Annual Report for U.S. DOE Office of Environmental Management: Year 2002–2003

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

Grant Number: DE-FG07-00ER62511

Date: June 11, 2003

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Research Objective

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

Research Progress and Implications

This report summarizes work after three years of a renewed three-year project. Significant progress has been made on all research objectives, as indicated in the following sections of this report.

Our research on extending our modeling of stochastic deposition of plutonium dioxide in the respiratory tract to account for variability between different individuals has been completed and key results presented at scientific meetings and in both published peer-reviewed and non-peer-reviewed papers. A stochastic version of the ICRP 66 respiratory tract deposition model was developed and implemented using Crystal Ball software. Key model

parameters are stochastic (i.e., have probability distributions). The distributions used are the same as introduced in the LUDUC (LUng Dose Uncertainty Code) model developed at the University of Florida. Our Crystal Ball stochastic deposition code is applicable to males and females, people of different ages, and people with different levels of physical activity. Further, the code can be applied to a variety of airborne toxic agents (including toxicants such as anthrax spores). We have applied our stochastic deposition code to inhalation exposure scenarios where adult male workers at the Rocky Flats Environmental Technology Site (Rocky Flats) inhale specific numbers of airborne particles of weapons-grade plutonium. Our focus was on evaluating the variability in radioactivity intake due to differing particle sizes and differences in respiratory parameters. Our results were compared with results from the deterministic program LUDEP associated with the ICRP 66 model. Our findings indicate that the widely used LUDEP software appears to incorporate a systematic error whereby radioactivity deposition of large respirable particles in bronchiolar and alveolar regions of the lung is significantly overestimated for many individuals. This overestimation would contribute to systematic errors when estimating cancer risks for humans.

Since the September 11, 2001, terrorist events in New York and Washington DC, the Department of Energy and other government agencies have realized the increased possibility of terrorists detonating radiological weapons within the continental U.S. and elsewhere. One possible scenario for a radiological weapon incident is the detonation of a source containing high specific activity plutoniun-238. This scenario is possible because the isotope can be purchased (e.g., in Russia) and is available to workers (e.g., disgruntled employees) in the U.S. involved in producing radioisotope thermoelectric generators. Its use would evoke high levels of fright and would render property unusable for extended periods. Also, inhalation exposure from such a radiological incident could lead to large intake of plutonium that could cause morbidity and fatalities associated with damage from large radiation doses to the lung. Risk models currently used for assessing risks of harm from non-cancer effects associated with large radiation doses are called hazard-function (HF) models and were first introduced by the U.S. Nuclear Regulatory Commission in July 1985 to assess nuclear accident risks.

Our EMSP-supported research team tested the validity of the HF models for lethality from radiation pneumonitis and for respiratory functional morbidity using both newly available animal data with long-term follow-up and data for humans exposed to plutonium-239 by inhalation (Mayak plutonium facility workers in Russia). Results of our study are reported in an in-press paper in *Health Physics* (Scott and Peterson) that is being used by the International Atomic Energy Agency to develop recommendations for medical intervention for plutonium inhalation. The HF model for morbidity induction was found to underestimate risk greatly; elevated risks were reported for Mayak workers for doses more than an order of magnitude below the expected threshold based on the HF model. The HF model for lethality also underestimates risks of fatalities but to a lesser extent than for morbidity.

Workers at Rocky Flats were reported to have plutonium isotopes in their urine from unknown exposures. We considered the possibility that at least some of the plutonium may have arisen from high-density, high-specific activity, weapons-grade plutonium (in dioxide form) penetrating respirator filters of workers carrying out decontamination and decommissioning (D&D) activities in high airborne concentrations of plutonium dioxide. Staff at DOE facilities where respirators are used to protect workers from inhaling plutonium and other radionuclides were contacted and asked to provide information on the types of respirator filters used. Based on information provided, we selected three types of respirator filters (MSA P100 Multigas, Survivair 7000 Series, and 3M 6000 Series) to study filter penetrations by high-density metals (surrogates for plutonium dioxide). The surrogate materials we used were ceric dioxide (density = 7.65 g/cm^3), hafnium dioxide (density = 9.68 g/cm^3), and lead dioxide (density = 9.64 g/cm^3). Our results indicate that all respiratory filters examined allow small numbers of high-density metal particles to occasionally penetrate and therefore likely pose varying risks to workers (depending on the filter type) for plutonium dioxide inhalation and deposition in the respiratory tract . More specifically, our results show that the 3M filters best protect workers from inhaling plutonium dioxide. The Suvivair filters provide the least protection and generally performed very poorly. Particles penetrating filters had aerodynamic diameters generally less than 4 micrometers and could therefore deposit in the deep regions of the respiratory tract. These results suggest that workers in plutonium-dioxide-contaminated, work-area air, risk chronic intake of plutonium dioxide through worker respirator filter penetration as well as inappropriate fitting of respirators, which might show up in urine bioassays.

Our modeling of radiation-induced stochastic effects in cells has led to a revised NEOTRANS$_2$ model for the induction of mutations and neoplastic transformation. Neoplastic transformation is considered an early step in

cancer induction. The current version of the NEOTRANS$_2$ model includes a protective bystander effect whereby existing problematic cells (e.g., neoplastically transformed cells, problematic mutations) can be signaled via other damaged cells to selectively undergo apoptosis. This leads to selective elimination of at least some problematic bystander cells after low doses, thereby protecting the cell community (group adaptation) from stochastic effects such as neoplastic transformation and cancer. Our current modeling results indicated that for exposure to efficiently-penetrating gamma rays in the dose range 0–100 mGy, the risk of neoplastic transformation (and possibly also cancer) can decrease rather than increase. Our results further indicated that when the gamma ray dose is delivered at very low rates, both the duration of the protection and dose range over which it occurs may be extended. Our results also indicate that for problematic cells induced by alpha radiation, low-dose or low-dose-rate gamma radiation may trigger the removal of at least some of these problematic cells via apoptosis.

For combined exposure to low-dose alpha particles and low-dose-rate gamma rays, our modeling results indicate that the risk of cancer could decrease initially, rather than increase. After the initial decrease in risk, the risk is then predicted to increase as the alpha radiation dose increases. Such a decrease with a subsequent increase has been called by some a "hormetic-type dose-response relationship." For such dose-response relationships, there is a threshold for excess risk. We show in a recently submitted paper (Proceedings for the BELLE 2003 Conference) that epidemiological data for Mayak workers exposed to low-dose-rate gamma rays in combination with alpha radiation from inhaled plutonium-239 are consistent with our predictions (hormetic-type dose-response relationship for relative risk for lung cancer). We also show in the paper how use of the linear, nonthreshold (LNT) risk model to extrapolate relative risk from moderate- and high-dose data to low doses introduced "phantom excess risks" (i.e., values above 1) at low doses where the relative risk appears to actually dramatically decrease below 1. Our evaluations indicate that the chronic gamma ray exposure may have protected from most all of the normally occurring spontaneous lung cancers and also from some alpha radiation-induced precancerous lesions. These results were obtained using baseline cancer rates derived from Russian national cancer statistics. Some studies by others (M. Kreisheimer et al., Radiation Research 154:3-11, 2000) using internal controls based on Mayak workers did not demonstrate this protective effect. We attribute this to their selecting a low-dose group of Mayak workers (irradiated over years) for evaluating the baseline cancer rate. These workers are likely to have been protected by their radiation exposure against cancer occurrence.

The current health risks assessment paradigm does not permit for relative risk for cancer induction by radiation to be less than 1, even at low doses, and is based on the LNT risk model. Relative risk is always assumed to be equal to or greater than 1 and to be increased by any radiation exposure. This risk assessment paradigm drives the billion-dollar cleanup costs associated with radionuclide-contaminated DOE sites. Our research results indicate that the current low dose risk assessment paradigm needs to be revised to allow for relative risks for cancer induction being less than one (i.e., a beneficial effect for the irradiated population). Our modeling results show that thresholds for inducing excess cancer should be expected for at least some types of cancer and exposure scenarios. These exposure scenarios include exposure at low-dose rates to gamma rays (and possibly also beta radiation) and combined exposure to gamma rays at low rates and low-dose alpha radiation.

We also have conducted case-control studies of cancer induction among Mayak workers chronically exposed to both alpha and gamma radiations and investigated the evidence for and against radiation threshold for inducing excess cancers. Although with such analyses internal controls were likely biased due to chronic exposure to low-LET radiation, our view is that thresholds for excess cancer induction may still be revealed, although demonstrating protective effects of low dose exposure would be more challenging than if baseline values were based on Russian national statistics. While our initial work focused on lung cancer, we have expanded our joint U.S./Russian Federation research to include liver and biliary cancers. We have used a multivariate regression approach to investigate associations between cancer and suspected key risk factors: plutonium-239 body burden (influences alpha radiation dose), external gamma-ray dose to the total body, and alcohol consumption. Chronic external gamma-ray exposure was not found to be associated with any cancer type. Thus, our results are consistent with the emerging view that for exposure at low-dose rates of low-LET radiation, thresholds (possibly quite large) may exist for inducing excess cancers. Plutonium-239 incorporation was found to be associated with lung cancer. For liver cancer, plutonium-239 incorporation was found to have the highest attributable risk for hemangiosarcoma occurrence. A significant association also was found between plutonium-239 incorporation and hepatocellular cancer. However, plutonium-239 incorporation was not found to be associated with biliary cancer. An association

between alcohol consumption and hepatocellular cancer was found also. Our results are consistent with an alpha radiation threshold for inducing excess lung, liver, and biliary tract cancers when the alpha radiation dose is accompanied by low-dose gamma rays. 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 plutonium-contaminated sites.

Planned Activities

Research in this project will continue (Phase III) via a recently approved renewal grant (second project renewal). Our future research activities will include the following: (1) concluding our evaluations of the Mayak worker clinical data and the associated biological dosimetry work and (2) developing improved estimates of dose thresholds for radiation-induced lung, biliary tract, stomach, and liver cancer.

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 2002–2003 publications fully or partially supported by this project follow:

Aden, J. and B. R. Scott. "Modeling variability and uncertainty associated with inhaled weapons grade PuO_2." *Health Physics* 84: 726-736, 2003.

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

Okladnikova, N. D., B. R. Scott, Z. B. Tokarskaya, G. V. Zhuntova, V. F. Khokhryakov, V. A. Syrchikov, and E. S. Grigoryeva. "Evaluation of genomic instability among Mayak workers that inhaled insoluble forms of Pu-239." *Medical Radiology and Radiation Safety Journal* (submitted, in Russian).

Schollnberger, 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* 15 (4), 387-399, 2002.

Schollnberger, H., B. R. Scott, M. Stafford, and S. V. Osovets. "Analytical solutions for mechanistic model for neoplastic transformation." Radiation Safety Problems, *Mayak Production Association Scientific Journal*, Russian Federation Ministry of Atomic Energy, No. 3:37-43, 2002 (in Russian).

Scott, B. R., D. M. Walker, Y. Tesfaigzi, H. Schollnberger, and V. Walker. "Mechanistic basis for nonlinear dose-response relationships for low-dose radiation-induced stochastic effects." *Nonlinearity in Biology, Toxicology and Medicine* 1 (1): 93-122, 2003.

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

Scott B. R., D. M. Walker, and V. E. Walker. "Low-dose radiation and genotoxic chemicals protect against stochastic biological effects." To be published in *Proceedings of the BELLE Conference on Nonlinear Dose-Response Relationships in Biology, Toxicology and Medicine* (submitted).

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* 83(6): 833-846, 2002.

Tokarskaya, Z. B., G. V. Zhuntova, B. R. Scott, V. F. Khokhryakov, Z. D. Belyaeva, and E. K. Vasilenko. "The influence of radiation and non-radiation factors on the incidence of liver and biliary tract malignant tumors among Mayak PA workers." *Health Physics* (submitted).

Walker, D. M., V. E. Walker, and B. R. Scott: "Modeling of low dose stochastic effects for the prototypic DNA alkylating agent ethylene oxide: Improved characterization using non-linear models." *Toxicological Sciences* (submitted).

Year 2002–2003 presentations fully or partially supported by this project follow:

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.

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, Liege, Belgiuim, September 4–7, 2002.

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.

Scott, 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.

Scott, B. R. and D. M. Walker. "Research on stochastic biological effects of low doses." Joint seminar presented at Lovelace Respiratory Research Institute, August 5, 2002.

Scott, B. R. and D. M. Walker "Have we been misinformed about low dose radiation being harmful?" Annual Meeting of the Environmental Mutagen Society, Miami, FL, May 10–14, 2003.

Scott, B. R., D. M. Walker, and V. E. Walker. "Low dose radiation and genotoxic chemicals protect against stochastic biological effects." BELLE Conference on Non-Linear Dose-Response Relationships in Biology, Toxicology and Medicine, University of Massachusetts, Amherst, MA, May 28–30, 2003.

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.

Optional Additional Information: None.

Optional Proprietary Information: None.