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HEALTH RISK EVALUATIONS FOR INGESTION EXPOSURE OF HUMANS TO POLONIUM-210

Bobby R. Scott □ Senior Scientist, Lovelace Respiratory Research Institute, Albuquerque, NM 87108

□ The incident in London during November 2006 involving a lethal intake by Mr. Alexander Litvinenko of the highly-radioactive, alpha-particles-emitting polonium-210 (Po-210) isotope, presumably via ingestion, sparked renewed interest in the area of Po-210 toxicity to humans. This paper is the result of assembling and interpreting existing Po-210 data within the context of what is considered a reliable risk model (hazard-function [HF] model) for characterizing the risk of death from deterministic effects of high alpha radiation doses and dose rates to body organs. The HF model 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 but not yet validated set of assumptions and using available megabecquerel (Po-210) to gray dose-conversion factors, acute lethality risk vs. dose curves were developed for circumstances of ingestion exposure to Po-210 by humans. 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 systemic Po-210 burden. Because of the unavailability of acute lethality data derived from human ingestions of high levels of Po-210, plausibility of risk calculations were evaluated based on data from studies of Po-210 injections in animals. The animal data, although limited, were found to be consistent with the theoretical risk calculations. Key findings are as follows: (1) ingestion (or inhalation) of a few tents of a milligram of Po-210 will likely be fatal to all exposed persons. (2) Lethal intakes are expected to involve fatal damage to the bone marrow which is likely to be compounded by damage caused by higher doses to other organs including the kidneys and liver. (3) Lethal intakes are expected to cause severe damage to the kidney, spleen, stomach, small and large intestines, lymph nodes, skin, and testes (males) in addition to the fatal damage to bone marrow. (4) The time distribution of deaths is expected to depend on the level of radioactivity ingested or inhaled, with deaths occurring within about a 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 a 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 for life shortening could be significant. New, funded experimental and modeling/theoretical research is needed to improve on these estimates.

Keywords: Po-210, toxicity, threshold, LD50

INTRODUCTION

Shortly after the beginning of the November 2006 incident in London involving human poisoning (Mr. Alexander Litvinenko) via pre-

Address correspondence to Bobby R. Scott, Senior Scientist, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108; Ph.: 505-348-9470; Fax: 505-348-8567, E-mail:bscott@LRRI.org

sumed ingestion exposure to the highly-radioactive, alpha-emitting radionuclide polonium-210 (Po-210), there has been much interest expressed in the news and other media about what amount of Po-210 when ingested constitutes a lethal intake for an adult male human. This paper presents scientifically based calculations of ingested amounts expected to be required for lethality from severe damage to body organs. The current focus in the area of radiological-terrorism-related research is on the conduct of experiments designed to develop new drugs to reduce radiation dose and to prevent harm from radiation exposure. Too little attention is being devoted to the need for supportive theoretical/modeling research related to assessing radiation doses and the risk of harm for the various radiological terrorism scenarios of interest. This has led to a shortage of experts with sufficient background for answering the types of questions that were raised last November related to the Po-210 incident in London. Five such question follow:

1. Is it possible to become ill within 24 h of ingesting Po-210, and if so, would it signal a lethal intake?
2. How much Po-210 is required for causing death via ingestion in foods or drinks?
3. Is it possible to deliver a lethal radiation dose within 22 days (currently presumed survival time of Mr. Litvinenko) after ingesting micrograms quantities of Po-210?
4. What are the appropriate medical countermeasures to be employed in the event of intake of a potentially lethal amount of Po-210?
5. What are the chances of survival when appropriate medical countermeasures are implemented in a timely manner?

The type of modeling presented here helps address questions 1 - 3. An extension of the modeling (not addressed here) would allow addressing question 5. Possible approaches to addressing question 4 are discussed by Rencová *et al.* (1994, 1995, 1997), Geber and Thomas (1992), and by Guilmette (see Roessler 2007) based on Po-210 decorporation studies in animals.

Speculations have been made in the news media and over the Web about how much intake via ingestion of Po-210 might be needed to cause death from deterministic radiobiological effects. Deterministic effects are threshold-type effects that include death via severe damage to the hematopoietic system, gastrointestinal system, pulmonary system, or other body targets (e.g., liver and kidney). Large radiation doses are required to cause death via severe deterministic effects. The severe damage involves massive cell killing, especially of stem cells, leading to organ dysfunction and possibly failure which can be fatal over a relative

short time period (e.g., days to several weeks) or after a long delay (months).

Some key references considered (especially studies in the former Soviet Union of human exposures to Po-210) were not directly available. In such cases I have relied on information about these studies provided in other publications (e.g., Moroz and Parfenov 1971; Cohen 1989).

Discovery, Sources and Physical Characteristics of Po-210

Polonium was discovered by Marie Sklodowska Curie and her husband Pierre in 1898 by purifying it from pitchblende. The element was named in honor of Marie's homeland Poland.

Because of the radioactive decay of the uranium-series radionuclides, very low levels of Po-210 are naturally in air we breathe, the water we drink, biota, and foods we ingest (Stannard 1988; Cohen 1989). An extensive review of the sources and distribution of environmental Po-210 and normal metabolic levels in humans was published years ago by Parfenov (1973) and by Moroz and Parfenov (1971).

Po-210 is used industrially (e.g., in devices designed to eliminate static electricity). The radionuclide decays mainly via the emission of 5.297-MeV alpha particles (Roessler 2007) that have a range of 40 to 50 μm in biological tissue (Harrison *et al.*, 2007). Its physical half-life is 138 days.

Po-210 occurs naturally in very low concentration in the earth's crust (about 1 part in 10^{15} [ANL 2005]) and can be produced in relatively large quantities in nuclear reactors. The main commercial method of producing Po-210 in nuclear reactors is to neutron-irradiate a bismuth target to obtain Bi-210 which beta decays with a 5-day half-life to Po-210. Each month about 8 g of Po-210 is shipped to the United States from Russia (Roessler 2007). This is equivalent to 1.33 PBq (1 petabecquerel = 10^{15} Bq). A becquerel (Bq) represents 1 nuclear disintegration per second.

Po-210 is found in small amounts in uranium ore, can be present in very small amounts in cigarette smoke, and can occur in very small amounts in the home via the decay of radon-222 and its daughters. Thus, we all have very small amounts of Po-210 in our bodies, providing support for the view that very low alpha radiation dose rates and doses are likely tolerated without causing diseases. Obviously, our natural defenses evolved to protect us from such mild natural insults.

The highly infrequent gamma-ray photon emission is essentially negligible with respect to the overall radiological damage caused by Po-210. The specific activity of Po-210 is 1.66 TBq/g, astonishingly high for an alpha radiation source. One TBq equals 10^{12} Bq. The indicated value of specific activity corresponds to 1.66MBq/μg, implicating that a mass of only 0.6 μg is needed in order to produce 1 MBq of radioactivity. One mg of Po-210 emits as many alpha particles as is emitted by 5 g of radium-226 (ANL 2005).

Average Daily Intakes of Naturally Occurring Po-210 by Humans

In 1965, average daily dietary intake of naturally occurring Po-210 was estimated to range from 37 to 370 mBq (Hill 1965). Millibecquerel quantities of Po-210 constitute very small (considered harmless) amounts of radioactivity. It takes 1 billion mBq to make 1 MBq (units used in this paper for toxicity assessment). Hill (1965) estimated an average intake of 118 mBq/d for persons then residing in Great Britain and Holtzman *et al.* (1976) estimated and average intake of 67 mBq/d for persons then residing in the United States, based on excreta analysis (Holtzman 1963). Excretion of Po-210 averaged 70 ± 17 mBq/d in feces and 23 ± 9 mBq/d in urine of not-specifically-exposed humans (Holtzman *et al.* 1976).

Naturally Occurring Po-210 in Human Tissue

Concentrations of naturally occurring Po-210 in human tissues have been evaluated in Great Britain, the United States, and the Former Soviet Union (Holtzman 1966; Blanchard 1967; Ladinskaya *et al.* 1973; Parfenov 1973; Cohen 1989). Concentrations in the skeleton ranged from 1,295 - 1,480 mBq/kg and exceeded the soft tissue Po-210 concentrations because of in-growth and physical trapping of Po-210 formed from the decay of lead-210 (Pb-210) within the bone matrix (Cohen 1989). However, unlike Pb-210, which has a relative long biological half-life in bone, approximately 50 % of the Po-210 from Pb-210 decay is transported to soft tissues and later excreted (Cohen 1989).

Hair had about 3000 mBq/kg of Po-210. This suggests that body hair follicles may be an important excretion route in addition to the fecal and urinary routes (Cohen 1989).

Po-210 soft-tissue concentrations were the highest in the liver and kidneys (Cohen 1989). Ladinskaya *et al.* (1973) reported concentrations of 973 and 762 mBq/kg (sampled from adults) and Blanchard reported concentrations of 537 ± 74 and 418 ± 81 mBq/kg (sampled from 18 individuals ranging in age from 6 - 78 y).

Some consideration has been given to the levels of Po-210 in tobacco because of the hypothetical role low dose radiation has in lung cancer induction. Reported dose estimate vary covering a range from probably insignificant to possibly significant, depending upon the importance assigned to effects from hot-particle geometry (BEIR 1988; Cohen 1989).

Gastrointestinal Absorption of Po-210

Mr. Litvinenko is presumed to have ingested possibly a massive amount or Po-210 (based on radioactivity rather than mass). Significant gastrointestinal absorption into blood of Po-210 would be necessary for severe radiation damage to the bone marrow, kidneys, spleen, and other

sites to occur. Some studies in animals and humans have been carried out related to evaluating the gastrointestinal absorption of Po-210. Among the heavy elements, polonium occupies an intermediate position with respect to gastrointestinal absorption. Po-210 is reported to be more readily absorbed (ICRP 1979, 1993) than the actinides (e.g., uranium and plutonium isotopes), but less easily absorbed than radium isotopes (Moroz and Parfenov 1972; Cohen 1989).

Radiation dose to internal organs will depend on the level of uptake of the ingested Po-210 from the gastrointestinal tract into the blood. The efficiency of uptake depends both on the physical and chemical characteristics of the Po-210, which has great propensity to form colloids. Moreover, according to Moroz and Parfenov (1971), absorption of Po-210 from the gastrointestinal track into blood also depends on the physiological state of the gastrointestinal tract and the composition of the diet. It has been demonstrated that considerable Po-210 absorption may occur from the stomach (Stannard and Casarett 1964). The colloid formation is significantly reduced by low pH, thus soluble complexes are probably the principle forms absorbed (Moroz and Parfenov 1971).

Gastrointestinal tract components at risk for deterministic effects from large alpha radiation doses from deposited Po-210 and from systemic burdens may include blood vessels and other structures in the mucosa and submucosa (Harrison *et al.* 2007). Target cells may therefore include vascular endothelial cells, mesenchymal fibroblast and other cell types (Harrison *et al.* 2007). Animal data revealed an association between ingested Po-210 and intestinal tissue. Autoradiography revealed that surface adherence occurred rather than uptake into the intestinal mucosa (Morrow *et al.* 1964; Harrison *et al.* 2007).

The intestinal epithelium of rats receiving Po-210 by oral administration was found to be severely damaged (Stannard and Casarett 1964). The observed damage was suspected by the researchers to be significant with regard to Po-210 toxicity in the first few months after intake. The indicated observations support the view that lethal damage to the gastrointestinal track may occur after ingesting Po-210. However, radiation doses to the gastrointestinal tract presented later for ingested Po-210 are based on biokinetic and dosimetric models of the International Commission on Radiological Protection (ICRP 1993; Leggett and Eckerman 2001) which only account for irradiation arising from material that enters the blood. Thus, gastrointestinal tract doses are likely underestimated (possibly to a large extent). *However, new funded research is needed to develop improved dosimetry models for human exposures to Po-210 that are applicable to deterministic effects.* Current models were mainly developed for assessing cancer risk.

In a study of two rats exposed by gavage to approximately 20 MBq/kg-body-mass of freshly neutralized Po-210 chloride, gastrointestinal absorp-

tion (fractional absorption, f_1, of the intestine deposited Po-210 into blood) was estimated as 0.024 (2.4 % of the intake) and 0.048 (4.8 %) (Cohen 1989). After gavage administration of 0.52 MBq/kg-body-mass to rats, f_1 was found to be approximately 0.03 - 0.05 (i.e., 3 - 5 %) (Spoerl and Anthony 1956). Stannard (1954, 1964) reported average f_1 values of 0.05 (5 %) for male rats and 0.045 (4.5 %) for female rats based on balance studies after correcting for the amount of Po assumed to be excreted into the intestine via the bile.

In a series of experiments by Morrow *et al.* (1964), cats were administered by gavage either a colloidal hydroxide or soluble citrate form of Po-210. After placing Po-210 in the stomach, significant amounts were absorbed (0.6 - 1.6%) from the stomach, independent of chemical form, over a 7-h period. However, significant differences were found for the two chemical forms when the solution was placed in isolated duodenal loops of the small intestine. During a 10-h period, absorption was up to 40 times greater for the citrate solution. The authors indicated that in the stomach, gastric acidity converted the colloidal Po-210 to a soluble form, making absorption comparable to the momomeric citrate form, in agreement with Moroz and Parfenov (1971). The percentage of administered dose absorbed in the cat was less than that for the rat, but because of the limited duration of the cat experiments (7 - 10 h), the total amount of absorption may have been underestimated.

A male patient who was hospitalized with chronic myeloid leukemia is reported to have volunteered to ingest Po-210 in the amount 7.0×10^{-6} MBq /kg-body-mass in drinking water (Cohen 1989). Absorption of Po-210 is reported to possibly have reached 10 % ($f_1 = 0.1$); however, the authors indicated that the estimate was largely conjectural and may have been considerably overestimated. Higher values for f_1 have been reported when Po-210 is ingested in foods (Harrison *et al.* 2007).

The behavior of ingested Po-210 in the body is influenced by the form in which it enters the body. However, a large portion of the ingested Po-210 is rather quickly removed from the body via excreta (ANL 2005). A significant proportion of the ingested Po-210 that enters the blood from the gastrointestinal track concentrates in the spleen, kidney, lymph nodes, liver, bone marrow, skin (especially hair follicles), testes and other sites (Moroz and Parfenov 1971; Legget and Eckerman 2001; Harrison et al. 2007). For lethal intakes of Po-210, substantial alpha radiation doses could be delivered to the spleen, kidney, lymph nodes, and liver with smaller doses to the bone marrow, gastrointestinal tract, and other body sites. Dose rates after lethal intakes are likely to be high for several months, especially when the alpha particle's relative biological effectiveness (RBE) for causing deterministic effects is taken into consideration. For a fixed level of intake (e.g., in megabecquerels), dose rate (whole-body) would be higher for a small child as compared to a large adult.

A more uniform radiation exposure throughout the body is thought to occur for ingested Po-210 than after ingesting other alpha-emitting radionuclides such as plutonium-238 (Pu-238) and Pu-239. However, for inhalation exposure, intake of airborne high-specific-activity Po-210 will likely vary for different persons breathing the same contaminated air for the same period of time (Scott *et al.* 1997; Scott and Fencl 1999; Aden and Scott 2003).

For estimating radiation doses to organs in the body of humans, calculated doses presented later in this paper are based on $f_1 = 0.1$, although the possibility for greater absorption cannot be ruled out. *New, funded research is needed to improve on this estimate and to address the associated uncertainties.*

Respiratory Tract Deposition of Inhaled Po-210

Inhalation of aerosols or particles that contain Po-210 can result in deposition of the radionuclide throughout the respiratory tract, including the surface of the lung. The amount retained after a given period depends on the aerodynamic characteristics of the aerosol, the physiological characteristics of the process of respiration, and respiratory tract geometry (Moroz and Parfenov 1971). For material deposited on the surface of lung, the lung epithelia will be irradiated by alpha particles. During and just after inhalation exposure, the ionic or soluble Po-210 can be absorbed into the bloodstream. Insoluble colloidal Po particles were reported to be eliminated from the lung with an effective half-time of 18 - 35 days (Moroz and Parfenov 1972). Because of the high-specific activity of Po-210, some aggregates may break up over time, thereby enabling additional absorption of Po-210 into the blood. Systemic uptake of Po-210 can also occur as a result of its transport up the mucociliary escalator in the bronchial tree, resulting in Po-210 being swallowed, thereby entering the gastrointestinal tract and being absorbed into the blood.

Rats exposed via inhalation to 0.28 μm mass median diameter (MMD) Po-210-chloride aerosol in 0.1 *N* hydrochloric acid had an estimated lung and trachea deposition of 25 % (relative to the total material presented for inhalation), with an equal amount of Po-210 found in the gastrointestinal tract following a 5-hour exposure (Berke and DiPasqua 1964; Cohen 1989). Twenty-minutes of nose-only exposure of rats to freshly neutralized Po-210 aerosol with 0.046 μm count median diameter (CMD; 0.34 μm MMD) resulted in an average pulmonary deposition of about 33 %, which was divided equally between the upper and lower portions of the respiratory tract (Casarett 1964; Cohen 1989).

A small number of dogs were exposed via inhalation to Po-210-chloride carried on a sodium-chloride aerosol, with a CMD of 0.04 μm (Smith *et al.* 1961). Average respiratory tract deposition was reported to be 64 %, with values ranging from 48 - 77 %, based on use of 6 dogs.

These results indicated that Po-210 could cause severe damage to targets in addition to the lung (e.g., gastrointestinal tract, liver, spleen, kidneys, bone marrow, skin, testes, and lymph nodes) when large amounts of radioactivity are inhaled.

Intake of Po-210 via the Skin

Po-210 is reported to penetrate the skin upon contact when in a soluble form (Cohen 1989). A Po-210 chloride solution placed on the bottom of the paws of mice was reported to be absorbed at the rate of 0.08 - 0.4 % per day (Cohen 1989). Fink (1950) investigated the absorption of Po chloride directly through human skin. It was concluded that absorption occurred at less than 2 % per day. These results would seem to indicated that a lethal amount of Po-210 could be administered via skin absorption into blood over an extended exposure period. Later in this paper, dose estimates based on ICRP models are provided for skin irradiation from Po-210 that enters the blood. It is shown that substantial radiation doses could be delivered to the skin after lethal amounts of Po-210 enter the blood via ingestion. This is also expected after lethal inhalation exposures.

Po-210 Distribution *in Vivo* after Large Intakes

Published studies of Po-210 distribution in the body were evaluated by Moroz and Parfenov (1971). Summarized, Po-210 is diffusely distributed throughout the body, predominately depositing in organs of the reticuloendothelial system. Thus, Po-210 can be detected in practically all body tissue after large intakes. Within minutes after being internalized, Po-210 appears in the blood, with the highest concentration in blood cells. Blood cell radioactivity concentration is about 20-fold larger than that for plasma. In neutral media in the body, Po-210 forms colloidal complexes with proteins. These radioactive hot particles are taken up by erythrocyte membranes, and the erythrocyte-hot-particle combinations are reported to be engulfed by macrophages and histocytes (Moroz and Parfenov 1971). This leads to accumulation over time of Po-210 in the reticuloendothelium in the form of large hot particles that can be detected as stars in autoradiograms. The largest concentrations of Po-210 were found in the lymph nodes, spleen, liver, and kidneys.

The mucous membrane and especially the epithelium of the intestines can contain substantial amounts of Po-210 as previously indicated. Po-210 is also detected in hair follicles, hair sheaths, the corneal epithelium of the eye, and in tear and mammary glands.

Po-210 Acute Toxicity in Laboratory Animals

The toxicity of Po-210 to mammals is discussed in two publications by Moroz and Parfenov (1971, 1972). Based on studies (presumed in the

Soviet Union) by a number of Soviet-era authors, when systemic burdens (subcutaneously injected) in dogs were 1.85 - 6.66 MBq/kg-body-mass, the animals developed acute radiation sickness (prodromal syndrome implied) and died from 10 days to 4 weeks after receiving the injections. Burdens of 0.74 - 1.11 MBq/kg-body-mass caused what was called "subacute radiation sickness" and were also lethal for the dogs. The lower burden of 0.0925 MBq/kg-body-mass apparently caused chronic radiation sickness in dogs leading to death between 6 and 12 months after administration. In rats, an injected burden of 1.45 MBq/kg-body-mass tended to cause deaths within 30 days (Rencova *et al.*, 1997).

A number of median lethal systemic burden (LD_{50}) studies in animals (rats, cats, rabbits, and dogs) have been summarized by Cohen (1989) and by Moroz and Parfenov (1971). Rats were reported to have similar radiosensitivity to Po-210 alpha irradiation as dogs. Rabbits were found to be more radioresistant than dogs and rats. Unfortunately, the studies focused on end-points such as $LD_{50/20}$ (i.e., lethal systemic burden for 50 % of the animals within 20 days), $LD_{50/30}$, and $LD_{50/40}$, which for Po-210 exposures means that results obtained are but snapshots in time reflecting the responses to the early radiation dose accumulation. Intakes found to harm 50 % of the exposed groups at 20, 30, or 40 days after intake of Po-210 would be expected to harm even more (possibly all) with longer follow-up, especially since alpha radiation is involved and radiation doses to target organs can increase significantly over a number of months. Indeed, the indicated systemic body burdens (e.g., 1.1 - 2.6 MBq/kg-body-mass) after injecting Po-210 appear to fall in the lethal-to-all range for the risk of death for humans after long-term follow-up, based on results presented later in this paper.

These results indicate that Po-210 ingestion-related deaths occurring within a month of ingestion would suggest a very large intake of radioactivity, even though the mass of Po-210 associated with the intake may be microgram quantities. Lower lethal amount could cause chronic radiation sickness with death occurring up to 1 year (or longer) after intake of Po-210.

Table 1 summarizes the hematological effects and histopathology for laboratory animals (rats, mice, cats, rabbits, and dogs) exposed to Po-210 as a function of the level of exposure (presumed systemic burdens) based on an adaptation of Table 2.4 from Cohen (1989). The cited table by Cohen appears to have incorrectly reported systemic burdensin kBq/kg-body-mass when kBq/g-body-mass appear to be the correct units. For example Moroz and Parfenov (1971) reported an $LD_{50/30}$ equivalent to 1.1 kBq/g-body-mass and an $LD_{50/20}$ equivalent to 1.9 kBq/g-body-mass for Po-210 injected into rats. On a per kilogram-body-mass basis, the estimates would be a 1,000-fold larger. Thus, values reported by Cohen (1989), which were similar in magnitude as the values indicated here (not a 1,000-fold higher), were interpreted to be in units of kBq/g-body-mass.

TABLE 1. Summary of toxic effects of single intakes of Po-210 by laboratory animals when evaluated as a function of the systemic burden in MBq/kg-body-mass (adapted from Cohen 1989).

Systemic burden (MBq/kg) *[Lethality]*	Animal type	Lethality period *[Comment]*	Histo-pathology	Hematological observations	Gross observations
1.9 - 3.7 *[All died from acute effects]*	Cat, dog, rabbit, mouse	20 days[a] *[$LD_{50/20}$ of 3 MBq/kg]*	Massive tissue destruction	Severe loss of lymphocytes, WBC[c], RBC[d], hemoglobin	Weight loss, lethargy, death
1.3 - 1.7 *[All died from acute effects]*	Rat	20 days[a] *[$LD_{50/20}$ of 1.5 MBq/kg]*	Massive tissue destruction	Severe loss of lymphocytes, WBC, RBC, hemoglobin	Weight loss, lethargy, death
0.37[b] - 1.1 *[All died, deaths were delayed]*	Rat	50-250 days	Rapid occurring kidney damage	Moderate to severe loss of WBC, effects on RBC and hemoglobin as rat is dying	Weight loss
0.37 *[All died, deaths were further delayed]*	Rat	300 - 500 days	Slowly-occurring kidney damage	Early WBC reduction, followed by recovery	Moderate weight loss
0.02[b] - 0.04 *[Possibly lethal]*	Rat	*[10 - 20 % reduced life-span]*	Occasional mild kidney and/or thyroid lesions	None	None
0 - 0.01 *[Not likely lethal]*	Rat	*[No early deaths]*	None	None	None

[a]At least 50 % of the deaths occurred within 20 days of Po-210 intake. No animals would be expected to survive past 4 weeks (Moroz and Parfenov 1971)

[b]Using results presented later for humans based on systemic Po-210 burden, burdens of 0.02 - 0.04 MBq/kg are close to the threshold for acute lethality.

[c]WBC = white blood cells

[d]RBC = red blood cells

Note that the results in Table 1 indicate that systemic burdens greater than about 1.1 MBq/kg-body-mass appear to be lethal (with no survivors) with 50 % of deaths apparently occurring within about 20 days, presumable via the hematopoietic mode. Harrison *et al.* reported results from a rat study showing that for systemic burdens > 4.4 MB/kg-body-mass, 50% of the animals died within 7 days, suggesting the possible occurrence of a mode of death other than the hematopoietic mode (possibly the gastrointestinal or another mode). For systemic burdens in Table 1 between 0.37 and 1.1 MBq/kg-body-mass, deaths are somewhat delayed (apparently occurring between 50 - 250 days, with no survivors), possibly associated with the lower radiation dose rates. For systemic burdens between 0.04 and 0.37 MBq/kg-body-mass, deaths appear even more delayed (with no survivors) apparently occurring between 300 and 500 days after Po-

210 exposure. Systemic intakes between 0.02 and 0.04 MBq/kg-body-mass appear to be associated with life shortening but apparently no deaths occur from acute effects. Systemic burdens lower than about 0.04 MBq/kg appear not sufficient for causing death via radiation-induced deterministic effects. The mortality frequencies presented in Table 1 are later compared to theoretical-model-based threshold, median-lethal, and the minimum dose for 100% lethality estimates and are shown to be in good agreement.

EVALUATIONS OF THE RISK OF DEATH FROM DETERMINISTIC EFFECTS FOR ADULT HUMANS

The risk of death for deterministic effects is evaluated here for a range of single ingestion intakes of Po-210 by humans. Results obtained are based on the following assumptions (*which require further research for validation*):

1. The systemic burden of Po-210 determines the absorbed alpha radiation doses to the bone marrow, kidney, spleen, and liver.
2. Lethal doses to the kidney, spleen, and liver are much higher than lethal doses to the gastrointestinal tract.
3. For the gastrointestinal tract, the large intestine is the critical target since waste transit times are slower (with related higher doses) for this compartment.
4. Death occurs via one of the two modes (among several possible modes) with the two lowest thresholds: hematopoietic and gastrointestinal.

Hazard Function Model

Risk of death is evaluated using the hazard function (HF) model developed at our Institute by this author. The HF model is quite general and can be adapted for application to a variety of radiation exposure scenarios (Scott and Hahn 1980; Scott 1988; Scott *et al.* 1988; Scott and Hahn 1989; Scott and Dillehay 1990; Scott *et al.* 1990, 1995, 1998; Scott 1993, 1995; Scott and Peterson 2003; Scott 2004, 2005). The HF model has undergone extensive peer review and is currently used internationally for radiological incident risk assessment by different, widely recognized organizations. This includes use by the U.S. Nuclear Regulatory Commission (USNRC 1998), by the U.K. National Radiological Protection Board (NRPB 1996) (Now the Health Protection Agency), and by the International Atomic Energy Agency (IAEA 2005). The model is also being used by scientists for assessing the expected health consequences of uses of radioactivity (radiological) dispersal devices by terrorists (F. Harper, Sandia National Laboratories, personal communications, 2006).

The HF model is briefly described here. For the competing modes of death, risk function, *R*, (i.e., individual probability of death) is given as a function of the total lethality hazard, H_{total}, (a cumulative hazard function) and survival probability, *S*, by:

$$R = 1 - S = 1 - exp(-H_{total}). \quad (1)$$

H_{total} represents the sum of lethality-mode-specific hazard functions. Here, only two modes of death are being assumed (hematopoietic and gastrointestinal) for ingested Po-210. In this case, H_{total} is given by the sum $H_{hematopoietic} + H_{gastrointestinal}$, with the subscript indicating the specific mode of death. Presently, inter-organ interactions are presumed accounted for by $H_{hematopoietic}$, which is largely based on data for total-body exposure and therefore includes inter-organ interaction effects. *Additional modes of death (lethal kidney damage, lethal spleen damage, lethal liver damage) could be added as needed via new, funded research.* Lethality hazard functions H_{spleen}, H_{liver}, and H_{kidney} could, in theory, be developed.

Evaluating Lethality-Mode-Specific Hazard Functions

The hazard function H_j, for the *j*th mode of death (e.g., *j = hematopoietic*), can be evaluated in different ways depending on the type of the exposure scenario considered. The RBE-weighted dose has been used when combinations of high- and low-LET radiations are involved (IAEA 2005). However, for Po-210, only alpha radiation needs to be considered because the gamma-ray component of the dose is insignificant. In this case, the risk for acute lethality can be adequately characterized using the un-weighted organ-specific absorbed alpha radiation dose *D*. The hazard function for the *j*th mode of death is evaluated as

$$H_j = ln(2)\,[\int \{y/D_{50}(y)\}dt]^V = ln(2)\,[X^V], \quad (2)$$

where *V* is the shape parameter; *y* is instantaneous dose rate for the target organ of interest; *X* is the corresponding normalized dose in units of the lethality-mode-specific, median-lethal dose D_{50}. While the notation D_{50} is used here for the median lethal dose (i.e., $D_{50} = LD_{50}$), it can also be used for the median effective dose (ED_{50}) for morbidity endpoints (Scott 2004). The value $X = 1$ corresponds to the D_{50}.

Functional Relationship Between D_{50} and Dose Rate

$D_{50}(y)$ has been demonstrated to be adequately characterized for death via the hematopoietic, gastrointestinal, and pulmonary modes using the empirical relationship (Scott and Hahn 1989; NRPB 1996; USNRC/CEC 1997)

$$D_{50}(y) = (\theta_1/y) + \theta_\infty, \quad (3)$$

that was developed for exposure to low-LET beta and/or gamma radiation. Similar relationships can be applied to morbidity risks (NRPB 1996). Beta and gamma radiations were treated as equally effective. Adjustments for high-LET alpha radiation are based on the relative biological effectiveness, $RBE_{\alpha,}$ for alpha radiation relative to gamma rays (USNRC/CEC 1997). The parameter θ_∞ is just the value (asymptotic value) of $D_{50}(y)$ at very high dose rates *y*. The term (θ_1/y) accounts for the steep rise in $D_{50}(y)$ as dose rate decreases to very low values allowing for more efficient recovery from radiation damage than after high rates (Scott *et al.* 1988; Scott and Hahn 1989). Values for θ_∞ and θ_1 appear to differ for the different modes of death *but new research is needed to resolve this*. No values have been estimated for lethal damage to the spleen, kidney, or liver.

For alpha radiation, parameters θ_1 and θ_∞ are different than for beta and gamma radiations (USNRC/CEC 1997). This causes RBE_α to be dose-rate-dependent. Previous research on RBE_α (USNRC/CEC 1997) led to reducing θ_∞ for gamma-ray exposure by the high-dose-rate RBE for alpha radiation (estimated to be 2 for deterministic effects in bone marrow) to obtain the corresponding parameter $\theta_{\infty,\alpha}$ for alpha radiation. However, the parameter θ_1 (0.07 Gy^2/h for bone marrow [Scott and Dillehay 1990]) in Equation 5 has to be reduced by the high dose rate RBE_α squared (USNRC/CEC 1997) in order to obtain the corresponding parameter $\theta_{1,\alpha}$ for alpha radiation. Using this approach, $\theta_{\infty,\alpha} = 1.5\ Gy$ and $\theta_{1,\alpha} = 0.0175\ Gy^2/h$ (central estimates).

Po-210 Ingestion Intake to Absorbed Radiation Dose Conversion Factors

In order to evaluate the risk of death after ingesting megabecquerel quantities of Po-210 using the HF model, one needs radioactivity intake to absorbed dose conversion factors (gray/megabecquerel/kilogram-body-mass) for each target organ of interest for the follow-up period of interest. The ICRP has used available information on the biokinetics and dosimetry of radionuclides to develop models for evaluating radiation dose per unit radioactivity intake as a function of time after ingesting or inhaling radionuclides (ICRP 1975, 1979, 1993, 1994a,b, 1996, 2006; Leggett and Eckerman 2001). Weighted dose (e.g., in Sv) is used for cancer risk assessment. However the cancer-induction-related weights have to be omitted for application to risk assessment for deterministic effects. The Acute Dose Calculator (USEPA 2006) implements ICRP models using the AcutDose Code and allows estimation of alpha radiation dose (un-weighted) to multiple organs from ingested Po-210 for different follow-up times according to the methodology described by Leggett and Eckerman (2001). The AcutDose Code provides results for both $f_1 = 0.1$

and $f_1 = 0.5$ for ingested Po-210. Because the indicated ICRP models were mainly designed for assessment of cancer risk at low doses, careful consideration needs to be given to their use for evaluating radiation deterministic effects (Harrison *et al.* 2007). In fact, absorbed radiation doses to the gastrointestinal tract relevant for deterministic effects are likely underestimated since only irradiation associated with Po-210 that enters the blood is accounted for with the code. However, this is not expected to impact on the accuracy of the calculated risk of death, since the hematopoietic mode is expected to predominate at doses just above the lethality threshold up to the minimum dose for 100% lethality. For higher doses, other modes of lethality are expected to come into play (e.g., gastrointestinal mode). For this higher dose range, the lethality risk can then be attributed to one or more modes as is done later for high-rate exposure to alpha radiation shortly after intake of Po-210 (e.g., within a month of intake).

Dose conversion factors for ingested Po-210 are presented in Table 2 for different organs of interest for a reference 70 kg adult male. Conversion factors are provided for the red bone marrow, lower large intestine (wall), liver, kidneys, spleen, skin, and stomach (wall). The skin was included to demonstrate the possibility for large radiation doses to the skin from Po-210 that enters the blood. The stomach was included to show that doses to the stomach wall could be large enough during day 1

TABLE 2. Organ absorbed dose (Gy)/MBq Po-210 intake, conversion factors for an adult human (70-kg reference adult male) based on the AcutDose Code (USEPA 2006)

Days After Ingestion	Red Bone Marrow	Lower Large Intestine Wall	Liver	Kidneys	Spleen	Skin	Stomach Wall
1	0.000278	0.000766	0.000641	0.00121	0.00105	0.0000598	0.000121
7	0.00307	0.00278	0.00758	0.0146	0.0126	0.000354	0.000416
14	0.00596	0.00311	0.0148	0.0286	0.0246	0.000656	0.000717
21	0.0085	0.00338	0.0211	0.0408	0.0352	0.00092	0.000982
22	0.00883	0.00342	0.0219	0.0425	0.0366	0.000955	0.00102
28	0.0107	0.00363	0.0267	0.0516	0.0444	0.00115	0.00121
30	0.0113	0.00369	0.0281	0.0544	0.0468	0.00121	0.00127
60	0.0179	0.00441	0.0444	0.086	0.074	0.0019	0.00196
90	0.0216	0.00481	0.0537	0.104	0.0895	0.00228	0.00234
120	0.0237	0.00504	0.059	0.114	0.0982	0.0025	0.00256
150	0.0249	0.00518	0.0619	0.12	0.103	0.00263	0.00269
180	0.0256	0.00525	0.0636	0.123	0.106	0.0027	0.00276
210	0.026	0.00529	0.0646	0.125	0.108	0.00274	0.0028
240	0.0262	0.00532	0.0652	0.126	0.109	0.00276	0.00282
270	0.0263	0.00533	0.0655	0.127	0.109	0.00276	0.00284
300	0.0264	0.00534	0.0656	0.127	0.109	0.00279	0.00284
360	0.0264	0.00534	0.0658	0.127	0.11	0.00279	0.00285
400	0.0264	0.00535	0.0658	0.127	0.11	0.00279	0.00285
500	0.0265	0.00535	0.0659	0.127	0.11	0.00279	0.00285

after a lethal ingestion intake to induce prodromal symptoms (e.g., vomiting). Other organs were included in addition to bone marrow to show reasons for expecting severe damage in multiple oranges after lethal intakes of Po-210.

Evaluating the Possibility of Prodromal Symptoms Being Caused by Ingested Po-210

A similar equation as Equation 3 also applies to prodromal symptoms (e.g. vomiting) (NRPB 1996). For high-rate exposure, $D_{50}(y)$ is essentially equal to θ_∞ and dose-rate effects can be neglected for both morbidity and lethality. Because the dose-conversion factors in Table 2 implicate large radiation doses to the stomach wall after ingesting hundreds of MBq of Po-210, one has to consider it possible that prodromal symptoms (e.g., vomiting, diarrhea) may be caused by ingested Po-210. Table 3 gives estimated thresholds and median effective absorbed radiation doses for the prodromal symptoms of vomiting and diarrhea based on $RBE_\alpha = 2$ for deterministic effects in the stomach derived from the corresponding published values for gamma rays (Scott 2004). The value of 2 for RBE_α is the same as has been recommended for bone marrow (discussed later). Using a dose conversion factor of 0.121 Gy/GBq (based on Table 2) for a 1-day absorbed alpha radiation dose to the stomach wall of a reference 70 kg adult from ingested Po-210, it would appear that an intake of about 2 GBq (1 gigabecquerel = 10^9 Bq) of Po-210 or larger via ingestion would be expected to be required to cause vomiting within 1 day after ingesting Po-210. Experiencing prodromal symptoms during the first (or even the second or third) day after ingesting (or inhaling) Po-210 would suggest a possible lethal intake.

Few human data are available that relates to Po-210 induced prodromal symptoms. However, a Russian inhalation exposure case was reported by Ilyin (2001; also discussed in Harrison *et al.* 2007) in which a male

TABLE 3. Central estimates of thresholds, median effective, and median lethal absorbed radiation doses for Po-210 alpha-radiation-induced deterministic effects after high-rate exposure at early times after radionuclide intake.

Symptom or Mode of Death	Region for Dose Evaluation	Threshold (Gy)[a]	Median Effective or Median Lethal Absorbed Radiation Dose (Gy)[a]
Vomiting	Stomach wall	0.25 (0.17,0.5)[b]	1
Diarrhea	Stomach wall	0.5 (0.33,1.0)[b]	1.5
Hematopoietic mode of death	Bone marrow	0.51 (0.34,1.0)[b]	1.5

[a]Based on $RBE_\alpha = 2$.

[b]Lower and upper bounds based on lower and upper bounds for RBE_α of 2 and 3.

worker accidentally inhaled Po-210. The individual survived for only 13 days after inhalation exposure. His total retention of Po-210 was estimated to be 100 MBq. Vomiting was severe at the time the individual was admitted to the clinic (two to three days after exposure) but there was no diarrhea. These data are consistent with the view that demonstrating prodromal symptoms within a few days of Po-210 intake would suggest a possible lethal intake.

Evaluating the Risk of Acute Lethality via the Hematopoietic Mode for High-Rate Exposure to Alpha Radiation

For high-rate, gamma-radiation-induced acute lethality (via the hematopoietic mode), θ_∞ = 3 Gy (lower and upper bounds of 2.5 and 3.5 Gy, respectively) to bone marrow (Scott 2004). For lethal damage to the bone marrow, the deterministic effects RBE_α has been estimated to be 2 (lower and upper bounds of 1 and 3, respectively) relative to gamma rays for high-rate exposure, based on limited data (Scott 1993, 2004). The value of 2 is presumed to also apply to the gastrointestinal tract for high-rate exposure to alpha radiation from ingested Po-210 as previously stated. *However, new funded research is needed to establish the best estimates of RBE for the different modes of death that could occur as a result of ingesting or inhaling Po-210.*

For the gastrointestinal mode of death (with doses evaluated to the large intestine), θ_∞ = 15 Gy (lower and upper bound of 10 and 20 Gy, respectively) (Scott 1993, 2004). These estimates are based on animal data.

For the hematopoietic mode of death, the shape parameter *V* has the central estimate 6 (lower bound 4 and upper bound 8) based on human data (Scott 1993, 2004; Scott and Peterson, 2003). For the gastrointestinal mode of death, the central estimate for *V* is 10 (based on animal data) and no uncertainty has been previously assigned (Scott 2003, 2004). *New funded research is needed to improve on these estimates and the associated uncertainty distributions.*

Figure 1 shows the dose-response curve for a reference adult human (a hypothetical 70-kg person) obtained for the risk (central estimate) of death vs. the ingestion intake of Po-210 when two competing modes of death were considered (hematopoietic and gastrointestinal) and when the follow-up period is 22 days over which high dose rates were presumed to persist. The 22 day period corresponds to the reported survival time of Mr. Litvinenko. The dose-response curve should be considered a snapshot in time, as additional dose and risk will occur well beyond 22 days. The curve is useful for addressing the question as to whether a lethal alpha radiation dose could accumulate within 22 days of intake of Po-210. The data points presented in Figure 1 represent the intake levels for which computations were carried out. Although two possible modes of death were considered, essentially all of the lethality risk was related in

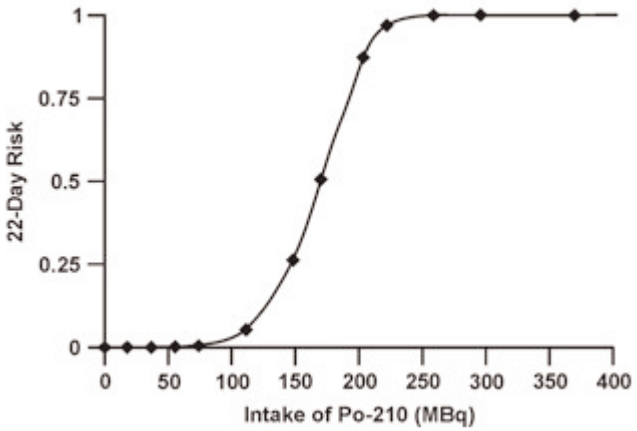

FIGURE 1. Central estimates of the risk of death from the hematopoietic or gastrointestinal modes as a function of the ingestion intake of Po-210 by adult 70-kg male humans. Systemic uptake of Po-210 into blood via gastrointestinal absorption is expected to be a factor of 10 smaller (central estimate) than the indicated intake values. Data points indicate where calculations have been conducted. For the range intakes shown, the hematopoietic mode of death was found to predominate (see Figure 2).

the calculation to bone marrow failure except for doses very much greater than the minimum dose for 100% lethality. The indicated curve should be regarded as possibly having large uncertainty which relates both to model and parameter uncertainties. *However, a comprehensive evaluation of uncertainties requires new, funded research.* Some uncertainties are addressed later in this paper using a rather crude approach.

Intakes of more than 260 MBq were calculated as being lethal with a probability of 1. This relates to lethal injury occurring with a 22-day exposure period. At 37 MBq intake, the calculated lethality risk (central estimate) was << 0.001 with respect to the dose that accumulates over the 22-day follow-up period. For longer follow-up, a 3 MBq dose may also turn out to be lethal. How to address this added risk as well as dose rate effects are discussed later.

Figure 2 relates to the attribution of the lethality risk among the two modes of death considered (hematopoietic and gastrointestinal) as a function of the Po-210 intake in gigabecquerels. Again, results presented are specific for a 22-day follow-up and for a 70-kg human. The risk attribution is expressed as a percent (%), representing the percentages of the total expected deaths ascribed to each of the two modes (hematopoietic and gastrointestinal). The gastrointestinal mode attribution (*GIMA*) was evaluated as $(R_{gastrointestinal}/R)*100$, where $R_{gastrointestinal}$ is calculated as $1 - exp(-H_{gastrointestinal})$ and R is evaluated based on Equation 1. The hematopoietic mode attribution (*HEMA*) is calculated as $[R_{hematopoietic}(1 - R_{gastrointestinal})/R]*100$. Implied here is a target population with groups of individuals (comprised of reference men) having the same intakes. The

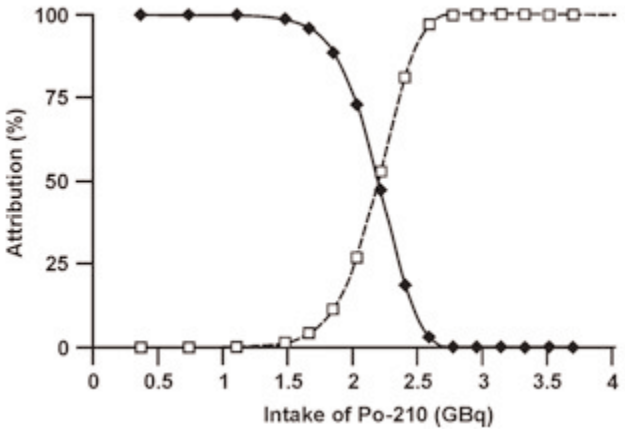

FIGURE 2. Attribution of risk between the hematopoietic (*HEMA*) and gastrointestinal (*GIMA*) modes based on the HF model applied to 70-kg adult male human for ingestion intake of Po-210. Diamonds represent the *HEMA* while squares represent the *GIMA*. Data points indicate where calculations have been conducted. Systemic uptake of Po-210 into blood via gastrointestinal absorption is expected to be a factor of 10 smaller (central estimate) than the indicated intake values.

sum *GIMA* + *HEMA* equals 100 %, for each intake level. The inclusion of the gastrointestinal mode in the risk attribution calculation is mainly based on animal data showing severe damage to the gastrointestinal tract after ingesting large amounts (based on radioactivity) of Po-210. However, the Acute Dose Calculate (USEPA 2006) may greatly underestimate the absorbed radiation dose to the gastrointestinal tract components because only irradiation arising from Po-210 that enters the blood is accounted for. Even so, for GBq quantities of Po-210 being ingested, severe damage to the gastrointestinal tract is being implicated even with doses likely being underestimated.

A high *GIMA* occurs (based on current dose estimates) essentially only at intakes that are lethal ($R = 1$) to the bone marrow (e.g., intakes > 2.3 GBq). The impact of the indicated gastrointestinal dose uncertainty is not on the lethality risk (which equals 1) but rather on judging what medical countermeasures would be appropriate for possible life saving.

For intakes below about 2.3 GBq, the hematopoietic mode is calculated to predominate (Figure 2). For higher intakes, the gastrointestinal mode is calculated to predominate (Figure 2). Preventing death via the gastrointestinal mode does not however guarantee survival of the hematopoietic mode. For Table 2 it can be seen that large radiation doses would also be expected to be delivered to the kidney, spleen, and skin over time. Thus, possibly lethal damage to multiple organs would need to be addressed via medical countermeasures employed. These results point out the importance of applying medical countermeasures, e.g., applications that remove Po-210 from the body early on after ingesting or inhaling possibly lethal amounts of Po-210. Some agent have successfully

removed Po-210 from the body of animals (Rencová *et al.* 1994, 1995, 1997; Roessler 2007).

In the very hypothetical case that a novel chelating agent was applied on day 22 and removed most of the remaining Po-210 from the body, Figure 1 would then reflect the residual risk for lethality at later times. With significant Po-210 remaining in the body, risks $R < 1$ could increase toward 1 at a rate that depends on the Po-210 body burden.

The risk vs. absorbed radiation dose curve obtained is presented in Figure 3 and applies to average absorbed dose rates greater than about 0.1 Gy/h, based on evaluating median lethal absorbed radiation dose as a function of absorbed dose rate using the HF model as applied to alpha radiation only (USNRC/CEC 1997). To obtain corresponding results as are presented in Figure 3 based on megabecquerel/kilogram-body-mass of ingested Po-210, one needs an appropriate dose conversion factor for the specific individual of interest. For a 70-kg male adult, and using a bone marrow dose conversion factor of approximately 0.0265 Gy/MBq for the total absorbed radiation dose (Table 2), one calculates an intake of 56 MBq of Po-210 as the median lethal intake associated with a risk of 0.5 of death from deterministic effects after long-term follow-up. The corresponding value in MBq/kg-body-mass is 0.8, and can be applied to all humans for which $f_1 = 0.1$ (which may exclude young children and the unborn fetus). The dose-response curve in Figure 4 is based on use of this value in Equation 7 along with $V = 6$. The corresponding value in μg/kg-body-mass is 0.5 (rounded), a very small mass. Corresponding systemic burdens (absorbed into the blood) are expected to be a factor of 10 smaller (0.08MBq/kg-body-mass and 0.05 μg/kg-body-mass) and to apply

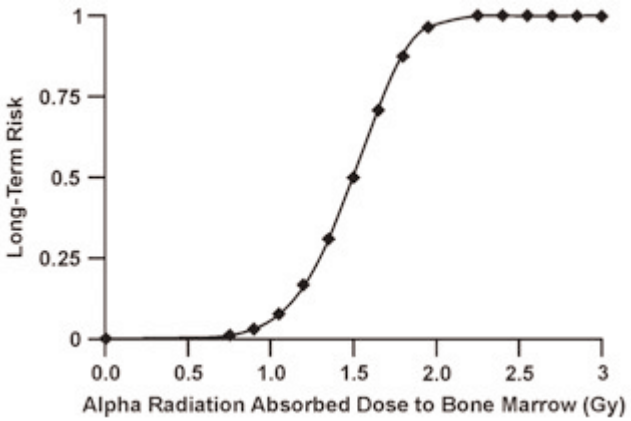

FIGURE 3. Calculated long-term risk (central estimates) of death via the hematopoietic mode after ingesting Po-210 based on the HF model and evaluated as a function of the absorbed alpha radiation dose to bone marrow (assuming $RBE_\alpha = 2$). Results apply to high-rate exposure and to all ages (except *in utero*). Radiation doses are total doses. Data points indicate where calculations were conducted.

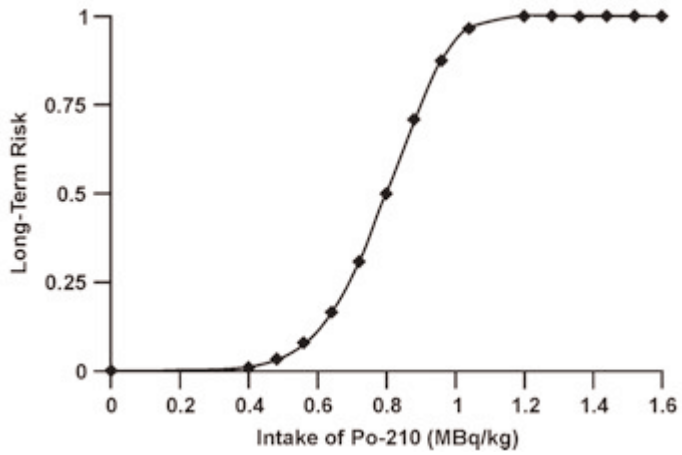

FIGURE 4. Calculated risk (central estimates) of death via the hematopoietic mode after ingesting Po-210 based on the HF model with risk evaluated as a function of the ingestion intake of Po-210 in megabecquerel/kilogram-body-mass. Results apply to high-rate exposure. Data points indicate where calculations were conducted.

to all ages (except for *in utero* exposure which has not been researched). The dose-response curve in Figure 5 is based on a median lethal systemic burden of 0.08 MBq/kg-body-mass along with with $V = 6$. The 0.08 MBq/kg-body-mass is consistent with the the animal data in Table 1. However dose rate effects have not yet been addressed. They are addressed in the next section.

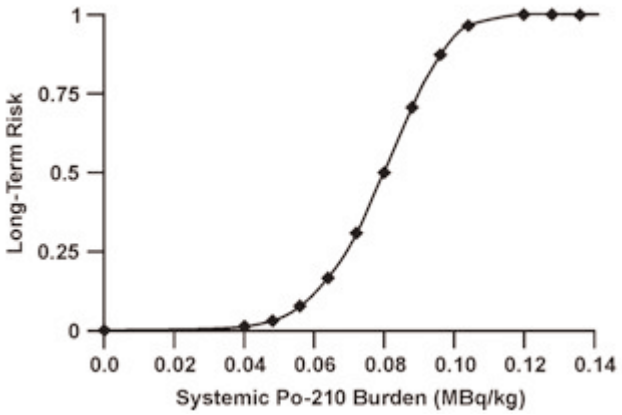

FIGURE 5. Calculated risk (central estimates) of death via the hematopoietic mode after ingesting Po-210 based on the HF model with risk evaluated as a function of the systemic burden of Po-210 in megabecquerel/kilogram-body-mass. Results apply to high-rate exposure and to all ages (except *in utero*). Data points indicate where calculations were conducted. For low-rate exposure, corresponding burdens would be higher.

Accounting for Exponentially Decreasing Dose Rate to Bone Marrow during Long-Term Follow-up

Risk estimates generated so far were based on assuming high-rate exposure to alpha radiation. For long-term follow-up, initially high dose rates to bone marrow will decrease to moderate and then to low rates. Some adjustments need to be made to account for such dose-rate changes. The following analytical solution for the normalized dose X in Equation 2 was previously published for a single-exponential-decreasing, dose-rate pattern to bone marrow (Scott and Dillehay 1990):

$$X = (D/\theta_{\infty,\alpha}) - (\theta_{1,\alpha}\, ln\{[(A\theta_{\infty,\alpha} + \theta_{1,\alpha}]/[A\theta_{\infty,\alpha}\, exp(-\lambda t) + \theta_{1,\alpha}]\})/\lambda\theta_{\infty}^{2}. \quad (4)$$

The parameter A is the initial dose rate to the target organ. The parameter λ relates to the effective retention halftime ($T_{1/2}$) of Po-210 in bone marrow according to the equation $\lambda = ln(2)/T_{1/2}$. Total-body retention of Po-210 has been reported to decrease exponentially with an effective retention half-time from about 30 to 60 days (Harrison e*t al.* 2007). It is assumed that Equation 4 can be applied to Po-210 that enters the blood and is taken up by bone marrow since it quickly enters the bone marrow from the blood (Harrison *et al.* 2007). Because the hematopoietic mode of death is expected to predominate at the lower end of the lethality risk dose-response curve up to the minimum dose for which $R = 1$, calculations are based solely on this mode. The parameter $T_{1/2}$ is assigned values of 30 and 60 to help bracket the range of uncertainty for X. RBE_{α} is assigned values of 1 and 3 in addition to the central estimate of 2, to further bracket the uncertainty in X and associated absorbed doses D. Three doses D are evaluated: threshold absorbed dose (evaluated at $R = 0.001$), median lethal absorbed dose, and minimum absorbed dose for which the risk $R = 1$ (evaluated at $R = 0.99$). This approach leads to the indicated doses being presented for two values of $T_{1/2}$ and for each halftime, lower-bound, central, and upper-bound estimates are provided for the indicated doses to bone marrow. Absorbed alpha radiation doses to bone marrow obtained are presented in Table 4 with corresponding systemic burdens of Po-210 presented in Table 5 based on a reference 70 kg adult male. The systemic burdens in Table 5 can be applied for all ages (except *in utero* which has not been researched).

Results in Table 5 can be compared to animal data in Table 1. The acute lethality threshold systemic burden is calculated to occur in the range 0.0183 to 0.148 MBq/kg-body-mass when both uncertainty in RBE_{α} and $T_{1/2}$ are taken into consideration. This finding is in good agreement with the data in Table 1 and suggests that the threshold intake in micrograms of Po-210 for acute lethality for a 70 kg adult male (*with* $f_1 = 0.1$)

TABLE 4. Lower-bound, central, and upper-bound estimates for the threshold, median lethal, and minimum alpha radiation dose for which the acute lethality risk $R = 1$, for exponentially decreasing dose-rate patterns to bone marrow.

Dose Category	$T_{1/2} = 0$ (high-rate exposure only)	$T_{1/2} = 30$ days	$T_{1/2} = 60$ days
Threshold dose in Gy (lower, central, upper)[a]	0.34, 0.51, 1.02	0.72, 1.08, 2.16	0.91, 1.37, 2.74
Median lethal dose in Gy (lower, central, upper)[a]	1.0, 1.5, 3.0	1.59, 2.38, 4.76	1.91, 2.86, 5.72
Minimum dose in Gy for $R = 1$ (lower, central, upper)[a]	1.37, 2.06, 4.12	2.14, 3.21, 6.42	2.51, 3.77, 7.54

[a]Lower-bound and upper-bound estimates are based on $RBE_{\alpha} = 3$ and 1, respectively. Central estimates are based on $RBE_{\alpha} = 2$.

may be as low as 1 μg. The median lethal systemic burden is calculated to be in the range 0.0539 to 0.308 MBq/kg-body-mass, taking into consideration the indicated uncertainties. This finding is also in good agreement with the data in Table 1. The minimum systemic burden for the risk $R = 1$ is calculated to be in the range 0.074 to 0.406 MBq/kg-body mass, which also is in good agreement with the data in Table 1. The corresponding range in micrograms of Po-210 is 0.0444 to 0.244 μg/kg-body-mass. For a 70 kg adult and $f_1 = 0.1$, the corresponding ingestion intake range would be 31 to 171 μg of Po-210. Thus intakes of a few tents of a milligram of Po-210 by humans of any age would be expected to be fatal with a probability of 1.

Data from other animal studies also appear to agree with the results in Table 5. When dogs were subcutaneously injected with 1.85 - 6.66 MBq/kg-body-mass they developed acute radiation sickness and died from 10 days to 4 weeks after injection (Moroz and Parfenov 1972). Based

TABLE 5. Lower-bound, central, and upper-bound estimates for the threshold, median lethal, and minimum systemic burden (megabecquerel/kg-body-mass) for which the acute lethality risk $R = 1$, for exponentially decreasing dose-rate patterns to bone marrow.

Systemic Burden Category	$T_{1/2} = 0$ (high-rate exposure only)	$T_{1/2} = 30$ days	$T_{1/2} = 60$ days
Threshold burden in MBq/kg (lower, central, upper)[a]	0.0183, 0.0275, 0.055	0.0388, 0.0582, 0.116	0.0492, 0.0739, 0.148
Median lethal burden (lower, central, upper)[a]	0.0539, 0.081, 0.162	0.0855, 0.128, 0.257	0.103, 0.154, 0.308
Minimum burden for $R = 1$ (lower, central, upper)[a]	0.074, 0.111, 0.222	0.115, 0.173, 0.346	0.135, 0.203, 0.406

[a]Lower-bound and upper-bound estimates are based on $RBE_{\alpha} = 3$ and 1, respectively. Central estimates are based on $RBE_{\alpha} = 2$.

on results in Table 5, these levels of intake would be expected be lethal with a probability of 1.

Lower systemic burdens in dogs of 0.74 - 1.1 MBq/kg-body-mass of injected Po-210 were also lethal for all (Moroz and Parfenov 1972), in agreement with results in Table 5, since acute lethality would be expected with a probability of 1. An even lower systemic burden of 0.093 MBq/kg-body-mass also was lethal to all exposed dogs but deaths occurred much later, between 6 and 12 months after intake (Moroz and Parfenov 1972). These data are also in good agreement with Table 5 since the indicated burden falls within the range of uncertainty for the lowest burden associated with a risk of 1 for acute lethality.

Evaluation of Available Human Data

Some human data for Po-210 exposure are also available but are not in a form such that it can be decided as to whether they agree or do not agree with Table 5. Workers reported to have had estimated Po-210 body burdens of 0.037 - 0.19 MBq/kg-body-mass developed hematologic changes, functional impairment of the liver, kidneys, and reproductive organs, but no deaths were apparently reported (Cohen 1989). It is unclear as to whether these burdens represent systemic burdens or intake. Results in Table 5 implicate intake rather than systemic burdens.

Two episodes have been reported where adolescents came in contact with a ruptured Po-beryllium (Be) source (Cohen 1989). In one incident, four individuals had an estimated Po-210 body burden that ranged from 0.019 - 0.41 MBq/kg-body-mass (Cohen 1989). There were no cases of radiation sickness over an 18-month follow-up period, but changes in liver function (increased blood levels of bilirubin) and kidney function (decreased flow of renal plasma) were observed. It is unclear as to whether the exposure units were for intake or systemic burden. Results in Table 5 implicate intake rather than systemic burdens. After the second incident, ten children with estimated Po-210 body burdens ranging from 0.0074 - 0.26 MBq/kg demonstrated no clear changes in general health over a 4-year follow-up period, although some impairment of the protein-forming function of the liver which began at 21 months was observed (Moroz and Parfenov 1971). It is unclear as to whether the exposure units were for intake or systemic burden. Results in Table 5 implicate intake rather than systemic burdens.

Three chemists inadvertently exposed to a Po-210 aerosol sustained estimated maximum doses of 0.0048, 0.007, and 0.042 MBq/kg-body-mass, corresponding to body burdens of 0.37, 0.44, and 3.3 MBq, respectively (Cohen 1989). No evidence of kidney damage was observed. Subclinical depression of the hematopoietic system was suspected for the individual receiving the two highest doses. However, the data were insuf-

ficient to support the findings. These data are consistent with results in Table 5 whether they represent intakes or systemic burdens.

Clinical observations were made 15 years after Po-210 inhalation by four individuals during an incident where the Po-210 escaped from a Po-Be source resulting in body burdens ranging from 0.0056 - 0.049 MBq (Jialiu *et al.* 1982). The general conditions of all the patients were good and no obvious abnormalities were found. However, small spots were observed on the lens epithelia of two of the individuals, possibly related Po-210 hot particles deposition in the eye. The indicated body burdens when expressed in MBq/kg-body mass would be expected to be < 0.0049, indicating that these data are also in agreement with Table 5.

Moroz and Parfenov (1971) evaluated the minimum lethal single dose (referred to as the minimum effective single dose) of injected Po-210 in rats. They reported that a body burden equivalent to 0.0093 MBq/kg-body-mass was the boundary between minimum effective and tolerable doses. Today such a dose would be called a threshold dose. Based on the results in Table 5, this estimate seems to fall below the threshold for acute lethality. Moroz and Parfenov (1971) gave an estimate of equivalent to 0.0001 MBq /kg-body-mass as the recommended maximum permissible systemic Po-210 body burden for humans. Based on results in Table 5, no harm would be expected to be associated with this level of exposure to Po-210.

Table 6 presents a summary of estimated Po-210 toxicity to humans (acute lethality related) based on animal data discussed in this paper and results presented in Table 5. Although the focus in this paper has been on the hematopoietic and gastrointestinal modes of death, radiation doses to the spleen, liver, and kidneys were calculated to be higher than those to the bone marrow and large intestine. Severe damage to liver, spleen, and kidney are expected when lethal damage to the large intestine or bone marrow occurs. Thus, even if medical countermeasures are applied to reconstitute bone marrow stem cells and counter infection associated with gastrointestinal damage, medical attention will also likely be needed related to severe damage to the spleen, liver, kidney, and possibly other sites. *New, funded medical countermeasures research is needed in this area.*

In the case of humans exposed via ingestion to Po-210, survivors of the acute radiation syndrome and chronic radiation sickness are likely at high risk of cancer occurrence for all heavily irradiated sites (kidney, liver, spleen, gastrointestinal tract, bone marrow, skin, and other sites), especially in light of the high alpha radiation-relative biological effectiveness for cancer induction and high absorbed radiation doses to target organs and tissues. Life shortening is also a risk of concern.

An area where large uncertainties remain relates to interorgan interaction effects. Serious damage to the spleen, liver, and kidney after intake of Po-210 could reduce the dose required for death via the hematopoiet-

TABLE 6. Expected Po-210 toxicity to humans as a function of the systemic burden in megabecquerel/kg-body-mass, based on animal data and the HF model.

Systemic burden range (MBq/kg-body-mass)	Central estimate of the risk (%) of death from deterministic effects	Expected survival time (days)	Expected histopathology	Expected hematological effects
> 1	100	1 to 28	Massive, rapidly-occurring damage to the kidney and other organs including bone marrow	Severe loss of lymphocytes, WBC[a], RBC[b], and hemoglobin
0.4 to 1	100	50 to 250	Rapidly occurring damage to kidney and likely other organs including bone marrow	Moderate to severe loss of lymphocytes, WBC; declines in RBC and hemoglobin at time of death
0.03 to 0.3	1 to 100	300 to 500	Slowly occurring damage to kidney and likely to other organs including bone marrow	Early WBC reduction followed by recovery; possibly delayed recovery since high-LET radiation is involved
0 to 0.02	< 1	Normal lifespan for most	Mild lesions in kidney and possibly other organs; cancers and life shortening possible	Minor effects if any

[a]WBC = white blood cells.
[b]RBC = red blood cells.

ic mode (the apparent principal determinant of the lethality risk) and reduce survival time. If so, even smaller Po-210 intakes than those calculated here as being lethal may also be lethal for some. *New, funded research is needed that addresses interorgan interaction effects.*

CONCLUSIONS

Each month about 8 g of Po-210 are shipped to the United States from Russia. Should such quantities of Po-210 be used by terrorist in a radiological incident (e.g., dirty bomb), havoc could ensue. Five questions were posed at the beginning of this paper which relate to managing mass casualties following a large-scale radiological event involving exposure to Po-210. The first three questions are now answered based on results presented. (1) It is possible to develop prodromal symptoms within 24 h of ingestion (or inhalation) intake of Po-210 and this would suggest a lethal intake. (2) An ingestion intake as small as 1 μg of Po-210 may be lethal for the most radiosensitive members of the population; ingesting (or inhaling) a few tents of a milligram would be expected to be lethal for all. (3) It is possible for a lethal radiation dose to accumulate

within as few as 7 days of ingesting (or inhaling) Po-210 for systemic burdens > 4 MBq/kg-body mass.

Lethal intakes of Po-210 would be expected to involve severe damage to the bone marrow, spleen, liver, kidney, skin, lymph nodes and possibly other sites in the body. The lung would also be an additional site of concern in the event of inhalation intake. Children would be expected to be at higher risk of harm than for adults for the same level of intake of Po-210 because of their smaller body masses and relatively higher radiation doses. Medical countermeasures implemented to compensate for radiation-induced damage to the bone marrow may not be lifesaving since lethal damage may be induced in multiple organs including the kidneys, liver, and spleen. Severe damage to the skin could also arise over time from systemic Po-210. *New, medical countermeasures-related as well as supporting and other modeling research is needed in order to be best prepare for dealing with mass casualties in the event of Po-210 use by terrorist for the purpose of causing harm to U.S. citizens and others.*

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