FINAL REPORT

U.S. Department of Energy

IMPROVED RADIATION DOSIMETRY/RISK ESTIMATES TO FACILITATE ENVIRONMENTAL MANAGEMENT OF PLUTONIUM-CONTAMINATED SITES

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Executive Summary

This report summarizes 4 years of research achievements in this Office of Science (BER), U.S. Department of Energy (DOE) project. The research described was conducted by scientists and supporting staff at Lovelace Respiratory Research Institute (LRRI)/Lovelace Biomedical and Environmental Research Institute (LBERI) and the Southern Urals Biophysics Institute (SUBI). All project objectives and goals have been achieved. A major focus was on obtaining improved risk estimates for deleterious effects of exposure via inhalation to plutonium (Pu) isotopes in the workplace (DOE radiation workers) and environment (public exposures to Pu-contaminated soil). To achieve project goals, a considerable effort was devoted to obtaining improved estimates of cancer risk associated with chronic exposure at low rates to alpha radiation alone or in combination with gamma rays. Dose-response modeling and epidemiological studies (Mayak plutonium facility worker population) were conducted. With the dose-response modeling, numerous published data on radiobiological effects from the molecular/cellular to the organ/tissue levels were acquired along with data from our epidemiological studies of lung and liver cancer among Pu-exposed humans as well as from many other epidemiological and ecological studies. The large number of data sets acquired were evaluated to determine whether they supported the linear-no-threshold (LNT) cancer risk model that drives current, low-dose radiation risk assessment and is the basis for establishing radiation exposure limits for humans and for establishing **r**adionuclide **s**oil **a**ction **l**evels (*RSAL*s) for radionuclide-contaminated soils.

Based on the LNT risk assessment paradigm, any amount of ionizing radiation exposure to DOE radiation workers or the public is expected to harm some among any large irradiated population, irrespective of the makeup of the population or the physical characteristic of the radiation. Our very significant findings were as follows: low doses and dose rates of sparsely ionizing radiation (e.g., X-rays, gamma rays, beta particles) activate a system of protective processes that include p53-related DNA repair/apoptosis, an auxiliary form of apoptosis (presumably p53-independent) that removes precancerous and other aberrance cells, and enhance immune functions (which contribute to suppressing cancer occurrence). We call this radiation **a**ctivated **n**atural **p**rotection (ANP). The level of ANP appears to increase with age and may provide little benefit to most children. The increased protection with age is considered to relate to an increase in the body's genomic instability burden, with protective signaling increasing as the number of unstable cells (which participate in the cross talk with normal cells to trigger removal of the aberrant cells) in the body increase. High radiation doses and dose rates appear to inhibit or suppress protective signaling. However, for sparsely ionizing radiation forms, reducing dose rate and extending the period over which the radiation dose is delivered appears to increase the protection efficiency and extend the range of protective doses. Alpha radiation by itself does not appear to induce any significant protection against spontaneous cancers.

For combined extended exposure at low rates to alpha radiation and low-dose gamma rays, gamma-ray ANP can completely suppress cancer induction by low-dose alpha radiation. However, high doses of alpha radiation appear to inhibit low-dose gamma-ray ANP. For high alpha radiation doses, lung cancer relative risk (*RR*) appears to approach a plateau rather than to continue to increase as dose further increases.

To incorporate this new knowledge into low-dose cancer risk assessment, we developed a biological-based cancer *RR* model. The model allows for an ANP-related reduction in cancer risk at low doses to below the spontaneous level and for gamma-ray ANP against alpha-radiation-induced cancer. Dose-response curves for which cancer *RR* first decreases to below 1 at low doses and then increases to above 1 at moderate and high doses are called hormetic. Thus, our model is called a hormetic *RR* (HRR) model. With the HRR model, there is a range of low doses from just above natural background radiation exposure over which ANP is maximal.

This dose range is called the Zone of Maximal Protection. For this dose zone, $RR \approx 1 - PROFAC$ (protection factor), where the *PROFAC* gives the expected proportion of protected individuals (i.e., those with ANP) that do not develop cancer that would have otherwise developed cancer in the absence of radiation exposure. Our research found values of *PROFAC* against cancer ranging from about 0.1 (10% protected from cancer) up to 1.0 (100% protected from cancer in one rat study involving combined exposure to alpha and gamma radiation).

In circumstances where only alpha radiation is involved, *PROFAC* appears to be *0* (or very close to zero). However, natural background low **l**inear **e**nergy **t**ransfer (LET) radiation exposure over an extended period and exposure to diagnostic X-rays could stimulate protecting signaling, leading to a small *PROFAC*. Repeated exposures to diagnostic X-rays therefore could significantly suppress lung cancer induction due to chronic exposure to low doses of alpha radiation from previously inhaled plutonium isotopes. Some Mayak plutonium facility workers who inhaled the alpha-emitter plutonium-239 (^{239}Pu) were also exposed over an extended period (years) to low doses and dose rates of gamma rays. Our analysis of data from a cohort study that used external controls revealed significant gamma-ray ANP against lung cancer ($PROFAC = 0.86 \pm 0.07$).

In our extensive review of adaptive response research results, we found that low-dose-radiation ANP has been demonstrated to:

- Protect against chromosomal damage!
- Protect against mutation induction by a high radiation dose if given before or after the high dose!
- Eliminate precancerous (neoplastically transformed) cells!
- Prevent chemically induced cancer!
- Prevent low-dose, alpha-radiation-induced cancer!
- Suppress metastasis of existing cancer!
- Protect against diseases other than cancer!
- Improve the efficacy of combined high-dose radiation plus gene therapy for cancer!
- Extend the lifespan of cancer-prone mammals!

It can now be stated with confidence that the LNT model does not apply to many real-world radiation-exposure scenarios, especially when adult humans are involved and when low-doses and dose rate of low-LET radiation occur alone or in combination with low doses of alpha radiation. These finding have important implications for regulating radiation exposure of workers and the public and for establishing *RSALs* for Pu-contaminated sites. Recommendations are made for adjusting current *RSAL*s to account for low-dose, low-LET-radiation ANP.

After the death of Mr. Alexander Litvinenko last November in London due to exposure to polonium-210 (^{210}Po), we began quickly modeling the toxicity to humans for this largely forgotten alpha-emitting radioisotope using our hazard-function model. We collaborated with other radiation research experts from around the world, including scientist at the Health Protection Agency (HPA) in London responsible for managing the incident. Our research findings are discussed in two publications on ^{210}Po toxicity that have been widely circulated. Key information related to ^{210}Po toxicity to humans was also provided to ABC News at their request.

1. Research Objectives (modified since project start date)

This project had the following four objectives:

1. To use available data from studies of Russians exposed by inhalation to plutonium-239 (^{239}Pu) (insoluble and soluble forms) and standard and novel analytical methods to *develop improved characterization of health risks to the public from inhaled plutonium (Pu)-contaminated soil* from pre- and post-remediated U.S. Department of Energy (DOE) sites.
2. To use available data from studies of Russians exposed to ^{239}Pu and standard and novel analytical methods to *develop improved characterization of health risks to DOE workers who inhaled airborne weapons grade (WG) Pu in dioxide form* during decontamination and decommissioning (D&D) operations.
3. To *develop improved biodosimetry capabilities for evaluating Pu intake* based on clinical data for Russians who inhaled plutonium-239 dioxide ($^{239}PuO_2$). (Work completed in year 1 with carryover funds).
4. *To continue to provide educational material about radiation and radiation issues to the public* and others via our project-related website: www.radiation-scott.org.

The following two goals were originally stated in our previous renewal application but because the requested funding was significantly reduced, the goals were unachievable with the funding level provided:

- To contribute significantly to improving the probabilistic approach for selecting **r**adionuclide **s**oil **a**ction **l**evels (*RSAL*s) for sites where soil is contaminated with Pu (e.g., Rocky Flats Environmental Technology Site).
- To design a reliable system of respirator protection for workers involved in D&D work for the DOE at Pu-contaminated sites.

2. Background

Research in this project has benefited from numerous publications (over 350) in different research areas, including radiobiological, biomathematical/statistical, dosimetric, and epidemiological/ecological research (Section 17, References). The main section of this report provides, in addition to background information on sources of ionizing radiation exposure and associated stochastic radiobiological effects, a description of research conducted and key findings. The main section is supported by three appendices (A – C). Appendix A presents key results from our previous project (under the same title as this renewal project) that relate to the stochastic deposition of insoluble plutonium dioxide (PuO_2) aerosols in the respiratory tract of adult radiation workers and that relate to measured aerosol filter penetrations by high density metal aerosols used as surrogates for PuO_2. Appendix B provides an in press paper by Scott (2007d) which proposes a new approach to regulating radiation exposure of humans that allows for adaptive-response-related thresholds doses for harm. Appendix C provides a submitted paper by Scott (2007e) demonstrating the efficient prevention of alpha-radiation-induced lung cancer by extended, low-rate exposure to low doses of gamma rays, which has important implications for establishing *RSALs* and for regulation exposure to Pu and other alpha emitting isotopes. A published paper by Scott and Di Palma (2006) relates to our modeling of cancer relative risk (*RR*) and accounting for radiation adaptive response (also called hormesis).

The indicated numerous publications (Section 17, References) related to the research carried out in this project include publications on radiation research (experimental and theoretical) at the molecular, cellular, organ/tissue, systemic, organism, and population levels as well as methods of analysis and integration of results from such studies over multiples biological scales. In carrying out our research, we reviewed previous health-risk-assessment-related,

dose-response modeling efforts that span biological scales from the molecular to the organism levels, as well as the current state of knowledge about the consequences of humans and other mammals being exposed to ionizing radiation. Such information is essential for understanding the true health risk to humans in the workplace (e.g., DOE radiation workers) and elsewhere from exposure to low and high levels of ionizing radiation, including alpha radiation from Pu isotopes. While our main focus has been on high linear-energy-transfer (LET) alpha radiation, considerable research has also addressed combined exposure to low- and high-LET radiations and exposure to only low-LET radiation. This is especially important in that exposure to high-LET alpha radiation is most often accompanied by exposure to low-LET radiation (e.g., as for radon in the home and for plutonium workers). Further, there is now abundant evidence for low-LET radiation **a**ctivated **n**atural **p**rotection (ANP) against cancer and other genomic instability diseases, including protection against alpha-radiation-induced cancer (Scott and Di Palma 2006; Scott 2007a,b,c).

Some background information is provided below on (1) the ionizing radiation environment on earth, including environmental Pu isotopes, (2) composition of weapons grade plutonium (WG Pu); (3) the current low-dose risk-assessment paradigm and associated controversy; (4) stochastic radiobiological processes and associated effects; and (5) low-dose, low-LET radiation ANP against cancer and other genomic-instability-associated diseases.

2.1 The Ionizing Radiation Environment on Earth

Natural background ionizing radiation on earth comes from the following three sources (Figure 1): the sun (solar radiation), outer space (cosmic rays), and terrestrial (e.g., radionuclides in our bodies and environment, and radon in the home). All organisms on earth are constantly bombarded by cosmic, solar, and terrestrial radiation sources. Our food, water, and air we inhale all contain radionuclides. Other sources of ionizing radiation exposure include diagnostic medical procedures (X-rays, isotopes used in nuclear medicine), televisions, smoke detectors, weapons fallout, and radioactive waste (Figure 2).

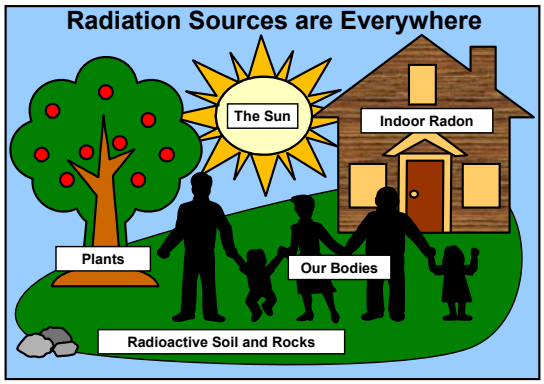


Figure 1. *Natural radiation sources.*

Figure 2. *Other sources of radiation exposure.*

2.1.1 *High- and Low-LET Radiations*

Two types of radiation (high and low LET) are usually distinguished when characterizing radiation risks to humans. High-LET forms include alpha particles, neutrons, and heavy ions that produce intense ionization patterns when interacting with biological tissue. Considerable energy is deposited when traversing a narrow thickness of tissue. Low-LET forms include X- and gamma rays and beta particles that deposit far less energy when traversing a narrow thickness of tissue.

2.1.2 *Units for Expressing Radiation Doses*

Radiation dose is expressed in different ways depending on the intended usage. A fundamental unit is the absorbed radiation dose, which is a measure of energy deposited in tissue (or other material) divided by the mass irradiated. Typical units of absorbed dose are the gray (Gy) which is equal to 1 joule/kg, and the milligray (mGy), which is one thousandth of a gray. These units can be applied when characterizing any type of radiobiological damage.

For regulating radiation exposure of humans (e.g., setting radiation exposure limits), establishing RSALs (and related remediation standards), and for low-dose cancer risk assessment, special radiation dose units have been established that are based on the linear-no-threshold (LNT) hypothesis (discussed in Section 2.2). These units are the result of applying statistical weights called *radiation weighting factors (W_R)* to radiation-specific doses and are expressed in units such as the sieverts (Sv) and millisieverts (mSv). These weighted doses are called *equivalent doses* and can be added for a given tissue. To account for differing sensitivities of different tissues, a second set of weights called *tissue weighting factors (W_T)* are employed to the equivalent doses. The resulting doubly weighted doses can also be added and the resultant dose is called *effective dose* and also expressed in sieverts or millisieverts. Under presumed LNT radiation dose-response functions for all cancer types, the effective dose represents the uniform gamma-ray dose to the total body that would incur the same overall cancer risk as is associated with the person's actual exposure, irrespective of its nonuniformity and irrespective of the types and energies of the radiations that are involved. Radiation dose limits are based on these weighted doses and the *LNT risk assessment paradigm*. Later, evidence pointing to a need to replace this approach with a more scientifically valid one is presented and an alternative regulatory paradigm is proposed in Appendix B.

2.1.3 *Current Radiation Dose Limits*

As already indicated, human radiation exposures are limited for nuclear workers, the public, and other groups based on restricting the effective dose. For example, the effective dose limit for nuclear workers is 50 mSv/y and 1 mSv/y for the public and is based on U.S. DOE and Nuclear Regulatory Commission regulatory policies (Metting 2005). The U.S. Environmental Protection Agency's regulatory policy limits on release of radioactivity to air is based on limiting the effective dose to humans to 0.1 mSv/y, and for public drinking water the corresponding limit is 0.04 mSv/y. For a point of reference, natural background radiation doses in the United States are associated with an effective dose of about 3 mSv/y (radon exposure included) (Metting 2005). For Ramsar, Iran, the corresponding dose associated with natural background radiation is about 200 mSv/y. Interestingly, such high background radiation doses appear to be associated with radiation hormesis-related protection against cancer (Frigèrio and Stowe 1976; Nambi and Soman 1987), i.e., a reduction in cancers. Similar reductions have been reported for lung and other cancers based on many epidemiological/ecological studies (Sanders and Scott 2007; Scott and Di Palma 2006).

2.2 LNT Risk-Assessment Paradigm and Associated Controversy

As previously indicated, the current low-radiation-dose, risk-assessment paradigm is based on the LNT hypothesis (Figure 3), which states that any increment of ionizing radiation dose can harm humans and other mammals via inducing stochastic effects such as cancer, and the risk for stochastic effects increases as an LNT function of radiation dose (NCRP 2001a; NRC 2005). The LNT assumption implicates possible harm from the smallest of ionizing radiation exposures, including natural background radiation exposure. Cancer risk estimates under the LNT hypothesis are largely derived based on victims of the atomic bombings in Hiroshima and Nagasaki. Cancer risk estimates derived from the very high-rate exposures and moderate and high doses that occurred are extrapolated to low doses using an LNT function (Figure 3). Corresponding risk estimates for low doses and dose rates (many orders of

magnitude lower rates than for the A-bombs) are obtained via use of what is called a low **d**ose and **d**ose **r**ate **e**ffectiveness **f**actor (*DDREF*). The *DDREF* is usually assigned the very small value of 2 (which may be appropriate for DNA repair effects) and is used to reduce the risk (or slope of the dose-response curve) by that amount to supposedly account for a lowered risk after low dose rates, regardless of how low the dose rate actually is. It is interesting that all of the complex biology associated with radiation-induced stochastic effects is presumed by many to be accounted for by the *DDREF*. Protective processes such as elimination of aberrant cells via apoptosis (Portess *et al.* 2007) and cancer suppression via immune system functions (Liu 2007) is totally disregarded.

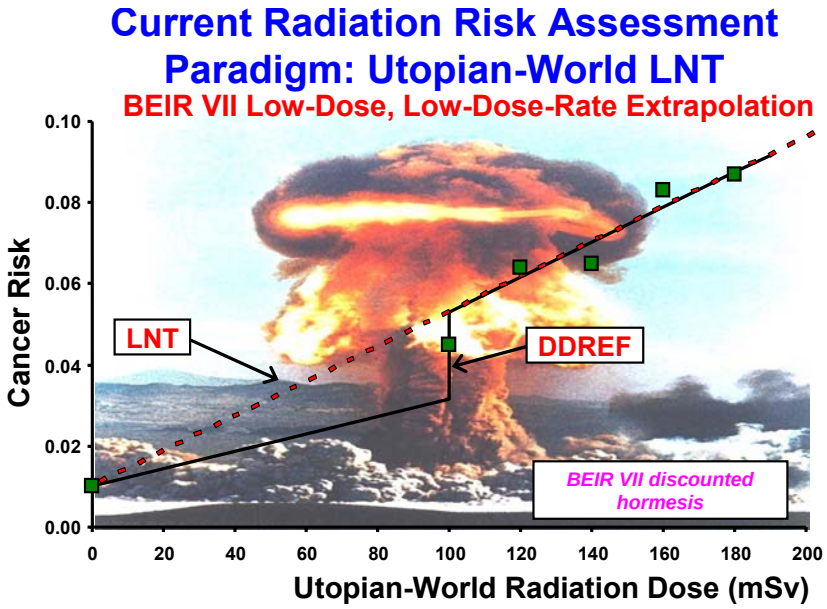


Figure 3. *Linear-no-threshold/low-dose low-dose-rate approach to cancer risk assessment. The approach precludes demonstrating adaptive response (hormesis) and uses what has been called utopian-world radiation dose units, which are based on the make-belief that a linear-no-threshold risk function is valid for all radiation types and exposures.*

We later show low-dose-rate data (many orders of magnitude lower dose rate than for the Hiroshima and Nagasaki bombs) where cancer risk is actually suppressed significantly below the spontaneous level, which cannot be accounted for with the utopian-world *LNT/DDREF* approach to low-dose risk assessment indicated in Figure 3.

The BEIR VII Report (NRC 2005) and the earlier NCRP Report 136 (NCRP 2001a) both recommended the continued use of the LNT supposition (any amount of radiation harms someone among a large population). However as we show in Appendices B and C, the LNT risk assessment practice appears to be incorrect for low-dose radiation exposures when involving low-LET forms or combinations of low- and high-LET forms. In fact, use of the LNT supposition is contributing to the *waste of possibly billions of dollars* related to excessive environmental remediation. Further, radiation phobia driven by the LNT risk perspective is likely to cause far more real casualties in the event of radiological terrorist act involving a dirty bomb than are likely to be related to actual radiation exposure (Figure 4). For a point of reference, LNT-driven radiation phobia was responsible for the loss of more than 100,000 lives through abortions in Eastern Europe following the Chernobyl accident (Ketchum 1987).

Figure 4. *LNT-idea driven radiation phobia is likely to cause more casualties following a dirty bomb incident than are associated with actual harm from radiation exposures.*

Radiobiological research carried out by numerous groups worldwide collectively does not support the LNT hypothesis for low-LET radiation (Ducoff 1975; Hoel *et al*. 1983; Bogen 1989; Azzam *et al*.1994,1996; Pollycove 1995; Mitchel *et al*. 1997; Redpath *et al.* 1998, 2001; Hoel and Lei 1998; Yamamato *et al*. 1998; Kondo 1999; Feinendegen *et al*. 1999, 2000; Pollycove and Feinendegen 1999, 2001;Yamamato and Seyama 2000; Feinendegen and Pollycove 2001; Bonner 2003; Hooker *et al*. 2004; Higson 2004; Sanders 2007; Sanders and Scott 2007; Scott 2007a,b,c). The recent report of the French Academies that addressed the validity of the LNT idea (Tubiana 2005; Tubiana *et. al.* 2005, 2006; Tubiana and Aurengo 2006) clearly articulated the lack of support. The French Academies report concludes the following:

"… this report raises doubts on the validity of using LNT for evaluating the carcinogenic risk of low doses (< 100 mSv) and even more for very low doses (< 10 mSv)."

The French Academies therefore came to a very different conclusion than was presented in the BEIR VII and NCRP 136 reports regarding the validity of the LNT model. Thus, the appropriateness of the current low-dose radiation risk assessment practice that is based on the LNT idea remains quite controversial. Research (modeling and epidemiological) conducted in this project has contributed significantly toward helping clarify when and when not LNT might be expected to apply. It would be expected to apply when humans at any age are exposed only to alpha radiation. However, when exposed to sparsely ionizing radiation (e.g., X-rays, beta particles, or gamma rays, or their combinations) LNT would not be expected to apply to persons already possessing a significant genomic instability burden (Scott and Di Palma 2006). A human's genomic instability burden increases with age and also with exposure to genotoxic agents in the environment, in the home, and in the workplace. Protective processes discussed in Section 2.4 can eliminate cells with genomic instability (e.g., precancerous cells). The protective processes can be stimulated by low doses and dose rate of sparsely ionizing radiation (Scott and Di Palma 2006)! When this occurs, benefit rather than harm is expected to be associated with the radiation exposure.

2.3 Stochastic Radiobiological Processes and Effects

Radiation-induced cancer is considered a stochastic effect (i.e., has a unknown probability of occurrence, but the probability can be estimated). Our research has focused on improved estimates of cancer risk after exposures to low doses of ionizing radiation, including alpha

radiation from inhaled alpha-emitting Pu isotopes and after combined exposure to alpha and gamma radiations. It is not widely known that radon exposure in the home involves combined exposure to alpha and gamma radiations.

Our risk modeling is biologically based and supported by epidemiological studies. In developing our biologically based cancer risk model for radiation exposure, we have considered the complex stochastic processes involved and the related biological outcomes. We also reviewed other quantitative models that describe both stochastic and deterministic biological effects caused by radiation or other toxicants (Whittemore and Keller 1978; Zaider and Rossi 1980; Barrett and Wiseman 1987; Bond *et al*. 1987; Brenner *et al*. 2001; Burkart *et al*. 1997; Calabrese and Baldwin 1999; Calkins 1971; Cucinotta *et al*., 2002; Elkind 1991, 1994;Crawford-Brown and Hofmann 1993; Feinendegen *et al*. 1999, 2000; Feinendegen and Pollycove 2001; Heidenreich *et al*. 1997; Hoel *et al*. 1983; Joiner *et al*. 1999; Luebeck *et al*. 1996; Moolgavkar *et al*. 1993; NCRP 2001a; Pollycove 1995; Pollycove and Feinendegen 1999, 2001; Portier 1987; Portier *et al*. 1990; Schöllnberger *et al*. 2001a-c; Scott 1981, 1983, 1984, 1986, 2004b, 2005c, 2007f; Scott and Dillehay 1990; Stewart 1999; Trott and Roseman 2000; Okladnikova *et al.* 2005a,b,c). This review helped to guide the cancer risk modeling conducted in this project.

Our cancer risk modeling was also supplemented by some modeling of radiation-induced deterministic effects (acute lethality). This modeling proved to be quite beneficial following the polonium-210 (^{210}Po) poisoning event that occurred during November 2006 in London. Our modeling of radiation deterministic effects risks help to clarify the likely intake of ^{210}Po by Mr. Alexander Litvinenko for the British Health Protection Agency (Harrison *et al.* 2007; Scott 2007f).

For low-dose radiation risk assessment, quite a lot is known about stochastic processes associated with radiobiological responses *in vivo* and *in vitro*. A key stochastic process is the induction of genomic instability (Kadhim *et al*. 1992, 1994, 1995, 1996, 1998; Kennedy *et al*. 1996; Little 1985, 1999; Little *et al*. 1990; Mauder and Morgan 1993; Morgan *et al*. 1996; Martins *et al*. 1993; Mothersill and Seymour 1998a,b; Wright 1998). A second key stochastic process relates to the occurrence of bystander effects, generally thought of as deleterious effects, based mainly on high-LET radiation studies (Brenner *et al*. 2001; Hei *et al*. 1997; Iyer and Lehnert 2002a,b; Little *et al.* 2002; Lyng *et al*. 2000; Mothersill and Seymour 1997, 1998a,b; Nagasawa *et al*. 2002; Seymour and Mothersill 2000). For low-LET radiation, the bystander effect has been found to be generally protective (Hooker *et al*. 2004, Redpath *et al*. 2001, Scott 2007a-c). A third key stochastic process is radiation adaptation, which is a form of hormesis (Liu 2007; Rithidech and Scott 2007; Redpath and Elmore 2007; Sanders 2007; Scott et al. 2007). A key stochastic effect at the cellular level associated with the indicated stochastic processes is the occurrence of genomically unstable cells (e.g., mutants and neoplastically transformed cells). Studies of neoplastic transformation (occurrence of precancerous cells) *in vitro* (Azzam *et al*. 1994, 1996; Ottolenghi *et al*. 1994; Redpath and Antoniono 1998; Redpath *et al*. 2001; Scott 1997; Scott *et al*. 2003) have provided useful information regarding the general shape of the dose-response curve for low-dose/dose-rate radiation-induced cancer.

Numerous researchers have attempted to link radiation-induced stochastic effects at the cellular level to cancer occurrence in humans by considering the general stages of initiation, promotion, and progression (Armitage and Doll 1954; Crawford-Brown and Hofmann 2002; Hoel and Li 1998; Kondo 1999; Mebust *et al*. 2002; Moolgavkar *et al*. 1993; Rossi and Zaider 1997; Tan 1991; Thorslund *et al*. 1987; Trott and Roseman 2000). However, these models did not adequately integrate the currently known underlying biological mechanisms of genomic instability, adaptive response, and bystander effects. We therefore developed a biologically based cancer *RR* model as a result of having carried out the indicated multi-scale integration via assuming a proportionality between cancer and neoplastic transformation *RR* (Scott 2007a,b,c).

2.4 System of Natural Protective Processes and the Control of Genomic Instability and Its Deleterious Consequences

Mammalian cellular communities are not complacent when threatened by environmental stresses such as ionizing radiation. The community reacts through a system of protective processes (when they are activated/stimulated by low doses of radiation) to limit deleterious biological consequences of irradiation (e.g., instability in the genome, mutations, neoplastic transformations, and cancer occurrence) (Makinodan and James 1990; Liu *et al*. 1994a,b; Liu, 2003, 2004; Sakai *et al*. 2003; Feinendegen *et al.* 2004; Scott 2004a; Lombard *et al.* 2005; Coates *et al*. 2005; Ljungman 2005). The protective processes include (1) detecting (sensing) DNA damage; (2) correcting the damage after its detection via activated low- or high-fidelity DNA repair; (3) removing cells with residual DNA damage (e.g., damaged cells that fail to undergo repair or misrepair their DNA damage) via apoptosis; and (4) stimulated immune functions.

DNA double-strand breaks may be the most disruptive form of damage to nuclear DNA (Chu 1997). They may occur by extrinsic insult from environmental sources or intrinsically as a result of cellular metabolism or a genetic program (Mills *et al.* 2003). Double-strand breaks are repaired by homologous recombination and by nonhomologous end-joining (Thompson and Schild 1999, 2001), which is the predominant mechanism in eukaryotes (Mills *et al*. 2003). Misrepair of DNA damage can lead to mutations and associated genomic instability (Tubiana *et al.* 2005). Cells that do not undergo p53-related repair of DNA damage can also be eliminated via p53-related apoptosis (Rothkamm and Löbrich 2003). An auxiliary **p**rotective **a**poptosis **m**ediated (PAM) process has also been described (Portess *et al.* 2007), partly due to research we carried out at our Institute (Scott *et al.* 2003; Scott 2004a). The PAM process seems to play a role in removing cells that develop genomic instability as a result of having undergone viable misrepair of DNA damage. This auxiliary protection, like repair of DNA double-strand breaks, appears to require a threshold level of mild stress, which seems to be caused by low doses (above an individual-specific threshold) of low-LET radiation forms such as X rays, gamma ray, and beta radiation (Scott *et al.* 2007).

Others have also proposed (Hanahan and Weinberg 2000; Tubiana *et al.* 2005) that apoptosis protects from stochastic effects such as cancer via eliminating genomically unstable cells. Hanahan and Weinberg (2000) in their classic paper entitled “The Hallmarks of Cancer” pointed out the following: “Collectively, the data indicate that the cell’s apoptotic program can be triggered by an over-expressed oncogene. Indeed, elimination of cells bearing activated oncogenes by apoptosis may represent the primary means by which such mutant cells are continually culled from the body’s tissues.”

Radiation-induced stimulation of the immune system provides additional protection against deleterious stochastic radiobiological effects (Anderson and Lefkovits 1979; Makinodan and James 1990; Liu 1998, 2003, 2004; James and Makinodan 1988; Shen *et al.* 1996, 1997; Hashimoto *et al*. 1999; Takahashi *et al*. 2000; Matsubara *et al*. 2000; Kojima *et al*. 2002; Liu *et al*. 1994a,b; Sakai *et al.* 2003, 2006; Tubiana 2005; Tubiana *et al.* 2005). Immunosurveillance systems can eliminate clones of transformed cells as seen in tumor cell transplants.

2.5 Radiation Adaptive Response/Hormesis, a Protective Bystander Effect

The above system of biological protection relates to radiation adaptive response. Classical two-dose, adaptive-response studies have involved administering a small adapting dose that after a time delay is followed by a larger test dose (Wolff 1996). Deleterious biological effects (usually expressed as a frequency) obtained are then compared to those observed after only administering the test dose. A reduced frequency of observed stochastic biological effects with the combined exposure is then interpreted to represent adaptation caused by the first dose. The first dose activates one or more components of the system of protection discussed in the

preceding section. For the two-dose adaptive response study design, it is clear that a low-dose-stimulated increased DNA repair capacity (a contribution to adaptation) likely plays a major role in the indicated reduction in the frequency of stochastic effects (Wolff 1996; Wolff *et al*. 1988; Mitchel 2004). The PAM process is also considered to play an important role in the indicated adaptive response. The indicated repair enhancement only occurs after a significant time delay and appears to require a threshold dose (Rothkamm and Löbrich 2003). However, cells with spontaneous and radiation-induced genomic instability (e.g., precancerous cells) can be eliminated via the PAM process, including cells that develop genomic instability as result of misrepair of DNA damage.

Azzam *et al.* (1996) and Redpath *et al.* (2001) introduced a novel experimental single-dose adaptive response study protocol whereby only the small adapting dose is administered. The yield of biological effects (neoplastic transformation *in vitro to* precancerous cells) was then compared to the spontaneous frequency for unirradiated cells. To the surprise of many, the adapting dose protected against spontaneous neoplastic transformation (adapted protection), yielding a decrease (rather than an increase) in the transformation frequency to below the spontaneous level. Others (Hooker *et al.* 2004; Day *et al.* 2006, 2007) also reported induced adapted protection for inversion mutation induction in spleen of pKZ1 mice exposed *in vivo* to low doses of 250-kVp X-rays. Because the single-dose form of protection can occur at low-LET radiation doses for which the vast majority of the target cell population receives no radiation hits, it is considered to be a *protective bystander effect* (Scott 2004a). These effects appear to be associated with low-LET radiation or combined exposure to low- and high-LET radiation but not with only high-LET alpha radiation (Scott 2004a, 2007a-b; Scott *et al*. 2003). This has an important implication for cleaning up environmental contamination caused by radionuclides released from DOE sites and other activities. Not only does potential harm from radiation need to be considered but also potential radiation-induced protection from harm (i.e., adaptive response, a benefit).

Low-dose-radiation adaptive response/hormesis is a manifestation of radiation ANP. Low doses and dose rates of sparsely ionizing radiations (X-rays, gamma ray, and beta radiation) have been found to:

- Protect against chromosomal damage (Azzam *et al.* 1996).
- Protect against high-radiation-dose-induced mutations if given before or after the high dose (Day *et al.* 2006, 2007).
- Eliminate precancerous (neoplastically transformed) cells (Redpath *et al.* 2001).
- Prevent chemically induced cancer (Sakai *et al.* 2003).
- Stimulate increased immune system functioning (Liu 2007).
- Suppress alpha-radiation-induced cancer (Tokarskaya *et al.* 1997a,b,c; Sanders 2007).
- Suppress metastasis of existing cancer (Sakamoto *et al.* 1997; Sakamoto 2004).
- Protect against diseases other than cancer (Sakai *et al.* 2006).

2.6 Environmental Plutonium

Plutonium (Pu) has the atomic number 94 and was discovered in 1941 by Glen Seaborg (Nobel Laureate), Arthur Wahl, and Joseph Kennedy, a group of chemist at Berkeley. In the winter of 1941, they bombarded uranium oxide with 16-Mev deuterons from the Berkeley cyclotron. They then chemically identified the isotope neptunium-239 (^{238}Np), which decayed by beta emission to an isotope of element 94 (Pu) that then emitted alpha particles. With the advent of the nuclear arms race in the 1950s, atmospheric nuclear tests were conducted

worldwide. During the 1960s, ownership of radioactive materials for energy production (e.g., nuclear power) became common. As a result, the levels of man-made Pu increased and continue to increase today. This has lead to workplace and environmental exposures of humans to Pu.

Our project has mainly focused on evaluating Pu toxicity to humans. Throughout the remainder of this report, the notation PuO_2 is used for Pu found in weapons-grade (WG) Pu and in soil when in dioxide form. The notation $^{239}PuO_2$ is specific for the dioxides of the isotope Pu-239. The notation $^{239,240}PuO_2$ refers to dioxides of mixtures of Pu-239 and Pu-240.

The element Pu is largely a human-made hazard produced in association with nuclear weapons and is contained in soils around the globe, partly as a result of atmospheric nuclear testing. Table 1 presents information about Pu inventories (kCi) in soil in the Northern and Southern Hemispheres arising from both nuclear weapons detonations and from SNAP devices, based on 1970 measurements. Higher inventories of $^{239,240}Pu$ from nuclear detonations were found in the Northern Hemisphere.

Table 1. Estimated fallout of Pu inventories (kCi) in soils around the globe[a]

Location	Weapons $^{239,240}Pu$	Weapons ^{238}Pu	SNAP ^{238}Pu
Northern Hemisphere	253 ± 33	6.1 ± 0.8	3.1 ± 0.8
Southern Hemisphere	67 ± 14	1.6 ± 0.3	10.3 ± 2.1
Total	320 ± 36	7.7 ± 0.9	13.4 ± 2.2

[a]Based on measurements of Pu from numerous locations (Holleman *et al.* 1987).

2.7 Main Isotopes of Pu

A typical, large nuclear power reactor creates about 230 kilograms of Pu per year. The main isotopes are:

- ^{238}Pu (*alpha emitter*), half-life 88 years;
- ^{239}Pu (*alpha emitter*), fissile, half-life 24,000 years;
- ^{240}Pu (*alpha emitter*), fertile, half-life 6,500 years;
- ^{241}Pu (*beta emitter*), fissile, half-life 14 years; and
- ^{242}Pu (*alpha emitter*), half-life 37,600 years.

Alpha particles from the Pu isotopes ^{238}Pu, ^{239}Pu, ^{240}Pu, or ^{242}Pu can harm humans only when taken inside the body though inhalation, ingestion, or a wound. The beta emitter ^{241}Pu emits low energy beta particles (*maximum energy = 21 keV*) and is therefore mainly a concern when inhaled or ingested. Controversial issues have arisen related to the concentrations of the indicated Pu isotopes, along with ^{241}Am (Americium-241, also an alpha emitter), that have remained in soil at the Rocky Flats Environmental Technology Site (herein called Rocky Flats) after site cleanup. Cleanup of such sites is risk driven, and risk of harm from radiation is normally evaluated based on the LNT model. Research results generated in this project and discussed in this report bring into question the validity of the LNT risk model for combined exposure of adults to alpha, beta, and gamma radiation or for exposure to low doses or low doses rates of sparsely ionizing radiation. The LNT model, however, may apply in rare circumstances where one is exposed only to high-LET alpha radiation (Scott and Di Palma 2006) or low-energy (high-LET) neutrons (Rithidech and Scott 2007).

Table 2 presents the constituents of WG Pu and their specific activities along with the relative radioactivity content (percent of total radioactivity) they represent with respect to the total mixture.

Table 2. Radionuclide-specific activities for WG Pu and relative radioactivity content for key alpha-emitting components (Scott and Peterson 2003).

Radionuclide[a]	Activity (Bq/g-mix)	Relative Radioactivity Content (%)
^{238}Pu	1.85×10^{8}	6.57
^{239}Pu	2.13×10^{9}	75.69
^{240}Pu	4.77×10^{8}	16.95
^{241}Am	2.22×10^{7}	0.79
Total	2.814×10^{9}	100.00

[a]Radionuclides not listed contribute little to total radiation dose.

3. Methods and Results from Epidemiological Studies of ^{239}Pu-Associated Lung Cancer among Mayak Production Association Workers

Only previously developed dosimetry and medical information were used in our studies of lung and liver cancer among Mayak Production Association (PA) workers. Medical examinations, interviews with patients, autopsy and biopsy protocols discussed here refer to work previously carried out by Russian physicians and scientists prior to initiating our epidemiological studies.

The Southern Urals Biophysics Institute (SUBI) assures that it complied with U.S. DOE regulations for protection of human research subjects (CFR 1-1-97) and the Russian Federation Law of Public Health Protection (Russian Federation 1993). In addition, the Western Institutional Review Board/Western International Review Board granted the project in which these studies (lung and liver cancer) were undertaken an exempt status.

To improve on cancer risk estimate for inhalation exposure of humans to environmental or workplace Pu isotopes, we conducted epidemiological studies of lung and liver cancers among Mayak PA workers (Tokarskaya *et al.* 2002, 2006).

3.1 Lung Cancer Cohort Characteristics

This was a nested, case-control study based on a population comprised of tens of thousands of humans exposed over years to alpha (from inhaled ^{239}Pu) plus gamma radiation (from external sources in the workplace). Our cohort comprised 4,390 (77% male) adult workers. The first criteria considered for inclusion in the cohort was that the Mayak PA worker started work between 1948 and 1970 (48% started work between 1948 and 1959) and that the worker was monitored for both external gamma-ray exposures and for body burdens of ^{239}Pu. The other criteria were that detailed information was available on the worker's smoking history and standard medical documentation was available.

The main factor associated with lung cancer induction among Mayak PA workers was previously identified to be ionizing radiation (Tokarskaya *et al.* 1995): high-dose external gamma rays and alpha radiation from inhaled ^{239}Pu (as inferred from internal Pu body burdens). During the first years of Mayak Pa operation, some workers were exposed to external gamma radiation that was significantly higher than permissible levels, i.e., > 50 mSv/y. The higher than permissible whole-body gamma-ray doses occurred between 1949 and 1957, and there was a

significant inhalation risk for airborne ^{239}Pu, with intakes possibly much higher than permissible (>1.48 kBq body burden) before the special respirator, "Lepestok," was adopted in 1957. From the 1960s, the whole-body gamma-ray exposure did not exceed the permissible level.

3.2 Dosimetry for Cancer Studies for Mayak PA Workers

Ionizing radiation (external gamma radiation and alpha radiation from inhaled ^{239}Pu aerosols) was the main occupational hazard. The Mayak Dosimetry Monitoring Service registered exposures to external gamma rays by using individual film badges (Vasilenko *et al.* 2000).

During the first years of operation (1948–1952), the estimated annual total-body, gamma radiation doses (D_γ) in some instances exceeded 1.0 Gy (maximum individual annual dose, 8.0 Gy). In this period, dose monitoring was carried out daily. During 1953–1955, the estimated maximum annual doses decreased to 1.0 Gy, and doses were monitored weekly. After 1968, individual annual total-body, gamma-ray doses did not exceed 50 mGy (corresponds to 50 mSv, the permissible level) for most workers. Film badge changes and registrations were performed monthly. Initially, the measurement error was approximately 60% (1948–1953); after 1985, it was approximately 30% due to improved technology. The thermoluminescent method has been used since 1988.

The SUBI Laboratory of Internal Dosimetry staff estimated a ^{239}Pu body burden based on spontaneous excretion of ^{239}Pu in urine (Khokhryakov *et al.* 1998a, 2000a,b). A systematic excreta-based program for monitoring workers' Pu exposures started in 1970. This program involves direct measurement of Pu in large urine samples. The estimates of ^{239}Pu body burden and alpha radiation absorbed dose (D_α) to select organs are based on a biokinetic model that uses information on the exposure history and transportability of Pu within the body as inputs into models for lung clearance (ICRP 1979; Suslova *et al.* 2002; Khokhryakov *et al.* 1995) and systemic plutonium excretion (Khokhryakov *et al.* 2004). Transportability of the ^{239}Pu aerosols at different work locations was determined using dialysis methods (Khokhryakov *et al.* 1998b).

The urine bioassay is based on the radiochemical technique of the double-phosphate precipitation of ^{239}Pu. The error did not exceed 30%; the detection limit was 0.26 kBq (Russian Federation 1993). The ^{239}Pu body burden and D_α were extrapolated for the period of interest using a retention function based on the indicated biokinetic model. The error in D_α may be higher than 30% because additional sources of error contribute to alpha-radiation doses (e.g., statistical and systematic error associated with the biokinetic model used to obtain doses) (Krahenbuhl *et al.* 2005). The risk of exceeding the permissible level for inhaled airborne ^{239}Pu remained high until a special respirator, "Lepestok," was introduced in 1957.

Both D_α and D_γ were estimated for each case and its control for the period from initial exposure up to the date of cancer diagnosis. Lagged doses (based on *lag = 10 years*) were used for characterizing dose responses for alpha and gamma irradiation. This may have introduced a systematic error favoring an LNT-type response over a threshold-type or hormetic response (Appendix B and Section 5.4).

3.3 Cigarette Smoking History

Prior to our study, data on the PA workers' smoking history were acquired during face-to-face interviews conducted via a standard method employed by medical personal at the SUBI (then FIB-1). The smoking index (SI) (a product of the number of years of smoking and the number of cigarettes smoked daily) was used as an integral (cumulative) index. Most smokers used "papiros" (cigarettes without filters) that were characterized by high tar and heavy metal contents.

The SIs ranged from 0 to 2000 [(cigarettes/day)*years]. The cigarette pack numbers ranged from one-quarter up to two packs per day. The duration of smoking ranged from several months to 45 years.

Cigarette smoking started before employment at the Mayak PA and continued at roughly a fixed level. At the time of employment, the SI was approximately 200. About 20 years of smoking were required to reach an SI of about 500. For an SI in excess of 900, more than 35 years of smoking were required.

3.4 Other Exposures Considered

Individuals who prior to employment at the Mayak PA worked at least 6 months at such facilities as a petroleum-chemical plant, a chemical plant that produced acids, explosives, stains, fertilizers, nonferrous metallurgy, or ferrous metallurgy were considered to have prior contact with chemicals.

3.5 Medical Monitoring of Mayak PA Workers

Early medical monitoring included a provisional examination (before starting work in a radiation area) and repeated prophylactic examinations (4 to 6 times/y) after first contact with workplace radiation. From 1960, annual examinations (that involved supportive therapy, neurology, blood analysis, and X-ray examination) were carried out. Periodically (once in 3 – 5 years), a large number of workers were examined in the clinic (located in the Radiation Medicine Department of the SUBI) by modern functional and other diagnostic methods.

3.6 Lung Cancer Cases and Associated Controls

The main group in the present study consisted of all lung cancer cases from 1966 to 1991 and were verified by morphological investigation among the staff that assembled the above-described cohort. There were 162 (148 men and 14 women) lung cancer cases.

The lung cancer cases were investigated in the Pathological Anatomy Laboratory of the SUBI hospital. Routine autopsy and histological methods were used: fixation in 10% formalin, embedding in paraffin, and staining with hematoxylin and eosin. When judged necessary, Schiff's periodic acid and mucicarmine were used as stains.

Routine optic microscope procedures were used. Histology was classified in accordance with the World Health Organization (WHO) classification scheme (WHO 1982). Controversial cases were evaluated by two or three pathologists. Surgical cases (23% of material) were evaluated in the pathological anatomy laboratories of special oncological clinics.

For the 162 workers who had lung cancer and formed the main group, matched controls (persons without lung cancer) were assigned. Each case was matched to two controls (1:2 ratio) for both men and women (total 324 controls). The matching was based on five factors: sex, year of birth (± 5 years), year work began (± 2 years), profession, and workplace (plant, sector, etc.).

Information about radiation contact, smoking history, and lung diseases was obtained after completing both the main and control groups and did not influence the control group matching. Matching on the five indicated factors limited the possible control selections for each lung cancer case to about three to five persons. This is why for each cancer case, two noncancer controls were selected that closely matched the lung cancer case for all five indicated factors. In some instances, it was not possible to match the profession exactly, and a different profession considered similar was therefore selected. The priority of the factors was as follows: sex, plant, year work began, birth date, and profession. Matching on profession, year work began, and workplace allowed controlling for possible other important industrial factors not considered.

3.7 Statistical Methods for Lung Cancer Incident Assessment

We investigated pair-wise interactions (additive, multiplicative, etc.) based the three uncorrelated factors, ^{239}Pu body burden, gamma-ray dose to lung, and cigarette SI, using the odds ratio (*OR*) approach. The *OR* was evaluated for individual factors, i.e., A (OR_A) and factor B (OR_B) and for their combination (OR_{AB}). Here subscripts A and B represent the factors being considered. The *OR* was also used to estimate *RR*.

Previously we evaluated the *OR* using the following equation for individual factors or for their combination (Tokarskaya *et al.* 1997c):

$$OR = \frac{m_I \cdot (n_{II} - m_{II})}{m_{II} \cdot (n_I - m_I)},$$

where m *is the number of persons with lung cancer, and (*n – m*) is the number of persons without lung cancer. The subscript* I *represents the exposed contingent, while the subscript* II *represents the unexposed contingent (i.e., not exposed to the factor or factors of interest).*

In conducting our study, we have instead estimated the *OR* based on the ratio of discordant pairs of type I (*DisI*) and type II (*DisII*) (Breslow and Day 1980). Thus,

$$OR = DisI/DisII.$$

Discordant pairs of type I occur when the case (with cancer) has the exposure, and the matched control (without cancer) has no exposure. Discordant pairs of type II represent the situation where the case has no exposure, and the control has the exposure. The number of concordant pairs (where both the case and control have been exposed or both have not been exposed) does not influence the calculation.

We evaluated the *OR* for different levels of a given factor. The groupings were made in the following way:

Group 1: High level of factor A and low level of factor B.

Group 2: Low level of factor A and high level of factor B.

Group 3: High levels of both factors.

Group 0: Low levels of both factors to which the other three groups were compared (i.e., group was taken as the uninfluenced reference group).

A statistical characterization of the association between factors was initially evaluated based on the comparison of the *OR* of three groups that had:

1. A high level of factor A only,
2. A high level of factor B only, or
3. High levels of both factors (AB).

For this grouping, the testing criteria were based on the following:

Additive effect of factors A and B, $OR_{AB} = OR_A + OR_B - 1;$ (1)

Multiplicative effect of factors A and B, $OR_{AB} = OR_A \cdot OR_B.$ (2)

A pooled analysis (unconditional logistic regression) was used for preliminary characterization of the disease distribution according to the dose levels, but not for interaction characterization. For interaction characterization, conditional logistic regression was used. Evaluation of homogeneity in *OR* was based on the McNemar's relationship (Breslow and Day 1980) specifically designed for matched data.

The homogeneity between discordant pairs was assessed via the χ^2 statistic (Breslow and Day 1980) whereby

$$\chi^2 = \frac{(|DisI - DisII| - 1)^2}{DisI + DisII}. \quad (3)$$

Corresponding calculations were also carried out based on the Mantel-Haenzel method (Fleiss 1981) but are not reported here as results were similar to results obtained with the above equation.

RR was estimated from *OR*. Pair-wise comparisons between factor-specific *RRs* were made to test the homogeneity of *RR* between factors A, B, and the combination AB. To carry out these evaluations, 2 x 2 contingency tables were created for which the usual corrected χ^2 (Breslow and Day 1980) was calculated for pair-wise comparisons (A to AB and B to AB). The observation of homogeneity was interpreted as an indication of a possible additive effect. The absence of homogeneity was interpreted as an indication of a possible interactive effect (sub-additive, multiplicative, supra-multiplicative, etc.).

To refine the characterization of interactions between factors A and B, a second approach was used whereby confidence intervals for the expected OR_{AB} under the additive and multiplicative models were generated via Monte Carlo calculations (10,000 realizations) assuming a normal distribution (Breslow and Day 1980) for the variable

$$\text{Prob} = \text{OR}/(\text{OR}+1), \quad (4)$$

with mean Prob_j *for a given factor assignment (i.e., j = A, B), where*

$$\text{Prob}_j = \text{OR}_j/(\text{OR}_j+1). \quad (5)$$

*The variance (*Var*) for* Prob *for a given factor assignment was evaluated as follows (Breslow and Day 1980):*

$$\text{Var}\{\text{Prob}\} = [\text{Prob}_j(1-\text{Prob}_j)/(\text{DisI} + \text{DisII})]. \quad (6)$$

Fifth and 95th percentile values for the Monte Carlo-generated distribution for OR_{AB} were evaluated using Crystal Ball (1996) under both the additive and multiplicative models based on *Prob* having the indicated normal distribution for individual factors A and B with the indicated *Var* (Equation 6). The *OR* was then used as an estimated *RR*.

The OR_{AB} distribution generated was skewed as expected. In some cases, negative values were obtained because of using the normal distribution for *Prob*. The Monte Carlo-generated percentiles were then compared with observed values for OR_{AB} to evaluate whether additive, multiplicative, or other associations were implicated by the data.

Criteria used for evaluating interactions were as follows:

- Sub-additive effect: If the observed OR_{AB} for the combined exposure to both factors A and B was less than the fifth percentile value of the Monte Carlo-generated OR_{AB} distribution under the additive model, then the data were judged consistent with a sub-additive effect of the combined exposure.
- Additive effect: If the observed OR_{AB} for the combined exposure to both factors A and B fell between the fifth and 95th percentile values of the Monte Carlo-generated distribution under the additive model and the fifth percentile under the multiplicative model is greater than the 95th percentile under the additive model, then the data were judged consistent with an additive effect of the combined exposure.
- Intermediate effect: If the OR_{AB} for the combined exposure to both factors A and B was greater than the 95th percentile value of the Monte Carlo-generated distribution

under the additive model but less than the fifth percentile value under the multiplicative model, then the data were judged consistent with an intermediate effect (i.e., between additive and multiplicative) of the factors.

- Multiplicative effect: If the observed OR_{AB} for the combined exposure to both factors A and B was greater than the 95th percentile value for the Monte Carlo-generated distribution based on the additive model but between the fifth and 95th percentile for the multiplicative model, then data were judged consistent with a multiplicative effect of the factors.

- Supra-multiplicative effect: If the observed OR_{AB} for the combined exposure to both factors A and B was greater than the Monte Carlo-generated 95th percentiles under both the additive and multiplicative models, then the data were judged consistent with a supra-multiplicative effect of the factors.

Although the above criteria are somewhat subjective and overly conservative, they are based on reasonable distribution-related considerations under the additive and multiplicative models.

Interactions between smoking and radiation were evaluated for middle (*SI = 200 to 900*) and high (*SI = 901 to 2000*) smoking levels. Only high levels of radiation were considered (*Gamma ray dose > 2 Gy*; *^{239}Pu body burdens > 2.3 kBq*) in interaction evaluations.

3.8 Results Obtained for Lung Cancer Occurrences among Mayak PA Workers

With our multivariate analysis of lung cancer occurrence among Mayak PA workers, we investigated the pair-wise interactions of previously identified three main etiological factors. These three factors are as follows: (1) body burden of ^{239}Pu, an influence on absorbed alpha-radiation dose; (2) cumulative, absorbed external gamma-radiation dose to the total body; and (3) level of cigarette smoking as indicated by the SI, which represents the number of cigarettes smoked per day times years smoking.

As already indicated, the Mayak PA workers were exposed by inhalation to both soluble and insoluble forms of ^{239}Pu. Based on using a cohort of 4,390 persons (77% male), our nested, case-control study of lung cancer induction was carried out using 486 matched cases and controls. As previously indicated, each case was matched to two controls. Matching was based on five factors: sex, workplace (plant), year work began, year of birth, and profession. 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.

Our study design used internal controls and dose groups comprised of widely varying doses so that we could not efficiently test for radiation adaptive response/hormesis at low doses (see Section 5.4). However, a previous publication not using discordant and concordant pairs

indicated a rather strong adaptive response (hormesis) after low doses of chronically delivered alpha plus gamma radiation doses (Tokarskaya *et al.* 1995, 1997c).

We also conducted a study using published Mayak PA worker data from a cohort study design with external controls based on Russian national statistics. The indicated data demonstrated a dramatic adaptive response (protection against lung cancer occurrence) and is discussed in Section 5 along with numerous data on protective effects of low doses and dose rates of ionizing radiation.

4. Methods and Results from Epidemiological Studies of ^{239}Pu-Associated Liver Cancer Among Mayak Production Association Workers

This Mayak-worker-based study focused on evaluating possible associations between malignant liver cancers and chronic alpha irradiation, chronic gamma irradiation, and nonradiation risk factors (alcohol consumption, smoking, viral hepatitis, chemical exposure, and chronic digestive diseases). This was the first multivariate study related to liver cancer among Mayak PA workers (Tokarskaya *et al.* 2006). Detail of the study design and key findings follow below.

4.1 Liver Cancer Cohort Characteristics

The study included 44 Mayak PA workers with morphologically confirmed (i.e., by histological studies) malignant liver tumors that were diagnosed during 1972 – 1999. These cases made up the "case" group. Cases of liver cancer (approximately 20 workers) diagnosed without any morphological confirmation, i.e., diagnosis based on death certificates, were not included in our study. The liver is one of the main sites for metastasis of malignant tumors (Tokarskaya *et al.* 2006). Thus, one cannot exclude the possibility that some liver cancer cases without morphological confirmation may represent metastases to the liver of an undetected primary tumor.

The "control" group consisted of 111 Mayak PA workers, who had no known liver cancers. The control group included workers from the same Mayak PA plants as the case group and was matched by sex, year of birth $\pm$ 5 years, year of starting work at the Mayak PA $\pm$ 2 years, and work assignment. The case-control ratio was 1:2 or 1:4.

4.2 Dosimetry

Dosimetry is explained in Section 3.2.

4.3 Alcohol Consumption Categories and Smoking Levels

The alcohol consumption was characterized using three disjoint levels:

a. Rare drinker: less than 40 mL ethanol per week.

b. Moderate drinker: about 200 mL ethanol per week.

c. Heavy drinker: much more than 200 mL ethanol per week.

Russian medical staff interviewed patients directly during visits to the SUBI Clinic to obtain the detailed smoking history (age started smoking, duration, number of cigarettes). The SI (product of daily smoked cigarettes and years of smoking) was used as a cumulative index.

4.4 Other Exposures Considered

Individuals who prior to employment at the Mayak PA worked at least 6 months at such facilities as a petroleum-chemical plant, a chemical plant that produced acids, explosives, stains, fertilizers, nonferrous metallurgy, or ferrous metallurgy were considered to have prior contact with chemicals.

4.5 Medical Monitoring

Medical follow-up of the case and control groups was the same as for all nuclear workers at the Mayak PA. The medical follow-up included an initial examination followed by annual ambulatory examinations (therapeutic, neurological, and blood analyses). Occasionally (once every 3–5 years), nuclear workers were examined in the Clinical Department of the SUBI.

Information on digestive diseases, viral hepatitis, prior exposure to chemical agents, and alcohol consumption was obtained from medical records (ambulatory cards, case histories). The information on individual alcohol consumption was verified in the Narcological Service Archive.

The Virology Laboratory provided information on markers of viral hepatitis B and C. However, viral hepatic marker information was available for < *10%* of the studied individuals. For individuals without viral hepatitis marker information, we evaluated the occurrence of viral hepatitis based on medical records. This diagnosis was therefore made based on the clinical data without any virological analysis. Most of such cases with hepatitis were registered during 1940 – 1960. Hepatitis A, which was not found to be associated with liver cancer, was prevalent in Russia during that period.

Data on liver tumor morphology (histological types) are based on autopsy or biopsy protocols established during 1972 – 1999. All cases were studied at the same pathology laboratory using routine autopsy and histological methods (Tokarskaya *et al.* 1995).

4.6 Auxiliary Controls

In addition to the control group used for case-control studies, another group (comparison group) was used for comparison when evaluating the frequency distribution (i.e., cancer spectrum) of different types of liver cancer among Mayak PA workers. The comparison group comprised cases (*n* = *28*) with malignant liver tumors diagnosed during 1972 – 1999 among Ozyorsk citizens who had never worked with radiation. Their ages and gender corresponded to the cancer cases among workers (those born during 1910 – 1946).

4.7 Statistical Methods for Liver Cancer Incidence Assessment

The case and control groups were compared using both single independent-variable and multivariate analyses. The "t" criterion was used for comparing sample averages. The "χ^2" criterion was used for comparing frequency ratios in univariate analyses. Nonparametric statistics (Man-Whitney U-test and Kolmogorov-Smirnov test) were used to account for the possibly skewed distributions (Handbook of Applicable Mathematics 1989).

Our main research objective was to study possible associations between several risk factors and the occurrence of liver tumors using multivariate methods. Two analytical approaches were used: (1) quantitative variables were grouped (i.e., categorized) and unconditional logistic regression was employed to obtain *OR* as an estimate of *RR*; (2) quantitative continuous variables were not grouped and conditional logistic regression analysis for matched case-control studies (SAS PHREG procedure) was employed to obtain the hazard ratio (*HR*) as an estimate of *RR*. Multivariate, conditional regression implemented with the PHREG routine (SAS Institute 2001) was used to estimate *HR* based on the Cox model. *Using SAS, the PHREG routine can be implemented in a mode that is equivalent to conditional logistic regression.*

Analyses were carried out separately for each type of liver cancer considered, as well as for all three types of liver cancers combined. Multiple logistic regression (based on the maximum likelihood criterion) was used in our multivariate analyses involving grouped data. The logistic regression procedure facilitated adjusting for confounding factors when calculating *OR* (Breslow and Day 1980). The quantitative risk factors considered included the following: ^{239}Pu body burden (or the corresponding absorbed alpha-radiation dose to the target tissue), the external gamma-ray dose to the total body, and the SI. Although these variables are continuous,

dose groups (categorized representation) were used for estimating crude odds ratios (OR_{cr}), adjusted odds ratios (OR_{ad}) in our multivariate analyses based on logistic regression and attributable risk (*AR*). Some additional nominal variables (e.g., alcohol abuse, chemical exposure) were represented as a binary variable.

Attributable risk was calculated for specific risk factors and specific liver cancer types using methods described in Fleiss (1981) and Rothman (1996). With the multivariate conditional regression analyses, our focus was on identifying significant contributions of specific risk factors (e.g., alpha-radiation dose, gamma-radiation dose, alcohol abuse) to the overall regression. For the continuous variable analyses, estimates of individual radiation doses and individual SI were used. Covariates included were D_α (linear [L] or quadratic [Q] forms), D_γ (L forms), and alcohol misuse (binary variable) (yes [1], no [0]). Using ungrouped doses avoids a systematic error linked to implementation of nonlinear models (i.e., modeling with Q forms) with dose groups.

A *p*-value ≤ 0.05 was considered significant in all statistical tests for associations. Also, *p*-values in the range $0.05 < p < 0.1$ were considered marginally significant and were interpreted as representing a weak association (Tokarskaya *et al.* 2006). All statistical calculations were carried out using SAS Version 8.02 (SAS 2001).

4.8 Results Obtained for Liver Cancer Occurrences among Mayak PA Workers

As indicated, the study was performed using the nested, case-control approach and included 44 cases of malignant liver tumors diagnosed from 1972 to 1999 and 111 matched controls. The OR_{ad} was evaluated relative to a group of workers with liver dose $D_\alpha < 2.0$ Gy (Tokarskaya *et al.* 2006). Dose estimates > *2.0 Gy* (corresponding ^{239}Pu body burden estimates > 20.4 kBq) were significantly associated ($p < 0.003$) with the occurrence of hemangiosarcomas (HAS) but only marginal significance ($0.05 < p < 0.1$) was found for hepatocellular cancers (HCC). The OR_{ad} for HAS was 41.7 (95% confidence interval [*CI*]: 4.6, 333) for a group with D_α in the range > *2.0 – 5.0 Gy* and was 62.5 (7.4, 500) for a group with $D_\alpha > 5.0 – 16.9$ *Gy*. The *AR* was calculated as 82%. For HCC, the OR_{ad} was estimated as 8.4 (0.8, 85.3; $p < 0.07$) for a group with D_α in the range > 2.0 – 9.3 Gy. For the indicated group, the *AR* was 14%. An association with high, external D_γ to the total body was revealed for both HCC and for combined liver cancers when dose was treated as a continuous variable. However, *we found no evidence that chronic low doses of gamma rays are associated with liver cancer occurrence*. Cholangiocarcinoma (CHC) was not associated with either alpha- or gamma-ray exposure. As expected, an association between alcohol abuse and HCC was inferred ($OR_{ad} = 3.3$ [*1.2, 9*]*; AR = 41%*) but not for CHC or HAS.

The study designed used involved averaging odds of cancer (relative to no cancer) over wide dose intervals and then using the interval specific average odds to obtain the *OR* as is done in most epidemiological studies (Scott 2007d). This, along with the use of internal controls (including Mayak PA workers also exposed to low-level radiation), made it difficult to test for radiation adaptive responses associated with the gamma-ray component of the total radiation dose (Scott and Di Palma 2006; Appendix B). However there is now abundant evidence for low-dose/low-dose rate radiation-related adaptive response/hormesis for cancer. Some of this evidence is presented in Section 5.

5. Modeling, Experimental, and Epidemiological/Ecological Evidence for Radiation Adaptive Response/Hormesis for Lung Cancer

5.1 Novel HRR Model for Cancer Induction

It is now known that through evolution, mammalian life forms have developed natural cancer preventative processes (chemically and biologically regulated) that are stimulated by low doses and dose rates of sparsely ionizing forms of radiation (e.g., X-rays, gamma rays, beta particles). Low doses and dose rates of these radiations stimulate protective intercellular and

intracellular signaling that lead to ANP (activated natural protection) against cancer and other genomic-instability-associated diseases (Scott and Di Palma 2006). The protective signaling appears to be a generalized response to mild stresses above an individual-specific threshold level.

Radiation ANP (also called radiation hormesis [Calabrese *et al.* 2007]) appears to be an evolutionary benefit of the interaction of low-level ionizing radiation with mammalian life forms on earth. Thus, ANP is evolutionary conserved (Mitchel 2007). High radiation doses and dose rates rather than preventing cancer, inhibit the protective processes that suppress cancer (Scott and Di Palma 2006). Appendix C discusses biological signaling associated with the PAM process which, when stimulated by low dose radiation, removes precancerous and other aberrant cells. The important role low-dose radiation-stimulated immune functions play in ANP against cancer and other genomic-instability-associated diseases is discussed in a number of papers (Liu 1988, 2003, 2004, 2007; Scott and Di Palma 2006).

Here, the focus is on application of our novel HRR model of lung cancer data for protracted exposure to low doses of alpha radiation in combination with very low doses of gamma rays to demonstrate the highly efficient prevention of lung cancer by gamma-ray ANP. Alpha radiation administered alone is a potent inducer of lung cancer. Small doses (close to natural background radiation levels) can cause a significant increased incidence (Lundgren *et al.* 1991; Sanders 2007). However, for combined exposure to low-dose alpha and very-low-dose gamma rays, the gamma-ray ANP can prevent cancer induction by alpha radiation. The level of protection can be quantified using our HRR model (Figure 5) as explained below.

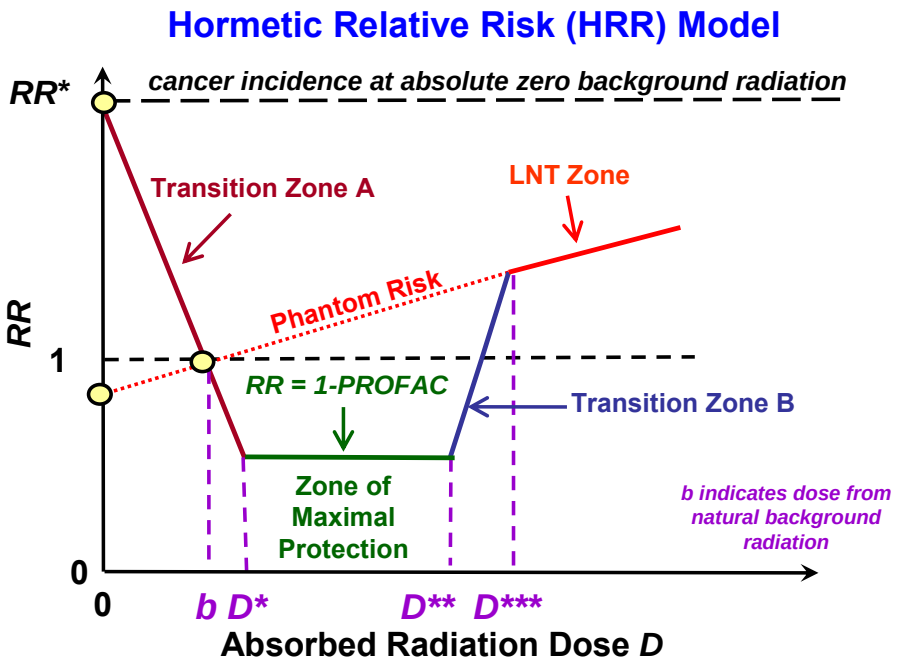


Figure 5. *Hormetic relative risk (HRR) model. Individual-specific threshold doses above absolute zero natural background are responsible for ANP and occur in Transition Zone A. The dose b is the current natural background dose. Everyone is protected for doses from D* to D** (Zone of Maximal Protection). Individual-specific threshold doses for suppression or inhibition of some ANP occur between doses D** and D*** (Transition Zone B). Only DNA repair is presumed to contribute to protection for doses > D***, and the RR curve intersects the LNT risk curve for a range of dose. Reducing doses to below < D* is expected to lead to harm, rather than to benefit due to loss of ANP. The LNT curve when extrapolated down to b gives phantom excess risk. Sharp bends are artificial and used only to clarify the different dose zones in a clear way.*

With the current version of our HRR model and for doses above the natural background dose *b* and below, the irradiated population is separated into two dose- and dose-rate dependent parts: (1) those that have ANP and (2) those without ANP. For persons with ANP, the population average cancer *RR* is given here by

$$RR_{ANP} = (1 - PROFAC)RR_{LNT} \quad (7)$$

where RR_{ANP} *is the* RR *for persons with ANP (i.e., protected individuals) and* RR_{LNT} *is the* RR *for persons without ANP and is based on the LNT assumption. Bayesian methods allow evaluating the expected proportion of the population that is protected for a given dose and dose rate, and radiation combination when formally fitting the model to data (Scott and Di Palma 2006).*

The protection factor (*PROFAC*) takes on values from 0 to 1 and here accounts for prevention of cancer via gamma-ray ANP. A value of *PROFAC = 0.25* would indicate that cancer would be expected to be prevented in 1 in 4 individuals among those with ANP. For a hypothetical population containing 1000 protected (by low-dose gamma-ray ANP) heavy cigarette smokers, if 100 were expected to develop lung cancer because of smoking, then with *PROFAC = 0.25*, 25 of the 100 would be expected to be prevented from developing smoking-related lung cancer. Thus, not every protected person is expected to escape lung cancer occurrence.

For alpha-radiation-induced lung cancer, RR_{LNT} is evaluated based on:

$$RR_{LNT} = 1 + [(1-B)/B]K_{\alpha}D_{\alpha}, \quad (8)$$

where *B* is the baseline (spontaneous) cancer incidence, K_{α} is the presumed always-positive slope parameter in the HRR model, and D_{α} is the alpha radiation dose. Equation 7 is used for evaluating cancer *RR* for combined exposure to low-dose alpha and gamma rays while Equation 8 applies to exposure only to alpha radiation (Scott 2007a,d). The *PROFAC* relates only to low-dose gamma rays (or a radiation type of similar interaction characteristics such as X-rays and beta radiation when used instead of gamma rays). Note that RR_{LNT} *in Equation 8 is a response surface that depends not only on dose* D_{α} *but also on the baseline cancer frequency B*. Thus, epidemiological studies using different dose groups with different baselines *B* for each group need to adjust to a common baseline in order to legitimately plot a single dose-response curve for *RR* vs. dose. The HRR model is applied elsewhere (Appendix B) to both animal and human data for the *RR* for lung cancer induction by combined chronic exposure to alpha and gamma radiations. Key findings are summarized in Section 5.2. *PROFAC* estimates for preventing different types of cancer derived from numerous epidemiological and ecological studies are summarized in Section 5.3.

5.2 Application of the HRR Model to Lung Cancer Data for Inhalation Exposure to Alpha or Alpha Plus Gamma Emitting Radionuclides

With the HRR model, exposure at low rates over an extended period to low doses of gamma rays is predicted to significantly suppress lung cancer induction by alpha radiation. However, for high doses of alpha radiation, the ANP-related signaling is presumed to be suppressed or overwhelmed by deleterious signaling (Appendix B). Lung cancer *RR* data and HRR-model-generated *RR* estimates are presented in Figure 6 for humans, dogs, and rats that were exposed to both low and high alpha-radiation doses alone or in combination with low-dose gamma rays. Lung cancer *RR* for Wistar rats that inhaled both the alpha emitter ^{239}Pu and the gamma emitter ytterbium-169 (^{169}Yb) are indicated by the filled squares and are based on data from Sanders (2007). Also shown is the adjusted *RR* for Wistar rats for inhalation exposure to only Pu-239 (filled circles) based on data from Sanders (2007), after adjusting to a baseline of 95/100,000 (same as for ^{239}Pu + ^{169}Yb-exposed rats). The adjusted *RR* for Beagle dogs (closed triangles) that inhaled the alpha emitter ^{238}Pu in an insoluble form based on data from

Muggenburg *et al.* (1996) after adjusting to a baseline of 95/100,000 is also presented. Logarithmic scales are used on both axes.

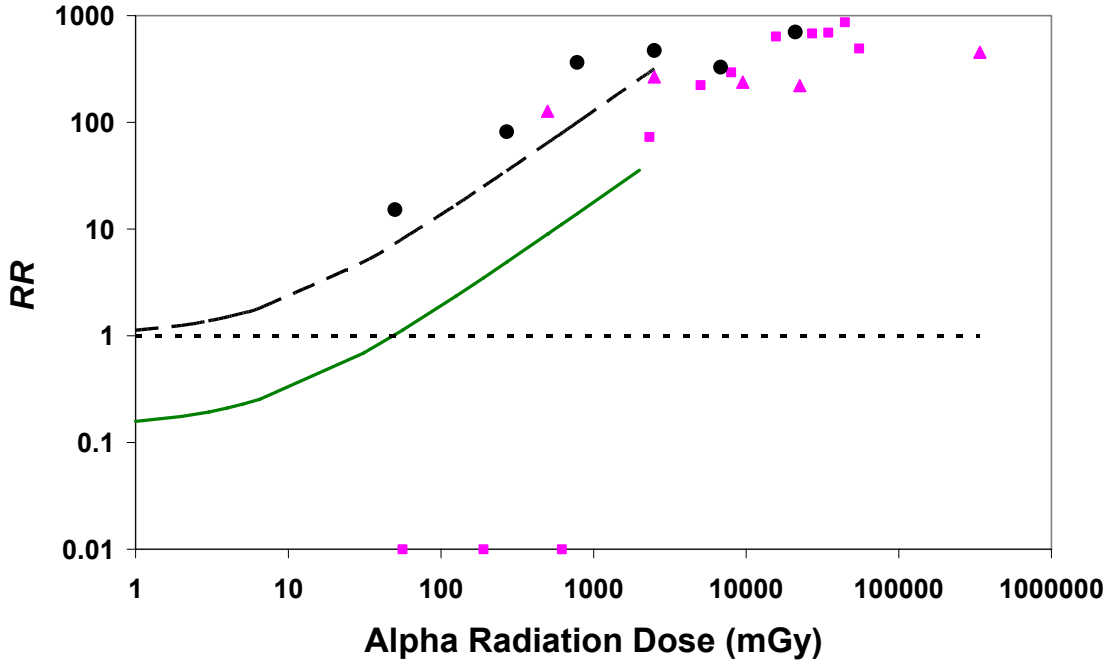


Figure 6. *Lung cancer RR data for Wistar rats exposed to low and high alpha radiation doses alone (filled circles) or in combination with low-dose gamma rays (filled squares) from a ^{169}Yb tag. Lung cancer data for beagle dogs exposed to very high alpha and low-dose gamma radiation (filled triangles). The lower smooth curve is based on fitting Equation 7 to human data (Mayak PA workers) using Bayesian inference and adjusting for a different baseline. All results in the figure relate to a baseline lung cancer incidence of B = 95/100,000. The upper smooth curve was obtained for unprotected humans by changing PROFAC = 0.86 (smooth curve for humans) to PROFAC = 0 (i.e., no protection; Equation 8). Values for RR = 0 are plotted at RR = 0.01. The zero dose groups for which RR = 1 are excluded. The horizontal line is for RR = 1.*

The expected adjusted *RR* for Mayak PA workers (smooth curve) exposed via inhalation to ^{239}Pu in combination with external gamma rays, based on fitting the HRR model to Mayak PA worker data from Kokhryakov *et al.* (1996) using Bayesian methods (Scott and Di Palma 2006) and adjusting for a baseline to 95/100,000 is also presented in Figure 6. The study used external controls, with a dose-group-specific baseline evaluated, based on Russian national statistics. This eliminates the systematic error associated with inclusion of persons receiving low-doses in the control group (a problem with most low-dose epidemiological studies). The upper dashed cure in Figure 6 is predicted for humans in the absence of the protective low-dose gamma rays based on Equation 8 and is in reasonable agreement with the data for Wistar rats (filled circles) that received only alpha radiation exposure. The rat and dog data converge at high doses where protection is presumed to be inhibited. The high-dose results can be presumed to also apply to humans for the indicated baseline. Interestingly, the *RR* seems to approach a plateau at very high doses (*> 10,000 mGy*), although a logarithmic scale is used and disguises large changes in the data.

For Wistar rats that receive average alpha radiation doses of 56, 190, and 620 mGy to the lung in combination with low-dose gamma rays, the expected *RR* assuming no gamma-ray ANP (based on low-dose data for rats exposed only to alpha radiation and Equation 8) was 13, 43, and 137, respectively. However, the observed *RR* values were zero in each case, implication *PROFAC = 1.0* (Equation 7) for gamma-ray ANP against lung cancer induction. *Thus, 100% of*

lung cancers (alpha-radiation-induced and spontaneous) were apparently prevented! However, for alpha radiation doses > 1000 mGy deleterious signaling is implied to predominate, thereby inhibiting or overwhelming protective signaling associated with the extended low-rate exposure to low doses of gamma rays for the ^{169}Yb tag. For Mayak PA workers chronically exposed to alpha and gamma rays over many years the estimated gamma-ray ANP was somewhat less (*PROFAC = 0.86 ± 0.07*). See Appendix B for more detail on the data in Figure 6.

5.3 Data Showing *PROFAC > 0,* Based on Radiation Epidemiological/Ecological Studies

Values of *PROFAC* significantly > *0* for cancer incidence (or mortality) demonstrate cancer prevention. Estimates of *PROFAC* for a number of irradiated human populations have been derived based on cancer mortality and incidence data and are presented in Table 3 (see Scott and Di Palma 2006 for additional data). Radiation exposures were presumed to have occurred in the Zone of Maximal Protection (i.e., maximal low-LET-radiation ANP) in cases where *RR* or *SMR* (standardized mortality ratio) was < 1. All indicated *PROFAC* values were significantly > 0 ($p < 0.05$). *PROFAC* values range from 0.15 to 0.97. Residing in U.S. states with high natural background appears to suppress cancer occurrence (*PROFAC = 0 .15*). *PROFAC* variation may relate, in part, to different genetic characteristics (e.g., polymorphisms) for the different irradiated groups.

Table 3. Central estimates of the presumed radiation-hormesis-related protection factor (*PROFAC*) against cancer in humans (Scott and Di Palma 2006).

Group	Effect	Radiation Types	*PROFAC*
Chernobyl accident recovery workers	Cancers	Low- plus high-LET	0.13[a]
USA, residents of high background states	Cancers	Low- plus high-LET	0.15[a]
British medical radiologists[b] after 1955-1979	Cancers	Low- plus high-LET	0.29[a]
High residential radon, USA	Cancers	Low- plus high-LET	0.35[a]
Canadian nuclear industry workers	Leukemia	Low- plus high-LET	0.68[a]
USA DOE facilities workers	Leukemia	Low- plus high-LET	0.76[a]
Russian Mayak plutonium facility workers	Lung cancer	Low- plus high-LET	0.86[a]
Taiwanese in cobalt-60 contaminated apartments	Cancers	Low-LET	0.97[a]

[a] *PROFAC* significantly > 0 ($p < 0.05$).
[b] Evaluated relative to all men in England and Wales.

The product *100*PROFAC* gives the expected number of deaths from cancer avoided due to radiation-induced adaptive protection (hormesis) for each 100 cases that would have otherwise occurred, when everyone is protected. Thus, for Mayak PA workers, 86 lung cancer deaths are expected to have been prevented for each 100 lung cancer deaths that would have otherwise occurred in the absence of their chronic exposure to gamma radiation. It was assumed that all workers were protected by their extended low-rate exposures to gamma rays. The gamma-ray ANP-related *PROFAC* of 0.86 is a pronounced level of protection against

normally occurring harm, including harm associated with cigarette smoking. The results presented for Taiwanese living in cobalt-60 contaminated apartments (*PROFAC = 0.97*) is based on controversial data. A lower *PROFAC* value may actually apply.

Other ANP-related *PROFACs* are presented in Table 4, based on data for persons residing in a high-level radon spa area in Japan (Mifune *et al.* 1992). Only the gamma-ray component to the radon dose is presumed to be associated with ANP (Scott and Di Palma 2006).

Table 4. Central estimates of high-level, radon-associated *PROFACs* against cancer at different sites in the body based on cancer mortality data for persons residing in a high-level radon spa area in Japan (Scott and Di Palma 2006)

	PROFAC	
Cancer Site or Type	Females	Males
Leukemia	0.47	0.56
Stomach	0.55	0.60
Breast	0.74	–
Lung	0.81	0.53
Colon/rectum	0.86	0.70

Figure 7 presents *PROFAC* against breast cancer occurrence in females as a function of age at exposure to diagnostic X-rays based on data from Nyström *et al.* (2002; Scott and Di Palma 2006). Female patients received fractionated diagnostic X-ray exposures (mammograms) related to breast cancer screening.

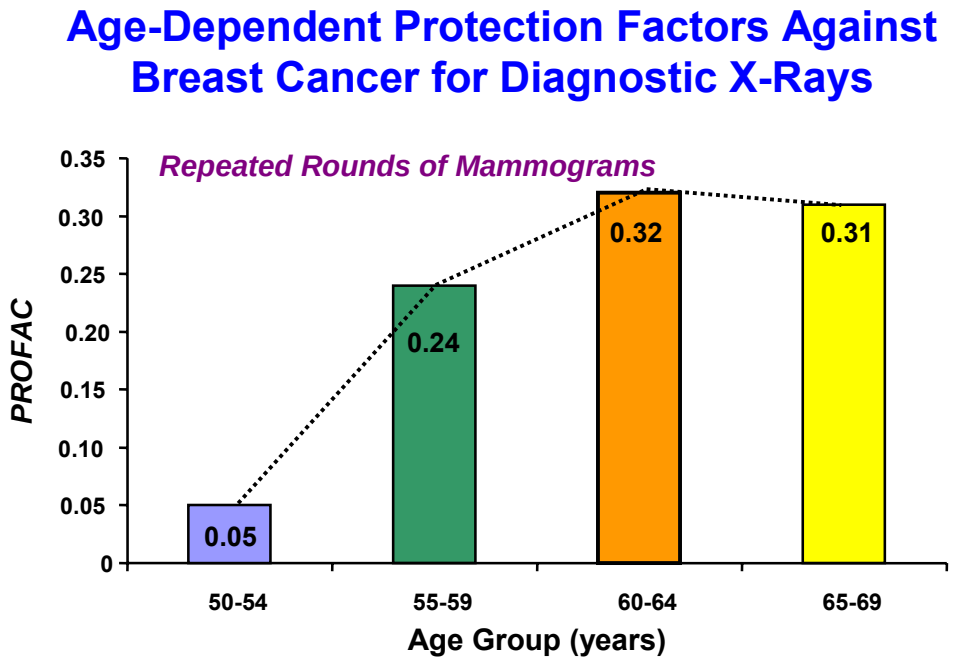


Figure 7. *X-ray PROFAC against breast cancer based on data from Nyström et al. (2002).*

A strong age dependency is implicated in Figure 7 for low-dose-radiation ANP against breast cancer in adult females. The *PROFAC* increases to a plateau as age increases. DNA repair fidelity is known to be reduced with increasing age. Thus, the genomic instability burden is expected to increase as we age because of reduced DNA repair. However, this increased genomic instability burden would be expected to be associated with an increased role of the PAM process and immune system stimulation in protecting against genomic-instability-associated diseases such as cancer. The PAM process involves signaling between normal and genomically unstable cells. The higher the concentration of unstable (aberrant) cells the stronger the signaling associated with the PAM process is expected to be, once signaling is initiated (Scott 2004a). Thus, one would expect the *PROFAC* to increase as age increases for a given genomic-instability-associated disease. The results appear to indicate that the aged benefit more from induction of the PAM process and enhanced immunity than do young adults. Whether or not the very young will benefit from the PAM process is unclear. Such persons without significant burdens of genomically unstable cells may not benefit from the PAM process.

5.4 Epidemiological Procedures Used that Hide Actual Departures from LNT Risk Functions

Appendix B presents an in press paper (Scott 2007d) that discusses procedures used in epidemiological studies to hide the presence of hormetic responses and thresholds in the dose-response curve for cancer induction. The epidemiological procedures are summarized below.

5.4.1 *Procedure #1: Dose Lagging*

Some of the actual radiation dose is discarded in many epidemiological studies that employ the LNT risk function. This process is called dose lagging. Throwing away dose is related to the view that some of the dose must be wasted. However, the notion of there being wasted dose and the dose-response curve being of the LNT type is a contradiction as explained in Scott and Di Palma (2006) based on more recent research. Throwing away dose can hide hormetic-type responses at low doses and thresholds for excess cancer risk. This was not realized when we conducted our lung and liver cancer studies related to Mayak PA workers.

5.4.2 *Procedure #2: Eliminating the Hormetic Dose Zone via Averaging over Dose Groups*

In case control studies, dose groups are often comprised of individuals with doses spanning a wide range. The statistical procedures used to obtain the *OR* (usually evaluated relative to the lowest dose group that includes exposed and unexposed individuals) essentially averages odds of cancer (against no cancer) over the indicated wide dose intervals. The averaged odds are then used to obtain the *OR* that, in turn, is used to estimate *RR*. As demonstrated in Appendix B, this procedure can change an actual hormetic-type, dose-response curve (with low-dose prevention of cancer) into what appears to be an LNT type curve (where any amount of radiation is implicated as being harmful). This was not realized when we conducted our lung and liver cancer studies related to Mayak PA workers.

5.4.3 *Procedure #3: Constraining the Slope of the Cancer Risk Dose-Response Curve to Always Be Positive*

With this procedure, high-dose data is always included in the analysis to ensure a positive slope to the LNT-type dose-response curve. It does not matter if the low-dose data show or suggest a reduction in *RR* to below 1. This is simply ignored (more weight given to the high-dose data). This leads to ignoring the hormetic implications of the low-dose data. Only the positive slope obtained for the dose-response curve is usually presented. The actual data used is often not presented so as to effectively hide the low-dose departure from linearity. See Appendix B for additional discussion.

6. Low-Dose-Radiation ANP Implications for Establishing RSALs

The cost of cleanup and the associated management costs of Pu and other radionuclide-contaminated sites, notably sites where processing of large amounts of nuclear materials has been done, are estimated to run into hundreds of billions of dollars in the United States alone (Makhihani and Gopal 2001). Ensuring the effectiveness of public expenditures in ways that are compatible with health and environmental protection for thousands of years is quite challenging. The level of cleanup is closely linked to the LNT risk model for cancer induction and the associated annual effective doses. Thus, any amount of residual radioactivity in soil, no matter how small, is calculated to be associated with an increased cancer risk. Having scientifically justifiable reasons for considering thresholds for radiation doses that cause harm could lead to greatly reducing the cost of cleaning up radionuclide-contaminated sites.

We discuss in an in press paper the implications of low-LET-radiation ANP for regulating worker and public exposures to ionizing radiation (Scott 2007d; Appendix B). Here, the focus is on implications for establishing more realistic *RSAL*s, taking into consideration low-LET-radiation ANP. *RSALs* are radionuclide concentrations in soil that when exceeded trigger an evaluation, remedial action, and/or management action, given the presence of institutional controls. Because of low-LET-radiation ANP, cancer risk after combined exposures to low doses of radiation from alpha, beta, and gamma-emitting radionuclides in soil of remediated DOE and other sites can be considerably less than would be expected based on the LNT hypothesis, and can actually be less than the risk would be in the absence of radiation exposure. However, the susceptibility characteristics of the at-risk human population are quite important. Radiation ANP considerations for adults would be different from those of children. Thus, for an industrial site established in a remediated area, risk considerations would likely relate to adults. However, for a family residing at the site (e.g., farming family) children could be at risk for radiation harm.

Under circumstances of combined exposure to low-LET beta and or gamma rays along with alpha radiation from contaminated soils, if the annual absorbed doses are low (up to 10 mGy of for each type), then for adults residing or working at such a location one would not expect any increase in cancer risk; and in fact, if the person is a heavy smoker their risk of cancer may be much less than if they received no radiation exposure from the indicated site. This points to the need for establishing *RSAL*s based on realistic risk of harm, rather than using the default LNT assumption. The **r**egulatory **r**adiation **a**bsorbed **d**ose **t**hreshold (*REGRADT*) that represent the radiation-specific minimum absorbed radiation dose (for the most sensitive person) to a given organ for the loss of ANP (lower end of Transition Zone B in Figure 5) could be used to obtained more realistic *RSALs*. Loss of ANP is equated with harm in that cancer risk is expected to increase because of this loss. *REGRADTs* are introduced in the in press paper by B.R. Scott (Appendix B) in connection with regulating worker and public exposures to ionizing radiation.

For a given radionuclide, the soil concentration for the exposure scenario could be considered an action level when evaluated at the concentration that corresponds to the *REGRADT* (evaluated as an annual dose), taking into consideration each type of radiation associated with the radionuclide and considering the likely low-LET radiation ANP below the action level. If $RSAL_j$ is used to represent the current soil action level for the j^{th} radionuclide based on an LNT extrapolation from high-dose data, then for circumstances where gamma- and/or beta-emitting radionuclides are present in soil and *min{PROFAC}* (i.e., the minimum *PROFAC* evaluated over all irradiation organs/tissue of the body) relates to the low-LET radiation exposure (low doses and dose rates presumed), then the modified action level:

$$RSAL_j^* = RSAL_j/(1 - min\{PROFAC\}) \quad (9)$$

would be a more scientifically justifiable choice than $RSAL_j$. As illustrated in Figure 5, $RSAL_j$ is based on phantom excess risk at low doses from radionuclides in soil when ANP occurs. In the absence of estimates of *min{PROFAC}*, a conservative value, e.g., 0.25, could be assigned. A similar approach could be used for beta- and gamma-emitting radionuclides.

If C_j is used to represent $RSAL_j^*$ for each radionuclide j, and c_j is the corresponding soil concentration for the radionuclide, then the action level for mixtures of radionuclides in soil could be evaluated according to the constraint:

$$\sum_{j=1}^{n} c_j / C_j < 1. \tag{10}$$

Exceeding the constraint in Equation 10 would trigger the appropriate evaluation, remedial action, and/or management action, given the presence of institutional controls.

Because ANP appears to decrease with decreasing age, special consideration needs to be given to the age when determining appropriate land uses for remediated radionuclide sites. In some instances, using land comprised of radionuclide-contaminated soil may be restricted to adults who would be expected to have high levels of ANP as compared to children. Thus, the contaminated site might be restricted to industrial applications where only adults had access to the site, rather than, for example, allowing the site to be used for farming activities by a family with children or with children planned. *New funded ANP-related research is needed to facilitate acceptance of Equation 10 by the general public and government agencies.*

7. Biological Dosimetry for Inhaled PuO_2

We explored the possible use of Mayak PA worker clinical data in biological dosimetry for inhaled ^{239}Pu. Our interest was in using the clinical data for Mayak PA workers with estimated ^{239}Pu body burdens and estimated radiation doses (alpha and gamma) to develop calibration relationships that could be used for other individuals with estimated gamma-ray doses (but not estimated ^{239}Pu intake) to estimate their ^{239}Pu incorporation and/or their radiation dose to a selected organ/tissue.

Based on exploratory analyses of the clinical data (chromosomal aberrations among peripheral blood lymphocytes, respiratory function measurements, and hematological data), empirical mathematical models were developed for use in creating calibration curves for biological dosimetry for both ^{239}Pu incorporation and alpha radiation dose (where possible). The chromosomal aberrations data appeared to be the most reliable, followed by data for peripheral lymphocyte depression. Respiratory function, although altered modestly by the combined alpha and gamma-ray exposures, was found to be the least reliable for use in biological dosimetry due to very large scatter. Our modeling of the respiratory function data is described in a recently submitted paper (Belyaeva *et al.* 2007).

Here, we briefly summarize results obtained based on chromosomal aberrations among peripheral blood lymphocytes. Stable and unstable aberrations were analyzed for a group of Mayak PA workers with body-burden estimates of ^{239}Pu in the range of 0 – 11.4 kBq. The dose-response curve for the average of the total aberrations (or for specific aberrations) was well characterized by the empirical nonlinear equation:

$$Y = E\{y\} = E\{ N - N_0\} = \alpha\, ln(X). \tag{11}$$

Here, the notation "$E\{y\}$" represents the expectation value of y. The random variable $y = N - N_0$, where the random variable N represents the measured aberrations (stable and unstable) per 100 cells scored; the random variable N_0 represents the corresponding spontaneous aberrations per 100 cells scored. D_α is the absorbed alpha-radiation dose to tracheobronchial lymph nodes;

$D_{\alpha,T}$ is a postulated threshold-absorbed alpha-radiation dose for excess aberrations, relative to the spontaneous level and conditional on chronic exposure over an extended period to both alpha and gamma radiations. The parameter α is the slope of the dose-response curve for *Y* when *ln(X)* is considered as an independent variable (e.g., *X* plotted on a logarithmic scale, i.e., log base "*e*"). The normalized dose *X* is given by

$$X = D_{\alpha}/D_{\alpha,T}. \quad (12)$$

Values of $Y < 0$ were not explored but would implicate gamma-ray ANP. The random variable *y* was modeled as having a normal distribution with mean *Y* and constant variance σ^2.

Figure 8 shows the calibration curve obtained in terms of D_{α} based on Equation 11. Data points plotted are means, and error bars are $\pm$ one standard deviation. Parameter estimates obtained were as follows: $N_0 = 1.3 \pm 0.2$ *per 100 cells*, $D_{\alpha,T} = 284 \pm 44$ *mGy*, and $\alpha = 1.63 \pm 0.04$ (has no units). Please note that the existence of a threshold for alpha radiation-induced excess aberrations long after initial exposure to ^{239}Pu is more complex than it may first appear. One has to consider that the workers whom the data represent were also chronically exposed over years to relatively low-rate external gamma rays. The gamma-ray dose was assumed to be protective.

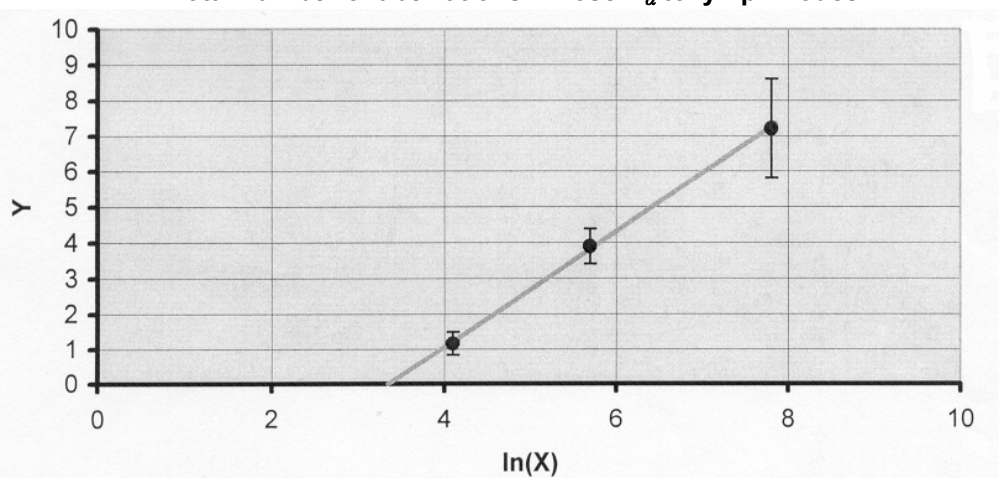


Figure 8. *Absolute threshold, calibration curve* (*Y vs. ln[X]*) *based on total chromosomal aberrations among 100 peripheral blood lymphocytes from Mayak workers chronically exposed to alpha and gamma-ray doses. The curve allows estimation of alpha radiation doses to tracheobronchial lymph nodes above a threshold* $D_{\alpha,T} = 290$ *mGy, and relates to years after initial intake of Pu. The curve is not expected to apply to early years after initial* ^{239}*Pu intake. Gamma-ray ANP over years is expected to have eliminated many of the aberrant cells induced by alpha radiation during early years of employment at the Mayak PA.*

The normalized dose, *X*, in Equation 11 can also be evaluated based on ^{239}Pu body burden (*BB*) for long-term follow-up. The corresponding threshold is given by BB_T (which replaces $D_{\alpha,T}$ in Equation 12). The resultant calibration curve is presented in Figure 9, where ^{239}Pu *BB* is in units of kilobecquerels. Model parameter obtained were $BB_T = 0.4 \pm 0.2$ kBq and $\alpha = 2.51 \pm 0.29$.

The absence of excess aberrations in Figure 8 below the threshold alpha dose $D_{\alpha,T}$ = 285 mGy is rather remarkable given that some workers had significant gamma-ray doses (in addition to significant alpha radiations doses), although they were delivered at relatively low rates over prolonged periods (Figure 10). The data are therefore quite consistent with repeated occurrence of the PAM process and repeated activation of high-fidelity DNA repair (gamma-ray ANP-

associated) under conditions of extended exposures at very low rates to gamma rays. The implications is that gamma-ray ANP eliminated alpha-radiation-induced and possibly also spontaneous aberrant lymphocytes from the body. Newly reported *in vitro* studies with human lymphocytes indicate that low-dose, gamma-ray ANP can indeed suppress spontaneous aberrant cells (micronucleated cells) (Rithidech and Scott 2007). Table 5 summarizes results from Rithidech and Scott (2007). Interestingly, the alpha radiation threshold of 284 mGy (tracheobronchial lymph node dose) in Figure 8 is quite consistent with the minimum doses to the lung, as shown in Figure 6 where gamma-ray ANP appears to be lost so far as preventing the occurrence of lung cancer in rats and dogs.

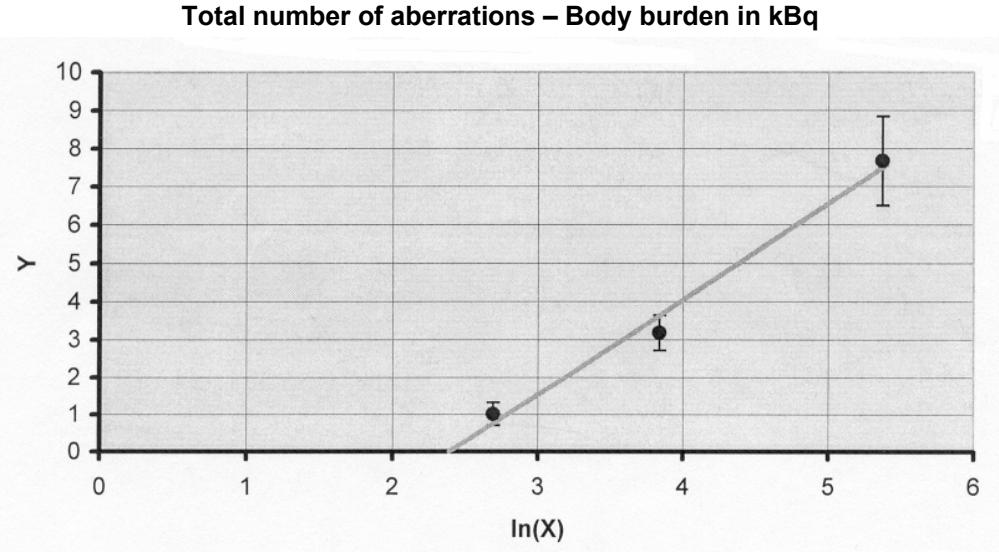


Figure 9. *Absolute threshold calibration curve [Y vs. ln(X)] based on total chromosomal aberrations among Mayak workers chronically exposed to alpha and gamma ray doses. Here the ^{239}Pu body burden is used for X in Equation 9. The curve allows estimation of the ^{239}Pu body burden for burdens above a threshold BB_T = 0.4 kBq and relates to years after initial intake of ^{239}Pu.*

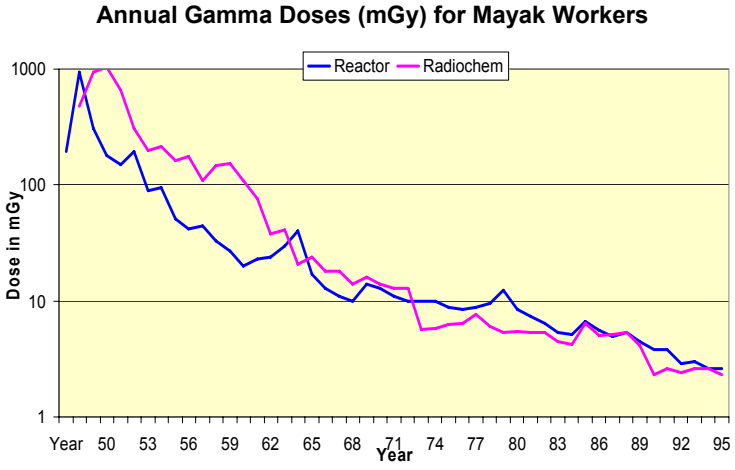


Figure 10. *Gamma-ray doses to the total body for Mayak PA workers (reactor and radiochemical physical workers). These dose rates appear to be in the dose rate range where natural protection is activated (Scott and Di Palma 2006).*

Table 5. Presence and absence of evidence for low-LET-radiation ANP against aberrant (micronucleated) cells among human lymphocytes exposed *in vitro* to different radiations based on data from Rithidech and Scott (2007).

Radiation Type	Low-LET Component to the Radiation Dose[a]	Evidence for Suppression in Aberrant Cells due to Low-LET-Radiation ANP
662-KeV gamma rays	100%	Yes
70-kVp X rays	100%	Yes
250-kVp X rays	100%	No
13.7 MeV neutrons	6% (from gamma rays)	Yes
5.9 MeV neutrons	6% (from gamma rays)	No
1.5-MeV neutrons	2% (from gamma rays)	Yes
0.44-MeV neutrons	1% (from gamma rays)	Marginal
0.22-MeV neutrons	1% (from gamma rays)	No

[a]The recoil proton contribution to the dose was not assessed.

8. Health Risks from High-Level Alpha Radiation Exposure

Health risk from high-level exposure to alpha radiation from inhaled PuO_2 aerosols has been extensively reported (Scott *et al.* 1990; Scott and Peterson 2003; Scott 2004b, 2005b,c). Here we summarize some of our more recent results (Scott 2007f) that relate to ingestion exposure to ^{210}Po.

The incident in London during November 2006 involving a lethal intake by Mr. Alexander Litvinenko of the highly-radioactive, alpha-particle-emitting isotope ^{210}Po sparked renewed interest in the area of ^{210}Po toxicity to humans. Because of the worldwide interest and wild, unfounded speculations in the news media, we quickly assembled information related to early studies of ^{210}Po toxicity and used our hazard function (HF) acute-lethality-risk model (Scott 2004b) to assess likely lethal intakes of ^{210}Po for adults. Key findings were discussed in the indicated paper by Scott (2007f) and some were also incorporated into another paper by Harrison *et al.* (2007).

The HF model (Scott *et al.* 1990; Scott and Peterson 2003; Scott 2004b, 2005b,c) was developed to address radiation exposure scenarios involving combined exposures to alpha, beta, and gamma radiations and can be used in circumstances where only one type of radiation is involved. Under a plausible set of assumptions (Scott 2007f) and using available megabecquerel (MBq) ^{210}Po intake to gray dose conversion factors, acute lethality risk vs. dose curves were developed for circumstances of human exposure to ^{210}Po by ingestion. Initial risk calculations were carried out for a reference adult male human (a hypothetical 70-kg person). Results were then modified for application to all ages (except the *in utero* child) via the use of a systemic (in blood) ^{210}Po burden that is assumed to apply to all modes of lethal intake. Because of the unavailability of acute lethality data derived from humans ingesting high levels (based on radioactivity) of ^{210}Po, the plausibility of risk calculations were evaluated based on data from studies of ^{210}Po injections in animals. The animal data, although limited, were found to be consistent with the theoretical risk calculations.

Key findings were as follows:

- Ingestion (or inhalation) of a few tenths of a milligram of ^{210}Po will likely be fatal to all exposed persons.
- Lethal intakes are expected to involve fatal damage to the bone marrow, which is likely to be compounded by severe damage caused by higher doses to the kidneys and liver.
- Lethal intakes are expected to cause severe damage to the kidney, spleen, stomach, small and large intestine, lymph nodes, skin, and testes (males) in addition to fatal damage to bone marrow.
- The time distribution of deaths is expected to depend on the level of radioactivity ingested or inhaled, with deaths occurring within about 1 month after very high levels of radioactivity intake (e.g., systemic burdens > 1 MBq/kg-body-mass) and occurring over longer periods, possibly up to or exceeding 1 year for lower but lethal intakes (systemic burdens from 0.1 to 1.0 MBq/kg-body-mass).
- Below a systemic burden estimate of 0.02 MBq/kg-body-mass, deaths from deterministic effects are not expected to occur but the risk of cancer and life shortening could be significant.
- New, funded experimental and modeling/theoretical research is needed to improve on these estimates.

We also compiled a Po-210 Information Sheet that is available through our project-supported website: http://www.radiation-scott.org/Polonium%20Fact%20Sheet_SM_C.htm.

9. Project Productivity

This project has accomplished all of its goals. We have achieved an impressive number of scientific publications and presentations (Sections 11 and 12) that include two Nova Publisher book chapters.

Annual project reports to DOE/BER were submitted in a timely manner for each the four years of this project. Our HRR model for radiation-induced cancer has attracted wide interest, as reflected by the numerous invitations for giving scientific presentations related to our research. This includes invited presentations at the National Institute of Allergy and Infectious Diseases, at Los Alamos National Laboratory, and at meetings sponsored by (1) the American Nuclear Society related to probabilistic risk analysis; (2) the DOE, related to their Low Dose Radiation Research Program; (3) the International Hormesis Society; (4) the Rio Grande Chapter of the Health Physics Society; and (4) Doctors for Disaster Preparedness. In addition, we assisted the U.K. Health Protection Agency in assessing toxicity to humans from ingested ^{210}Po that resulted in two publications that have attracted wide interest. Key information on ^{210}Po toxicity was provided to ABC News personnel at their request. Key research findings have been published in peer-reviewed journals (see Section 11).

10. Personnel Supported

A number of talented persons have contributed to this project. They are listed below.

Co-investigators at the SUBI: Dr. Z. B. Tokarskaya, Dr. G. V. Zhuntova, Dr. S. V. Osovets, Dr. Z. D. Belyaeva, Dr. V. Pesternikova (now retired), Dr. V. F. Khrokhryakov, and Dr. N. D. Okladnikova (now retired)

Co-investigators at Mayak PA: Dr. V. Syrchikov and Dr. E. K. Vasilenko

Translators at SUBI: O. Danilova, A. Danilova, and O. Lifanova

Graduate Student at LRRI: M. Haque

Undergraduate Student and Administrative Assistant at LRRI: J. Di Palma

11. Publications

Publications fully or partially supported by this DOE/BER project are listed below (PR = peer-reviewed; NPR = not peer-reviewed):

Belyaeva ZD, Osovets SV, Scott BR, Zhuntova GV, and Grigoryeva ES (2007, submitted). Respiratory system dysfunction among nuclear workers. Dose-Response. [PR]

Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, Cedergreen N, Cherian MG, Chiueh CC, Clarkson TW *et al.* (2007). Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. Toxicol Appl Pharmacol 222:122-128. [PR]

Day TK, Zeng G, Hooker AM, Bhat M, Scott BR, Turner DR, and Sykes PJ (2006). Extremely low priming doses of X radiation induced and adaptive response for chromosomal inversions in pKZ1 mouse prostate. Radiat Res 166:757-766. [PR]

Day TK, Zheng G, Hooker AM, Bhat M, Scott BR, Turner DR, and Sykes PJ (2007). Adaptive response for chromosomal inversions in pKZ1 mouse prostate induced by low doses of X radiation delivered after a high dose. Radiat Res 167:682-692. [PR]

Okladnikova ND, Osovets SV, and Kudryavtseva TI (2005a). Plutonium-239 and chromosomal aberrations in human peripheral blood lymphocytes. Radiobiology and Radioecology (in Russian) [PR].

Okladnikova ND, Scott BR, Tokarskaya ZB, Zhuntova GV, Khokryakov VF, Sirchikov VA, and Grigorieva ES (2005b). Level of stable and non-stable chromosome aberrations in incorporation of non-transportable ^{239}Pu compounds. Medical Radiology and Radiation Safety 50(6):23-32 (in Russian).[PR]

Okladnikova ND, Tokarskaya ZB, Scott BR, Zhuntova GV, Khokhryakov VF, Syrchikov VA, and Grigoryeva ES (2005c). Chromosomal aberrations in lymphocytes of peripheral blood among Mayak facility workers who inhaled insoluble forms of ^{239}Pu. Radiat Prot Dosimetry 113(1)3-13. [PR]

Osovets SV (2005). Dose rate factor at assessment and modeling of deterministic effects at external exposure. Medical Radiology and Radiation Safety 50:12-17 (in Russian). [PR]

Rithidech K and Scott BR (2007). Evidence for radiation hormesis in human lymphocytes. Dose-Response (submitted). [PR]

Sanders CL and Scott BR (2007, in press). Smoking and hormesis as confounding factors in radiation pulmonary carcinogenesis. Dose-Response. [PR]

Scott BR (2004a). A biological-based model that links genomic instability, bystander effects, and adaptive response. Mutat Res 568:129-143. [PR]

Scott BR (2004b). Health risks from high-level radiation exposures from radiological weapons. Radiat Prot Management 21(6):9-25. [NPR]

Scott BR, Walker DM, and Walker VE (2004). Low-dose radiation and genotoxic chemicals protect against stochastic biological effects. Nonlinearity Biol Toxicol Med 2:185-211. [PR]

Scott BR (2005a). Evaluating residual risks for lethality from deterministic effects after application of medical countermeasures against damage from inhaled radioactivity dispersal device released gamma-emitting radionuclides. Radiat Protec Management 22(3):7-26. [NPR]

Scott BR (2005b). Low-dose radiation risk extrapolation fallacy associated with the linear-no-threshold model. BELLE Newsletter 13(2), Part 2:22-27, December 2005. [NPR]

Scott BR (2005c). Stochastic thresholds: A novel explanation of nonlinear dose-response relationships. Dose-Response 3:547-567. [PR]

Scott, BR and Guilmette RA (2005). Radiation Toxicology, Ionizing and Nonionizing. In Encyclopedia of Toxicology (P. Wexler, editor), Elsevier Limited, Oxford, Volume 3, pp. 601-614. [NPR]

Scott BR (2006). Risk of thyroid cancer after exposure to ^{131}I in childhood. J Natl Cancer Inst 98(8):561(Correspondence). [NPR]

Scott BR (2007a). Health risk evaluations for ingestion exposure of humans to polonium-210. Dose-Response 5:94-122. [PR]

Scott BR (2007b). Low-dose radiation-induced protective process and implications for risk assessment, cancer prevention, and cancer therapy. Dose-Response 5(2):131-149. [PR]

Scott BR. (2007c). Natural background radiation-induced apoptosis and the maintenance of mammalian life on earth. In: Vinter CV (ed.), New Cell Apoptosis Research, Nova Sciences Publishers, Inc. Hauppage, NY, pp. 1-35. [NPR]

Scott BR (2007, in press). It's time for a new low-dose-radiation risk assessment paradigm — one that acknowledges hormesis. Dose-Response. [PR]

Scott BR (2007, in press). Low-dose radiation risk extrapolation fallacy associated with the linear-no-threshold model. J Human Exper Toxicol. [NPR]

Scott BR (2007). Radiation hormesis and the control of genomic instability. In: Gloscow EJ (ed), New Research on Genomic Instability. Nova Sciences Publishers, Inc. Hauppage, NY, pp. 139-180. [NPR]

Scott BR and Di Palma J (2006). Sparsely ionizing diagnostic and natural background radiations are likely preventing cancer and other genomic-instability-associated diseases. Dose-Response 5:230-255. [PR]

Scott BR, Haque M, and Di Palma J (2007, in press). Biological basis for radiation hormesis in mammalian cellular communities. International Journal of Low Radiation. [PR]

Scott BR (2007, submitted). Low-dose-radiation stimulated natural chemical and biological protection against lung cancer. Dose-Response, submitted. [PR]

Tokarskaya ZB, Zhuntova GV, Scott BR, Khokhryakov VF, Belyaeva ZD, Vasilenko EK, and Syrchikov VA (2006). Influence of radiation and non-radiation risk factors on the incidence of malignant liver tumors among Mayak PA workers. Health Phys 91(4):296-310. [PR]

12. Interactions

12.1 Invited Presentations and Other Activities by B. R. Scott that Involved Interactions with Research Peers

Invited speaker, Society of Toxicology Roundtable on low-dose extrapolation of cancer risks, 2004.

Invited presentation, “Low-dose radiation-induced protective process and implications for risk assessment, cancer prevention, and cancer therapy.” International Hormesis Conference, University of Massachusetts, Amherst, MA, June 8-10, 2004.

Invited Plenary Session presentation, “Stochastic thresholds: A novel explanation for nonlinear dose response.” Plenary session presentation, International Hormesis Conference, University of Massachusetts, Amherst, MA, June 6-8, 2005.

Invited session chair, session organizer, International Hormesis Conference, 2005, 2006, 2007.

Invited LNT Plenary Session participant, “The LNT hypothesis may have outlived its usefulness for low-LET radiation.” American Nuclear Society Meeting Plenary Session on “Has the LNT outlived its usefulness?” San Francisco, CA September 13, 2005.

Invited seminar, “The LNT hypothesis may have outlived its usefulness.” Los Alamos National Laboratory, November 10, 2005.

Invited seminar, “The LNT hypothesis vs. radiation hormesis: Implications for managing radiological terrorisms events.” NIAID/NIH, Bethesda, MD, February 14, 2006.

Invited plenary presentation, “The LNT hypothesis vs. radiation hormesis: Implications for managing radiological terrorisms events.” Rio Grande Chapter, Health Physics Society Meeting, Albuquerque, NM, June 2, 2006.

Invited presentation, “Alternative radiation risk models that include a system of protective processes.” Workshop, Diagnostic Imaging Radiation-Associated Risk-Benefit: A Resource for Clinicians, Kansas City, MO, June 10, 2006.

Invited Medical Session presentation, “Medical and therapeutic radiation hormesis: Preventing and curing cancer.” International Conference on Hormesis, June 6-8, 2006.

Invited presentation, “Low-dose/dose-rate low-LET radiation protects us from cancer.” DOE/BER Low Dose Investigator’s Workshop, Washington, DC, July 31-August 2, 2006.

Invited presentation, Radiation Carcinogenesis Workshop, NIH/NCI, Bethesda, MD, September 10-12, 2006.

Invited presentation, “Its time for a new low-dose radiation risk assessment paradigm—one that acknowledges hormesis.” The 6th International Conference on Hormesis: Implications for Toxicology, Medicine and Risk Assessment, University of Massachusetts, Amherst, MA, May 1-2, 2007.

Invited Keynote Presentation, “Polonium-210: A highly toxic substance.” Rio Grande Chapter Health Physics Society Meeting, Hilton, Santa Fe, NM, May 4, 2007.

Invited Presentation, “Low level radiation and health.” 25th Annual Meeting Doctors for Disaster Preparedness, "Category 5 Denial" vs. Confirming the Real Threats to America. Hilton Oakland Airport Hotel, Oakland, CA, August 3-5, 2007.

12.2 Other Project-Related Presentations Involving Interactions with Research Peers

Belyaeva ZD, Zhuntova GV, Osovets SV, and Grigoryeva ES. "Influence or radiation and smoking on respiratory function among nuclear enterprise Mayak PA." Fifth Russian Congress on Occupational and Health, Moscow, Russia, October 30 – November 2, 2006 (in Russian).

Di Palma J, "The implications of radiation hormesis: A student's understanding." Poster presentation, University of New Mexico Undergraduate Research and Creativity Symposium, Albuquerque, New Mexico, November 21, 2005.

Di Palma J and Scott BR, "Expected lives saved due to medical, therapeutic, environmental and other forms of radiation hormesis." Poster presentation, 5th International Conference on Hormesis: Implications for Toxicology, Medicine and Risk Assessment, University of Massachusetts, Amherst, Massachusetts, June 6-8, 2006.

Osovets SV, Belyaeva ZD, Scott BR, Tokarskaya ZB, Zhuntova GV, and Grigorieva ES. "Threshold model for estimation of external respiration indexes in combined chronic plutonium and smoking exposure on Mayak PA workers." Third International Symposium "Chronic radiation exposure: Biological and health effects", Chelyabinsk, October 24-26, 2005.

Scott BR. "New data support revised low dose extrapolation models." Presentation in Roundtable on "Low-Dose Extrapolation: Time for a Fresh Look at an Old Problem." 43rd Annual Meeting & Toxexpo™ of the Society of Toxicology, Baltimore, MD, March 21-25, 2004. Video of the roundtable available via http://www.radiation-scott.org.

Scott BR. "Low dose radiation induced protective apoptosis-mediated process." 51st Annual Meeting of the Radiation Research Society, St. Louis, Missouri, April 24-27, 2004.

Scott BR. "A little dab of radiation could protect us from cancer." Seminar presented at Lovelace Respiratory Research Institute, Albuquerque, New Mexico, June 21, 2004.

Scott BR. "Stochastic thresholds cause nonlinear dose-response curves for mutations and neoplastic transformation." DOE/BER Workshop on Biologically-Based Modeling of Human Health Effects of Low Dose Ionizing Radiation. Fred Hutchinson Cancer Research Center, Seattle, Washington, July 28-29, 2005.

Scott BR. "Background radiation may be protecting us from cancer and other diseases." Seminar presented at Lovelace Respiratory Research Institute, Albuquerque, New Mexico, August 8, 2005.

Scott BR, Haque M, and Di Palma J, "Basic research results do not support the BEIR VII conclusion regarding the linear-no-threshold risk hypothesis." Poster presentation at 9th International Conference on Environmental Mutagens and 36th Annual Meeting of the Environmental Mutagen Society, San Francisco, California, September 3-8, 2005.

Scott BR, "Some new low-dose studies should relate to mechanistic basis for radiation hormesis." Low Level Radiation Effects Summit, Carlsbad, New Mexico, Jan 15-18, 2006.

Scott BR and Di Palma J, "Biological-based cancer hormetic relative risk model and implications for low dose radiation risk assessment, cancer prevention, and cancer therapy." Poster presentation, Low Dose Investigator's Workshop, Washington, D.C., July 31-August 2, 2006.

Tokarskaya ZB, Zhuntova GV, Scott BR, Belyaeva ZD, Khokhryakov VF, and Syrchikov VA. Factors of lung cancer risks in nuclear Mayak PA workers. 11th International Congress of the International Radiation Protection, Madrid, Spain, May 23-28, 2004.

Tokarskaya ZB. “Lung cancer in human and ionizing radiation (review of current literature).” Presentation given at the Southern Urals Biophysics Institute, June 13, 2006.

Zhuntova GV, Tokarskaya ZB, Belyaeva ZD, and Sirchikov VA. "Role of radiation exposure in stomach cancer occurrence in Mayak PA personnel." Third International Symposium “Chronic radiation exposure: Biological and health effects”, Chelyabinsk, October 24-26, 2005.

Zhuntova GV, Tokarskaya ZB, Belyaeva ZD, Syrchikov VA, and Grigoryeva ES. "Influence of radiation and non-radiation factors on pancreatic cancer incidence among Mayak PA workers. Second European Congress on Radiation Protection, Paris, France, May 15-19, 2006.

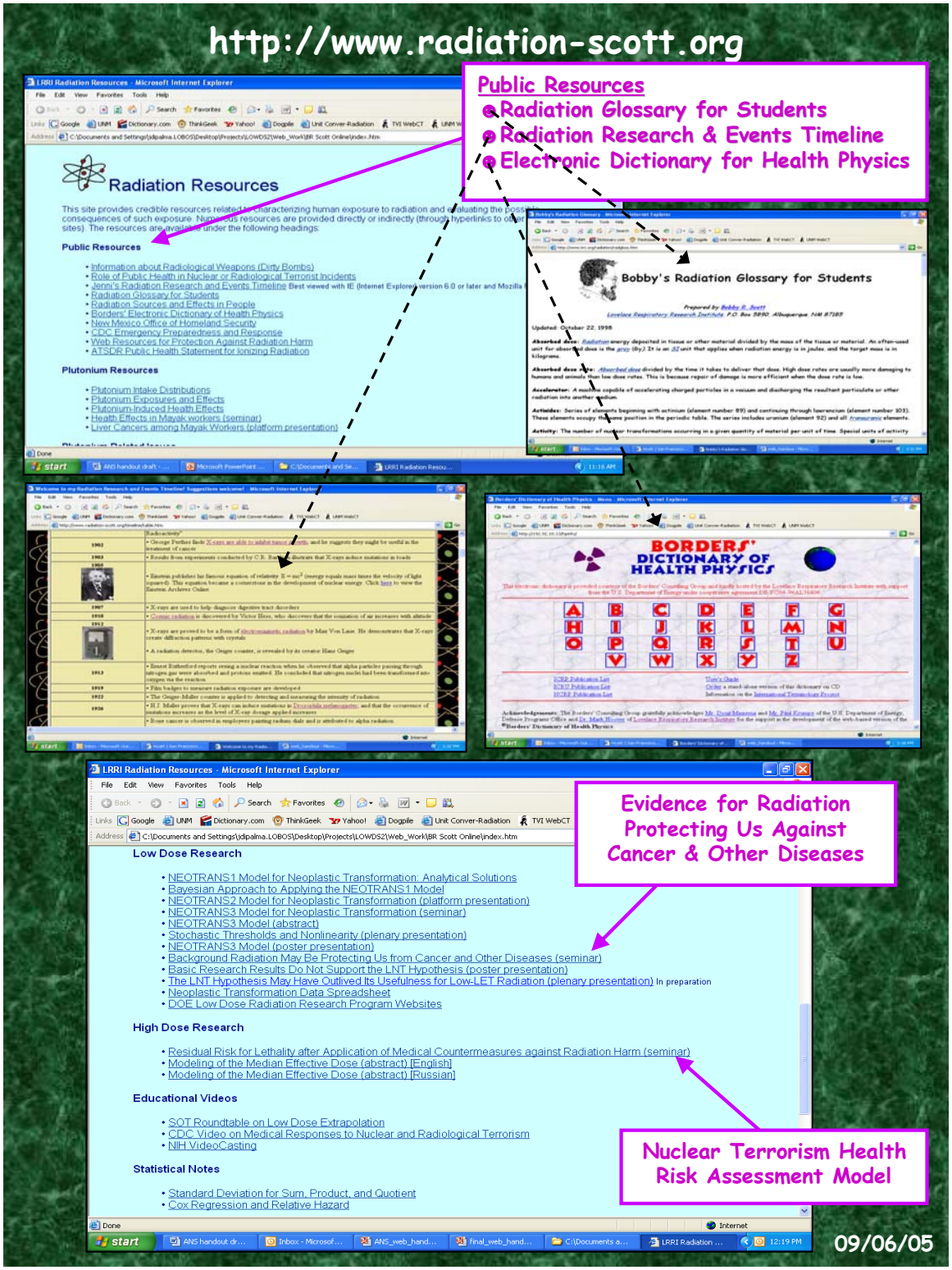
Zhuntova GV, Tokarskaya ZB, Belyaeva ZD, Syrchikov VA, and Grigoryeva ES. "Radiation and non radiation risk factors effect on the large intestine cancer morbidity among Mayak nuclear workers." 28th International Congress on Occupational Health, Milan, Italy, June 11-16, 2006.

Zhuntova GV, Tokarskaya ZB, Belyaeva ZD, Grigoryeva ES, and Syrchikov VA. “Kidney cancer risk factors among Mayak PA workers”, Fourth International Scientific-and-Practical Conference, Medical and Ecological Effects of Ionizing Radiation, Tomsk, Russia, April 11-13, 2007 (in Russian).

Zhuntova GV, Tokarskaya ZB, Belyaeva ZD, Grigoryeva ES, and Syrchikov VA. "Multivariate analysis of radiation and non-radiation risk factors influence on kidney cancer incidence among Mayak PA workers. 13th International Congress of Radiation Research, San Francisco, CA, USA July 7-12, 2007.

12.3 Project Related Website

Our project-related website provides additional information related to radiation inducted stochastic and deterministic effects: http://www.radiation-scott.org .


http://www.radiation-scott.org
Public Resources
Radiation Glossary for Students
Radiation Research & Events Timeline
Electronic Dictionary for Health Physics
Radiation Resources
Public Resources
Information about Radiological Weapons (Dirty Bombs)
Role of Public Health in Nuclear or Radiological Terrorist Incidents
Jenni's Radiation Research and Events Timeline
Radiation Glossary for Students
Radiation Sources and Effects in People
Borders' Electronic Dictionary of Health Physics
New Mexico Office of Homeland Security
CDC Emergency Preparedness and Response
Web Resources for Protection Against Radiation Harm
ATSDR Public Health Statement for Ionizing Radiation
Plutonium Resources
Plutonium Intake Distributions
Plutonium Exposures and Effects
Plutonium-Induced Health Effects
Health Effects in Mayak workers (seminar)
Liver Cancers among Mayak Workers (platform presentation)
Bobby's Radiation Glossary for Students
BORDERS' DICTIONARY OF HEALTH PHYSICS
LRRI Radiation Resources - Microsoft Internet Explorer
Low Dose Research
NEOTRANS1 Model for Neoplastic Transformation: Analytical Solutions
Bayesian Approach to Applying the NEOTRANS1 Model
NEOTRANS2 Model for Neoplastic Transformation (platform presentation)
NEOTRANS3 Model for Neoplastic Transformation (seminar)
NEOTRANS3 Model (abstract)
Stochastic Thresholds and Nonlinearity (plenary presentation)
NEOTRANS3 Model (poster presentation)
Background Radiation May Be Protecting Us from Cancer and Other Diseases (seminar)
Basic Research Results Do Not Support the LNT Hypothesis (poster presentation)
The LNT Hypothesis May Have Outlived Its Usefulness for Low-LET Radiation (plenary presentation) In preparation
Neoplastic Transformation Data Spreadsheet
DOE Low Dose Radiation Research Program Websites
High Dose Research
Residual Risk for Lethality after Application of Medical Countermeasures against Radiation Harm (seminar)
Modeling of the Median Effective Dose (abstract) [English]
Modeling of the Median Effective Dose (abstract) [Russian]
Educational Videos
SOT Roundtable on Low Dose Extrapolation
CDC Video on Medical Responses to Nuclear and Radiological Terrorism
NIH VideoCasting
Statistical Notes
Standard Deviation for Sum, Product, and Quotient
Cox Regression and Relative Hazard
Evidence for Radiation Protecting Us Against Cancer & Other Diseases
Nuclear Terrorism Health Risk Assessment Model
09/06/05

13. Transitions

Through our DOE/BER-supported research, we have assisted the scientific communities worldwide in becoming better aware of health risks associated with exposure of humans to Pu isotopes. In addition, we have informed the research community about the serious consequences of using the LNT cancer risk model for regulating radiation worker and the public exposures to ionizing radiation. The LNT risk model creates phantom excess risk at low doses for most exposure scenarios of interest that involve low-LET radiation or low- plus high-LET radiation. This is especially true for exposures involving residual radioactivity after remediation of radionuclide-contaminated DOE sites.

Through our many publications, seminars, and presentations at scientific meetings we have alerted the scientific community to the enormous potential for using low-LET-radiation ANP for both preventing future cancers in high risk groups of individuals and for the possibility of combining low-dose-radiation ANP with other agents (e.g., biological [gene therapy] and/or chemical [e.g., resveratrol]) that sensitize cancer cells to undergo apoptosis in order to cure existing cancer with a low-dose paradigm (e.g., multiple low, harmless doses of diagnostic X-rays plus resveratrol). Low-dose radiation therapy would eliminate the type of patient suffering that is associated with the current high-dose radiation and chemotherapies which destroys large amounts of normal tissue. Multiple, essentially harmless doses (milligray quantities) of X-rays spread over an extended period, for example, could be used in treating lung and other cancers.

Our risk modeling of deterministic radiation effects proved to be very beneficial to the world community after the death of the Mr. Alexander Litvinenko last November in London, due ^{210}Po exposure. We began quickly researching this largely forgotten alpha-emitting radioisotope. We also collaborated with other radiation research experts including scientist at the Health Protection Agency (HPA) in London responsible for managing the incident. The research led to a publication on ^{210}Po toxicity (Scott 2007f) as well as another joint publication with John Harrison (first author) of the HPA entitled "Polonium-210 as a Poison" that was published in the March 2007 issue of the Journal of Radiological Protection. A feature article about our timely ^{210}Po research entitled "One of the Most Dangerous Radioisotopes Known to Man: Polonium-210" was published by our Institute in its Spring 2007 issue of the Gift of Breath newsletter that was circulated in the United States. We also assisted ABC News personnel in understating the toxicity of ^{210}Po to humans at their request.

14. Acknowledgments

We are very grateful to the Department of Energy (DOE/BER) for having supported our research in this project and in the previous projects with the same titles. Some of this earlier research was also supported by the DOE Office of Environmental Management via the Environmental Management Science Program. We are also very grateful for that support. We have benefited greatly in this project from knowledge gained in our earlier projects in the DOE/BER Low Dose Radiation Research Program. Knowledge provided in this report and some of our many project-related publications represent an integration of all of the stated research and is likely to benefit mankind for many years to come.

15. Patents

No patents were developed in this project.

16. Future Work

Although there is need for future work related to toxicity to humans from low- and high-level exposures to radionuclides and external radiation (e.g., gamma rays, neutrons, protons), there is currently no DOE research program that is funding such research. New research that focuses on cancer prevention and cancer cures using low-dose-radiation ANP would also be quite beneficial to mankind. Modeling/theoretical and experimental research related to evaluating residual risk of acute lethality after application of medical countermeasures following a dirty bomb incident involving the intake of large quantities of radionuclides would also be quite beneficial. While our research group is quite capable of conducting such research, currently there are no DOE research programs that support such research. Epidemiological studies specifically designed to reveal low-dose-radiation ANP would also be quite beneficial in light of the misleading information published in the BEIR VII Report regarding cancer risks from low dose radiation. A combined case-control and cohort design would be expected to be optimal, allowing for controlling for confounders and addressing the systematic error introduced by including low-dose persons (possibly with ANP) in the control (unirradiated) group. Our research team is also quite capable of conducting such studies and would be happy to participate in such research should funding opportunities become available in the near future.

17. References

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APPENDIX A

Stochastic Deposition of PuO_2 Aerosols in the Respiratory Tract and Respirator Filter Efficiencies for Preventing Intake via Inhalation

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Abstract

This appendix summarizes previous work carried out related to theoretical modeling of plutonium-dioxide (PuO_2) aerosols deposition in the human respiratory tract and experimental results related to respiratory filter efficiencies for preventing inhalation intake of the high-density material (surrogates for PuO_2). Results that follow were reported in a previous Department of Energy project final report with the same title as the current renewal project. The results are being reported here because of their relevance to the current project.

1. Theoretical Approach to Estimating Plutonium Dioxide Intake via Inhalation

Here, we summarize our theoretical approach to calculating radioactivity intake distributions for populations of individuals with varying breathing characteristics. The approach helps to explain the large variability in radioactivity intake by inhalation observed in association with the Los Alamos, New Mexico, incident on March 16, 2000 (Table 1), where a glovebox leaked high-specific-activity, alpha-emitting (HAS-αE) plutonium dioxide-238 ($^{238}PuO_2$) to room air, which was inhaled by at least some of the eight workers in the room. Scientists at our Institute participated in characterizing the source term for the Los Alamos incident.

Table 1. Nasal-swipe measurement for ^{238}Pu for eight Los Alamos workers involved in the March 16, 2000, glovebox incident at the Pu Processing and Handling Facility (TA-55) (DOE, 2000).

Affected Employee[a]	Nasal Swipe Results (dpm)[b] (left nostril/right nostril)
ET	99,271/68,536
RCT-1	5,807/1,161
RCT-2	1,048/193
CPT-1	2,502/NDA[c]
CT-2	159/NDA[c]
CPT-3	NDA/NDA[c]
CPT-2	NDA/NDA[c]
CT-1	NDA/NDA[c]

[a]ET = Electrical Mechanical Technician (one person); RCT = Radiological Control Technician (two persons); CPT = Chemical Process Technician (three persons); CT = Chemical Technician (two persons). [b]dpm = disintegrations per minute; [c]NDA = no detected amount.

1.1 Single-Particle-Associated Radioactivity Intake Distributions

We indicate the single-particle-associated radioactivity intake distribution as $f_1(A|pop, aero)$, where A is the radioactivity intake associated with the single particle deposited in the respiratory tract (e.g., specific region) via inhalation; the abbreviation *pop* (for populations) accounts for all the key population characteristics (distributions); and the abbreviation *aero* (for aerodynamic) accounts for the aerodynamic characteristic of the aerosol considered. The vertical bar "|" is used to indicate that the amount of radioactivity, A, deposited in the respiratory tract as a result of a single-particle deposition event depends on the population characteristics (*pop*) in addition to the aerodynamic characteristic (*aero*) of the aerosol. For a heterogeneous population, *pop* accounts for all relevant distributions (e.g., distribution in breathing frequencies, in tidal volumes, in fraction of air entering via the nose, etc.). For reference individuals (e.g., a

70-kg reference adult male), *pop* would then relate to fixed values for these variables assigned to the reference individual. Our early publications were based on reference individuals (Scott *et al.* 1997; Scott and Fencl 1999). This work relates to populations (i.e., a large group) of individuals (e.g., adult male workers involved in light, work-related exercise).

For a reference individual, the distribution $f_1(A|pop, aero)$ depends on the region of the respiratory tract, the individual's age, the physical activity level, and the particle size distribution $\Phi(d)$, where d is the aerodynamic diameter. For a heterogeneous population (e.g., adult male workers) with different breathing characteristics, the calculated distribution $f_1(A|pop, aero)$ depends on the distributions assigned to key respiratory variables and parameters. Our calculations (explained in detail in Aden and Scott 2003) are based on distributions published by Bolch and colleagues (2001) that relate to their stochastic version of the International Commission on Radiation Protection (ICRP) 66 respiratory tract dosimetry model (ICRP 1994).

The product $f_1(A|pop, aero)dA$ gives the fraction of single-particle associated radioactivity intakes (via single particles) with radioactivity in the very small interval (A, $A+dA$). The distribution $f_1(A|pop, aero)$ does not depend on particle presentation (defined below), Ω, but accounts for particle inhalability, $P_I(d)$, and particle deposition probability, $P_{Dep}(d)$ (Scott *et al.*, 1997; Scott and Fencl, 1999). In addition, both $P_I(d)$ and $P_{Dep}(d)$ depend on particle density, size, and shape.

The presentation, Ω, is the mean number of particles presented to a human receptor for inhalation over the period of interest (Scott *et al.*, 1997). For the stochastic intake (StI) paradigm, the number of particles presented can be presumed to come from a Poisson distribution (Scott *et al.* 1997; Scott and Fencl, 1999). We have used the notation $P(n|\Omega)$ to indicate the Poisson probability that exactly the number, n, of airborne particles of interest are presented to an individual for inhalation during the period of interest. $P(n|\Omega)$ is useful for conducting evaluations over many inhalations (breaths) and is related to the particle availability, $P_A(d)$, which is associated with a single breath (Scott *et al.*, 1997).

The $P_A(d)$ represents the probability that a particle of interest will be contained in a tidal volume of air just before inhaling (Scott *et al.*, 1997). Calculated availability of monodisperse, low-specific-activity, alpha-emitting (LSA-αE) and HSA-αE PuO_2 aerosols is presented in Figure 1 as a function of particle equivalent-volume diameter, d_{ev}, when the air radioactivity concentration is 1 DAC (derived air concentration) (Scott *et al.*, 1997). Calculations were based on a 1.3-L tidal volume, a particle density of 10 g/cm^3 (Kotrappa *et al.*, 1972; Raabe, 1994), and ICRP Publication 30 DACs (ICRP, 1979).

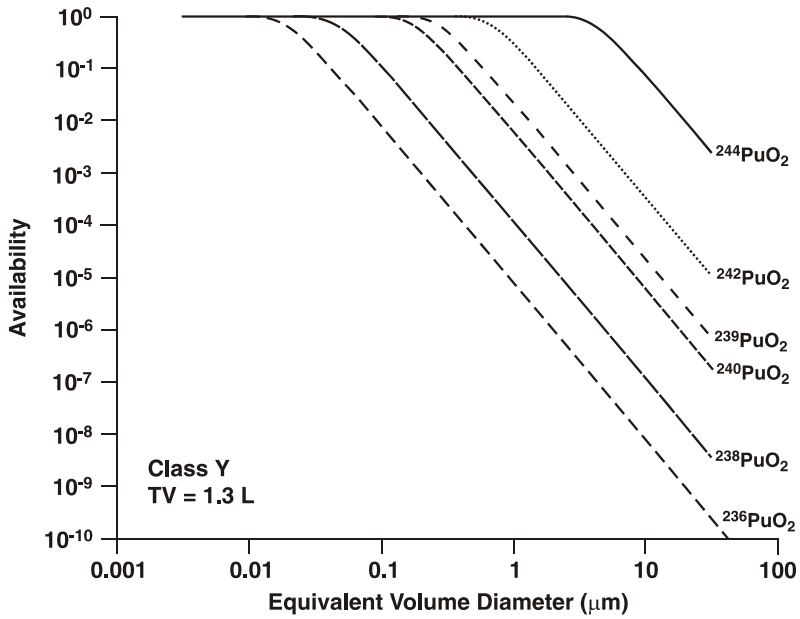

Figure 1. Availability of airborne, monodisperse, PuO_2 particles evaluated at the derived air concentration (Scott *et al.*, 1997).

The d_{ev}, is the diameter of a sphere with the same density and mass as the particle of interest. Use of equivalent-volume diameter facilitates evaluating particle radioactivity for irregularly shaped particles. We calculate equivalent-volume diameter using mathematical equations presented in ICRP Publication 66 (1994).

For the StI paradigm, where at most relatively small numbers of airborne particles are inhaled, the particle presentation Ω and associated Poisson probability, $P(n|\Omega)$, are important in characterizing the variability of the unconditional intake of radioactivity (Scott and Fencl, 1999).

1.2 Convolution Method for Multiple Particle Intakes

The radioactivity intake distribution for inhaling two particles of interest, sampled by inhalation from an airborne particle-size distribution, $\Phi(d)$, is given by $f_2(A|pop, aero)$ where

$$f_2(A \mid \text{pop}, \text{aero}) = \int_0^A f_1(x \mid \text{pop}, \text{aero})\, f_1(A - x \mid \text{pop}, \text{aero})\, dx. \quad (1)$$

The integral and those that follow can be evaluated numerically as described elsewhere (Aden and Scott 2003). The radioactivity intake distribution for inhaling three particles of interest, sampled from a given $\Phi(d)$, is given by $f_3(A)$, where

$$f_3(A \mid \text{pop}, \text{aero}) = \int_0^A f_1(x \mid \text{pop}, \text{aero})\, f_2(A - x \mid \text{pop}, \text{aero})\, dx. \quad (2)$$

Similarly, for $n + 1$ particles the radioactivity intake distribution is given by

$$f_{n+1}(A \mid \text{pop}, \text{aero}) = \int_0^A f_1(x \mid \text{pop}, \text{aero})\, f_n(A - x \mid \text{pop}, \text{aero})\, dx. \quad (3)$$

We were not able to develop an analytical solution for $f_1(A|pop, aero)$. However, an empirical distribution was developed based on particle-size-dependent deposition efficiencies (adjusted for inhalability) associated with our stochastic version (Crystal Ball based [Decisioneering, 1996]) of the ICRP 66 respiratory tract deposition model. The convolutions for multiple-particle intake were carried out via the standard Monte Carlo method using our Crystal Ball program developed by Jay Aden and Pamela Longmire (both were graduate students when they were at our Institute). The use of Crystal Ball software facilitates the later addition of risk distribution calculations. As opposed to a programming language such as Fortran Visual Basic or C++, Crystal Ball provides a much more user-friendly and efficient way for obtaining summary statistics and graphics for the distributions generated, and facilitates outputting distribution data generated for use in other analyses. It also allows the parameter values and distributions to be easily adjusted for other genders and age groups. The Crystal Ball software runs inside of Excel, which allows use of Excel macros. The output of the Monte Carlo evaluations is an empirical radioactivity intake distribution that varies because of sampling, via inhalation, from a distribution $\Phi(d)$ and because of sampling over-distributions of respiratory parameters and variables representative of the population of interest.

Particle radioactivity was calculated via a macro that accounted for particle shape, mass, etc., and converted aerodynamic diameter d to the equivalent-volume diameter d_{ev}.

Inhaling relatively small amounts of PuO_2 via resuspended PuO_2-contaminated soil could cause lung, liver, and bone cancers in the general population (e.g., citizens who live near Rocky Flats). Inhaling large amounts of PuO_2 in the nuclear workplace could lead to radiation deterministic effects such as radiation pneumosclerosis (Okladnikova, 1994b). Radiation pneumosclerosis is a disease observed among Mayak Production Association (PA) workers that inhaled large amounts of ^{239}Pu, possibly milligram quantities (Scott and Peterson, 2003). Thus,

for years, environmental and workplace exposure to Pu and associated health risks have been topics of interest to many scientists and clinicians (Altman *et al.*, 1992; DOE/EPA/CDPHE, 1996; Gilbert *et al.*, 2000; Hoover and Newton, 1993; Kreisheimer *et al.*, 2000; Koshurnikova *et al.*, 2000; Jones and Zhang, 1994; NCRP, 1996, 1999; Newton *et al.*, 1986, 1987; Okladnikova and Burak, 1993; Okladnikova *et al.*, 1992a, b, 1993, 1994a, b; RSALOP 1999a-d; Scott, 1995; Scott *et al.*, 1990, 1993; Tokarskaya and Basogolov, 1995; Tokarskaya and Khokhryakov, 1975; Tokarskaya *et al.*, 1995, 2002; US DOE, 1996)

We carried out basic and applied research related to developing improved radiation dosimetry and risk estimates to facilitate environmental management of Pu-contaminated sites. Our early research focused largely on the StI paradigm, where some of the at-risk population may inhale relatively large amounts of radioactive particles while other may inhale none. Similar consideration would apply to polonium-210 aerosols. Some consideration has also been given to the deterministic intake (DI) paradigm, where every member of the at-risk population would be expected to inhale large numbers of radioactive particles. As may be expected, the StI paradigm relates to relatively small numbers of LSA-αE or HSA-αE PuO_2 particles being presented for inhalation (e.g., particles that penetrate respirator filters when carrying out deactivation and decommissioning [D&D] operations in PuO_2 environments). Examples of HSA-αE particles are $^{236}PuO_2$, $^{238}PuO_2$, $^{240}PuO_2$, $^{241}AmO_2$ (americium-241 dioxide) and $^{242}CmO_2$ (curium-242 dioxide). Examples of LSA-αE particles are $^{239}PuO_2$, $^{242}PuO_2$, and $^{244}PuO_2$ (Scott *et al.*, 1997).

For the DI paradigm, every person who inhales the radionuclide-contaminated air takes in radioactivity with essentially a probability equal to 1. There is no issue of whether a person has intake. In contrast, with the StI paradigm, some individuals may have intakes but others may not for the same incident, same duration of exposure, and same location (e.g., same room). Our research has demonstrated that for the StI paradigm, point estimates of radioactivity intake and associated dose are highly unreliable, and instead should be replaced by distributions for possible intakes and doses (Scott *et al.*, 1997; Scott and Fencl, 1999; Aden and Scott, 2003). With the distribution framework, each possible intake of radioactivity as well as each absorbed radiation dose will have an associated probability.

We previously constructed theoretical, conditional PuO_2 intake (via inhalation) distributions for adult males engaged in light work-related exercise, using the convolution method briefly summarized below. The conditioning relates to the number of particles inhaled. For example, the conditioning could be that exactly 10 PuO_2 particles are inhaled and deposited in the respiratory tract (or specific region or subregion) from airborne PuO_2 (with a specified particle size distribution and physical characteristics). Table 2 gives summary statistics for calculated radioactivity intake for exactly 1, 10, or 100 PuO_2 particles depositing throughout the respiratory tract of adult male workers engaged in light work-related exercise and not wearing respirators (Aden and Scott, 2003). For these evaluations, variability between different individuals in physiological and anatomical characteristics was accounted for using a stochastic version of the ICRP 66 respiratory tract deposition model implemented with Crystal Ball software. Our stochastic version of the ICRP 66 particle deposition model is based on parameter and input variable distributions established by Bolch *et al.* (2001) in developing their FORTRAN-based, stochastic model known as LUDUC (LUng Dose Uncertainty Code). Our Crystal Ball software allows for particle polydispersity, which Bolch *et al.* (2001) did not address.

Results presented in Tables 2 and 3 apply to a population (large group) of adult male worker engaged in light, work-related exercise. Variability indicated relates to sampling from a polydisperse particle size distribution and over a population with differing breathing characteristics. Evaluations were carried out for a log-normal distribution of PuO_2 particle size distributions with an activity median aerodynamic diameter of 5 μm and geometric standard deviation of 2.5.

Table 2. Statistics for radioactivity from the deposition of 1, 10, and 100 particles (par) of weapons grade Pu in the respiratory tract of adult males engaged in light work-related exercise. Statistics are based on data measured in becquerels.

Statistics	1 par	10 par	100 par
Mean/n*	1.67	1.73	1.68
Median/n*	0.1	0.631	1.39
Mode/n*	0.03	0.172	0.964
Std. Dev	9.75	34.4	104
Variance/n*	95	119	108
Skewness	11.80	5.17	1.61
Kurtosis	168.37	38.5	6.61
CV[a]	5.83	1.99	0.62
Minimum	<0.01	0.10	19.1
Maximum	172	446	1060
Std. Error	0.10	0.34	1.04

*Indicated statistic has been divided by the number, *n* of particles deposited.
[a]Coefficient of Variability

Table 3. Statistics associated with calculated respiratory tract regional radioactivity intake for exactly 1, 10, or 100 particles of PuO_2 depositing in the respiratory tract of adult males engaged in light work-related exercise.

	Particles (n)	Mean/n	Median/n	Var*/n	Skew-ness	Kur-tosis	Coeff. variation	Min	Max
	1	2.6	0.14	187	12.63	206.5	0.19	0	325
ET1[a]	10	2.64	0.10	246	4.81	33.53	1.88	0.22	632
	100	2.71	0.22	288	1.63	6.39	0.63	36.95	1,375
	1	2.56	0.09	331	16.94	350	0.14	0	470
ET2	10	2.26	0.85	228	5.9	50.2	2.11	0.13	855
	100	2.42	0.19	278	1.76	6.72	0.69	20.82	1,407
	1	0.28	0.041	1.44	21.43	758	0.23	0	52.19
BB	10	0.275	0.17	1.44	6.75	79	1.38	0.09	63.6
	100	0.283	0.25	1.86	2.51	11.95	0.48	7.18	143
	1	0.06	0.014	0.017	6.37	64.4	0.43	0	2.4
bb	10	0.059	0.048	0.018	2.03	9.77	0.73	0.03	4.82
	100	0.059	0.057	0.018	0.59	3.64	0.23	2.22	14.1
	1	0.02	0.005	0.0016	5.58	47.7	0.45	0	0.78
AI	10	0.02	0.017	0.002	1.75	8.01	0.7	0.01	1.6
	100	0.02	0.02	0.002	0.57	3.52	0.22	0.88	4.18

[a]Regions: ET (1 & 2), extrathoracic; BB, bronchial; bb, bronchiolar; AI, alveolar.
[b]Var = variance.

The results in Table 2 and 3 apply to persons not wearing respirators. In Table 3 we divided the following statistics by the number of particles depositing in the indicated region of the respiratory tract: mean, median (Med), and variance (Var). We call the respective results: normalized mean, normalized median, and normalized variance. It can be seen that the normalized mean is quite stable for a given region (i.e., it is not influenced very much by the number of particles depositing in a given region). This is also true of the normalized variance. It can also be seen that with penetration into the respiratory tract, the mean radioactivity per particle (normalized mean) depositing greatly decreases between the extra thoracic region (ET) and the bronchial region (BB). Similar decreases are indicated for going from the BB to the bronchiolar (bb) region and from the bb region to the alveolar (Al) region. The reductions are not due to a reduced number of particles (since this number was fixed in our calculations) but to a shift in the particle size distribution toward smaller particles with penetration into the respiratory tract.

In our previous publication (Aden and Scott 2003), we have compared our generated distributions for regional deposition efficiencies to deterministic results (point estimates) generated with the LUDEP computer program used by many to implement the ICRP 66 deposition calculations. We found that LUDEP appears to involve a systematic error for the efficiency at which large particles deposit in the deep regions of the respiratory tract (greatly overestimating deposition). This systematic error would contribute to overestimating the risk for cancer induction when evaluated with a model that depends on absorbed dose to the pulmonary region. Further, it appears that LUDEP evaluates radioactivity deposition in the deep lung based on scaling the radioactivity presented for inhalation by the averaged particle deposition efficiency for the region. This appears to introduce systematic error in that the radioactivity distribution changes with penetration into the respiratory tract (See Aden and Scott 2003), whereas the method apparently used in LUDEP to calculate radioactivity deposition seems to assume that the radioactivity distribution (when normalized) is independent of the respiratory tract region.

1.3 Using Conditional Intake Distributions

The conditional distributions can be used to evaluate probabilities for exceeding, via inhalation, the intake of a specified amount of radioactivity (e.g., Annual Limit on Intake [ALI]). One of our earlier publications (Scott and Fencl, 1999) shows how to carry out the necessary calculations as well as how to address mixtures of different alpha-emitting isotopes.

2. Respiratory Filter Penetration Concerns

Earlier, it was recognized through routine monitoring of workers at Rocky Flats that employees who carried out D&D work occasionally showed Pu in their urine even though they were well protected (via special protective garments and devices [e.g., respirators]) in conducting their job duties. We have previously hypothesized that small high-density PuO_2 particles might with low frequency penetrate respirator filters, and over time the intake of PuO_2 could increase to detectable levels in urine.

To test the indicated hypothesis, Yue Zhou and Yung-Sung Cheng previously conducted experimental, respirator filter penetration studies using high-density metal dioxide particles (CeO_2, density = 7.65 g/cm^3; HfO_2, density = 9.68 g/cm^3; and PbO_2, density = 9.64 g/cm^3). Test aerosols were generated by a small-scale powder disperser (SSPD, Model 3433, TSI Inc., St. Paul, MN). The SSPD consisted of a rotational disk coated with powder and a suction tube to take up the powders from the disk and disperse them as an aerosol. The aerosol was delivered at a flow rate of 22.5 L/min and passed into an 85Kr discharger tube to neutralize the particles, through a dilutor to maintain proper concentration, and into the test chamber where a flow laminator distributed the flow evenly. The test chamber was a cylinder (12 in. I.D. x 17 in. long), and the aerosol consternations were uniform. Pre-filter and post-filter probes were located in the

test chamber to sample the aerosol. An aerodynamic particle sizer (APS, TSI Inc.) was connected to the sample probes and measured the particle concentrations before and after the filter, from which the filter penetration frequency could be calculated.

Three types of respirator filters were used in this study, according to the recommendations of the Department of Energy (DOE) laboratories contacted: 1) MSA P100 Multigas (Model 00817887, MSA, Pittsburgh, PA), 2) Survivair 7000 Series MC-Multi-Contaminant/P100 (Survivair, Santa Ana, CA), and 3) 3M 6000 Series Particulate P100 (Model 2091, 3M, St. Paul, MN). Hundreds of thousands of inlet particles were used.

Mean penetration frequencies are presented in Table 4. The best performing filter was the 3M. The worst performing filter was the Survivair. Thus, our results suggest that the Pu appearing in urine of workers at Rocky Flats may have arisen via respirator filter penetration events for small PuO_2 particles (density approximately 10 g/cm^3). As the number of work days (with protective garments and devices) in PuO_2 environments increases, the intake of PuO_2 would be expected to increase to a level possibly detectable in urine. Thus, routine monitoring of workers' urine (as appears is already being done at DOE facilities such as Rocky Flats) appears to be a good defendable practice.

Table 4. Measured respirator filter penetration frequencies for high-density metal surrogates for PuO_2[a]

	Average particles penetrating filter per million inlet particles		
High-density Metal	3M	MSN	Survivair
CeO_2	6.3	43.4	616
HfO_2	6.6	34.6	1178
PbO_2 (study #1)	6.9	6.4	53.8
PbO_2 (study #2)	15.3	10.3	35.4

[a]Most airborne particles had aerodynamic diameters less than 12 μm.

2.1 DI Paradigm: Inhaling PuO_2 in Resuspended Dust

We have conducted similar evaluations for inhalation exposure of members of the public to PuO_2-contaminated soil. We have only carried out a calculation for reference male adults. However, the results can also be applied to reference female adults for a first approximation. Thus, the variability addressed here relates only to sampling from a polydisperse particle size distribution. Because the radioactivity is diluted by mixing with soil, the specific activity of the contaminated soil can be much lower than for pure PuO_2. Thus, to inhale the same amount of radioactivity as that of pure metal PuO_2, large numbers of contaminated dust particles may need to be inhaled (possibly over many years). We were interested in starting from the StI paradigm and systematically increasing the number of particles inhaled until we crossed the boundary between the StI and DI paradigms.

Thus, for PuO_2-contaminated soil we have evaluated conditional radioactivity intake distributions. We started from a single dust particle and by convolution generated conditional intake distributions for up to 5 million dust particles. Again, the numerical convolution approach was used. For Pu-contaminated soil, we used a density of 2 g/cm^3 and a reference specific activity of 1 Bq/g (27 pCi/g) for PuO_2-contaminated dust particles. With this approach, results can be scaled to any specific activity of interest for the soil/PuO_2 combination. Evaluations were carried out for reference adult males engaged in light exercise based on respiratory tract parameters for males but are assumed to apply to both sexes.

Results for 100, 10,000, and or 1,000,000 dust particles are presented in Figures 2–4.

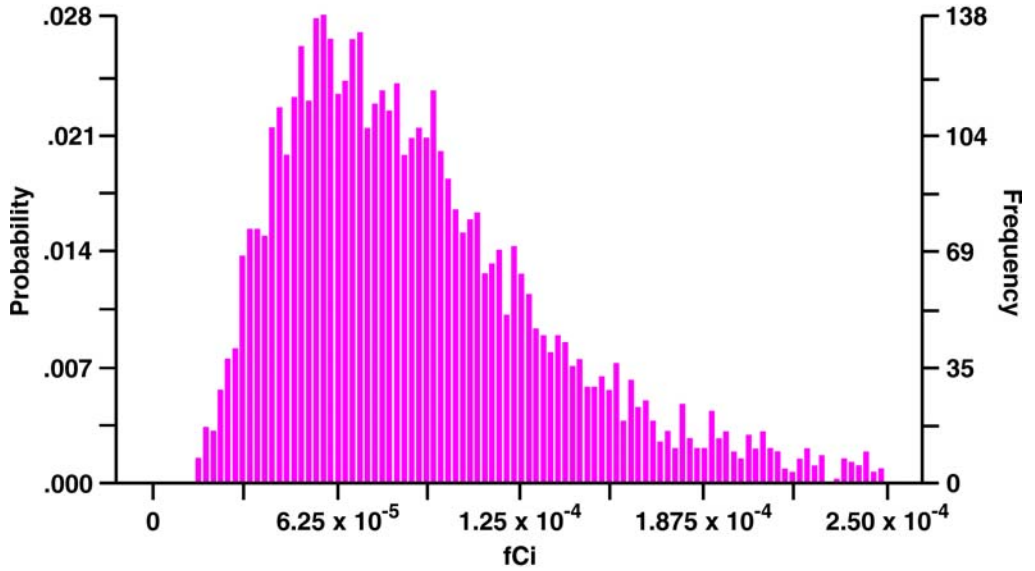

Figure 2. Conditional radioactivity-intake distribution, $f_{100}(A|pop, aero)$, for a 100 PuO_2-contaminated dust-particle intake by reference adults (Scott *et al.*, 1999) when the contaminated dust has a specific activity of 1 Bq/g. The distribution was evaluated numerically based on 10,000 Monte Carlo trials, a polydisperse size distribution with an activity median aerodynamic diameter of 1 μm, and a geometric standard deviation of 2.5.

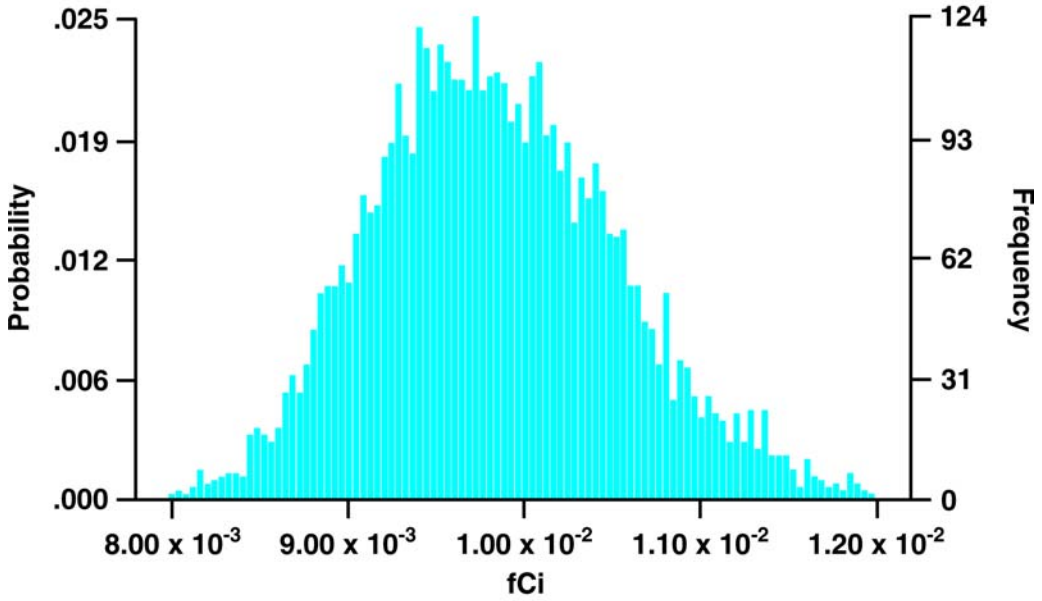

Figure 3. Conditional radioactivity-intake distribution, $f_{10,000}(|pop, aero\ A)$, for a 10,000 PuO_2-contaminated, dust-particle intake by reference adults (Scott *et al.*, 1999) when the contaminated dust has a specific activity of 1 Bq/g. The distribution was evaluated numerically based on 10,000 Monte Carlo trials, a polydisperse size distribution with an activity median aerodynamic diameter of 1 μm, and a geometric standard deviation of 2.5

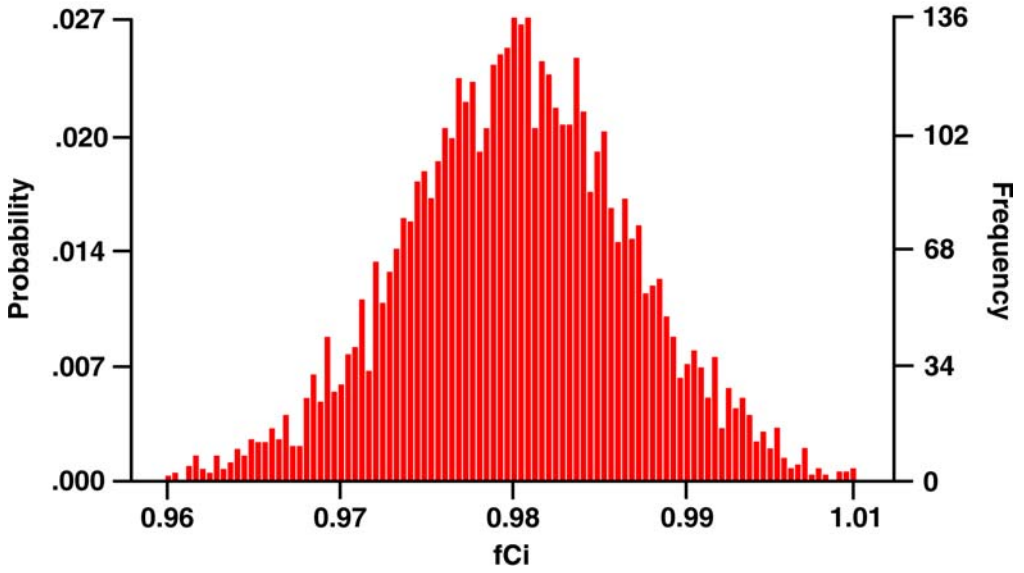

Figure 4. Conditional, radioactivity-intake distribution, $f_{1,000,000}(A|pop, aero)$, for a 1,000,000 PuO_2-contaminated, dust-particle intake by reference adults (Scott *et al.*, 1999) when the contaminated dust has a specific activity of 1 Bq/g. The distribution was evaluated numerically based on 10,000 Monte Carlo trials, a polydisperse size distribution with an activity median aerodynamic diameter of 1 μm, and a geometric standard deviation of 2.5.

Note that as the number of particles deposited in the respiratory tract increases, the shape of the radioactivity intake distribution shifts from having a long tail to the right toward roughly a normal distribution with little variability. The 1,000,000-particle intake distribution is clearly in the deterministic paradigm as the variability in intake related to particle polydispersity (varying sizes) has almost vanished (compare max and min radioactivity values for the distribution). A more variable distribution is expected to emerge when we add variability in breathing characteristics as was done earlier for pure metal PuO_2. Our earlier work suggests that when millions of dust particles are inhaled over years (as may occur for a family living at a remediated DOE site), variability in lifestyle may be a much more important influence on radioactivity intake than is variability in dust particle size distribution. Based on this research, specific recommendations were made related to developing final radionuclide soil action levels (RSALs) for the Rocky Flats site. These recommendations were placed on our Pu web site (www.radiation-scott.org) and presented at the American Chemical Society National Meeting & Exposition, New Orleans, LA, August 22-26, 1999 (Scott *et al.*, 1999).

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APPENDIX B: Dose-Response (in press)

It's Time for a New Low-Dose-Radiation Risk Assessment Paradigm — One that Acknowledges Hormesis

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Running Head: New low-dose-radiation risk assessment paradigm

Abstract

The current system of radiation protection for humans is based on the linear-no-threshold (LNT) risk-assessment paradigm. Perceived harm to irradiated nuclear workers and the public is mainly reflected through calculated hypothetical increased cancers. The LNT-based system of protection employs easy-to-implement measures of radiation exposure. Such measures include the equivalent dose (a biological-damage-potential-weighted measure) and the effective dose (equivalent dose multiplied by a tissue-specific relative sensitivity factor for stochastic effects). These weighted doses have special units such as the sievert (Sv) and millisievert (mSv, one thousandth of a sievert). Radiation-induced harm is controlled via enforcing exposure limits expressed as effective dose. Expected cancer cases can be easily computed based on the summed effective dose (person-sievert) for an irradiated group or population. Yet the current system of radiation protection needs revision because radiation-induced natural protection (hormesis) has been neglected. A novel, nonlinear, hormetic relative risk model for radiation-induced cancers is discussed in the context of establishing new radiation exposure limits for nuclear workers and the public.

Indexing Terms: hormesis, radiation, adaptive response, risk assessment

1. Introduction

The current system of limiting human exposure to ionizing radiation is based on the premise that the risk of deleterious stochastic effects such as cancer increases as a linear-no-threshold (LNT) function of the absorbed radiation dose (i.e., radiation energy deposited in tissue divided by the tissue mass). This is known as the LNT hypothesis and has no scientific basis. The linearly increasing risk function is also often called the LNT model. Such a linear relationship, if correct, means that doubling the radiation dose doubles the risk of harm. Conversely, reducing the dose one million-fold is supposed to reduce the risk by the same factor.

Some basic terminology is explained below to facilitate following the later sections of this paper.

1.1 High- and Low-LET Radiations

Two types of radiation (high and low linear energy transfer [LET]) are usually distinguished in characterizing radiation risks to humans. High-LET forms include alpha particles, neutrons, and heavy ions that produce intense ionization patterns when interacting with biological tissue. Considerable energy is deposited when traversing a narrow thickness of tissue. Low-LET forms include x and gamma rays and beta particles that deposit far less energy when traversing a narrow thickness of tissue.

1.2 Units for Expressing Radiation Doses

Radiation dose is expressed in different ways depending on the intended usage. A fundamental unit is the absorbed radiation dose, which is a measure of energy deposited in tissue (or other material) divided by the mass irradiated. Typical units of absorbed dose are the gray (Gy) which is equal to 1 joule/kg, and the milligray (mGy), which is one thousandth of a gray. These units can be applied when characterizing any type of radiobiological damage.

For regulating radiation exposure of humans (e.g., setting radiation exposure limits) and for low-dose risk assessment, special radiation dose units have been established that are based on the linear-no-threshold [LNT] hypothesis. These units are the result of applying statistical weights called *radiation weighting factors (W_R)* to radiation-specific doses and are expressed in units such as the sieverts (Sv) and millisieverts (mSv). These weighted doses are called *equivalent doses* and can be added for a given tissue. To account for differing sensitivities of different tissue, a second set of weights called *tissue weighting factors (W_T)* are employed to the

equivalent doses. The resulting weighted doses can also be added and the resultant dose is called effective dose and expressed in sieverts or millisieverts. Under presumed LNT dose-response functions for all cancer types, the effective dose represents the uniform gamma-ray dose to the total body that would incur the same overall cancer risk as is associated with the person's actual exposure, irrespective of its nonuniformity and irrespective of the type and energies of the radiations that are involved.

1.3 Radiation Dose Limits

Human radiation exposures are limited for nuclear workers, the public, and other groups based on limiting the effective dose. For example, the effective dose limit for nuclear workers is 50 mSv/y and for the public is 1 mSv/y based on U.S. Department of Energy and Nuclear Regulatory Commission regulatory policies (Metting 2005). The U.S. Environmental Protection Agency's regulatory policy limits on release of radioactivity to air is based on limiting the effective dose to humans to 0.1 mSv/y, and for public drinking water the corresponding limit is 0.04 mSv/y. For a point of reference, natural background radiation doses in the United States are associated with an effective dose of about 3 mSv/y (radon exposure included) (Metting 2005). For Ramsar, Iran, the corresponding dose associated with natural background radiation is about 200 mSv/y. Interestingly, such high background radiation doses appear to be associated with radiation hormesis-related protection against cancer (Frigèrio and Stowe 1976; Nambi and Soman 1987), i.e., a reduction in cancers.

1.4 Low Dose/Dose Rate Cancer Risk Assessment within the LNT Framework

Under the LNT risk assessment framework, effective doses for individuals can be added to obtained person-sievert (a collective dose) for population exposure, and the collective dose can be used to calculate the expected number of cancers among an irradiated population. Similarly, effective dose can be used to assign an individual specific cancer risk. However, low doses are often delivered at low rates and a correction is made for a reduction in harm after low-rate exposure as compared to high-rate exposure. For low doses and dose rates, a low-dose and dose-rate effectiveness factor (*DDREF*) is used to reduce the slope of the cancer risk curve by a fixed amount, usually a factor of 2 (Mitchel 2006). However with the LNT framework, reducing the effective dose by a factor of 2 has the same effect. By using the LNT-based *DDREF* approach for low-dose, low-dose-rate risk assessment, one essentially dismisses the possibility of radiation-induced protective effects (hormesis), as the dose-response curve slope is constrained to be positive.

1.5 Hormetic Dose-Response Curves

With hormesis, low doses of radiation protect against cancer, leading to a negative slope in the low-dose region for the dose-response curve. High doses, however, inhibit protection causing risk to then increase as dose increases. This yields what has often been called a U- or J-shaped dose-response curve (Calabrese and Baldwin 2001 a,b; Calabrese 2004, 2005; Calabrese *et al.* 2006).

2. Different Classes of Radiation-Associated Hormesis

This paper distinguishes three classes of radiation hormesis based on the recent recommendations of Calabrese *et al.* (2007):

5. *Radiation conditioning hormesis:* This form of hormesis relates to circumstances where a small radiation dose (mild stress) or moderate dose administered as a low rate (prolonged mild stress) activates protective processes that in turn suppress harm from a subsequent damaging large radiation dose.

6. *Radiation hormesis:* A small radiation dose (mild stress) or a moderate dose given at a low rate (recurring mild stresses) activates protective processes and reduces the level of biological harm to below the spontaneous level.

7. *Radiation post-exposure conditioning hormesis:* Damage normally caused by a large radiation dose or large dose of some other agent is reduced as a result of a subsequent exposure to a small radiation dose (mild stress) or a moderate dose delivered at a low rate (repeated mild stresses).

Sheldon Wolff's group (Olivieri *et al.* 1984; Wolff 1989, 1996) were the first to demonstrate and publish radiation conditioning hormesis data. When human lymphocytes were cultured with tritiated thymidine, which was a source of low-level chronic beta radiation, and then briefly exposed to 1500 mGy of x rays, the yield of chromatid aberrations from the x-ray exposure was suppressed. In a 1988 publication (Wolff *et al.* 1988) by his group, it was also demonstrated that human lymphocytes exposed to low doses of ionizing radiation (mild stress) became refractory to chemical mutagens that induced double-strand breaks in DNA. Howard Ducoff (1975) was the first to demonstrate radiation hormesis in insects. This author benefited greatly by participating in some of Dr. Ducoff's research as a graduate student at the University of Illinois. Members of this research group are now known as the *Irradiating Illini*.

T.D. Luckey, in his 1991 book entitled *Radiation Hormesis*, reported extensive data on the indicated topic, including data showing that repeated mild stresses associated with chronic low-rate exposure (involving low-LET radiation or low- plus high-LET radiation) significantly reduced the cancer incidence or mortality to below the level for spontaneously occurring cancers. Recently, such *chronic radiation hormesis* has been demonstrated for lung cancer in a very large number of epidemiological and ecological studies (Sanders and Scott 2007).

Ullrich *et al.* (1976) were the first to demonstrate a pronounced radiation hormesis effect (for lung cancer) in gamma-ray irradiated female RFM mice. The mice had a *high spontaneous frequency* of cancer implicating high genomic instability burdens. The pronounced radiation hormesis effect was similar in magnitude to the radiation hormesis demonstrated for neoplastic transformation by Azzam *et al.* (1996) for mouse embryo fibroblast cells exposed to x rays *in vitro*. Further, dose-response curves for neoplastic transformation were remarkably similar to those reported by Ullrich *et al.* (1976) for lung cancer. Just as in the Ullrich *et al.* study with high spontaneous lung cancer, there was a *high spontaneous frequency* of transformations for the mouse embryo fibroblasts, implicating a high genomic instability burden for the unirradiated cells. Such hormetic observations now are thought to relate to a dependency of protective intercellular signaling on the concentration of cells bearing genomic instability (Bauer 1996, 2000; Portess *et al.* 2007; Scott 2007a,b,c). Protective signaling intensity for protective apoptotic pathways is thought to increase with increasing numbers of genomically unstable cells (Scott 2004; Scott *et al.* 2007), i.e., a form of natural protection. The distribution of mild radiation hits among the target cell population appears also to be an important determinant of the protective signaling intensity (Bond *et al.* 1987; Feinendegen *et al.* 2004; Rithidech and Scott 2007), including signaling related to induced immunity (Laster *et al*. 2007).

Ullrich and Storer (1979) apparently attributed the radiation-hormesis-like observation for lung cancer in mice to systematic errors in lung cancer detection based on the methodology used. However, such a systematic error should operate at all dose levels, including those for the controls; and thus correcting such an error would not be expected to eradicate the hormetic dose-response curve shape. This can be demonstrated by assigning an arbitrary large systematic error (e.g., 50%) to each dose group including the controls and correcting the data. When evaluating relative risk, the correction is canceled so the hormetic curve shape remains. In addition, the study by Ullrich *et al.* (1976) not only demonstrated radiation hormesis for lung cancer, but it was also demonstrated for reticulum cell sarcoma for both gamma-ray and neutron exposures.

Edouard Azzam (Azzam *et al.* 1996) and colleagues were the first to demonstrate radiation hormesis *in vitro* by exposing mouse embryo fibroblasts in culture to low doses of x-rays. Their findings were later confirmed by Redpath *et al.* (2001, 2003). Studies by Dr. Redpath's group also demonstrated the importance of the type of radiation as well as dose rate in radiation hormesis response (Redpath *et al.* 2001, 2003; Ko *et al.* 2004, Elmore *et al.* 2005; Redpath and Elmore 2007). At the encouragement of this author, Day *et al.* (2007) performed the first studies demonstrating radiation post-exposure conditioning hormesis in mice (prostate gland). Chromosomal inversions associated with a large radiation dose were completely prevented by a subsequent small radiation dose (mild stress). Now there are many publications related to the indicated classes of radiation-associated hormesis (e.g., Liu *et al.* 1987, 1994; Hosoi and Sakamoto 1993; Cohen 1995; Howe 1995; Khokhryakov *et al.* 1996; Wolff 1996; Jaworowski 1997, 2001; Rossi and Zaider 1997; Hashimoto *et al.* 1999; Tokarskaya *et al.* 1995, 1997, 2002; Redpath *et al.* 2001, 2003; Nyström *et al.* 2002; Wei and Sugahara 2002; Liu 2003, 2004, 2007; Mitchel *et al.* 2003; Pollycove and Feinendegen 2003; Sakai *et al.* 2003; Chen *et al.* 2004, Feinendegen *et al.* 2004; Hooker *et al.* 2004; Ko *et al.* 2004; Mitchel 2004, 2005, 2006, 2007; Scott 2004, 2005a,b, 2007a,b,c; Scott *et al.* 2004; Zaichkina *et al.* 2004; Elmore *et al.* 2005; Ina and Sakai 2005; Tubiana 2005; Tubiana *et al.* 2005; Boreham *et al.* 2006; Mothersill and Seymour 2006; Redpath 2006; Pollycove 2007; Portess *et al.* 2007; Sanders and Scott 2007; Scott and Di Palma 2007; Scott *et al.* 2007). For an extensive listing of the many early radiation-associated hormesis publications, see Dr. Luckey's (1991) book entitled *Radiation Hormesis*.

The indicated radiation-associated hormesis publications and others collectively demonstrate that low doses/dose rates of low-LET radiation:

- Activate protective apoptosis signaling pathways and stimulate immunity.
- Protect against spontaneous chromosomal damage, mutations, neoplastic transformation, and cancer.
- Protect against high dose chemical- and radiation-induced cancer.

In spite of these now widely published hormetic effects, regulatory agencies still use the LNT-based system for regulating human exposure to ionizing radiation and for low-dose cancer risk estimation. Use of the LNT-based system is considered justifiable by many outside the hormesis community in light of publications such as the BEIR VII Report (NRC 2006), published by the U.S. National Research Council/National Academy of Science. The BEIR VII report concluded that the LNT approach to low-dose risk assessment was valid and essentially dismissed radiation-associated hormesis. A corresponding French Academies report did not come to the same conclusions (Tubiana 2005; Tubiana et al. 2005) when examining essentially the same data that were reviewed in the BEIR VII report. The French report found hormesis to be plausible and the LNT risk function to be invalid for low-LET radiation doses < 100 mGy and especially for doses < 10 mGy.

In the next section, three epidemiological tricks are discussed that when used helps to justify continued use of the LNT framework for low-dose-radiation risk assessment. An approach for accounting for radiation-associated hormetic effects in regulating radiation exposure is then discussed.

3. Epidemiological Tricks that Favor a LNT Dose-Response Curve

3.1 Trick #1: Throwing Away Radiation Dose

With many previous epidemiological studies of radiation-induced cancer, the researchers somehow came to the conclusion that radiation dose was wasted. Thus, in order to correct for the so-called wasted dose, one has to lag (throw away) some of the dose. However, if the dose-

response curve is indeed of the LNT type, then each fixed infinitesimally small increment, *dD*, in the radiation dose, *D*, would be expected to be associated with the exact same increment in the cancer risk (i.e., risk per individual). Stated mathematically, if *R(D)* is the dose-dependent LNT risk function and *D* is the radiation dose and α is the slope of the LNT dose-response curve, then the fixed increment in risk is $dR(D) = \alpha dD$; each small increment *dD* in the dose increases the risk by the amount αdD. Now there is a problem! If each increment in dose is equally effective in increasing risk, how can one conclude that dose is wasted? One cannot in one breath claim the existence of a LNT risk function, then in the next breath claim dose wasting and throw away dose. It is wrong to simply throw away radiation dose in order to obtain a LNT dose-response curve!

When studying DNA double-strand break induction by radiation, one usually observes a LNT-type dose-response curve at low doses (NRC 2006). This seems to be the basis for the expectation by many experts that cancer risk is also a linear function of dose. Interestingly, no dose lagging is used when evaluating DNA double-strand break dose-response curves; possibly because the inappropriateness of doing so would be immediately realized by many if not most radiation researchers.

To illustrate how radiation hormesis can be hidden by this dose lagging trick, data are presented in Figure 1 for *in vitro* neoplastic transformation after brief high-rate exposure to gamma rays, based on studies of Redpath *et al.* (2001). The cells used were HeLa x skin fibroblast, and relative risk (*RR*) for these cells has been demonstrated to agree quite well with *RR* data for cancer (leukemia and solid tumors) induction in humans after brief high-rate exposure (Redpath *et al.* 2001). Note the hormetic zone between 0 and 100 mGy (which corresponds to the hormetic zone demonstrated by Azzam *et al.* (1996) using x rays and mouse embryo fibroblast cells) where *RR* is suppressed to < *1*. Figure 2 shows the same data as in Figure 1 with doses lagged by 100 mGy. The radiation hormesis has magically disappeared! There is no longer a hormetic zone. This dose lagging trick is still widely used in epidemiological studies but needs to be stopped. Publishers should no longer allow this trick to be used to deceive the readers and funding agencies. Use of the indicated trick contributed indirectly to the radiation phobia that led to more than 100,000 misinformed physician-recommended abortions of wanted births after the Chernobyl accident (Ketchum 1987).

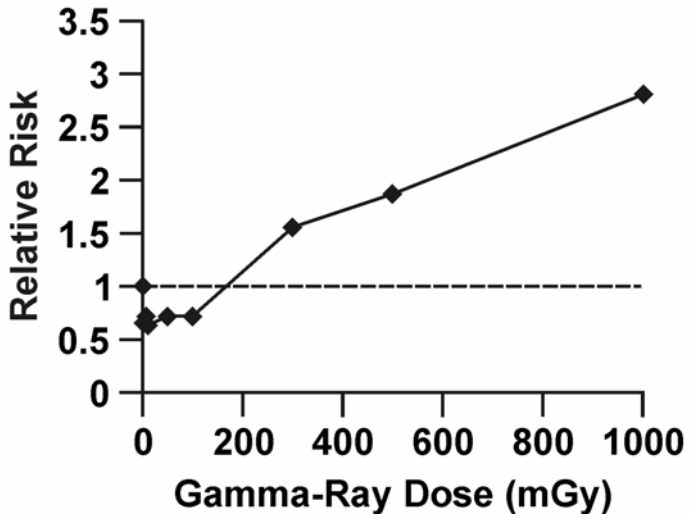

Figure 1. Relative risk dose-response relationship for gamma-ray induced neoplastic transformation of HeLa x skin fibroblast human hybrid cells by brief high-rate exposure, based on *in vitro* data from Redpath *et al.* (2001).

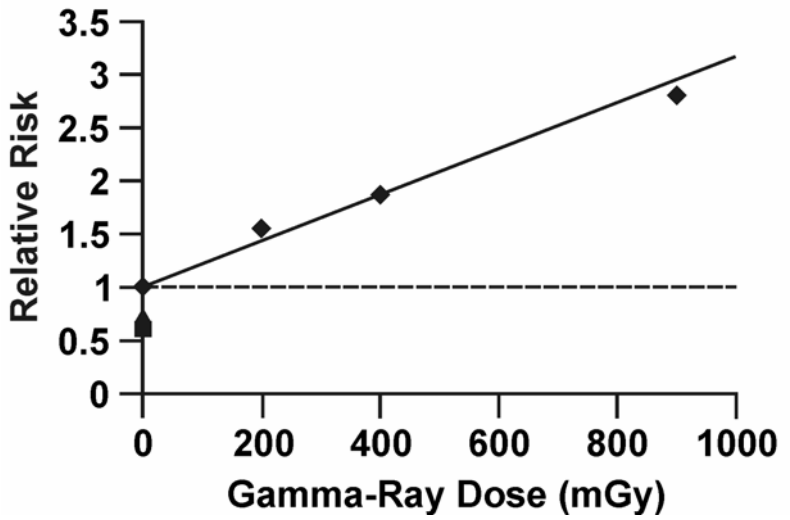

Figure 2. Application of dose lagging (100 mGy) to the data in Figure 1. Analysis based on data from Redpath *et al.* (2001).

3.2 Trick #2: Eliminating the Hormetic Zone via Averaging over Dose Groups

The second trick relates to forming dose groups comprised of persons having received widely varying radiation doses (i.e., the minimum and maximum doses [often reconstructed] for each dose group differs greatly). Such dose groups are usually necessary in case-control studies and are also often used in cohort studies of irradiated populations. Here the focus is on case-control study design and the use of odds ratio (*OR*) as an estimate of *RR*.

The neoplastic transformation frequency data used for the *RR* curve presented in Figure 1 can also be converted to odds of neoplastic transformation and the odds used to obtain *OR* relative to controls which are point estimates (without grouping) as indicated in Figure 3. Note that the hormetic zone is still present and that the dose-response curve is almost identical to the curve in Figure 1. For low frequency stochastic biological effects, *OR* and *RR* are quite similar. Dose groups were then formed over the following intervals: 0 to 100 mGy, 101 to 300 mGy, 301 to 500 mGy, and 501 to 1000 mGy. The odds for neoplastic transformation were then averaged over these intervals. Then, these averages were used to calculate *OR* relative to the lowest dose group, which corresponds to the averaging carried out and methodologies employed in case-control studies of cancer induction. The results obtained are presented in Figure 4, with the lowest dose group plotted at a dose of 0 (as is done in some epidemiological studies) and the results for the other dose groups plotted at the group midrange dose. Note that the hormetic zone has again disappeared. Thus, odds averaging over wide dose groups when evaluating *OR* can also vanish the hormetic zone. Journal editors and the general public need to be aware of this averaging trick when they are told that the dose-response data from case-control studies are consistent with the LNT hypothesis, which implies that any amount of radiation is harmful no matter how small. Users of the odds averaging trick with no previous knowledge of its hormetic zone vanishing capabilities should be more cautious of how they interpret their research findings.

Dose-grouping in cohort studies of radiation-induced cancer can also vanish the hormetic zone when persons who received low doses are included among the control group (representative of unexposed individuals). This is because the study design has reduced power for demonstrating suppressed risk at low doses when irradiated persons with radiation doses in the hormetic zone are included in the control group (used to represent unirradiated persons).

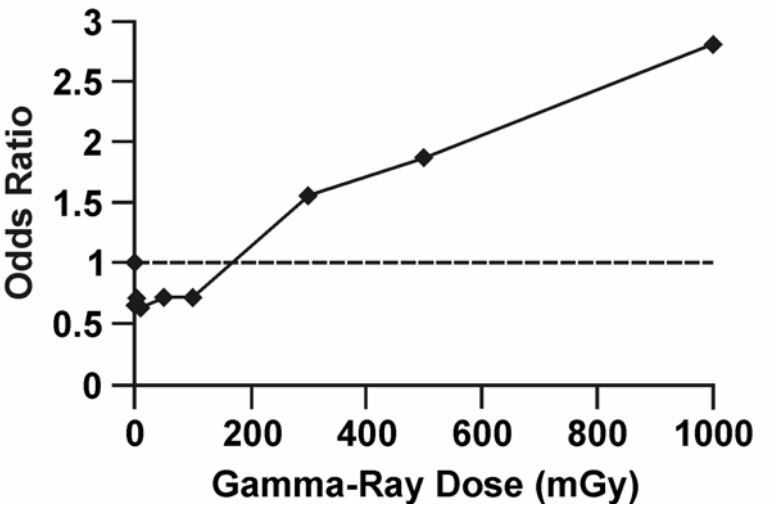

Figure 3. Odds ratio relative to controls for the neoplastic transformation data presented in Figure 1 for gamma-ray exposure of HeLa x skin fibroblast human hybrid cells.

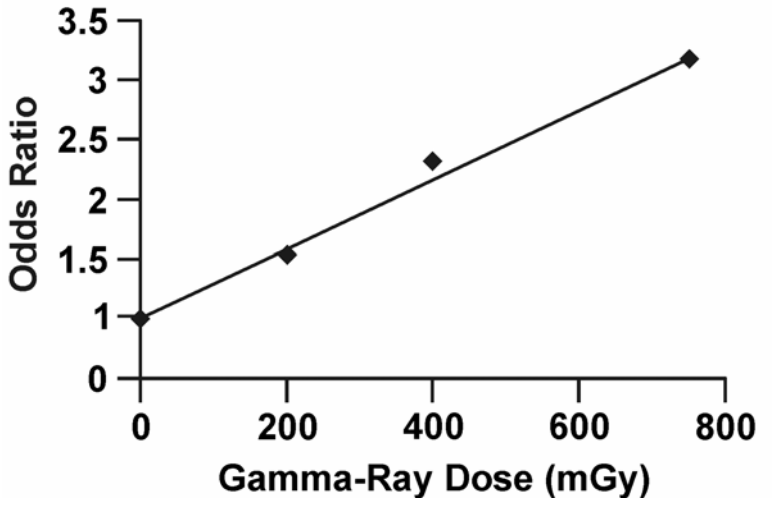

Figure 4. Ratio of dose-interval-specific average odds for neoplastic transformation based on data in Figure 3. Ratio of average odds evaluated relative to the lowest dose group. The lowest dose group was plotted at dose = 0 mGy. Other data plotted at the midrange of the dose intervals are used.

3.3 Trick #3: Constraining the Slope of the Cancer Risk Dose-response Curve to Always Be Positive

A trick often employed in cohort and case-control studies is to constrain the slope of the dose-response curve to be positive while including high-dose, high-risk data in the analysis of the dose-response curve fit. This is especially true when a LNT function has been presumed to apply at low doses by the researchers. Irrespective of the low-dose data, an increase in risk is predicted as dose increases for all such studies. The conclusion that any dose is harmful then follows. Low-dose hormetic (U- and J-shaped) data departing from the LNT characteristic is often simply ignored. It is wrong to portray such data as part of a LNT curve! Low-dose risk assessments should account for the hormetic shape to the dose-response curve.

4. Hormesis Implications for Regulatory Policy

In Zbigniew Jaworowski's1997 article, *Beneficial Effects of Radiation and Regulatory Policy*, he states the following:

"Adaptive stimulating effects of ionizing radiation occur at near natural doses. This disagrees with linear, no-threshold hypothesis on the dose/effect relationship, which is a basis of the current radiation protection. Vast literature demonstrates that such effects, usually known as hormetic ones, occur at molecular, cellular and population levels, and often result in increased longevity and decreased cancer incidence… After the Chernobyl accident, adverse health effects and vast material losses were induced in the former USSR by practical implementation of the ICRP radiation protection recommendations. A revision of the current approach to managing the risk of ionizing radiation is needed for the public interest."

Here, an approach to regulating radiation exposure is recommended that allows for the existence of a hormetic dose zone just above natural background radiation. The approach relates to the hormetic relative risk (HRR) model previously developed by this author (Scott 2007 a,b,c), which is summarized below in a more general form.

4.1 Hormetic Relative Risk Model

With the HRR model for low-dose radiation-induced cancer, doses at or slightly above normal monthly natural background low-LET radiation levels are presumed to fall within the what is currently considered the hormetic zone. This hormetic zone starts at natural background radiation and spans a relative wide dose range, possibly exceeding 1000 mGy of low-LET radiation when radiation dose is delivered at a low rate. However, protective effects associated with hormesis may also occur at below current natural background levels for some individuals. For low-LET radiation doses in the hormetic zone, cancer *RR* from exposure to low-LET radiation in excess of natural background is expected to remain < 1 for most if not all members of the population. Also, for combined exposure to low doses of low- and high-LET radiations above natural background radiation levels, the low-LET component of the dose activates protective hormetic processes and prevents cancer *RR* from increasing above 1. The risk may decrease as a result of hormetic processes that are regulated by protective intercellular and intracellular signaling.

The protective signaling, presumed activated with low doses and dose rates of low-LET radiation, relates to removal of aberrant cells from the body via p53-dependent and independent apoptosis signaling pathways and stimulated immunity (Scott 2007 a,b,c; Scott and Di Palma 2007; Scott *et al*. 2007). The protective signaling can also involve DNA repair pathways if a damage threshold is exceeded (Rothkamm and Löbrich 2003). Possible exceptions to full hormetic protection are the very young and children who may not have significant burdens of genomically unstable cells that participate in the signaling associated with protective p53-independent apoptosis (Scott and Di Palma 2007).

Stochastic thresholds (StoThresh) that vary between different individuals are required in the HRR model for activating the protective signaling. However, somewhat higher doses (also StoThresh) inhibit protection causing an increase in the *RR* as dose increases up to a point at which protection is suppressed in all individuals. At this point, a linear response that extrapolates to *RR = 1* at background radiation *b* is presumed to apply (Fig. 5). This corresponds to use of the LNT model to extrapolate from high to low doses.

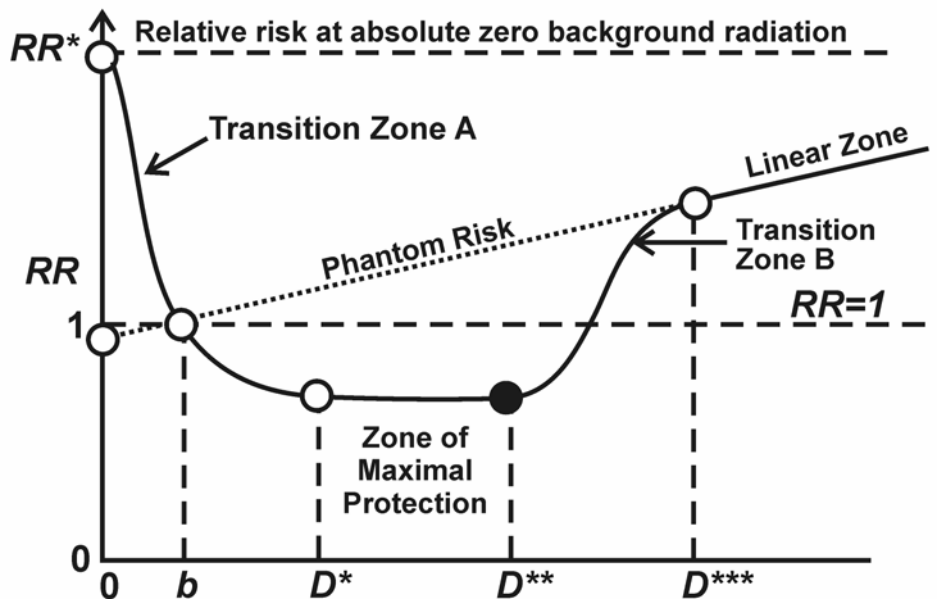

Figure 5. Schematic representation of the hormetic relative risk model. The model is presented as a function of the total absorbed radiation dose *D* to allow for a two-dimensional representation. The dose scale ranges from hypothetical absolute zero natural background radiation dose (*D = 0*) to doses in excess of the current dose *b* from natural background. Doses *D**, *D*** and *D**** define the different dose zones indicated. The *RR* at absolute zero radiation is indicated by *RR**. The exponential rise as dose decreases below *b* is supported by epidemiological data (Cohen 1995) for environmentally irradiated humans and is presumed to relate to reduced DNA repair capacity (Rothkam and Löbrich 2003), the loss of protective apoptosis (Scott and Di Palma 2007), and the loss of stimulation of immune functions (Liu *et al.* 1987).

The mathematical functions discussed in this paper relate to radiation doses equal to or greater than natural background radiation. For this dose range, the indicated nonlinear hormetic *RR(**D**)* function (population average) can be evaluated as arising from a weighting between two *RR(**D**)* function components: a LNT component (RR_{LNT}) that applies to unprotected individuals and a hormetic component (RR_{HORM}) that applies to protected individuals. The weighting function, *PROTEC(**D**),* is the probability function for activated protection (radiation hormesis) as a function of the dose vector, ***D*** (called a covariate dose vector by some), which relates to all relevant radiation doses (from low- and high-LET sources) in excess of natural background. *PROTEC(**D**)* represents the proportion of the irradiated population that is protected via p53-independent apoptosis and induced immunity and is expected to depend on genetic and other characteristics of the population. The *RR*(***D***) for persons with the same nonzero dose vector ***D*,** under this model is given by

$$RR(\mathbf{D}) = PROTEC(\mathbf{D}) \bullet RR_{HORM}(\mathbf{D}) + (1 - PROTEC(\mathbf{D}))RR_{LNT}(\mathbf{D}). \quad (1)$$

Equation 1 is used to characterize the population average *RR* and applies to radiation doses in excess of natural background. Equations that relate to below natural background radiation exposures are not addressed in this paper. The function $RR_{HORM}(\mathbf{D}) = 1 - PROFAC$ is for doses in the hormetic zone and equals 1 otherwise (Scott 2007a). The protection factor (*PROFAC*) gives the expected proportion of cancer cases that are prevented due to radiation hormesis and only relates to the low-LET component of the total radiation dose. The *PROFAC* relates both to protective apoptosis (presumed p53-independent) and immune functioning but does not relate to DNA repair (Scott 2007a). The function $RR_{LNT}(\mathbf{D})$ simply adds to *RR = 1* (with no radiation exposure) the sum ***K'D***, where ***K'*** is a row vector of radiation-specific slope factors for excess cancers for matching radiation-specific doses in the dose vector ***D*** (a column vector). For a

single radiation type $\boldsymbol{K'D} = kD$, where k is the excess RR per unit dose and D is the individual radiation dose. Components of the vector $\boldsymbol{K'}$ depend on DNA repair capacity (Scott 2007a) which is expected to be greatly reduced in below natural background radiation environments (Rothkam and Löbrich 2003). Components of $\boldsymbol{K'}$ are expected to increase as DNA repair capacity decreases, which is expected to be the case for below natural background radiation exposure. For above natural background radiation exposures, components of $\boldsymbol{K'}$ are currently modeled as being constant.

For just above natural background radiation exposure $PROTEC(\boldsymbol{D})$ is evaluated presently as 1, decreasing only when one exits the hormetic zone (through a transition zone) at moderate to high doses. For natural background radiation exposure, $RR(\boldsymbol{D}) = 1$. The RR dose-response curve associated with Equation 1 when plotted as a function of the total radiation dose (indicated by D in this example) has the general features as indicated in Figure 5 for doses $\geq$ natural background b. The figure however presents doses ranging from absolute zero natural background radiation exposure to doses considerably in excess of background radiation exposure.

What has traditionally been considered the hormetic zone comprises the above natural background range of radiation doses for which $RR < 1$. However, for doses below and above this zone, protective effects can be operational for some individuals. With the HRR model, RR increases above 1 to RR^* as the radiation dose decreases below natural background to absolute zero radiation, due to a progressive loss of protected individuals. Over the dose range for which $RR < RR^*$, the dose-response curve is expected to have a U- or J-shape. The schematic exponential increase of RR in Figure 5 as dose decreases below natural background b is supported by data on human lung cancer mortality rates (Cohen 1995) and data revealing a loss of essential DNA repair capacity in low-dose radiation environments (Rothkamm and Löbrich 2003).

Transition Zone A in Figure 5 is where StoThresh for activating protective signaling are progressively exceeded as radiation dose increases. When protective signaling is activated in all members of the population, then the RR is roughly constant through what is called the Zone of Maximal Protection. At doses just above this zone, StoThresh for inhibiting protective signaling (immune system stimulation, protective p53-independent apoptosis, but not p53-related DNA repair) are progressively exceeded as dose increases (Transition Zone B). At somewhat higher doses, protection is suppressed in everyone (except for p53-related DNA repair) and what is called here the Linear Zone then emerges. This zone was previously called the LNT Zone because of intersection of a LNT line (Scott and Di Palma 2007), but this proved to be confusing terminology. The Linear Zone corresponds to the dose region where most epidemiological studies have mainly been conducted that claimed a LNT dose-response curve. For this zone, $PROTEC(\boldsymbol{D}) = 0$, so that $RR(\boldsymbol{D}) = RR_{LNT}(\boldsymbol{D})$. For very high doses, departure from linearity can again emerge due to lethal damage to body organs such as the bone marrow.

Over Transition Zone A, $PROTEC(\boldsymbol{D})$ increases from zero to 1 and remains at 1 over the Zone of Maximal Protection. Over Transition Zone B, $PROTEC(\boldsymbol{D})$ decreases from 1 to 0.

4.2 Regulatory Threshold with Respect to Cancer Induction

It is beneficial to define a **reg**ulatory **r**adiation **a**bsorbed **d**ose **t**hreshold (REGRADT) based on the StoThresh, $T_{j,i}$, for loss of protection against cancer in tissue, j, due to dose from the i^{th} radiation type of interest. The indicated REGRADT can be assigned as the radiation-specific dose that corresponds to the minimum individual dose for transitioning from the Zone of Maximal Protection to Zone B. Let $T_{j,i}\{min\}$ represent the tissue-j-specific minimum absorbed dose from radiation of the i^{th} radiation type (e.g., x rays, gamma rays, electrons, positrons, protons, muons, neutrons, alpha particles, fission fragments, nonrelativistic heavy nuclei, etc.), for Zone B. The REGRADT is therefore determined by the most sensitive member of the

population, related to loss of protection over Transition Zone B. The REGRADT therefore likely depends on the types of radiation involved, dose rates, radiation energies, the population at risk, and the tissue of interest. The dose D^{**} in Figure 5 corresponds to the proposed REGRADT. Higher doses produce harm in part via loss of hormetic protection.

One can then use the normalized stochastic effect dose, S_j, for tissue j as defined below to limit radiation-induced cancers (with respect to preventing excess cancers relative to the spontaneous frequency):

$$S_j = (D_{j,1}/T_{j,1}\{min\}) + (D_{j,2}/T_{j,2}\{min\}) + \ldots + (D_{j,n}/T_{j,n}\{min\}) < 1, \quad (2)$$

for all tissues j and all n radiations of interest. A value $S_j = 0.5$ means that only one half of the require radiation exposure for loss of adaptive protection by the most sensitive member of the population has occurred.

This example does not account for genetic effects. However, it is widely known that genetic effects are much less likely to be induced than cancer (NRC 2006). Thus, limiting testicular and ovarian cancer occurrence would be expected to also limit genetic effects. There is also some evidence for dose-response relationships for genetic effects in humans being of the hormetic type with respect to low-rate exposure to gamma rays (Chen *et al.* 2007). Limiting both cancer and genetic effect occurrences would be expected to also limit shortening of life due to deleterious genetic effects and cancer.

The REGRADT as defined would apply both to population and individual exposures. *New, funded research is needed in order to properly assign appropriate values for $T_{j,i}\{min\}$ for different radiations, radiation energies (e.g., neutron energy), different cancer types, and for different populations*.

5. Conclusions

There is abundant evidence for radiation-associated hormesis. However, dismissal of radiation-associated hormesis is in many instances based on epidemiological tricks that include dose lagging, odds averaging over wide dose ranges when evaluating *OR*, and forcing a positive slope to the *RR* dose-response curve.

Its time for new, low-dose radiation risk assessment and regulatory paradigms that allow for hormesis. Normalized stochastic effects dose, based on radiation-, radiation-energy-, and dose-rate-specific REGRADTs could be used to limit radiation exposure. For S_j limited to < 1, for all tissues, cancer $RR \leq 1$ would be expected.

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APPENDIX C: Dose-Response (submitted)

Low-Dose-Radiation Stimulated Natural Chemical and Biological Protection against Lung Cancer

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Running Head: Stimulated natural protection against lung cancer

Abstract

Research is being conducted world-wide related to chemoprevention of future lung cancer among smokers. The fact that low doses and dose rates of some sparsely ionizing forms of radiation (e.g., x rays, gamma rays, beta radiation) stimulate transient natural chemical and biological protection against cancer in high-risk individual is little known. The cancer preventative properties relate to radiation adaptive response (radiation hormesis) and involve stimulated protective biological signaling (a mild stress response). The biological processes associated with the protective signaling are now better understood and include: increased availability of efficient DNA double-strand break repair (p53-related and in competition with normal apoptosis), stimulated auxiliary apoptosis of aberrant cells (presumed p53-independent), and stimulated protective immune functions. This system of low-dose radiation activated natural protection (ANP) requires an individual-specific threshold level of mild stress and when invoked can efficiently prevent the occurrence of cancers as well as other genomic-instability-associated diseases. In this paper, low, essentially harmless doses of gamma rays spread over an extended period are shown via use of a novel biological-based, hormetic relative risk (HRR) model to be highly efficient in preventing low-dose, alpha-radiation-induced lung cancer in both rats and humans.

Indexing Terms: chemoprevention, cancer, radiation, hormesis, adaptive response

1. Introduction

Lung cancer is the leading cause of cancer death worldwide and cigarette smoking is considered a major risk factor. Because the population of smokers worldwide continues to be very large, effective lung cancer preventative modalities that could be implemented in a clinical setting for such high-risk individual are needed. In this paper evidence is provided that low doses and dose rates of sparsely ionizing gamma radiation over and extended period can efficiently prevent lung cancer among high-risk populations via stimulating and prolonging the body's natural defenses (natural chemical and biological prevention).

Ionizing radiation has been present in the environment since the beginning of the universe. Radiation sources remain everywhere, including in our bodies, in our homes, in the soil, in plants and animals we ingest, and in the air we breathe (including polonium-210). The sun we depend on for sustaining life on earth is also a source of ionizing radiation, as well as other entities in space. It is now known that through evolution, mammalian life forms have developed natural cancer preventative processes (chemically and biologically regulated) that are stimulated by low doses and dose rates of sparsely ionizing forms of radiation (e.g., x rays, gamma rays, beta particles). Low doses and dose rates of these radiations stimulate protective intercellular and intracellular signaling that leads to activated natural protection (ANP) against cancer and other genomic instability associated diseases (Scott and Di Palma 2007). The protective signaling appears to be a generalized response to mild stress above an individual threshold level.

Radiation ANP (also called radiation hormesis [Calabrese *et al.* 2007]) appears to be an evolutionary benefit of the interaction of low-level ionizing radiation with mammalian life forms on earth. Thus, ANP is evolutionary conserved (Mitchel 2007). High radiation doses and dose rates rather than preventing cancer, inhibit the protective processes that suppress cancer (Scott and Di Palma 2007).

1.1 Low-Dose Radiation ANP

Low-dose radiation ANP involves induced high-fidelity DNA repair in corporation with normal apoptosis (presumably p53-dependent), activation of an auxiliary **p**rotective **a**poptosis-**m**edicated (PAM) process that selectively removes precancerous (Scott *et al.* 2003; Scott 2004;

Portess *et al.* 2007) and other aberrant cells, and induced immune functions (Scott and Di Palma 2007). However, the protective processes are transient.

Bauer (2000) has summarized what is known about the PAM process among fibroblasts based on numerous signaling studies by his research group. Figure 1 relates to the summary. The protective process involves a sophisticated system of interdependencies and interactions of reactive oxygen and nitrogen species. The release of transforming growth factor beta (TGF-β1) by transformed cells is a key early event. Nontransformed cells, when activated, release a novel peroxidase (P) and nitric oxide (•NO). Superoxide anions (O_2^-•) generated and released by transformed cells participate in the intercellular signaling and make transformed cells the selective target for intercellular induction of apoptosis (i.e., transformed cells are selectively removed via apoptosis). Chloride ions (Cl^-) and hydrogen peroxide (H_2O_2) also participate in the intercellular signaling. The interactions of the indicated molecules result in two currently known major signaling pathways to protective apoptosis that are based on hypochlorous acid (HOCl)/hydroxyl radicals (•OH) and •NO/peroxynitrite ($ONOO^-$). H_2O_2 plays a key role by fostering the HOCl/•OH pathway and inhibiting the •NO/$ONOO^-$ pathway. Additional pathways to apoptosis are likely associated with the auxiliary PAM process, with the selected path possibly depending on the cell type to be eliminated via apoptosis (mutants, neoplastically transformed cells, micronucleated cells, etc.), its local cellular environment, and the nature of the damage to DNA (Scott and Di Palma 2007).

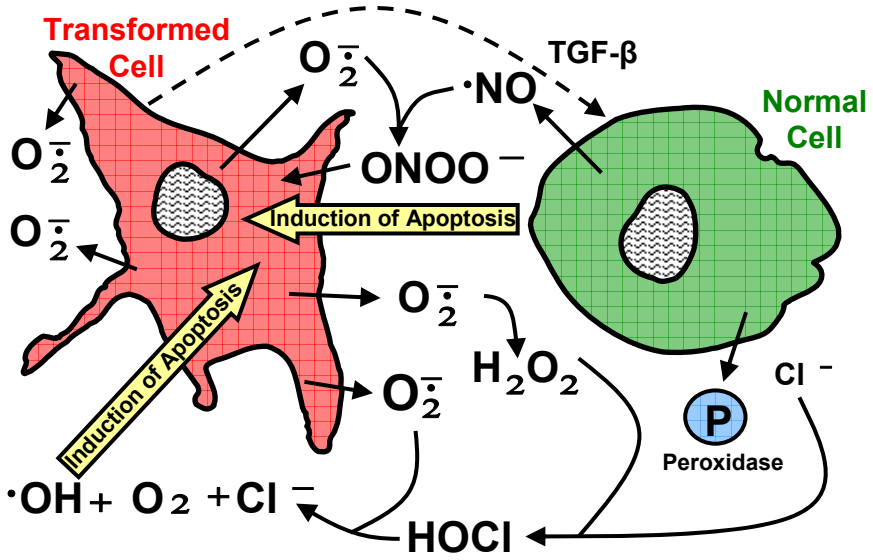

Figure 1. Signaling pathways for the protective apoptosis mediated (PAM) process in fibroblast (Scott and Di Palma 2007). See main text for an explanation of symbols used.

Stochastic threshold radiation doses (which are presumed to differ for each person and body organ/tissue) are required for ANP. However, somewhat higher doses can inhibit protective signaling (e.g., signaling related the PAM process) and also suppress the immune system.

1.2 Demonstrated Benefits of Radiation ANP

Low doses and dose rates of sparsely ionizing radiations have been found to:

- Protect against chromosomal damage (Azzam *et al.* 1996).
- Protect against mutation induction by a high radiation dose if given before or after the high dose (Day *et al.* 2006, 2007).

- Eliminate precancerous (neoplastically transformed) cells (Redpath *et al.* 2001).
- Prevent chemical-induced cancer (Sakai *et al.* 2003).
- Stimulate increased immune system functioning (Liu 2007).
- Suppress cancer induction by alpha radiation (Tokarskaya *et al.* 1997; Sanders 2005).
- Suppress metastasis of existing cancer (Sakamoto *et al.* 1997; Sakamoto 2004)
- Protect against diseases other than cancer (Sakai *et al.* 2006)

Based on our adaptive-response research carried out over a number of years, we developed a biological-based, hormetic relative risk (HRR) model for cancer induction (Scott 2007; Scott and Di Palma 2007) that accounts for radiation ANP. The current version of the model is discussed in the Methods section.

2. Methods

2.1 Computational and Statistical Approaches

For fitting *RR* equations to lung cancer data for humans exposed to alpha and gamma radiations, Bayesian inference methods implemented via Markov chain Monte Carlo (MCMC) were employed, based on uniform priors for parameters to be estimated and a very long single chain (Scott 2007). Judgments about convergence were based on comparing the Monte Carlo error and posterior distribution standard deviation. Ratios of the Monte Carlo error for parameters to the posterior distribution standard deviation that were < 0.05 were considered consistent with convergence. Autocorrelation were also monitored during our MCMC runs to facilitate judging how long to run the chain. Where *RR* data were compared for different species (dogs, rats, humans), they were adjusted to a common baseline incidence. Standard errors for cancer incidence were evaluated based on the binomial distributions. Subjective upper bounds were used for reported zero cancer incidences. The bounds were set equal to two standard errors for the cancer frequency, based on 1 assigned cancer case.

Here the focus is on application of the HRR model (Scott 2007) to lung cancer data for protracted exposure to low doses of alpha radiation in combination with very low doses of gamma rays to demonstrate the highly efficient prevention of lung cancer by gamma-ray ANP. Alpha radiation administered alone is a potent inducer of lung cancer. Small doses (close to natural background radiation levels) can cause a significant increased incidence (Lundgren *et al.* 1991; Sanders 2007). However, for combined exposure to low-dose alpha and very-low-dose gamma rays, the gamma-ray ANP could possibly prevents cancer induction by alpha radiation. The level of protection can be quantified using our HRR model.

2.2 Hormetic Relative Risk Model

With the current version of our HRR model, the irradiated population is separated into two dose- and dose-rate dependent parts: (1) those that have ANP and (2) those without ANP. For persons with ANP, the average cancer relative risk is given here by

$$RR_{ANP} = (1 - PROFAC)RR_{LNT} \quad (1)$$

where RR_{ANP} is the relative risk for persons with ANP (i.e., protected individuals) and RR_{LNT} is the relative risk for persons without ANP and is based on the linear-no-threshold (LNT) assumption. Risk is evaluated relative to an unirradiated population. Bayesian methods allow evaluating the expected proportion of the irradiated population that is protected for a given dose and dose rate and radiation combination when formally fitting the HRR model to data (Scott 2007).

The protection factor (*PROFAC*) takes on values from 0 to 1 and here accounts for prevention of cancer via gamma-ray ANP. A value *PROFAC=0.25* would indicate that cancer would be expected to be prevented in 1 in 4 individuals among those with radiation ANP. For a hypothetical population containing 1000 protected (by low-dose gamma-ray ANP) heavy cigarette smokers, if 100 were expected to develop lung cancer because of smoking, then with a gamma-ray *PROFAC = 0.25*, 25 of the 100 would be expected to be prevented from developing smoking-related lung cancer. Thus, not every protected person is expected to escape lung cancer occurrence.

For alpha-radiation-induced lung cancer, relative risk, RR_{LNT} can be evaluated based on a linear-no-threshold (LNT) function which includes the baseline cancer incidence (Scott 2007):

$$RR_{LNT} = 1 + [(1-B)/B]K_{\alpha}D_{\alpha}, \quad (2)$$

where B is the baseline (spontaneous) cancer incidence, K_{α} is the presumed always-positive slope parameter in the HRR model and D_{α} is the alpha radiation dose to the target organ. Equation 1 is used for evaluating cancer *RR* for combined exposure to low-dose alpha and gamma rays while Equation 2 applies to exposure only to alpha radiation and relates to low, moderate, and high doses but not very high doses (Scott 2007). The *PROFAC* relates only to low-dose gamma rays (or a radiation type of similar interaction characteristics such as x rays and beta radiation when used instead of gamma rays).

In circumstances where one has an estimate of RR_{ANP} (based on exposure to alpha plus gamma radiation) when every one is presumed protected and RR_{LNT} (for exposure only to alpha radiation) when no one is presumed protected, you can estimate the *PROFAC* for a given dose level D_{α} using the baseline-independent (baseline dependence cancels) relationship:

PROFAC = 1 – {(observed RR under alpha plus gamma irradiation)/(observed RR under exposure only to alpha radiation)}.

3. Results

3.1 Estimates of *PROFAC* and K_{α} for Different Species

Table 1 shows *PROFAC* estimates (*=1*) and subjective lower bounds for low-dose, low-dose-rate, gamma-ray prevention of lung cancer among alpha-radiation exposed female Wistar rats that either inhaled the alpha-emitter plutonium-239 (Pu-239) alone or Pu-239 labeled with a gamma-ray-emitting ytterbium-169 (Yb-169) tag (label), based on studies conducted years ago and reported recently by Sanders (2007) that were revaluated in the context of radiation hormesis. Here gamma-ray doses are presumed sufficient for ANP for every rat but not high enough for its inhibition. Also, alpha radiation doses in Table 1are presumed not to be high enough to overwhelm or suppress gamma-ray-induced protective signaling. The gamma-ray doses in Table 1 are similar in magnitude to essentially harmless doses received form single diagnostic x-ray exposures. However, for the data in Table 1, the gamma-ray exposure was protracted over several months (physical half-life for Yb-169 = 32 d). Extending the length of exposure is considered to prolong the time period over which protective signaling occurs, thereby increasing the efficiency of protection as has been demonstrated for eliminating precancerous cells *in vitro* (Elmore *et al.* 2006).

The Wistar rat lung cancer incidence data for combined alpha plus gamma radiation exposure is presented in Table 1. A subjective upper bound on each zero incidence is reported and is based on assigning 1 lung cancer case and assuming a binomial distribution for cases, with 2 standard errors for the assigned frequency being presented in Table 1. Calculated values for RR_{LNT} based on fitting Equation 2 (re-expressed as an absolute risk) to lung cancer incidence data for rats exposed only to plutonium-239 (Sanders 2007) to estimate K_{α} are also included in the table and are based on the assumption that no rats were protected (i.e.,

PROFAC = 0). The dose-group-specific excess absolute risk per unit dose was used to obtain six estimates of K_α that were then averaged, assuming no rats were protected. The average obtained for K_α was $2.1 \times 10^{-4} \pm 1.6 \times 10^{-4}$ mGy[1], which is close to the value of $1.2 \times 10^{-4} \pm 9.0 \times 10^{-5}$ mGy^{-1} previously reported for lung cancer in Mayak plutonium facility workers (Scott 2007) based on Equation 1 and the value of $1.0 \times 10^{-4} \pm 5.0 \times 10^{-5}$ mGy^{-1} previously reported for lung cancer in F344/Crl rats that inhaled the alpha emitter Pu-239 (Scott 2007), based on studies conducted by Lundgren *et al.* (1991). Using the lowest two dose groups reported by Muggenburg *et al.* (1006) for Pu-238 alpha-particle-induced lung cancer in beagle dogs, a slope parameter of $1.7 \times 10^{-4} \pm 1.0 \times 10^{-5}$ mGy^{-1} was obtained and is consistent with the result obtained for rats and humans.

Table 1. Lung cancer incidence among Wistar rats that inhaled Pu-239 + Yb-169 and associated expected (assuming no protection) and observed *RR* and related gamma-ray associated protection factor against cancer

Average alpha radiation dose (mGy)	Average gamma radiation dose (mGy)	Number of animals	Lung cancer incidence	Expected relative risk[a]	Observed relative risk	Protection factor
0	0	1052	0.00095 ± 0.00095	1	1	
56	1	1389	0 (0.00072)[b]	13	0 [1][c]	1.0 [0.92][d]
190	2	343	0 (0.0029)[b]	43	0 [1][c]	1.0 [0.98][d]
620	1	145	0 (0.014)[b]	137	0 [1][c]	1.0 [0.99][d]

[a]Based on rats not exposed to gamma rays from a Yb-169 tag and Equation 2 (upper dashed curve in Figure 2) with *RR* evaluated based on *B = 0.00095* rather than the value of 0.00150 reported by Sanders (2007).

[b]Bionimal distribution standard error had exactly on rat developed lung cancer, given that none did. An average of 1.6 spontaneous lung cancers was expected among all 1677 irradiated rats.

[c]Subjective upper bound (*RR = 1)*.

[d]Subjective lower bound on *PROFAC* based on an upper bound of 1 for the observed *RR*.

The slope parameter estimates are summarized in Table 2 and differ by less than a factor of 2.2. Genetic polymorphisms that impact on DNA repair efficacy are expected to impact on the parameters K_α and *B* but not the *PROFAC* (Scott 2007). Thus, the similar results in Table 2 for K_α for the different genetic backgrounds suggest that genetic polymorphisms related to DNA repair may not greatly impact K_α. For a point of reference, studies on relative susceptibility for lung cancer occurrence for pair-wise comparisons for different genetic polymorphisms that impact on DNA repair show relative susceptibility factors < 1.5 (Hu *et al.* 2004; Hung *et al.* 2005; Benhamou and Sarasin 2007; Schwartz *et al.* 2007). Genetic polymorphisms that impact on the PAM process and immune system functioning are expected to influence the *PROFAC* and *B* but not K_α.

Table 2. Evidence for slope parameter K_α for lung cancer induction being similar for different species and rodent strains.

Animals	Radiation Types	K_α in mGy^{-1}	Equation Used	Estimated or implicated value for *PROFAC*
Humans	Alpha + gamma	$1.2x10^{-4} \pm 9.0x10^{-5}$	Equation 1	0.86 ± 0.07
F344/Crl rats	Alpha + gamma	$1.0x10^{-4} \pm 5.0x10^{-5}$	Equation 2	0 (high dose data only)[a]
Wistar rats	Alpha	$2.1x10^{-4} \pm 1.6x10^{-4}$	Equation 2	0
Beagle dogs	Alpha + gamma	$1.7x10^{-4} \pm 1.0x10^{-5}$	Equation 2	0 (high dose data only)[a]

[a]The protective signaling induced by low-dose gamma rays is assumed to be inhibited or overwhelmed by very high doses of alpha radiation.

Note from Table 1 that the very small, essentially harmless protracted gamma-ray doses (1 to 2 mGy) appeared to completely prevented (*PROFAC = 1.0*) the occurrence of lung cancer (spontaneous and alpha-radiation-induced) for alpha radiation doses up to 620 mGy. However, subjective lower bound on *PROFAC* presented in Table 1 would allow for a possible lower level of protection (*PROFAC* as low as 0.92).

Where the *RR* was expected to be 137 in the absence of ANP (Table 1), based on data for exposure only to alpha radiation (presumably unprotected rats), adding an essentially harmless protracted gamma-ray dose (1 mGy) appears to have protected against 100 % of the expected lung cancers. Thus, all of the gamma-ray irradiated rats were apparently very well protected from lung cancer occurrence for the alpha radiation dose range (0 to 620 mGy) in Table 1. A similar level of protection might be expected against smoking-related lung cancer in humans.

The indicated level of protection is even higher than we previously reported (*PROFAC = 0.86 ± 0.07* [Scott 2007]) for Mayak plutonium facility workers that were chronically exposed over years to alpha and gamma radiation in connection with the production of plutonium-239 for use in nuclear weapons. The workers inhaled Pu-239 and were also exposed to external gamma-ray sources (Khokhryakov *et al.* 1996). However, not only did the gamma rays appear to protect against low-dose alpha-radiation-induced lung cancer among Mayak facility workers, but also against cigarette-smoking related lung cancers (Scott 2007). Many of the male workers were heavy smokers (Tokarskaya *et al.* 2002*)*.

3.2 Lung Cancer *RR* Dose-Response Relationships for Different Species

Figure 2 shows the lung cancer *RR* data for combined alpha and gamma-ray exposure of Wistar rats and beagle dogs. The Wistar rat data of Sanders (2007) for exposure only to alpha radiation are also included for comparison and to demonstrate the dramatic protection implicated to be associated with low-dose gamma-ray exposure when the alpha radiation dose is less than about 1000 mGy (1 Gy). The beagle dog data are from Muggenburg e*t al*. (1996) and relate to inhalation exposure to the alpha emitter Pu-238 in an insoluble oxide form with a Yb-169 gamma-ray tag. The observed *RR* values for dogs and for Wistar rats exposed only to alpha radiation were adjusted so as to be applicable to a baseline cancer incidence of 95/100,000 =0.00095 as was reported for Wistar rats exposed to both alpha and gamma radiations (Sanders 2007). Thus, relative risk is expressed based on a common baseline. For making the indicated adjustments, it was assumed that the *PROFAC = 0* for the alpha-irradiated

dogs, because of the mainly very high radiation doses involved. Similarly *PROFAC* was assumed equal to zero for Wistar rats exposed only to alpha radiation.

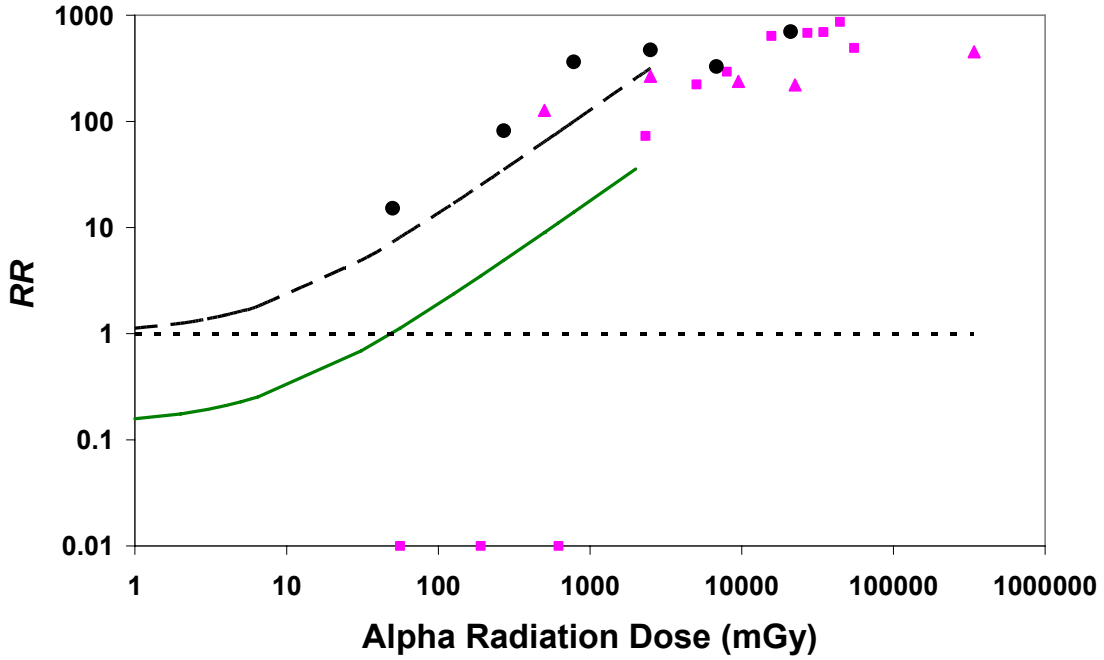

Figure 2. Lung cancer relative risk: Wistar rats that inhaled Pu-239 + Yb-169 (filled squares) based on data from Sanders (2007); adjusted *RR* for Wistar rats for inhalation exposure to only Pu-239 (filled circles) based on data from Sanders (2007) after adjusting to a baseline of 95/100,000; Expected adjusted *RR* for Mayak plutonium facility workers (filed diamonds) exposed via inhalation to Pu-239 in combination with external gamma rays, based on fitting data from Kokhryakov *et al.* (1996) and adjusting for a baseline to 95/100,000; adjusted *RR* for Beagle dogs(closed triangles) that inhaled Pu-238 in an insoluble form based on data from Muggenburg *et al.* (1996) after adjusting to a baseline of 95/100,000. Logarithmic scales are used on both axes. The upper dashed curve though the rat data for Pu-239 only (open circles) is based on Equation 1. Values for *RR = 0* are plotted at *RR = 0.1*. The zero dose-group for which *RR = 1* is excluded. The horizontal line is for *RR = 1*.

Note that the adjusted *RR* in Figure 2 seemed to converge for the different species an approach an asymptotic value as the alpha radiation dose increased above 10,000 mGy (10 Gy). The mainly very high alpha radiation doses received by dogs (500 to 340,000 mGy) appear to have completely inhibited or overwhelmed protective signaling associated with gamma-ray ANP.

Human lung cancer *RR* data in Table 3 from Khokhryakov *et al.* (1996) could not be directly adjusted (since *PROFAC > 0* implicated) for a baseline of 95/100,000 but were fitted to Equation 1 [work previously carried out Scott 2007)] assuming alpha radiation doses for each dose group were uniformly distributed over the dose intervals indicated and gamma-ray doses were negligible, except for their influence on protective signaling which is accounted for via *PROFAC*. All exposed workers were assumed to be protected by gamma-ray ANP for the range of alpha radiation doses in Figure 2. The simulated lower smooth curve for humans in Figure 2 is based on Bayesian analysis posterior mean values previously obtained for model parameter K_α *(=1.2x10^{-4} ± 9.0x10^{-5} mGy^{-1})* and *PROFAC (= 0.86 ± 0.07)* in fitting the data in Table 3 via Markov chain Monte Carlo (Scott 2007). The MCMC analysis comprised 1 million iterations with the first 800,000 results discarded as burn-in. For the results for humans in Figure 2, the

baseline *B* was fixed at 95/100,000. The upper dashed curve in Figure 2 for exposure only to alpha radiation also applies to humans and was obtained by setting *PROFAC = 0*.

Table 3. Unadjusted lung cancer *RR* for Mayak plutonium facility workers based on data from Khokhryakov *et al.* (1996)

Alpha Radiation Dose Range (mGy)	Mean Baseline Incidence per 100,000[a]	Observed Unadjusted *RR*	Expected Unadjusted *RR*, HRR Model[b]	Expected Adjusted *RR*, HRR Model[c]
0 – 2	41 ± 25	0.39	0.36 ± 0.07	0.24 ± 0.07
12.1 – 50	57 ± 41	0.53	0.56 ± 0.09	0.40 ± 0.07
51 – 200	76 ± 55	1.58	1.59 ± 0.14	1.30 ± 0.12
201 – 800	86 ± 93	4.65	4.66 ± 0.23	4.24 ± 0.21
801 – 3200	99 ± 106	28.1	28.1 ± 0.53	29.2 ± 0.55

[a]Based on Russian national statistics (Khokhryakov *et al.* 1996)

[b]Based on unadjusted results from previous application of HRR model to these data using Bayesian inference methods to address stochastic thresholds for ANP and for protection inhibition (Scott 2007).

[c]Expected *RR* based on the HRR model when the baseline *B=95/100,000* (same as for Wistar rats exposed to Pu-239 + Yb-169).

All results presented in Figure 2 therefore relate to a common baseline incidence, *B = 95/100,000*. Table 3 also provides predictions for the adjusted lung cancer *RR* for humans based on *B = 95/100,000* with doses assumed uniformly distributed over the group-specific dose intervals indicated in the table. Evaluations were carried out via MCMC analysis based on posterior distributions for model parameters K_α and *PROFAC*. This was achieved by rerunning the MCMC analysis previously used to estimate HRR model parameters but this time also making prediction of RR_{ANP} for *B = 95/100,000*. The results in Table 3 suggest that low baselines *B* can obscure the reduction in lung cancer *RR* associated with low-dose ANP.

Alpha radiation doses > 2000 mGy appeared to have inhibited protective signaling (e.g., related to the PAM process) for rats and dogs and the same is implicated for humans based on the convergence of the dose-response data (for protected and unprotected groups) at high doses.

3.3 Gamma-Ray ANP for Humans vs. Rats

Protection provided to humans and Wistar rats by low-dose/low-dose-rate gamma-ray ANP can be assessed relative to the upper dashed curve and filled circles in Figure 2 that relate to only alpha radiation exposure. Humans appear to be somewhat less protected than were Wistar rats, even when the uncertainty in *PROFAC* for rats (Table 1) is considered. Many of the male Mayak facility workers were heavy smokers and this may have impacted on the level of ANP-related protection that occurred. Genetic differences may also be important.

The results in Figure 2 are consistent with the view that low doses and dose rates of gamma rays activate the body's natural defenses (biological and chemical protection), which in turn can significantly reduce the risk of cancer from exposure to carcinogenic doses of other

agents. Similar results have been demonstrated for suppression of chemical-induced cancer via low-dose-rate exposure to sparsely ionizing radiation (Mitchel *et al.* 1999; Sakai *et al.* 2003). For alpha radiation doses > 2000 mGy in Figure 2, there is no evidence for gamma-ray ANP. This suggests that deleterious biological signaling associated with very high alpha radiation doses may overwhelm or suppress protective signaling in all mammalian species (including humans) that is associated with low dose gamma-ray ANP.

4. Implications for Other Radiations and Other Diseases

Gamma rays, x rays, and beta radiation have similar physical characteristic with respect to their interacting with biological tissue. Thus, extended exposures to essentially harmless low doses of any of these sparsely ionizing radiations would also be expected to efficiently stimulate protective signaling associated with ANP against lung cancer. Repeated (over and extended period) very small x-ray doses could be administered from machines in hospitals used for administering diagnostic x-ray procedures. Beta radiation sources used in nuclear medicine could also be administered in very small harmless quantities in clinical settings for achieving ANP against future cancer for high risk groups of adults. Special radiation ANP rooms (e.g., exercise, lounges) with elevated background radiation (e.g., from potassium-40) could be used in medical facilities for implementing natural protection from lung cancer for long-time heavy smokers.

Most children are unlikely to be at high-risk for cancer. Thus, using low-dose-radiation ANP to prevent cancer among children may be inappropriate in most cases.

The indicated low-dose radiation ANP is not restricted to preventing lung cancer but could be implemented in a clinical setting to possibly prevent any type of cancer for high-risk adults as well as for other genomic-instability associated diseases.

Many other agents are also being researched related to possibly preventing lung and other cancers among high risk populations and individuals. It may be beneficial to consider combining low-dose radiation (harmless doses) with other cancer preventative agents, *but new funded research is needed in this area.*

5. Conclusions

The results presented demonstrate that low doses of gamma rays when spread over time are a potent inducer of natural chemical and biological protection against lung cancer. Because gamma rays, x rays, and beta radiation have very similar physical characteristics related to their interaction with biological tissue, low x-ray and beta-radiation doses when spread over time (e.g., repeated very low doses of x rays, or continuous very-low levels of beta irradiation) are also expected to be potent inducers of natural chemical and biological protection against lung cancer. Similar protection is also expected against other types of cancer and for other genomic-instability-associated diseases.

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