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Project Title: Improved Radiation Dosimetry/Risk Estimates to Facilitate Environmental Management of Plutonium Contaminated Sites

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Research Objective

Our phase-II research relates to evaluating health risks associated with inhaled plutonium (Pu). Our current research objectives are as follows: (1) to extend our stochastic model for deposition of plutonium (Pu) in the respiratory tract to include additional key variability and uncertainty; (2) to generate and analyze risk distributions for deterministic effects in the lung from inhaled Pu that reflect risk model uncertainty; (3) to acquire an improved understanding of key physiological effects of inhaled Pu, based on evaluations of clinical data (e.g., hematological, respiratory function, chromosomal aberrations in lymphocytes) for Mayak workers in Russia that inhaled Pu-239; (4) to develop biological dosimetry for Pu-239 that was inhaled by some Mayak workers (with unknown intake) based on clinical data for other workers with known Pu-239 intake; (5) to critically evaluate the validity of the linear no-threshold (LNT) risk model as it relates to cancer risks from inhaled Pu-239 (based on Mayak worker data); (6) to evaluate respirator filter penetration frequencies for airborne Pu aerosols using surrogate high density metals.

Research Progress and Implications

This report summarizes work after 2 years of a renewed 3-year project. Significant progress has been made in several areas of our research and are summarized below.

Our research on extending our modeling of stochastic deposition of PuO_2 in the respiratory tract to account for variability between different individuals has been quite successful. A stochastic version of the ICRP 66 respiratory tract deposition model has been prepared and is implemented

using Crystal Ball software. Model parameters are stochastic (i.e. have probability distributions). The distributions we used are essentially the same as those used in the LUDUC (LUng Dose Uncertainty Code) model developed at the University of Florida. Our Crystal Ball based stochastic deposition model is applicable to males and females, to persons of different ages, and to different levels of physical activity. Further, the model can be applied to a variety of airborne toxic agents (including anthrax). We have applied our stochastic deposition model to inhalation exposure scenarios where adult male workers at Rocky Flats inhale specific numbers of airborne particles of weapons grade Pu (WG Pu). Our focus was on evaluating variability in radioactivity intake due to differing particle sizes and differences in respiratory parameters. Our results were compared with result from the deterministic program LUDEP associated with the ICRP 66 model. Our finding indicate that the widely-used LUDEP software appears to incorporate a systematic error whereby particle deposition in bronchiolar and alveolar regions of the lung are significantly overestimated for many individuals for large respirable particles. This implies that cancer risk evaluated based on LUDEP doses are possibly greatly overestimated.

The terrorist events on September 11th of last year led to a heightened awareness of the possibility of other terrorist acts in the U.S. and around the world, including nuclear terrorist acts. We have extended our research focus to include evaluating consequences to workers (e.g. at Rocky Flats) and the public from nuclear terrorist acts involving the airborne release of large amounts of WG Pu. For such exposure scenarios, it is likely that existing risk models presented by the Nuclear Regulatory Commission in a series of NUREG/CR-4214 reports would be used to evaluate health consequences. These models would also likely be used for scenarios involving nuclear accidents at Rocky Flats. Our research has focus on using the NUREG/CR-4214 risk models for morbidity and lethality to make calculations of morbidity and lethality risks for inhalation exposure of adult males to WG Pu and to compare our findings to newly available data from Mayak workers in Russia that inhaled large amounts of Pu-239 as well as to results form long-term animal studies carried out at our Institute involving inhalation exposure to PuO_2 aerosols. Our findings indicate that morbidity risks based on the NUREG/CR-4214 model appears to be greatly underestimated at low doses and lethality risk slightly underestimated (at high doses). Further, the high level of morbidity (from pneumosclerosis) observed at low doses cannot be explained based on radiation dose (too small). We have therefore introduced the possibility that the morbidity observed in Mayak workers that received low radiation doses from inhaled Pu-239 were caused by non-radiation factors that include chronic loading of the lung with metal (Pu) particles. Heavy cigarette smoking may have also contributed to the morbidity.

Related to plutonium worker (e.g. at Rock Flats) risks, we have investigated the possibility that even when wearing respirators and other protective gear in carrying out job duties, some small numbers of airborne PuO_2 particles could penetrate respirator filters and over time present a heath risk to the nuclear worker. We have therefore conducted respirator filter penetration studies. Three type of respirator filters (MSA P100 Multigas, Survivair 7000 Series, and 3M 6000 Series) were used in accordance to recommendations of DOE laboratory personnel interested in filter performance. Three high density surrogate, nonradioactive aerosols were used: cerium dioxide (density=7.65 g/cm^3) hafnium dioxide (density=9.68g/cm^3), and lead dioxide (density=9.64g/cm^3). Because the test particles have high densities, the generating system could not disperse large particles. Large particles that could be seen under the microscope could not pass through the generating system into the chamber used. The count median diameter of the test particles in the test chamber was around 2-3 μm. Our results showed that the 3M filters had the highest collection efficiencies while the Survivair filters had the lowest. For the high density test materials used, small numbers of particles penetrated the test filters. Most particle penetrating the filters had aerodynamic diameters less than 4 μm. These results suggest that small PuO_2 particles likely pose the highest risks to DOE workers engaged in deactivation and decommissioning operations that require working in high airborne concentration of PuO_2. Thus, over time Pu might be detectable in urine as a result of chronic intake via respirator filter penetration.

Our modeling of radiation induced stochastic effects in cells continues and has led to a revised $NEOTRANS_2$ model for the induction of mutations and neoplastic transformation. The current version includes a protective bystander effect whereby already existing problematic cells can be signaled via other damaged cells to selectively undergo neoplastic transformation. This leads to selective elimination of at least some problematic cells after low doses, thereby protecting the cell community (group adaptation) from stochastic effects such as neoplastic transformation. We have applied the model to available data for gamma-ray induced neoplastic transformation and have demonstrated a sizable threshold for excess transformants. Taking into consideration the observation by Dr. Leslie Redpath that relative risk for neoplastic transformation in vitro appears to have a very similar dose-response characteristic at low doses as for relative risk for specific radiation induced cancers, we have concluded that quite large thresholds may exist for low-LET induced cancer. Further, our revised model for neoplastic transformation suggests that when radiation dose (alpha, beta, or gamma radiations) is protracted and remains relatively low, the protective bystander apoptosis effect may be much more pronounced, extending the threshold for excess stochastic effects. Thus, large thresholds could possibly exist for chronic alpha, beta, or gamma irradiation induced excess stochastic effects as well as for combined exposure to these radiations.

In our joint research with scientists at the Southern Ural Biophysics Institute we have investigated lung cancer induction among Mayak workers in Russia chronically exposed to gamma rays and alpha radiation from inhaled Pu-239. We have used a multivariate analysis approach to investigate the pair-wise interactions of the previously identified three main etiological factors for lung cancer induction in Russian Mayak workers. These three factors are as follows: (1) body burden of inhaled plutonium-239 (^{239}Pu), an influence on absorbed alpha-radiation dose; (2) cumulative, absorbed external gamma-radiation dose to the lung; and (3) level of cigarette smoking as indicated by a smoking index (SI). The SI represents the cigarettes smoked per day times years smoking. The Mayak workers were exposed by inhalation to both soluble and insoluble forms of ^{239}Pu. Based on a cohort of 4,390 persons (77% male), we conducted a nested, case-control study of lung cancer induction using 486 matched cases and controls. Each case was matched to two controls. Matching was based on five factors: sex, year of birth, year work began, profession, and workplace. Three levels of smoking were considered: low (SI = 1 to 499), used as a reference level; middle (SI = 500 to 900); and high (SI = 901 to 2000). For lung cancer induction, a supra-multiplicative effect was demonstrated for high external gamma-ray doses (> 2.0 Gy) plus high ^{239}Pu intakes (body burden > 2.3 kBq). This observation is consistent with the hypothesis of curvilinear dose-response relationships for lung cancer induction by high- and low-LET radiations. The interaction between radiation (external gamma rays or ^{239}Pu body burden) and cigarette smoke was found to depend on the smoking level. For the middle level of smoking in combination with gamma radiation (>2.0 Gy) or ^{239}Pu body burden (>2.3 kBq), results were consistent with additive effects. However, for the high level of smoking in combination with gamma radiation (> 2.0 Gy) or ^{239}Pu body burden (> 2.3 kBq), results were consistent with the occurrence of multiplicative effects. These results indicate that low-dose risk estimates for radiation-induced lung cancer derived without adjusting for the influence of cigarette smoking could be greatly overestimated. Further, such systematic error may considerably distort the shape of the risk vs. dose curve and could possibly obscure the presence of a dose threshold for radiation-induced lung cancer. We have previously reported that when adjusting for the influence of cigarette smoking, our research results are consistent with a threshold for alpha radiation induced lung cancer of approximately 1 Gy. This observation is consistent with predictions of the mechanistic $NEOTRANS_2$ model for radiation induced stochastic effects.

While our initial work focused on lung cancer among Mayak workers, we have expanded our joint U.S./Russian Federation research to include liver and biliary cancers. We have used a multivariate unconditional, logistic regression approach to investigate associations between liver and biliary cancer with suspected key risk factors: Pu-239 body burden, total external gamma dose, chemical-agent (unspecified) exposure, alcohol consumption, viral hepatitis history, and chronic digestive disease history. Both odds ratio (OR) and attributable risk (AR) were

evaluated. The cohort was comprised of 63 cases and 147 controls with appropriate matching. Pu-239 was found to have the highest attributable risk for hemangiosarcoma occurrence. A significant association was also found between Pu-239 incorporation and hepatocellular cancer. Pu-239 incorporation was not found to be associated with biliary cancer. Chronic external gamma ray exposure and smoking were not found to be associated with any cancer type. An association between alcohol consumption and hepatocellular cancer was also found. The cited results are preliminary. Our results are consistent with a large alpha radiation threshold ($\geq$ 2 Gy) for liver cancer induction and a corresponding large threshold for chronic gamma induced liver (and biliary) cancer. These observations are in agreement with predictions of the NEOTRANS$_2$ model and have important implications for radiation protection, risk assessment, and environmental management of Pu contaminated sites.

Planned Activities

Our future research activities will include the following: (1) using Mayak worker clinical data in developing a better understanding of morbidity effects of chronic exposure of humans to alpha and gamma radiations; (2) using the Mayak worker cytogenetic data (peripheral blood cells) for biological dosimetry for Pu-239 intake; and (3) developing improved risk estimates for radiation induced lung, bone, and liver cancer and leukemia.

Information Access

Web resources arising from full or partial support from this project follow:

See following site for numerous web resources: http://www.radiation-scott.org

Year 2001-2002 publications fully or partially supported by this project follow:

Gerde, P. and B. R. Scott: A model for absorption of low-volatile toxicants by the airway mucosa. Inhalation Toxicology 13: 903-929, 2001.

Schöllnberger, H., B. R. Scott and T. E. Hanson: Application of Bayesian inference to characterize risks associated with low doses of low-LET radiation. Bulletin of Mathematical Biology 6: 865-883, 2001.

Schöllnberger, H., J. Aden, and B. R. Scott: Respiratory tract deposition efficiencies and evaluation of impacts from smoke released in the Cerro Grande forest fire. Journal of Aerosol Medicine (in press).

Scott, B. R., Y. Tesfaigzi and H. Schöllnberger: Radiation induced apoptosis could lead to dose thresholds for stochastic effects such as neoplastic transformation and cancer. Radiation Protection Dosimetry (revised, resubmitted).

Tokarskaya, Z. B., B. R. Scott, G. V. Zhuntova, N. D. Okladnikova, Z. D. Belyaeva, V. F. Khokhryakov, H. Schöllnberger and E. K. Vasilenko: Interaction of radiation and smoking in lung cancer induction among workers at the Mayak enterprise. Health Physics (in press).

Walker, D. M., V. E. Walker and B. R. Scott: Modeling of low-dose stochastic effects for a prototypic DNA-alkylating agent, ethylene oxide: Characterization by non-linear models is superior to the linear nonthreshold model. Proceedings of National Academy of Sciences (submitted).

Scott, B. R. and V. L. Peterson: Risks estimates for deterministic effects of inhaled weapons grade plutonium. Health Physics (submitted).

Aden, J. and B. R. Scott: Modeling variability and uncertainty associated with inhaled PuO_2 for the stochastic intake paradigm. *In* Proceedings of the ANS Radiation Protection and Shielding Division 12th Biennial Topical Meeting, Santa Fe, NM, April 14-18, 2002.

Aden, J. and B. R. Scott "Modeling variability and uncertainty associated with inhaled weapons grade PuO_2." Health Physics (submitted).

Year 2001-2002 presentations fully or partially supported by this project follow:

Scott, B. R., Y. Tesfaigzi, J. Aden, H. Schöllnberger and D. Walker. "Thresholds for radiation-induced mutations and neoplastic transformation could arise from apoptosis and error-free repair." DOE Low Dose Radiation Research Program Investigators Workshop III, Rockville, MD, March 25-27, 2002.

Scott, B. R., D. Walker and V. E. Walker. "Low dose extrapolation: Evidence against the validity of the linear nonthreshold hypothesis." Presented to American Conference of Governmental Industrial Hygienist (ACGIH) representatives, Lovelace Respiratory Research Institute, Albuquerque, NM April 13, 2002.

Aden, J. and B. R. Scott. "Modeling variability and uncertainty associated with inhaled PuO_2 for the stochastic intake paradigm." ANS 12th Biennial Radiation Protection and Shielding Division Topical Meeting, Santa Fe, NM, April 14-18, 2002.

Soctt, B. R., D. M. Walker, V. Walker, G. Aden and Y. Tesfaigzi. "Low-dose protective mechanisms: Implications for risk assessment." BELLE Conference, Non-linear Dose-response Relationships in Biology, Toxicology and Medicine, University of Massachusetts, Amherst, MA, June 11-13, 2002.

Scott, B. R. and V. L. Peterson "Use of NUREG/CR-4214 models to estimate risks for deterministic health effects of inhaled weapons grade plutonium." American Radiation Safety Conference and Exposition, Health Physics Society's 47th Annual Meeting, Tampa, Fl. June 16-20, 2002.

Tokarskaya, Z., G. Zhuntova, B. Scott, V. Khokhryakov and E. Vasilenko. "Influences of radiation and non-radiation factors in the occurrence of liver and biliary tract malignancies among plutonium production workers". American Radiation Safety Conference and Exposition, Health Physics Society's 47th Annual Meeting, Tampa, Fl. June 16-20, 2002.

Henderson, R. and B. R. Scott. "Proteomics at LRRI." Joint seminar presentation at Lovelace Respiratory Research Institute, Albuquerque, NM, July 8, 2002.

Osovets, S. V. and B. R. Scott. "Modeling the dependence of the median effective dose on dose rate". 32nd Annual Meeting of the European Society for Radiation Biology (to be presented).

Optional Additional Information: None

Optional Proprietary Information: None