TOXICITY OF INHALED ALPHA-EMITTING RADIONUCLIDES - STATUS REPORT

Abstract — The toxicity of inhaled alpha-emitting radionuclides is being investigated in a series of interrelated dose-response studies. Dogs, rodents, and nonhuman primates have been exposed to monodisperse or polydisperse aerosols of the oxides of ^{239}Pu, ^{238}Pu, ^{241}Am, or ^{244}Cm to measure the relative importance of average organ dose, local dose around particles, specific activity, chemical form, particle size, and number of particles inhaled to the development of biological effects. The influence of animal species, age at exposure, and pre-existing lung disease, as well as the effects of repeated exposure, are also being studied, because they may influence the toxicity of these radionuclides.

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The continued use of light-water reactors as energy sources and the production of nuclear weapons materials assure that large quantities of alpha-emitting radionuclides will continue to be present in the United States' nuclear inventory. Because of this, there is a potential for human exposure to these radionuclides, either from environmental pathways or as a result of occupational exposures. Inhalation is the most likely route of exposure.

To provide important information needed for assessing the risks from inhalation exposures, studies of the toxicity of plutonium and other transuranic elements are being conducted at this Institute. These studies constitute a series of integrated experiments with laboratory animals exposed to well-defined aerosols so that we may better understand the relationships between exposure atmosphere, deposition and retention patterns, radiation dose patterns, and resulting biological effects. A number of factors influence the dose to the lung and other tissues and the subsequent biological effects from an inhalation exposure. For inhaled alpha-emitting radionuclides, factors associated with the aerosols include the elemental characteristics of the material, its chemical form, specific activity, and particle size distribution. Factors associated with the host include the age at the time of exposure, the laboratory animal species, its health status, and individual response.

The basic experimental approaches used in the dose-response studies with alpha-emitting radionuclides are presented here. These approaches have been designed to provide a broad base of information that can be applied to a wide variety of possible exposure situations, including those that may be encountered in accidents in the nuclear industry.

Detailed progress reports for most of the studies are presented elsewhere in this document. Additional information and a more detailed discussion of the relationships of these dose-response studies to other studies being conducted at this Institute have been published in the scientific literature[1,2] and in previous annual reports.

Studies in Beagle Dogs

The major study in progress involves groups of Beagle dogs exposed as young adults to graded radioactivity levels of $^{238}PuO_2$ or $^{239}PuO_2$ in monodisperse particles of different sizes. A schematic representation of the experimental design for this study is shown in Figure 1, where each cube represents one dog. Five different aerosols have been used, each resulting in particles with different levels of alpha-emitter radioactivity. For each aerosol, a randomized block design was used that is similar to that used for the beta-gamma dose-response studies (this report, pp. 157-163).

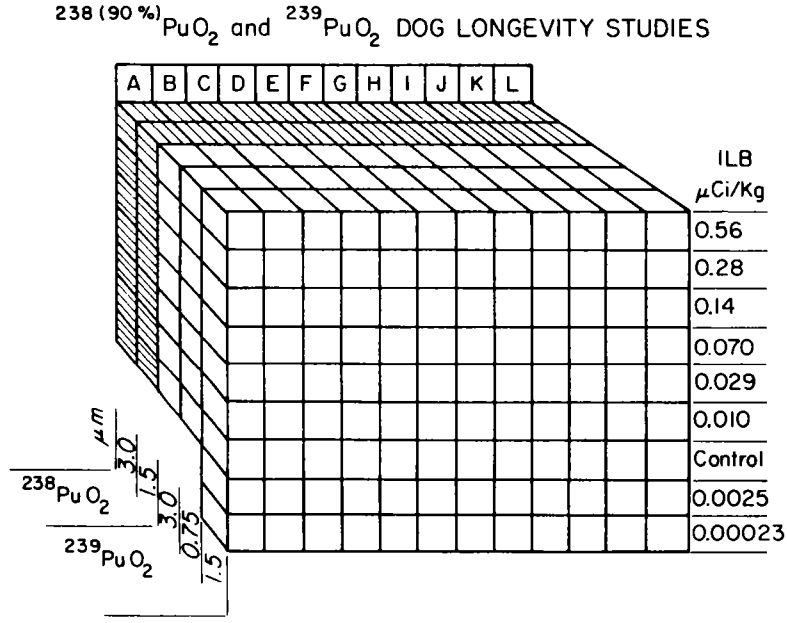

Figure 1. Schematic representation of the experimental design for life-span studies involving dogs exposed to different monodisperse aerosols of $^{238(90\%)}PuO_2$ or $^{239}PuO_2$. Each cube represents one dog entered into the experiment at 12-14 mo of age.

Twelve blocks of dogs were exposed to each aerosol to achieve graded initial lung burdens (ILB) ranging from 0.01-0.56 μCi (0.37-21 kBq) Pu/kg body weight. Sixty control dogs were included, 12 for each aerosol. Two additional ILB levels of 0.0025 and 0.00023 μCi (93 and 8.5 Bq) Pu/kg body weight were included for the studies in which young-adult dogs and immature dogs inhaled $^{239}PuO_2$ aerosols of 1.5-μm activity median aerodynamic diameter (AMAD). An ILB of ^{239}Pu of 0.00023 μCi (8.5 Bq) Pu/kg body weight in a Beagle dog is equivalent to a lung burden of 0.016 μCi (590 kBq) Pu in a 70-kg human.

The information given in Table 1 and in Figure 1 was used to calculate the initial dose rate averaged over the total lung and the local dose rate around each particle, for each particle size and activity level shown in Figure 2. With two different radioisotopes of plutonium and three different particle sizes, the alpha activity per particle and the corresponding idealized local dose rate to a sphere of lung tissue with a radius of 180 μm (density = 0.22 g/cm^3) surrounding an individual particle varied by a factor of ~ 40,000. Also, the use of six activity levels for each aerosol resulted in a difference of about a factor of 50 in the initial dose rate, averaged over the entire lung. Thus, these five experiments permit comparison of both local dose rates and

Table 1

Some Characteristics of Aerosol Particles of Pure Transuranic Alpha-Emitting Radionuclides

Aerosol	Specific Activity (Ci/g)	Activity (picocuries) per Particle[a,b] AMAD[c] = 0.75 μm RD[d] = 0.18 μm	AMAD = 1.5 μm RD = 0.44 μm	AMAD = 3.0 μm RD = 0.96 μm
$^{239}PuO_2$	0.0541	0.0013	0.020	0.20
$^{238}PuO_2$	15.3	0.38	5.5	58
$^{241}AmO_2$	3.05	0.075	1.1	11
$^{244}CmO_x$	74.7	1.8	27	270
$^{242}CmO_x$	2990	73	1100	11000

[a]A density of 8 was used for these calculations. This is the measured density for $^{238}PuO_2$ and $^{241}AmO_2$ particles produced by standard methods at this Institute.

[b]The ^{238}Pu used at this Institute contained 10% ^{239}Pu by weight. This produced a specific activity of 13.9 Ci/g (5.14 x 10^5 kBq) and particle activities of 0.34, 4.9, and 51 pCi (9.2, 132, and 1379 Bq), respectively, for 0.75-μm, 1.5-μm, and 3.0-μm AMAD particles.

[c]AMAD = Activity median aerodynamic diameter of monodisperse particles (geometric standard deviation < 1.2).

[d]RD = Geometric diameter of the particle.

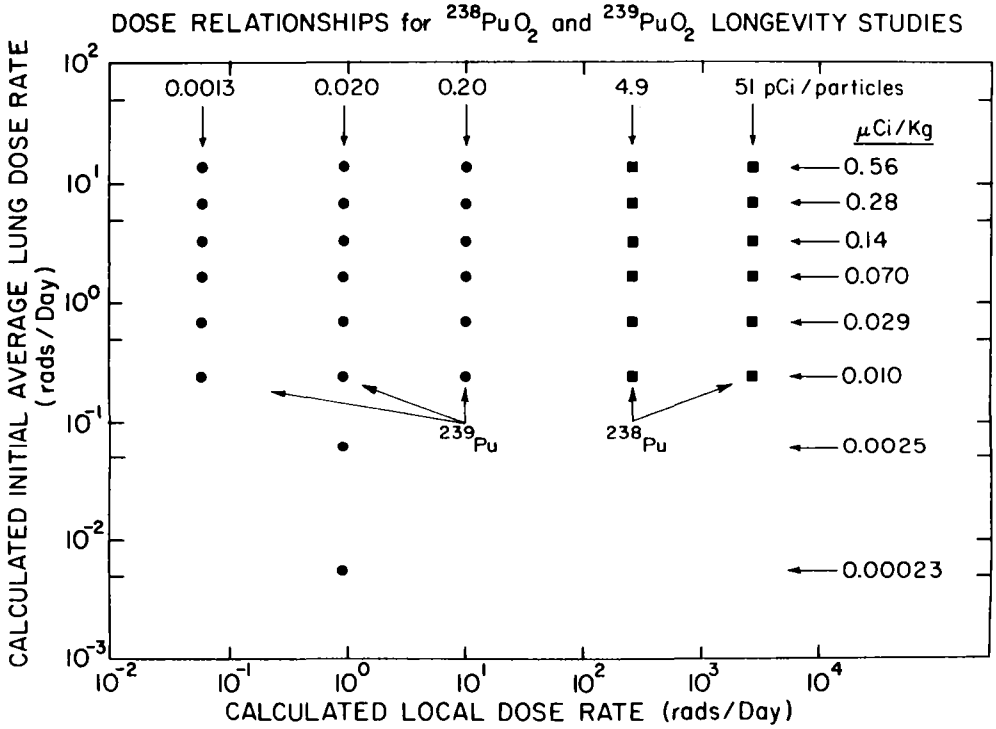

Figure 2. Calculated dose relationships for the five life-span studies involving dogs that inhaled monodisperse aerosols of $^{238}(90\%)PuO_2$ or $^{239}PuO_2$. Local dose rate was computed in a 180-μm sphere of lung tissue (density = 0.22 g/cm^3). The calculation of average dose rate was based on a 110-g lung. Self-absorption of alpha energy by the particles was negligible.

average dose rates in producing long-term biological effects. The average dose rate to the lung will decrease with time after exposure because of clearance of plutonium from the lung. The local dose rate can decrease or increase because of particle movement, aggregation, dissolution, or particle breakup in the lung.

Inherent in the experimental design is a difference in the number of particles associated with a given ILB level for each aerosol (Figs. 1 and 2). An estimate can be made of the fraction of the lung irradiated by assuming a spherical irradiation volume of 2.4×10^7 μm^3 around each particle, and determining how many of these volumes are present in the volume of a 110-g lung. Results of such a theoretical calculation are presented in Figure 3. When the number of these irradiation volumes exceeds 2.1×10^7, the calculated fraction of lung irradiated exceeds 1.0. For values > 1.0, some or all portions of the lung would be irradiated by the alpha emissions from more than one particle of plutonium, even if the particles are assumed to be uniformly distributed in the lung tissue and geometrical considerations are ignored. Our experimental evidence suggests that inhaled particles are not uniformly distributed, but are randomly deposited in the lung. This random distribution indicates that theoretical calculations of the fraction of lung irradiated are slight overestimates. All of the ILB levels for the exposures to 0.75-μm AMAD particles of $^{239}PuO_2$, the upper four levels for the exposures to 1.5-μm AMAD particles of $^{239}PuO_2$, and the highest level for the exposure to the 3.0-μm AMAD particles of $^{239}PuO_2$ gave calculated fractional irradiations > 1.0. The remaining $^{239}PuO_2$ ILB levels and all of the $^{238}PuO_2$ exposure levels resulted in calculated values < 1.0 for fractions of lung irradiated. Because of the overlap in fractions of lung irradiated for the several different size aerosols, the effects of local dose rate are being studied while the fraction of lung irradiated is held constant. To obtain more detailed dosimetric information, parallel studies have been conducted in dogs and

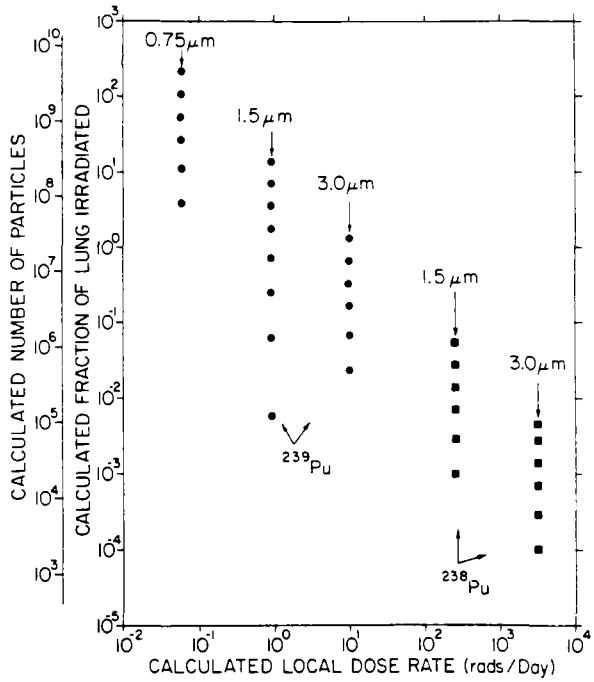

Figure 3. Calculated numbers of particles and fractions of lung irradiated based on the sphere of irradiation associated with each particle (2.4×10^7 μm^3) and a determination of how many of these volumes could be contained in the lung before overlapping occurred. Self-absorption of alpha energy by the particles is negligible.

rodents exposed to $^{239}PuO_2$ and $^{238}PuO_2$ aerosols and serially sacrificed at selected times after exposure. These studies have provided valuable data on the organ and tissue distribution of plutonium with time after exposure.

To study the effects of age at exposure on the resulting dose-response relationships, immature (3 mo old) and aged (8-10.5 yr old) dogs were exposed once, by inhalation, to graded activity levels of $^{239}PuO_2$ in 1.5-μm aerodynamic diameter particles, and are being held for life-span observations in the same manner as used for the studies with young-adult dogs discussed above. The results of these studies are providing important information on the possible range of dose-response relationships that might be observed in an accidental exposure of the general population.

In each of the above studies, all of the dogs received a single inhalation exposure. Recognizing that some inhalation exposures to plutonium or other transuranic radionuclides in humans may be repeated or chronic exposures, it is also important to examine the dose-response relationships after repeated exposures to determine the extent to which results from single exposure studies can be used to predict the results from repeated or chronic exposure studies.

Studies in Rodents

Several major studies have been and are being conducted in rodents to complement the dog studies. The first of these rodent studies at the ITRI was conducted in Syrian hamsters [SCH:(SYR)]. These studies included animals exposed to monodisperse aerosols of $^{238}PuO_2$ or $^{214}AmO_2$, or to polydisperse aerosols of $^{239}PuO_2$. More recently, young-adult F344/N rats were exposed to 1.0 or 2.85 μm AMAD particles of $^{239}PuO_2$ and were observed over their life spans. An additional group of rats was exposed to an aerosol of 1.0 μm AMAD particles of $^{239}PuO_2$ when the rats were 18 mo old (aged). A study with graded lung burdens of $^{244}Cm_2O_3$, an alpha-emitting radionuclide with a higher specific activity than ^{239}Pu or ^{238}Pu, is being conducted in young adult F344/N rats for comparison with the results from the plutonium isotopes.

Pre-existing lung diseases are being evaluated as possible dose-modifying factors in F344/N rats. In two different studies, pulmonary fibrosis was induced by the administration of bleomycin, or pulmonary emphysema was induced by the intratracheal instillation of elastase. Once the pulmonary disease was present, the rats were exposed by inhalation to aerosols of $^{239}PuO_2$. Clearance of the radionuclide was followed by the serial sacrifice of a limited number of rats, while the remaining rats were held for observation of biological response over their life spans.

Repeated inhalation exposures of Syrian hamsters, mice, and rats to aerosols of $^{239}PuO_2$ have also been conducted for comparison with the single-exposure data. The purpose of all these studies is to develop interspecies comparisons among the dog, rat, mouse, and Syrian hamster to strengthen the extrapolation of these results to potential human exposure situations.

Studies of the effects of nonuniform alpha irradiation of the liver from injected Thorotrast vs. more uniform irradiation from ^{239}Pu have been conducted in Chinese hamsters. The data from this hamster study will be compared directly to a human data set derived from people that have been injected with Thorotrast.

Studies in Nonhuman Primates

To strengthen the interspecies comparison of biological effects from inhaled plutonium aerosols, a small group of nonhuman primates was exposed to a polydisperse aerosol of $^{239}PuO_2$ to achieve graded activity levels in the lung. To date, one monkey has died with a fibrosarcoma of the lung. Only one other nonhuman primate has been reported to have developed a lung tumor from inhaled $^{239}PuO_2$.[3] Although only a few nonhuman primates have been exposed to plutonium aerosols by inhalation, these animals should provide important information on the relative radiosensitivity of the primate respiratory tract, as compared to that of the dog and several rodent species.

STATUS

It is now 13-15 yr after exposure for the experiments in young-adult Beagle dogs exposed once to $^{238}PuO_2$ (this report, pp. 196-205). and are 10-12 yr after exposure for those dogs exposed once to $^{239}PuO_2$ (this report, pp. 206-214). These dogs are being maintained for life-span observation, and the major diseases of interest are radiation-induced cancers. The current status of these studies is summarized in Table 2. Dogs at the highest exposure levels died from non-neoplastic radiation effects, primarily radiation pneumonitis and pulmonary fibrosis. In contrast to the results seen with beta-emitting radionuclides, where radiation pneumonitis and pulmonary fibrosis were seen mainly during the first 500 days after exposure, these effects continue to be seen in the plutonium-exposed dogs many years after the inhalation exposure.

Table 2
Current Status of Life-Span Studies of Beagle Dogs
That Inhaled Aerosols of $^{238}PuO_2$ or $^{239}PuO_2$

	Number in Study		Alive 9/30/88	
Study	Exposed	Control	Exposed	Control
$^{238}PuO_2$ - Young-Adult				
1.5 μm	72	12	4	2
3.0 μm	72	12	3	4
$^{239}PuO_2$ - Young-Adult				
0.75 μm	48	12	6	8
1.5 μm	96	12	29	11
3.0 μm	72	12	10	10
$^{239}PuO_2$ - Immature	96	12	66	11
$^{239}PuO_2$ - Aged	48	12	0	0
$^{239}PuO_2$ - Repeated Exposure	72	12	26	9
Total	576	96	144	56

The principal long-term neoplastic effects observed after inhalation of $^{238}PuO_2$ have been cancers in the skeleton, lung, and liver, whereas lung cancer has been the only long-term neoplastic response observed to date after inhalation of $^{239}PuO_2$. These effects continued to be observed during this past year in the studies in dogs. Differences in the dose-response relationships for two different isotopes of plutonium reflect differences in the biokinetics of these two isotopes, apparently resulting from differences in their specific activities. Some differences in the biological effects from plutonium inhaled by dogs of different ages are beginning to emerge. Few dogs exposed as immature animals have developed radiation pneumonitis and pulmonary fibrosis, whereas nearly all of the dogs exposed when aged have developed this disease. All of the dogs exposed to ^{239}Pu when they were 8-10.5 yr of age have now died. Only one of these dogs died from a primary cancer of the lung; five other dogs had lung cancers as an incidental finding. Six of the dogs that were exposed to ^{239}Pu when immature died during the past year. All six of these dogs had lung cancers. Because cancer is the main long-term effect from internally deposited radionuclides, it has been possible to collect specimens for oncogene analysis as these dogs die. We have initiated a search for the genetic changes responsible for the development of these cancers by comparing and contrasting the expression of known oncogenes in the above samples with both spontaneous tumors obtained from unexposed dogs and normal dog tissues (this report, pp. 333-337).

Parallel studies using polydisperse aerosols of $^{238}PuO_2$ and $^{239}PuO_2$ are in progress at the Battelle Pacific Northwest Laboratories.[4] The parallel nature of these studies in both laboratories is an important aspect of this major effort to study the inhalation toxicology of actinide aerosols. Qualitatively, the results to date have been similar in both laboratories, both regarding the types of cancers being observed and the differences in cancers produced by inhaled $^{238}PuO_2$ and $^{239}PuO_2$. The quantitative relationships remain to be developed as these studies move toward their conclusions.

In the studies involving rodents that have inhaled actinide radionuclides, all of the animals are now dead. Histopathologic examinations are complete except for a few animals in the bleomycin-induced pulmonary fibrosis study, a few of the rats exposed once when aged, and 75% of the rats that inhaled $^{244}Cm_2O_3$. The clearance of the $^{239}PuO_2$ was decreased in the rats with pre-existing pulmonary fibrosis, but no effect on clearance was observed in the rats with pulmonary emphysema (this report, pp. 256-261 and pp. 262-268). The presence of pulmonary emphysema did not appear to have modified the biological effects of inhaled $^{239}PuO_2$ when compared to normal rats exposed to ^{239}Pu. The presence of pulmonary fibrosis slightly decreased the survival times of exposed rats. Of particular interest will be the results for inhaled $^{239}PuO_2$ in the rat compared with those for $^{239}PuO_2$ in the dog, and of a comparison of the effects from inhaled $^{244}CmO_2O_3$ and $^{239}PuO_2$ in the rat.

A completed study on the effects of repeated inhalation exposure of mice to an aerosol of $^{239}PuO_2$ has indicated that protraction of the alpha dose to the lung through repeated exposures may increase the carcinogenic risk of inhaled $^{239}PuO_2$ in mice.[5] This is the only repeated exposure study conducted at the ITRI to date that has indicated that protracted dose can increase the carcinogenic risk. Similar studies in rats and still in progress in dogs, indicate that repeated exposures are not more carcinogenic and suggest that the findings in the mouse are a true species difference. The similarities and differences among these studies need to be examined further to understand the interspecies relationships and their implications for different types of human exposures.

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