Evaluation of the Carcinogenic Risk of Depleted Uranium in the Lungs of Gulf War Veterans

Prof. Asaf Durakovic, MD, Ph.D. - Leonard A. Dietz, M.Sc. - Isaac Zimmerman, B.Sc.

Uranium Medical Research Centre

476 Parliament St. Suite 302 - Toronto, Ontario, Canada, M4X 1P2 - www.umrc.net - asaf@umrc.net

Abstract

The aim of this work was to determine the burden of inhaled depleted uranium (DU) oxide particles in the lungs of British, Canadian, and US Gulf War I veterans at time-zero of exposure. In a group of thirteen veterans whose urine was quantitatively analyzed for DU isotopes by thermal ionization mass spectrometry (TIMS) nine years after exposure, five tested positive for the presence of DU. Our method presents a new, non-invasive technique for calculating a cumulative alpha-particle radiation dose from DU isotopes in the lungs of exposed veterans.

We have utilized a method of determining the minimum biological half-life of DU from the derivation of the Battelle Model of simulated interstitial lung fluid. The values of the minimum biological half-life determined the total inhalational exposure to DU isotopes at time-zero. The integration of the total number of alpha particle events from time-zero to ten years after exposure has been calculated as a radiation dose.

The average of 24-hour urine specimens of veterans containing 3.89 x 10^{-2} micrograms (µg) of DU corresponds to inhalational exposure of 0.40 milligrams (mg) of DU at time-zero with an alpha radiation dose to the lungs of 1.14 milliSieverts (mSv) during the first year and a total of 5.77 mSv over ten years. The determined values slightly exceed the maximum permissible inhalational dose of uranium and suggest a need for additional research on metabolic pathways, biological half-life, and DU induced risk of malignant alterations in the respiratory system of the exposed population.

Introduction

Depleted uranium, a heavy metal with radiation and chemical toxicological properties was used in the conflicts in the Gulf War and Kosovo, presenting a health hazard to the exposed military personnel and civilian population. Recent studies confirm well described uranium toxicological properties including renal damage[1], neurological alterations[2], induction of mutagenesis[3] and neoplastic disease[4], as well as adverse environmental effects[5].

DU presents little risk by its external radiation, but may cause significant health consequences in the internal environment of the body[6] by the long biological half-life and alpha emission. While inhaled soluble uranium particles are rapidly transported to the extracellular fluid and either excreted through the kidney or incorporated in the bone, the insoluble DU compounds remain in the lungs for a long time and are either slowly dissolved or transported by the macrophages to the tracheobronchial lymph nodes. Inhalational exposure to insoluble uranium dust presents a potential radiation hazard with established dose-dependent radiation effects including fibrotic and neoplastic changes in experimental animals[7]. The experimental research postulates species differences in animals and has been even less well studied in man. The estimation of the risk of alpha radiation in the lung tissue is still an area of controversy of the alpha dose assessment in the lung[8]. The malignant alterations of the lung tissue by inhaled alpha emitters in humans indicates that basal cells are more susceptible to small energy transfer alpha particles than secretory cells. The linear stochastic extrapolation has been recently challenged in estimating cancer risk of low dose alpha radiation with non-hit cells contributing to the response of irradiated cells[9].

Slow pulmonary clearance of insoluble oxide compounds of depleted uranium may pose a significant radiological risk by the long retention in the lung tissue and pulmonary clearance rate demonstrated to be several years by the Battelle studies of simulated interstitial lung fluid[10]. Our work attempts to better understand the hazards of milligram and microgram quantities of inhaled depleted uranium aerosols in Gulf War veterans.

Materials & Methods

Eleven British, Canadian, and United States Gulf War veterans with verified inhalational exposure to dust containing DU during the Operation Desert Storm, 8-9 years prior to sample collection, participated in the study. Each subject gave signed informed consent and had a 24-hour urine sample analyzed for total uranium concentration and the quantity and ratio of four uranium isotopes: ^{234}U, ^{235}U, ^{236}U, and ^{238}U. The analysis was done by thermal ionization mass spectrometry (TIMS) at the Radiogenic Isotope Facility, Department of Earth Sciences, Memorial University of Newfoundland, Canada.

The analytical methodology involved evaporation, oxidation of organic matter with concentrated nitric acid, purification by ion-exchange chemistry, and mass spectrometry using a Finnigan MAT 262V thermal ionization multi-collector mass spectrometer operating in peak jumping mode using the secondary electron multiplier ion counting detector system to determine the isotopic composition.

Exposure to depleted uranium was indicated by an upward shift in the isotopic ratio of $^{238}U/^{235}U$ away from the natural uranium ratio of 137.9. The ratio of 141.0 was taken as the cutoff point for definitive exposure to DU. From the isotopic ratios of natural and depleted uranium and the ratio of the uranium in the sample, the percentage of the uranium that came from a DU source (DU fraction) could be calculated.

Five of the eleven subjects tested positive for DU with a mean $^{238}U/^{235}U$ ratio of 191.00 ± 2.90. For these subjects with definitive DU exposure 8-9 years prior to sample collection, the alpha radiation dose from inhaled uranium was calculated.

Sample preparation using Eichrom UTEVA columns

Uranium sample just prior to loading on the filament

Sample loaded and dried down on the filament

Finnigan MAT 262V solid source thermal ionization mass spectrometer with 8 faraday detectors and one secondary electron multiplier – ion-counting system

Results

The alpha radiation dose from depleted uranium particles in the lungs can be calculated from the DU fraction (table 1), DU concentration in the urine (table 2), and the biological half-time of DU particles in the lungs.

The rate of DU excretion, dN/dt, is proportional to the amount of DU in the lungs, N (eq1). Solving (eq1) for N gives the traditional decay equation with N_o as the quantity of DU in the lungs at time-zero (eq2). N_o can also be found from the current rate of excretion by substituting (eq1) into (eq2) and solving for N_o (eq3). Integrating the right-hand side of (eq3) with respect to time gives the number of alpha-events over a given time period, N_α, where c is the conversion factor between grams of DU to alpha-particle events per day, 25,252 Bq/g (eq4). By substituting (eq3) into (eq4) for N_o an equation relating the rate of uranium excretion to the number of alpha-events over a specified time period is obtained (eq5). From this mathematical derivation the number of alpha-events and resulting radiation dose to the lungs from inhaled depleted uranium can be calculated.

The weighted average alpha-particle energy for the four isotopes was found to be 4.27 MeV per alpha-particle (table 3). The total number of alpha-events over a time period from (eq5) multiplied by the average alpha-particle energy gives the total energy imparted to the lungs. This is averaged over 2 kg of lung tissue to convert to units of Grays. The weighting factors meant to modify absorbed dose to reflect no-threshold effects as a function an internal radiation event in the body are equal to 20 for a quality factor as a function of linear energy transfer. The dose in Gray multiplied by the value of the relative biological effect of alpha particles on the tissue in the units of milliSieverts.

Table 4 shows the grams of DU present in a 24-hour urine sample, the number of alpha-particles this amount of DU gives off per day, and the total number of alpha-particles and the resulting milliSievert dose over the first year and the first decade.

Eq 1: $$\frac{\partial}{\partial t} N = -\lambda N \qquad \text{where} \qquad \lambda = \frac{\ln(2)}{T}$$

Eq 2: $$N = N_o \, \mathbf{e}^{(-t)}$$

Eq 3: $$N_o = \frac{\left(\frac{\partial}{\partial t} N\right) \mathbf{e}^{(\lambda t)}}{\lambda}$$

Eq 4: $$N_\alpha = c \, N_o \int \mathbf{e}^{(-\lambda t)} \, dt = \frac{N_o \left(\mathbf{e}^{(-\lambda t_1)} - \mathbf{e}^{(-\lambda t_2)} \right)}{\lambda}$$

Eq 5: $$N_\alpha = \frac{c \left(\frac{\partial}{\partial t} N\right) \mathbf{e}^{(\lambda t)} \left(\mathbf{e}^{(-\lambda t_1)} - \mathbf{e}^{(-\lambda t_2)} \right)}{\lambda^2}$$

Conclusion

Recent experimental studies of the carcinogenic and mutagenic risks of depleted uranium (DU) could be a contributing factor in the development of neoplastic disease in humans. The inhalation of DU insoluble oxide compounds with a long biological half-life and slow pulmonary clearance warrants further studies of lung neoplastic risks of inhaled DU compounds. Our studies indicate that 24 hours urine specimens of Gulf War veterans containing 3.89 x 10^{-2} µg of DU corresponds to 0.40 mg of DU at time zero with an alpha radiation dose to the lungs of 1.14 mSv during the first year and a total of 5.77 mSv over 10 years. These values slightly exceed the maximum permissible doses of inhaled uranium and indicate a need for sustained interdisciplinary research on DU induced risk of malignant alterations in the respiratory system of DU dust-exposed human population.

References

1. Edwards R: Too hot to handle, New Scientist 1999; 162, 2189: 20-1.

2. Pellmar TC, Keyser DO, Emery C, Hogan JB: Electrophysiological changes in hippocampal slices isolated from rats embedded with depleted uranium fragments, Neurotoxicology 1999; 20, 5: 785-92.

3. Miller AC, Fuciarelli AF, Jackson NE, Ejnik EJ, Emond C, Strocko S, Hogan J, Page N, Pellmar T: Urinary and serum mutagenicity studies in rats implanted with depleted uranium or tantalum pellets, Mutagenesis 1998; 13, 6: 643-8.

4. Miller AC, Xu J, Stewart M, McClain D: Suppression of depleted uranium-induced neoplastic transformation of lumen cells by the phenyl fatty acid, phenyl acetate: chemoprevention by targeting the p21 RAS protein pathway, Radiation Research 2001; 155 (1 part 2): 163-70.

5. Edmands JD, Brabander DJ, Coleman DS: Uptake and mobility of uranium in black oaks: implications for biomonitoring depleted uranium-contaminated groundwater, Chemosphere 2001; 44, 4: 789-95.

6. Miller AC, Xu J, Stewart M, Prasanna PG, Page N: Potential late health care effects of depleted uranium and tungsten used in armor-piercing munitions: comparison of neoplastic transformation and genotoxicity with the known carcinogen nickel, Military Medicine 2002; 167, supplement 2, 120-122.

7. Hahn FI, Guilmette RA, Hoover MD: Implanted depleted uranium fragments cause soft tissue sarcomas in the muscles of rats, Environmental Health Perspectives 2002; 110, 1: 51-59.

8. Durante M, Pugliese M: Estimates of radiological risk from depleted uranium in war, Health Physics 2002; 82, 1: 14-20.

9. Little MP, Wakeford R: The bystander effect in experimental systems and compatibility with radon-induced lung cancer in humans, Journal of Radiological Protection 2002; 22, 3A: A27-31.

10. Mishima J, Parkhurst MA, Sherpelz RI, Hadlock DE: Potential behavior of depleted uranium penetrators under shipping and bulk storage accident conditions, Prepared for US Department of the Army under a Relate Service Agreement with the US Department of Energy Contract DE-A-C06-76RLO 1830, Pacific Northwest Laboratory Operated for US DOE by Battelle Memorial Institute, March 1985.

Table 1

Isotopic Data for Individual Samples

Subject	% ^{238}U	% ^{235}U	$^{238}U/^{235}U$	% DU
1	99.3154	0.6758	146.96	8.52
2	99.4280	0.5663	175.58	29.64
3	99.5603	0.4304	231.34	55.86
4	99.4876	0.4945	200.77	43.28
5	99.4862	0.4966	200.34	43.08

Table 2

Gravimetric Data for Individual Samples

Subject	U ng/L	U / 24hrs (mg)	DU / 24hrs (mg)	T_0 DU Lung Burden (mg)
1	13.07	1.29 x 10^{-6}	1.10 x 10^{-7}	1.13 x 10^{-3}
2	2.77	1.41 x 10^{-5}	4.18 x 10^{-6}	4.29 x 10^{-2}
3	77.96	2.68 x 10^{-4}	1.50 x 10^{-4}	1.54
4	163.02	8.20 x 10^{-5}	3.55 x 10^{-5}	3.64 x 10^{-1}
5	2217.04	1.14 x 10^{-5}	4.92 x 10^{-6}	5.05 x 10^{-2}

Table 3

Radioactive Decay of Uranium Isotopes in Natural and Depleted Uranium

Isotope	Natural U (Bq/g)	DU (Bq/g)	Half-life (years)	Alpha-Particle Energy (MeV)
^{234}U	12,242	1,815	2.45 x 10^5	4.76
^{235}U	568	159	7.04 x 10^8	4.39
^{236}U	0	71	2.34 x 10^7	4.48
^{238}U	12,342	12,406	4.47 x 10^9	4.19
Totals	**25,252**	**14,451**		**4.27**

Table 4

Radiation Dose to the Lungs from Depleted Uranium

Subject	First Year (alphas)	First Year (mSv)	First 5 Years (alphas)	First 5 Years (mSv)	First Decade (alphas)	First Decade (mSv)
1	4.70 x 10^5	0.00	1.69 x 10^6	0.01	2.38 x 10^6	0.02
2	1.79 x 10^7	0.12	6.45 x 10^7	0.44	9.07 x 10^7	0.62
3	6.41 x 10^8	4.38	2.31 x 10^9	15.8	3.25 x 10^9	22.2
4	1.52 x 10^8	1.04	5.47 x 10^8	3.74	7.69 x 10^8	5.26
5	2.11 x 10^7	0.14	7.59 x 10^7	0.52	1.07 x 10^8	0.73
Average	**1.66 x 10^8**	**1.14**	**6.00 x 10^8**	**4.10**	**8.44 x 10^8**	**5.77**
Std Dev	2.72 x 10^8	1.86	9.80 x 10^8	6.71	1.38 x 10^9	9.43
Std Err	1.22 x 10^8	0.83	4.38 x 10^8	3.00	6.17 x 10^8	4.22