micrograms (364 millionths of a gram, or less than ½ of a milligram, or about 1/5 of the amount of uranium that he was excreting into urine yearly while he was employed). This estimate is a very good estimate, and was based on actual measurement of uranium concentration in about 80 soft tissue sites (which allowed the authors to calculate the uranium loads of for essentially every individual organ in the body) and about 140 bony sites.

So, what does this information mean so far? Since the man died at age 83 of stroke, his uranium exposure had pretty obviously not significantly shortened his life. Also, it means that while the man did retain uranium in his body for very long times (e.g. 4 or 5 decades), the amount retained overall was incredibly small, maybe only about 2 thousandths of the amount that had entered his body (based on assuming 20 mg per year times 10 years = 200 mg total intake into his body, and 0.4 mg [the 364 micrograms converted to milligrams] left in his body at his death, making a ratio of 0.4/200 = 0.2/100 = 2/1000). His body had actually been very efficient at clearing the uranium.

The paper goes on to present a detailed analysis of where the uranium had been found in the man's body, and compared some of this information to the relatively small amount of available information about storage of uranium in individuals who had just had normal daily life exposures to trace uranium from the environment. The appendix to the paper

has the most detailed information, and covers separately the 80 soft tissue and 140 bony sites for which they had detail. The man's exposure had predominately apparently been through inhalation of uranium containing dusts, and much of the uranium remaining in his body was concentrated in the lymph nodes (primarily those draining the respiratory tract), lung, and trachea. The concentration in the lymph nodes was the highest reached in the body, and was 1,133.83 nanograms per gram of tissue. A nanogram is a *billionth* of a gram, or a thousandth of a microgram, or a millionth of a milligram. The concentration in the trachea was 375.48 nanograms per gram of tissue, and that in the left lung was 267.98 nanograms per gram of tissue.

Mr. Salsman cites this paper because of his concern about the accumulation of uranium in the testes. The raw data reported in the appendix of the paper shows the man's right testes had a uranium concentration of 5.92 nanograms per gram of tissue (i.e. the ratio of uranium to everything else was about 6 parts in a billion) and the uranium concentration of the left testes was 3.43 nanograms per gram of tissue. These values were in the mid ranges of the concentrations reported, much less than those seen in the lymph nodes and respiratory tract, and greater than those seen in muscle, which tended to have uranium concentrations less than 1 nanogram per gram of tissue. Many other body tissues had uranium concentrations similar to that of testes, including eyes (7.50 nanograms per gram tissue), thyroid (9.81 nanograms per gram tissue), hair (6.48 nanograms per gram tissue), and diaphragm (2.48 nanograms per gram tissue). No one is suggesting that these organs tend to accumulate toxic doses of uranium.

6 parts in a billion doesn't look to me like the testes is accumulating much uranium. Mr. Salsman may have assumed that just because our modern measuring techniques have gotten so sophisticated that we can pick up extraordinarily tiny concentrations of materials, it means that they are always causing problems. That of course doesn't follow, anymore than it would mean that because a child wrote on his skin with a magic marker, it must be that the magic marker poisoned him.

Incidentally, the last paragraphs in this paper discuss the autopsy findings. Having done many autopsies myself, two things stand out in the discussion of the autopsy findings. The first is that the findings seen were typical of an older patient with severe atherosclerosis that affected many vessels in many sites of the body, and none of them would be unexpected in an older patient who had never been exposed to uranium. The second thing that stands out is that there is no mention at all of the testes (which would have certainly been sampled as part of the autopsy protocol), which means to me that the testicular findings were so typical of what is usually seen in an autopsy of an older individual, that the authors didn't even choose to comment on them - which certainly wouldn't have been the case if the paper authors had thought that the testes were a significant source of uranium pathology.

Mr. Salsman in his Internet writings makes reference to a second important paper that is worth discussing here in the context of his letter to your committee. This paper is "A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development", by Darryl P Arfsten, Kenneth R Still, and Glenn D Ritchie (Toxicology

and Industrial Health 2001; 17:180-191). These authors are at Wright-Patterson Air Force Base, and have been concerned about the potential effects on Persian Gulf and Kosovo veterans of having been exposed to depleted uranium. Their paper is a well-referenced review paper (with no new data) that explores what we know about uranium and depleted uranium and their effects of reproduction and fetal development.

One point that the authors of this paper make with which I strongly agree is that there may be a significant possibility of true uranium poisoning if shrapnel composed of depleted uranium is left permanently in someone's body because it has lodged in a surgically inaccessible site. Because of the possibility of long-term effects, I think we would probably be wise to try to remove if at all surgically feasible, any shrapnel fragments that do contain uranium. However, that topic lies beyond the scope of what your committee is trying to do, and has no bearing on whether our present occupational exposure limits for uranium are set correctly. A person who gets in a war-time setting a piece of depleted uranium containing shrapnel lodged permanently in his body has probably massively exceeded current occupational limits anyway. Whether the very real protection offered against munitions by depleted uranium (which is one of the physically strongest material we have) shielding (with potential of significantly saving lives in a wartime setting) outweighs the risks of poisoning if shrapnel cannot be removed is a question for the military, and does not seem to be to apply to the decisions your committee is making. Additionally, even if we were to choose to not use the depleted uranium, exposures could still occur if the enemy force used it against our troops in shield penetrating munitions.

The Arfsten paper reviews the scanty human literature pertaining to uranium effects on human reproduction and fetal development. One paper they cite had found an altered frequency of female offspring among male uranium workers, which was interpreted as suggesting a possible effect on sperm. To me this sounds like suggestive data, but too weak to base a specific decision on at this point. Another study the Arfsten paper mentions looked at male uranium miners from Namibia, Africa (who probably had very different occupational exposures and general medical backgrounds that American uranium miners) and found increased levels of sister chromosome exchanges in white blood cells (a marker for potential genetic abnormalities in sperm) and decreased testosterone levels as compared to control subjects who did not work in the uranium industry. A third paper cited by the Arfsten paper reported a statistical association between maternal exposure to mine tailings and unfavorable birth outcomes in Navajo Indians living near Shiprock, New Mexico. While the exposure was cited as maternal exposure to mine tailings, I wondered when thinking about this topic whether a more likely source of exposure might be from private well water containing high concentrations of naturally occurring uranium in this uranium rich area, which might have ground water with uranium concentrations up to two orders of magnitude greater than what is allowed in public water supplies. (The permissible concentration of uranium in private wells is at the moment unregulated due to a loophole in the current federal drinking water standards.) In any event, if the report is reliable, it does suggest the possibility of adverse effects, but does not address the topic of whether the exposures producing the effects were already above existing standards or not.

The Arfsten paper also reviews several studies that followed Persian Gulf War veterans that had been in tanks and fighting vehicles hit with (presumably enemy) munitions containing depleted uranium penetrators. Some of these veterans had been hit with uranium containing shrapnel that could not be surgically removed, and in follow-up, a few of these veterans were excreting heavy concentrations of uranium in urine (up to 39.1 micrograms of uranium per gram of creatinine, which is up to 1000 to 10,000 times that excreted by unexposed individuals). Some of the individuals had also been exposed to aerosolized uranium in the attacks. This population appears to have developed some statistically significant level of subtle neurocognitive (brain reasoning) impairment. The results on sperm numbers and motility were much more equivocal - the 1997 study showed no difference in sperm characteristics, while the 1999 study showed significantly elevated sperm counts and sperm motility (e.g. improved rather than impaired sperm physiology). Again, to put the studies in context, carrying uranium containing shrapnel around in your body almost certainly exceeds current occupational limits for uranium exposure.

The Arfsten paper also looked at papers reporting on the effects on rat reproductive and developmental problems related to exposures to uranium. One study that looked at depleted uranium pellets implanted into female rats was unable to demonstrate any impact on maternal or fetal parameters related to the rats' pregnancies. Other studies of rats fed very high concentrations of uranium nitrate (e.g. 2% of the food was uranium; a corresponding dose in humans might be a tablespoon of uranium salts daily - compare that to the doses that the man whose body after death was evaluated for uranium concentrations got!) showed a decrease in litter frequency with the high uranium doses. Other high dose rodent studies showed testicular atrophy in rats.

Despite these fairly convincing rodent studies, the significance in the context of your committee is unclear. Partly, these studies were all at such high dose studies that it is unclear that the present uranium exposure limits aren't already set low enough that people in whom the occupational exposures are within current limits aren't already protected. Additionally, the studies don't have enough dosing information in them to be able to accurately estimate what human levels of toxicity would trigger the reproductive effects. This means that, even if your committee were to decide that you wanted to worry about the reproductive toxicity effects, it is not at all clear that you would be able to figure out what an appropriate acceptable exposure would be. We just aren't at the point that new standards can be set, if desired, in a reasonable way.

This is a developing field, and, because of the interest in the Gulf War veterans exposures, we can anticipate that the problem of whether or not there is any significant reproductive toxicity at current levels of acceptable uranium exposures (which I anticipate will prove adequately protective) will become better defined over the next ten years. In the mean time, we already have strict occupational exposure limits about uranium, and I personally do not think that you need to tinker with them at this time.

I appreciate your having read this long letter and I hope that my comments may be of

some value to your committee. With thanks for your attention,

Nancy Standler, MD PhD

Nancy Standler, MD PhD, pathologist
Valley View Hospital, Cedar City, Utah

From: Carol Gallagher
To: Evangeline Ngbea
Date: 8/23/05 9:49AM
Subject: Comment on PRM-20-26

Van,

Attached for docketing is a comment letter on the above noted PRM from Marion Loomis, Wyoming Mining Association, that I received via the rulemaking website on 8/22/05.

Carol

Mail Envelope Properties (430B2955.BFF : 3 : 886)

Subject:	Comment on PRM-20-26
Creation Date:	8/23/05 9:49AM
From:	Carol Gallagher
Created By:	CAG@nrc.gov

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Files	**Size**	**Date & Time**
MESSAGE	648	08/23/05 09:49AM
1564-0010.pdf	669696	08/23/05 09:43AM

Options

Expiration Date:	None
Priority:	Standard
Reply Requested:	No
Return Notification:	None
Concealed Subject:	No
Security:	Standard