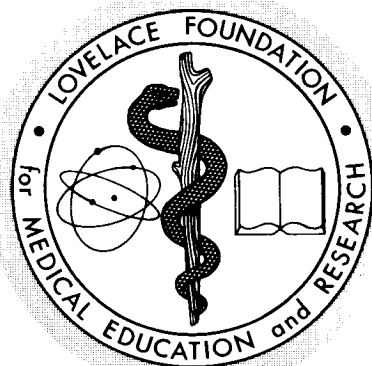


**REVIEW OF JOHN GOFMAN'S PAPERS ON  
LUNG CANCER HAZARD FROM INHALED PLUTONIUM**

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**September 1975**



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REVIEW OF JOHN GOFMAN'S PAPERS ON  
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September 1975

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## ABSTRACT

John W. Gofman released two papers recently on behalf of the Committee for Nuclear Responsibility. Using what is in effect an extension of the "hot particle" hypothesis, he defines the critical tissue in lung of humans to comprise 1 gm of bronchiolar epithelium which has a 500-day half-life for clearance of a small portion of inhaled plutonium particles which deposit on or become trapped on this epithelial region of the lung after clearance from alveoli. The effect is to extend to the sensitive bronchiolar region a long-term burden of inhaled plutonium. The slowed clearance is presumed by Gofman to be the result of impaired ciliary activity because of smoking. His hypothesis is invalidated by recognition that if it were true smokers would eventually accumulate sufficient cigarette smoke residue in the lungs to cause blockage of small airways and cessation of ventilation. Gofman's use of "lung cancer dose" in his risk analyses is misleading and obscures reality; for example, the risk from natural background radiation is projected to be considerably greater than for fallout plutonium when analyzed using Gofman's approach. Defining lung cancer risk from inhaled plutonium in terms of risk per pound or ton of plutonium does little beyond impress or confuse the average reader with large numbers. His risk estimates for human lung cancers caused by plutonium from worldwide fallout are based entirely on his preposterous model for long-term retention of inhaled plutonium in bronchioles. In summary, Gofman's approach to estimation of excess lung cancer from inhaled plutonium is uncertain, unscientific and is not substantiated by current knowledge of the toxicity of plutonium.

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INTRODUCTION

John W. Gofman recently released two papers (1,2) on behalf of the Committee for Nuclear Responsibility in which he developed lung cancer hazard estimates for inhaled plutonium and estimates for numbers of human lung cancers related to worldwide fallout of plutonium. These papers are apparently intended for the non-scientific reader and consist mainly of assumptions, simple mathematical derivations and predictions. The predictions and derived large numbers of lung cancers predicted for fallout plutonium serve only to confuse or impress the reader and have little scientific validity. These papers represent a very non-constructive approach to the problem of lung cancer risk due to inhaled plutonium.

Gofman states that his approach does not involve the "hot particle" hypothesis which precipitated considerable controversy in 1974. However, his approach to this problem is in fact an extension of the hot particle hypothesis. He defines the critical tissue in lung to be bronchial epithelium comprising 1 gm of sensitive epithelium. This was necessary because it then becomes possible to discuss this tissue as highly sensitive to irritants which leads to the production of cancer of bronchiogenic origin. The next problem, irradiation of this sensitive tissue for sufficient time to cause lung cancer, is solved by Gofman by making the remarkable prediction that some plutonium particles which deposit on that sensitive epithelium or move onto it from alveoli are trapped there with a 500-day half-life. He therefore conveniently defines a long-term burden of plutonium or other alpha-emitting particles for a known sensitive 1 gm region of lung tissue. The fallacy of this approach will be pointed out later.

Another thing Gofman does is avoid the use of absorbed dose for relating the amount of inhaled plutonium to possible risk. He uses the concept of "lung cancer dose", which is very misleading in that it cannot be readily defined or compared with reality. Moreover, Gofman failed to consider that

background radiation constitutes a significantly greater hazard than plutonium in worldwide fallout if also expressed in the meaningless units of "lung cancer dose".

Our approach to reviewing these papers was to point out the major assumptions in these two papers and develop real-life tests for his hypotheses where applicable. A test of such hypotheses is to see if predicted results make any sense in the real world. This was done for Gofman's prediction of a 500-day half-life for clearance of a portion of inhaled plutonium deposited on bronchial epithelium and for Gofman's prediction of the carcinogenicity of a "lung cancer dose". Both predictions are incompatible with the real world.

#### SUMMARY OF CNR REPORT 1975-1 and 1975-2

In CNR Report 1975-1, Gofman derives an estimate of lung cancer risk per unit mass of plutonium inhaled. This calculation is similar in its initial goals to the Radiological Effects of Ionizing Radiation (BEIR) Report (3); however, it attempts to develop separate risk estimates for cigarette smokers as compared to nonsmokers. Throughout the report, comparisons of the Gofman-Tamplin risk estimates are made with the author's extensions of the BEIR report data. It should be clearly noted that risk values indicated as "BEIR" estimates do not come directly from that report but represent Gofman's personalized extension of the BEIR report data. In general, the "Gofman" risk estimates for lung cancer in nonsmokers are reasonably close to his BEIR report data extensions. The major differences occur in his modification of risk factors as applied to cigarette smokers. Risk probabilities for smokers are several orders of magnitude greater than for nonsmokers exposed to the same plutonium inhalation dose. He then extends these risk values from the amount of  $^{239}\text{Pu}$  inhaled to the number of "lung cancer doses" that would exist in a pound of  $^{239}\text{Pu}$  or reactor grade plutonium if it were inhaled.

In the second paper (CNR Report 1975-2), Gofman uses his plutonium lung cancer probabilities to estimate expected lung cancer incidence in the population exposed to nuclear weapons fallout. Because of Gofman's estimated higher risk to cigarette smokers compared to nonsmokers inhaling the same quantity of plutonium, the over-whelming majority of lung cancers are projected to occur in smokers. If cigarette smokers were excluded from Gofman's model, plutonium would not represent a significant hazard. Very major objections should be

raised to the methods used in applying a new model with several unproven assumptions for clearance of inhaled plutonium in smokers. These assumptions and models are not valid. If they are applied to other poorly soluble materials inhaled along with plutonium during the normal course of life, small airways would become obstructed in smokers, preventing small airway ventilation. Therefore, the poor risk estimators developed in the first paper produce an untenable result when applied to nuclear weapons fallout in the second paper. Detailed comments directed to specific areas of the papers follow.

Specific Comments Related to CNR 1975-1:

A. Basic Risk Assumptions:

A major assumption of the BEIR committee, Gofman and others is that risk estimates based upon irradiation at high dose rates may be extrapolated to large populations irradiated at low dose rates. The extrapolation is considered to be linear. Risk estimates for lung cancer were:

	<u>BEIR</u>	<u>Gofman</u>
Absolute risk (Cases per $10^6$ people years/rem)	1 to 2	None given
Relative risk (% increase in rate/yr/rem)	0.2 to 0.5%	2%

There is an initial difference of a factor of 4 or more in the initial risk estimates at the beginning of Gofman's discussion. The Gofman relative risk factor, 2%/year/rem, was taken from a previous publication of Gofman and Tamplin (4), an estimate that was not accepted by the BEIR Committee.

The spontaneous rate for lung cancer in males over 25 years of age is  $1.27 \times 10^{-3}$ /yr as derived by Gofman. It is recognized that males over 25 years of age are a high risk in part because of the large number of individuals in this group who smoke. The incidence in women is about  $0.35 \times 10^{-3}$ /yr and the risk is extremely small for all individuals under 25 years of age. Thus, it is inappropriate to use any single one of these risk estimates to calculate a cancer risk which is to be applied to the population as a whole. In addition, if as Gofman suggests, the current lung cancer rate of 63,500 deaths/yr in men represents an epidemic which may be attributed in part to plutonium inhalation, then the values of  $1.27 \times 10^{-3}$  or  $0.35 \times 10^{-3}$  are not baseline values to which



the relative risk escalation due to plutonium inhalation may be added. It is already represented in these values. A more representative rate for spontaneous cancer induction in the total U.S. population is  $4.0 \times 10^{-4}$  deaths/yr (63,000 deaths/yr for men + 17,600 deaths/yr for females/200 million people). Use of a relative risk of 0.5%/year/rem would lead to 2 additional cases per  $10^6$  people years/rem. Curiously enough, Gofman back-calculates this number for the "BEIR" estimate from his own data to be 6.3 cases per  $10^6$  people years/rem to lung (Gofman's page 6 - CNR Report 1975-1).

B. "Lung Cancer Dose":

Gofman's definition of "lung cancer dose" is 1/risk, where risk is the spontaneous lung cancer incidence multiplied by 2% per year per rem of exposure. He next multiplies by 30 to derive a lifetime risk estimate, which he takes the reciprocal of to derive "lung cancer dose" in units of man-rem. He next uses the assumption that 1  $\mu$ Ci delivers a cumulative infinite dose of 2000 rems. Dividing his lung cancer dose in man-rems by 2000 rems yields values for lung cancer dose in units of  $\mu$ Ci. The concept of "lung cancer dose" for inhaled plutonium, which may be considered similar to a "drowning dose" for water or a "burning death dose" for fire, is not truly scientific. It is more akin to a quantity which if deposited in lung would give a certain probability for lung cancer among members of a given population. Its use does have a practical advantage for Gofman's point of view in that it avoids the problem of relating absorbed radiation dose to anticipated biological effects. Thereby, it obscures comparisons with background radiation dose levels which exceed lung irradiation due to past plutonium inhalation by several orders of magnitude.

C. Lung Cancer Dose per Unit Mass:

Tables 1 and 2 on page 10 yield estimates for lung cancer risk due to deposited  $^{239}\text{Pu}$  or reactor grade plutonium. The "Gofman-Tamplin" and "BEIR" estimates differ by a factor of 4, for reasons previously stated. Since the BEIR Committee estimate is the currently accepted estimate of the scientific community, it is the only meaningful comparison to the "Gofman-Tamplin" estimates. Further, extrapolations of data to numbers of cancers per pound or ton of plutonium or other toxicant have little significance. These estimates provide no additional useful data and serve only to confuse or impress the reader with large numbers. It should be emphasized that lung cancer risk is associated

with radioactive material deposited in the lung; any expression of risk in terms of tons of something is essentially useless.

D. Determination of Relevant Tissue at Risk and Dose Calculations:

The mass of a tissue used for radiation dose calculations is the total mass in which the energy is deposited. Since the range of alpha particles in tissue of unit density is on the order of 40  $\mu\text{m}$ , energy is deposited in blood and lymphatic fluid, insensitive components of lung structure and, especially in the case of smokers, debris contained in the lung. Selecting a lung weight of 570 gm (an estimate for mass of bloodless lung for man) for energy deposition will not produce a result greatly different from using 1000 gm. Further reduction to a weight for sensitive tissue of 1 gm is inconsistent with biological and physical properties of the lung. Gofman assumes a sensitive tissue mass of 1 gm which naturally leads to an extremely large radiation dose estimation per unit mass of plutonium inhaled.

The origin of tumors which might be produced in man due to inhalation and retention in lung of  $^{239}\text{Pu}$  is uncertain as no such tumors have been identified to date. Cigarette smokers do develop bronchial tumors, but the site of irritation or exposure for carcinogens derived from cigarette smoke may be substantially different from  $^{239}\text{Pu}$ . Long-term retention of  $^{239}\text{Pu}$  in lung tissue primarily occurs in alveoli. Gofman assumes the critical tissue for  $^{239}\text{Pu}$  is the bronchial epithelium whereby a very small lung volume and related tissue mass becomes the sensitive region of interest. This was represented by about 1 gm of tissue. Plutonium-239 trapped in this small volume was assigned a clearance half-time of 500 days due to destruction of cilia in this region from contact with tobacco residues in smokers.

E. Testing the Gofman Hypothesis in Human Smokers:

Gofman emphasizes the role of cilia in bronchi as the sole determinant for clearance of inhaled particles which initially deposit there or pass during lung clearance from alveoli. There may be a reduction in active cilia in smokers, slowing movement, but lung clearance still continues in these bronchi. Albert et al. (5) reported on bronchial deposition and clearance of aerosols for cigarette smoking and nonsmoking humans. Their conclusion was that "It is disappointing...that there is so little effect on the overall time for bronchial clearance in cigarette smokers.... But this is understandable since

backup mechanisms for bronchial clearance must operate effectively to maintain airway patency." In essence, clearance mechanisms were unaltered by smoking. Lourenco et al. (6) noted essentially the same results, with a delay of tracheo-bronchial clearance of 1-4 hours after inhalation in smokers. The notion that cilia are absolutely necessary for clearance is not substantiated. All bronchial areas in the human lung have goblet cells which secrete mucus. To maintain airway patency the mucus thus produced must move continuously and towards the pharynx or small airways will become obstructed and ventilation will cease. Lung bronchial regions clear constantly in healthy humans and smokers since airways must be patent to allow respiration. At most, only a slight delay in clearance rate could be possible, otherwise the small bronchioles would plug and death would soon follow.

Assuming Gofman's model did apply to cigarette smokers, then the inert material inhaled in smoking will be retained in the same manner as he projects for plutonium particles. The amount of smoke inhaled by a person smoking one filter cigarette is approximately 16.1 mg (7). If a smoker consumed 20 cigarettes per day each day of a year, then 118 gm would be inhaled each year. Assuming Gofman's value of 2.7% deposition in the sensitive region, 3.2 gm of material would collect each year, with a 500-day retention half-time representing a 720-day ( $\sim 2$  yr) mean residence time, about 6.4 gm would accumulate in this volume of  $20 \text{ cm}^3$  surrounded by Gofman's sensitive bronchiolar tissue of 1-gm mass. Thus, ventilation would cease or be seriously impaired in heavy smokers. Other environmental contaminants would also contribute to such a blockage. The fact that smokers may live a nearly normal lifespan compromises such a model of bronchiolar clearance - it is not compatible with life. This potential respiratory blockage would also serve two functions in altering the dose to the bronchial epithelium: (a) to provide considerable self-absorption for plutonium co-deposited with the smoke residue and (b) to minimize further deposition of inhaled plutonium and provide a protective function.

Gofman presents a risk estimate on page 19 of  $1.27 \times 10^{-3}$ /year for "spontaneous" lung cancer rate for men (USA) over 25 years of age. This value does not represent a spontaneous rate, rather a base rate already affected by lung cancer deaths due to cigarette smoking and inhalation of industrial and environmental toxicants, either naturally occurring or man-made. Two addi-

tional risk estimates, one for smokers and one for nonsmokers, are also derived. The value of  $2.3 \times 10^{-4}$ /year for male nonsmokers over 25 years of age would more closely represent the spontaneous incidence rate (without the influence of cigarette smoking) than the combined rate of  $1.27 \times 10^{-3}$ /year.

In the "Step 3 Calculation..." on page 20, Gofman ignores the fact that there are no goblet cells in alveoli but they are present in ciliated regions of the lung and that mucus will move in airways with or without local ciliary action. The pulmonary region does not fill up with the normally occurring naturally generated aerosols of dust, etc. because large particles deposit in the upper airways where they are readily cleared with the mucus flow. Small particles which reach the alveoli may be retained there with relatively long half-times.

Data included in Table 10 (page 24) are probably reasonable for both the "Gofman-Tamplin" and "BEIR" estimates of micrograms of plutonium per gram of lung needed to induce or initiate lung cancer in nonsmokers. These values should also represent the risk for smokers, excluding the added risk due to cigarette smoking. The difference between the Gofman-Tamplin and BEIR estimates, only a factor of 4, is much less than biological variability observed in many experiments.

On the bottom of page 24 and top of page 25, Dr. Gofman states that "Since ciliary function is the mechanism counted upon for differentiating rapid clearance in the bronchi versus slow clearance in the pulmonary region, the absence of effective ciliary function makes it reasonable, ..., to expect clearance times to become identical. If there is any intrinsic more rapid clearance mechanism (aside from cilia) for bronchial cells than for pulmonary cells, such mechanism is totally hypothetical. Indeed, the effect can be such as to worsen the estimates." This statement ignores the possibility that the cough, mechanical breathing action, surface phenomena, etc. may also serve to move mucus in airways. That airways do not congest in smokers indicates that either ciliary action is not seriously impaired or that ciliary action is not exclusively responsible for lung clearance.

G. Comments Related to Gofman's General Discussion:

Experimental studies in Beagle dogs have indicated that 27.1  $\mu\text{g}$  of  $^{239}\text{Pu}$  is carcinogenic (8). This compares with 28.8  $\mu\text{g}$  from Gofman's extension

of the "BEIR" data and 7.3  $\mu\text{g}$  as his cancer producing dose in nonsmokers, Table 10. These are reasonable comparisons. It is noteworthy, however, that this amount of activity in dogs did not produce demonstrable lifespan shortening. It may be appropriate therefore to make a distinction between life-shortening and the presence of a lung tumor.

In considering the risk to the public-at-large, pp. 28-30, Gofman ignores the fact that exposure standards are modified by the "low as practicable" criteria. Each individual will not accumulate a maximum burden - whatever the associated hazard. For nonsmokers, Gofman presents a risk estimate of 2000 deaths per year due to lung cancer for a 20-year period of nuclear industry operation giving uniform maximum population exposure. This estimate is quite large because individuals in the population cannot be exposed to maximum levels for 20 years. However, while this estimate is large, it is not large in comparison to other risks taken voluntarily and involuntarily by the U.S. population and the fact that approximately 1.9 million U.S. citizens die every year from one cause or another. His estimated risk for smokers is probably 400 times too high. A factor of 4 is due to excessive risk assumed for each rem of population exposure and a factor of 103 due to the application of a pre-posterous model for bronchiolar clearance of plutonium particles. Dividing by 400, the risk for smokers in the general population would be 6000 deaths per year for a maximum permissible burden of 16 nCi in each individual. Being mindful that

- 1) the U.S. population will not be exposed to the maximum permissible burden,
- 2) about 84,000 U.S. citizens presently die from lung cancer each year, 45,000 die as a result of automobile-related accidents and  $1.9 \times 10^6$  deaths occur each year in total (9),
- 3) The cancer risk estimate given in CNR Report 1975-1 for smokers is probably a factor of 400 too high,
- 4) Gofman's approach to estimation of lung cancer risk is uncertain, unscientific and cannot be related to radiation doses from plutonium,

then the plutonium hazard from nuclear fallout is truly less dramatic than Gofman might imagine.

## Specific Comments Related to CNR 1975-2:

### A. Introduction:

In CNR Report 1975-1, estimates were derived for lung cancer risk per unit mass of deposited plutonium in cigarette smokers and nonsmokers. The estimates for nonsmokers were about 4 times higher than might be developed from data included in the BEIR report. Estimates for smokers were about 400 times too high due mainly to application of an absurd model for describing bronchial clearance processes. In CNR Report 1975-2, these risk estimates are applied to nuclear weapons fallout in estimating its impact upon U.S. and world population lung cancer incidence. In fact, Gofman's entire argument in CNR Report 1975-2 is based on his assessment of risk in CNR Report 1975-1. That risk estimates in the first report can be invalidated essentially nullifies risk estimates in the second report.

Gofman suggests that the current lung cancer rate - 63,500 deaths per year for men and 17,000 deaths per year for women - is due in part to fallout plutonium. This may be a true statement; however, in view of the fact that no sex-related differences in lung cancers due to radiation exposure have been demonstrated, lung cancer patterns in the general population probably reflect smoking patterns in males and females.

### B. Fallout:

As a result of atmospheric weapons testing, an estimated 320,000 Ci (11,500 lbs.) of long-lived plutonium isotopes has been deposited on the surface of the earth; of this, about 250,000 Ci deposited on the northern hemisphere and 16,000 Ci on the United States (10). Machta et al. (11) has stated that deposition of environmental pollutants is approximately 90% by rain droplet washout. Thus, of the total amount deposited, perhaps only 1150 pounds or 32,000 Ci of weapons plutonium would have reasonably been available for inhalation by inhabitants of the northern hemisphere. Using the Bennett (12) estimate of 42 pCi/person for inhaled plutonium, citizens of the United States would have accumulated approximately 8.5 mCi or  $5 \times 10^{-7}$  of the total 16,000 Ci deposited on the United States. This indicates a deposition factor of  $10^{-7}$  to  $10^{-8}$  for that activity dispersed into the atmosphere.

### C. Lung Cancer Risk from Natural Background Based on Gofman's Model:

Gofman proceeds to equate 7.3 micrograms of  $^{239}\text{Pu}$  deposited or 450 pCi,

to the "lung cancer dose" for nonsmokers. Using the assumption that 1  $\mu\text{Ci}$  yields a lifetime dose in humans of 2,000 rem, 450 pCi would yield a lifetime dose of 0.9 rem. Therefore, the nonsmoker would accumulate an average dose to lungs of approximately 10 millirem per year for a 70-year lifespan. Natural background radiation contributes approximately 150 millirem per person per year. Background radiation dose to lung would therefore be 15 times greater than from 450 pCi of  $^{239}\text{Pu}$ . Thus, using the Gofman risk evaluation, about 15 times as many lung cancer deaths would be related to background radiation for any given time period for the U.S. population as would be related to inhaled plutonium; this would apply, anyway, for nonsmokers. Using lung cancer risk per unit mass of plutonium rather than rem dose tends to obscure this comparison.

D. Human Experience:

The workers in the Manhattan Project as well as those exposed during the Rocky Flats fire in 1965 have not developed a single lung cancer. Perhaps the latent period is not over. In any event, this again emphasizes that latency period and age may both be important factors in influencing the potential for detecting lung cancer resulting from  $^{239}\text{Pu}$  deposited in the lung. Life shortening has not occurred in either group and perhaps will not, even if one or more of these workers eventually develop lung tumors relatable to their plutonium exposures.

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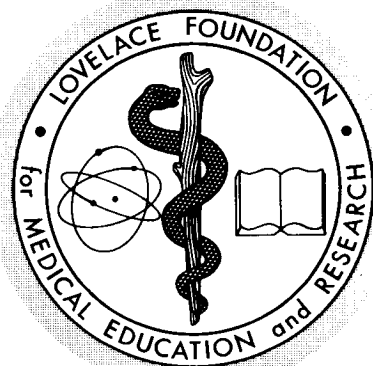


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**ESTIMATES OF MORTALITY DUE TO RADIATION  
PNEUMONITIS AND PULMONARY FIBROSIS AFTER EXPOSURE  
TO RADIONUCLIDE RELEASES IN HYPOTHETICAL  
LIGHT WATER REACTOR ACCIDENTS**

**F. F. Hahn**

**September 1975**



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September 1975

by

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## ABSTRACT

Estimates of incidence of early effects in people after exposure to radionuclide releases in hypothetical light water reactor accidents are necessary for benefit risk analysis of various energy sources. Because no human data exist which directly apply to this problem, estimates must be made from experimental data in animals. This report makes such estimates based on hypothetical releases and radiation doses estimated in WASH-1400 and experimental data derived from Beagle dogs exposed to various radionuclides.

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ESTIMATES OF MORTALITY DUE TO RADIATION PNEUMONITIS  
AND PULMONARY FIBROSIS AFTER EXPOSURE TO RADIONUCLIDE  
RELEASES IN HYPOTHETICAL LIGHT WATER REACTOR ACCIDENTS

by

F. F. Hahn

INTRODUCTION

Irradiation of the lung may occur either from external sources, such as x-ray therapy or  $^{60}\text{Co}$  machines, or from internally-deposited radionuclides such as inhaled radioactive particles. The radiation dose patterns to the lung from these two types of exposures are quite different and therefore not easily compared, but in sufficiently high doses, either can cause radiation pneumonitis (inflammation or irritation of the lung) which may lead to pulmonary fibrosis (scarring of the lung). Death due to cardiopulmonary insufficiency (malfunction of the heart and lungs) may occur within days after exposure due to radiation pneumonitis or as long as many months after exposure due to radiation pneumonitis and/or pulmonary fibrosis. The sequence of events may proceed even though the time of actual radiation exposure is brief and/or the radioactivity is no longer present in the body.

Factors which influence the development of radiation pneumonitis include the total dose of radiation, the fractionation of the radiation dose, the type of radiation, the volume of lung affected, pre-existing diseases and modifying drugs.

REVIEW

Considerable data concerning radiation pneumonitis have been reported from studies related to radiation therapy of tumors arising in the lung or other thoracic structure. Radiation pneumonitis was first described as a clinical entity by Groover et al.<sup>1</sup> They recognized it as an untoward effect associated with irradiation of thoracic tumors.

Warren and Spencer<sup>2</sup> described the pathology of radiation pneumonitis. They divided the reaction into three stages: acute, late and late with superimposed acute radiation pneumonitis. They also noted that probably the earliest effect is one of mild injury to the alveolar lining cells and capillary endothelium. This suggestion has since been confirmed by numerous

studies with electron microscopy.<sup>3,4</sup> Edema, swelling, necrosis and proliferation of endothelium and alveolar epithelium follow. With severe or repeated injury and attempts for repair, chronic changes such as fibroblastic proliferation occur within alveolar walls. The changes are not unique to the radiation reaction but very prominent edema and enlarged epithelial and endothelial cells in the absence of much exudate are suggestive of radiation pneumonitis.

Rubin and Casarett<sup>5</sup> described the clinical course of patients receiving thoracic irradiation and used the clinical categories of acute, subacute and chronic. These three periods are separated mainly on the basis of time after exposure and overlap one another. Typically, the onset occurs 1 to 3 months after completion of a 4 to 6 week course of x-irradiation, but may be delayed 6 months or longer. The acute clinical period may be clinically silent depending on the degree of pulmonary involvement. As the volume of injured lung increases, dyspnea and coughing become apparent. When more than 75% of the lung reacts to irradiation, respiratory distress is severe and death may occur from cardiopulmonary insufficiency. The respiratory system does not exhibit a distinctly recognizable subacute clinical syndrome in the radiation reaction as is encountered in other organ systems, but generally it blends into the chronic period. Symptoms may be seen in this period 6 to 12 months after irradiation if secondary pulmonary infections are present. The chronic clinical period occurs about 1 year after exposure. Symptoms are directly related to the degree and extent of lung damage. Scarring limited to 50% of one lung is well tolerated and rarely symptomatic. Progressive changes involving extensive portions of the lung may lead to right heart failure or severe chronic dyspnea.

The time dose factors involved in the production of radiation pneumonitis in man from therapeutic irradiation of the thorax are difficult to derive because exposure of the lesions is maximized and exposure of the normal lung is minimized. Generally, doses to the lung cannot be accurately calculated. Several studies, however, have been reported which involved irradiation of the entire thorax in treatment regimens for metastatic tumors in the lung. Baeza<sup>6</sup> found that 9 of 39 patients with tumor doses (which approximate lung doses) greater than 1500-2000 delivered rads in 2-3 weeks had radiation pneumonitis (Table 1). The average time of onset after exposure was 2.7 months for the entire group of patients. Newton<sup>7</sup> found that two patients receiving

Table I  
Summary of dose-response data for man and dog exposed to external thoracic radiation

Species	Treatment Parameters			Dose		Effects	
	Radiation	Number of Exposures	Treatment Period (Days)	Area Irradiated	Total* Dose (rads)		NSD** (rets)
Man	<sup>60</sup> Co or Mega Voltage x-rays	(?)	7-74	(> 75% of one lung)	550 — — 6600	0-750 750-900 900-1200 > 1200	Incidence of radiation pneumonitis (clinical and radiographic) { 0/25 = 0% <sup>a</sup> 1/8 = 13% <sup>a</sup> 2/4 = 50% <sup>a</sup> 5/5 = 100% <sup>a</sup>
Man	<sup>60</sup> Co or kilo voltage x-rays	(?)	(10-49)	Whole thorax	740-1220 1500-2000		Incidence of radiation pneumonitis (clinical) { 4/23 = 17% <sup>b</sup> 9/39 = 23% <sup>b</sup>
Dog	1000 KVP	1	-	Upper Body	1775		LD <sub>50/30</sub> <sup>c</sup>
Dog	260 KVP	1 15	- 105	Whole thorax	1000-2900 3000-4800	930-1500	8/8 = 100% dead in 2.5 months <sup>d</sup>
Dog	<sup>60</sup> Co	1	-	Whole thorax	1250		5/5 = 100% dead in 3 months <sup>e</sup>

\* Total dose in rads = N x d

\*\* Nominal Standard Dose in rets = total dose x N<sup>-0.24</sup> T<sup>-0.11</sup>

N = number of fractions    T = time in days    d = dose per fraction

<sup>a</sup>Wara et al. (1973)

<sup>b</sup>Baeza et al. (1975)

<sup>c</sup>Hansen et al. (1961)

<sup>d</sup>Sweany et al. (1959)

<sup>e</sup>Tyree et al. (1966)

3000R thoracic irradiation in two weeks at a rate of 300R per day died with radiation pneumonitis.

A quantitative approach to time dose factors for the production of radiation pneumonitis has been published.<sup>8</sup> They studied the incidence of radiation pneumonitis in a series of 51 patients treated with irradiation of at least 75% of one whole lung for metastatic pulmonary disease. Using probit analysis, they determined the dose response curve for development of radiation pneumonitis as determined by clinical symptoms and radiographic changes. These data are shown in Table 1 and indicate that the nominal standard dose (NSD) which will produce radiation pneumonitis in 50% of those exposed, is about 1050 rets. The NSD is a mathematically derived term representing the extrapolation of the dose time relationship back to a single fraction, taking into account the number of fractions and the total time separately<sup>9</sup>. The NSD is expressed in "rets," or rad equivalent therapeutic. It is used to compare doses from multiple exposures with those of single exposures.

Only a few studies of the effects of inhaled radionuclides in man have been reported. The exposures have either resulted in no effects being observed<sup>10,11</sup> or late effects seen and related to metaplasia and neoplasia.<sup>12,13</sup> One exception is a report of a case of a radium plant worker developing radiation pneumonitis presumably caused by inhalation of radon and radon daughters.<sup>14</sup> This early report contains few details and little quantitative information can be obtained from the paper.

Numerous animal studies describing radiation pneumonitis after external irradiation have been published and reviewed.<sup>15</sup> Davis<sup>16</sup> was the first to publish extensive experimental studies designed to determine the histologic reaction of normal lung to radiation. Using dogs and rabbits, he determined that the reactions seen in animals were similar to man. Engelstad<sup>17</sup> used rabbits to study the temporal sequence of the pulmonary lesions after thoracic irradiation. He described stages similar to those seen in man.<sup>2</sup> Generally, similar findings have been reported in rats,<sup>18</sup> dogs,<sup>19</sup> Syrian hamsters<sup>20</sup> and mice.<sup>21</sup> More recent studies of the ultrastructural lesions at early times after irradiation show focal lesions in many types of lung parenchymal cells,<sup>22</sup> including the pulmonary capillaries<sup>3</sup> and granular pneumocytes.<sup>23</sup>

Several quantitative dose response studies have been reported in animals exposed to thoracic irradiation. Hansen et al.<sup>24</sup> determined the LD<sub>50/30</sub> for single upper body exposure of dogs to x-rays to be 1775 rads. These dogs died with pulmonary congestion and fibrinous pneumonia but also had other complicating factors such as neuroendocrine abnormalities and infection. Sweany et al.<sup>25</sup> exposed the thorax of dogs to single doses of x-rays ranging from 1000 to 2900 R. All 8 of the dogs were dead within 2.5 months. Dogs were also exposed to 15 fractions in 105 days resulting in a radiation dose of 3000 to 4800 R. Four of 7 dogs died within 6 months. The NSD calculated for these dogs was 930-1500 rets. Tyree et al.<sup>26</sup> reported a study in which 5 of 5 dogs exposed to 1250 rads thoracic radiation were dead within 3 months. They commented, however, that secondary infections were an important complicating factor in the death of these dogs. These data are shown in Table 1.

Phillips and Margolis<sup>21</sup> have developed a dose-response relationship for mice exposed to thoracic x-radiation. The LD<sub>50/160</sub> was determined to be 1350 ± 50 rads. They also used fractionated doses over a period of days to more closely compare the findings with radiation therapy patients. In these studies the NSD ranged from 1438 to 1596 rets. Field and Hornsey<sup>27</sup> reported an LD<sub>50/180</sub> for thoracic irradiated mice to be about 1170 ± 100 rads.

Experimental studies of radiation pneumonitis after inhalation of radionuclides have been reported. Lesions have been described in a dog after inhalation of <sup>144</sup>CeO<sub>2</sub>,<sup>28</sup> <sup>144</sup>Ce in fused clay particles,<sup>29</sup> or <sup>90</sup>Y in fused clay particles<sup>30</sup>; in rats after inhalation of <sup>144</sup>Ce OH<sup>31</sup> or intratracheal injection of <sup>144</sup>CeCl<sub>3</sub><sup>32</sup>; and in dogs after inhalation of <sup>239</sup>PuO<sub>2</sub>.<sup>33</sup> Radiation pneumonitis induced by these internally-deposited radionuclides is, in general, similar to that induced by external irradiation. Pulmonary lesions consist of (1) alveolar accumulations of fibrin, red blood cells, hemosiderin, macrophages and cellular debris, (2) alveolar septal thickening due to accumulations of inflammatory cells and hypertrophy and hyperplasia of alveolar lining cells, (3) interstitial accumulations of chronic inflammatory cells around vessels and airways, (4) bronchiolar epithelial injury characterized by focal denudation and hyperplasia, (5) vascular changes characterized by fibrous subintimal proliferations in elastic pulmonary arteries, fibrinoid necrosis in muscular pulmonary arteries and perivascular fibrosis, (6) pulmonary

fibrosis characterized by fibrillar thickening of alveolar septae of pleura and large dense scars which obliterated the normal alveolar pattern, and (7) focal emphysema related to large scars or thrombosis of small muscular arteries. The time and tissue distribution of these lesions may differ from those seen in externally irradiated animals because of nonuniform localization of the radionuclide in the lung, dose distribution of its emitted radiation, and the half-life of the material in lung which determines the time over which the radiation dose is delivered.

Quantitative dose response studies with dogs that have inhaled various beta gamma emitting radionuclides have been reported.<sup>29,34,35</sup> Groups of Beagle dogs received single, nose-only exposures of  $^{90}\text{Y}$ ,  $^{91}\text{Y}$ ,  $^{144}\text{Ce}$  or  $^{90}\text{Sr}$  incorporated into aerosols of relatively insoluble particles. These particles with their incorporated radionuclide were retained in the lung wherein the varying physical half-lives of the 4 radioisotopes resulted in varied effective half-lives in the lung ranging from 2.6 days for  $^{90}\text{Y}$  to about 400 days for  $^{90}\text{Sr}$ . Because of the protracted irradiation of the lung with  $^{144}\text{Ce}$  and  $^{90}\text{Sr}$  very high radiation doses to lung were accumulated by the time of death. Maximum cumulative doses ranged from 9000 rads for the short half-life isotope  $^{90}\text{Y}$  to 140,000 rads for the long half-life isotope  $^{144}\text{Ce}$ . In general, dogs exposed to  $^{90}\text{Y}$  and  $^{91}\text{Y}$  had shorter survival times than those exposed to  $^{144}\text{Ce}$  or  $^{90}\text{Sr}$ . The doses which produced death from radiation pneumonitis and/or pulmonary fibrosis are shown in Table 2.

Animals dying at relatively early times after inhalation exposure (< 500 days) had various degrees of radiation pneumonitis and pulmonary fibrosis and succumbed because of respiratory insufficiency. Pulmonary lesions induced by all 4 radionuclides were generally similar except for the short-lived isotope ( $^{90}\text{Y}$ ) which caused squamous metaplasia in bronchioles and the long-lived isotope ( $^{90}\text{Sr}$ ) which caused generally more severe lesions.

Table 2

Radiation doses to lung and time of death after exposure for dogs dying with radiation pneumonitis after inhalation of various beta-emitting radionuclides.

Radionuclide (inhaled in relatively insoluble form)	Time of death after exposure (days)		Dose to lung at death (rads)	
	Median	Range	Median	Range
$^{90}\text{Y}$	99	7- 903	16,000	9,300 - 70,000
$^{91}\text{Y}$	181	113-1011	29,000	8,300 - 60,000
$^{144}\text{Ce}$	211	143-410	57,000	28,000 -140,000
$^{90}\text{Sr}$	262	159-477	60,000	40,000 - 96,000

Catastrophic light water reactor accidents may result in the release of radioactive materials and expose the general population to both external radiation and airborne radionuclides. The magnitude of hypothetical releases and the resultant radiation doses to various organs of individuals in the hypothetically exposed population are estimated in Reactor Safety Study, WASH-1400.<sup>36</sup> The highest predicted doses to lung as a result of a "maximum" release are shown in Table 3. They are based on estimates of irradiation of the lung from external sources, inhaled radioactive particles and gases and from inhaled and deposited radionuclides.

Table 3

Predicted radiation doses to lung as a result of a "maximum" release nuclear accident.

<u>Days after exposure</u>	<u>Dose to lung (rads)</u>
2	16,000
7	21,000
30	30,000
180	35,000
365	38,000

The temporal radiation dose pattern to the lung from this exposure can be seen in Figure 1 which shows the percent of the total radiation dose absorbed at various times after exposure. Initially, the dose is accumulated very rapidly. To achieve 38,000 rads infinite dose to the lung with this dose pattern the initial dose rate is about 7000 rads per day.

Estimation of the morbidity and mortality due to radiation pneumonitis and pulmonary fibrosis resulting from hypothetical exposure of people to predicted releases in nuclear reactor accidents is difficult. There are no human data relating effects to pulmonary dose from irradiation due to inhalation of radioactive particles. There is only one case reported of radiation pneumonitis after inhalation of radionuclides but doses to lung are unknown.<sup>14</sup> Studies of radiation therapy patients cannot be applied directly to the problem since both the temporal and spatial radiation dose patterns are very different.

Mortality estimates can be made for dogs exposed to the estimated maximum releases in a nuclear reactor accident. The temporal radiation dose pattern to the lung is somewhat similar to the radiation dose patterns in the studies described by McClellan et al.<sup>29</sup> and Hobbs et al.<sup>30</sup> for  $^{90}\text{Y}$  or  $^{91}\text{Y}$  in fused clay particles shown in Figure 1. Because the early effects of inhaled  $^{90}\text{Y}$  in fused clay particles are usually more severe than those of  $^{91}\text{Y}$  in fused clay particles due to the more rapid delivery of the dose to the lung,  $^{90}\text{Y}$  was chosen for estimates of death from radiation pneumonitis or pulmonary fibrosis. Figure 2 shows the cumulative incidence of death from radiation pneumonitis and pulmonary fibrosis to 365 days after exposure of dogs to  $^{90}\text{Y}$  in fused clay particles. Incidence rates were determined using a procedure based on life table methods.<sup>37</sup> Doses to lung to 365 days after exposure (infinite dose) of 20,000 rads or greater resulted in 100% cumulative incidence of radiation pneumonitis. A similar analysis of dogs exposed to aerosols of  $^{91}\text{Y}$  in fused clay particles (Figure 3) shows that pulmonary doses of 30,000 rads or greater resulted in 100% cumulative incidence of radiation pneumonitis. Thus, it can be predicted that 100% of dogs receiving the pulmonary dose (38,000 rads in 1 year) calculated from a maximum release accident would be dead from radiation pneumonitis and/or pulmonary fibrosis at the end of 1 year. Mortality incidence estimates for lower doses can also be made from Figures 2 and 3.



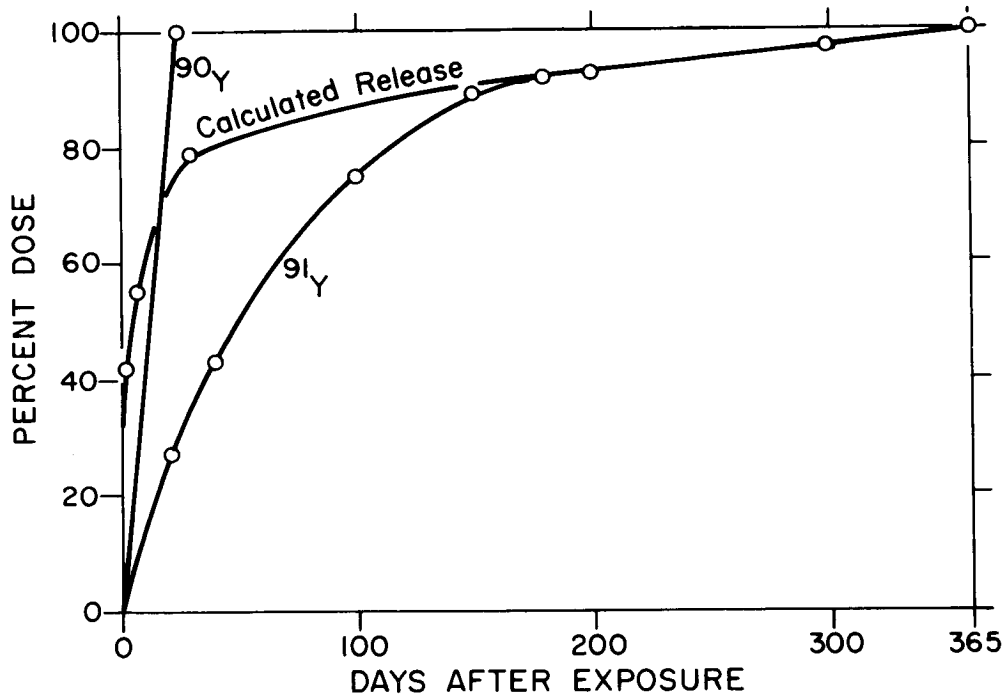


Figure 1. Dose accumulation in lung for man for a hypothetical maximum release from a nuclear reactor accident and for dog from inhalation exposure to  $^{90}\text{Y}$  and  $^{91}\text{Y}$  in fused clay particles.

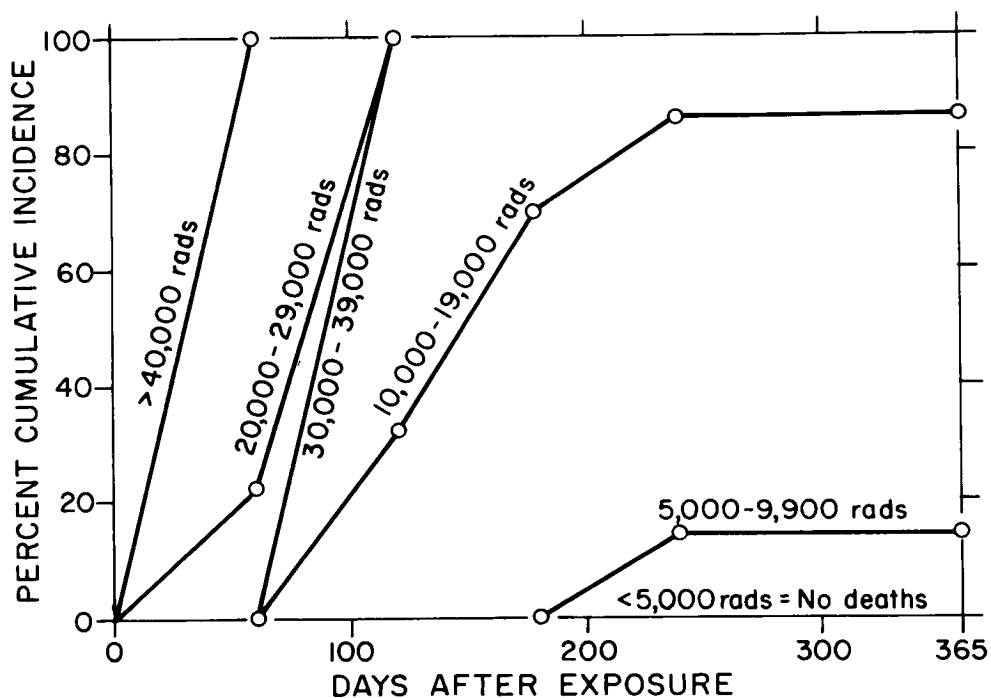


Figure 2. Cumulative incidence of deaths from radiation pneumonitis and/or pulmonary fibrosis in dogs after inhalation of  $^{90}\text{Y}$  in fused clay particles (doses to lung at 365 days after exposure).

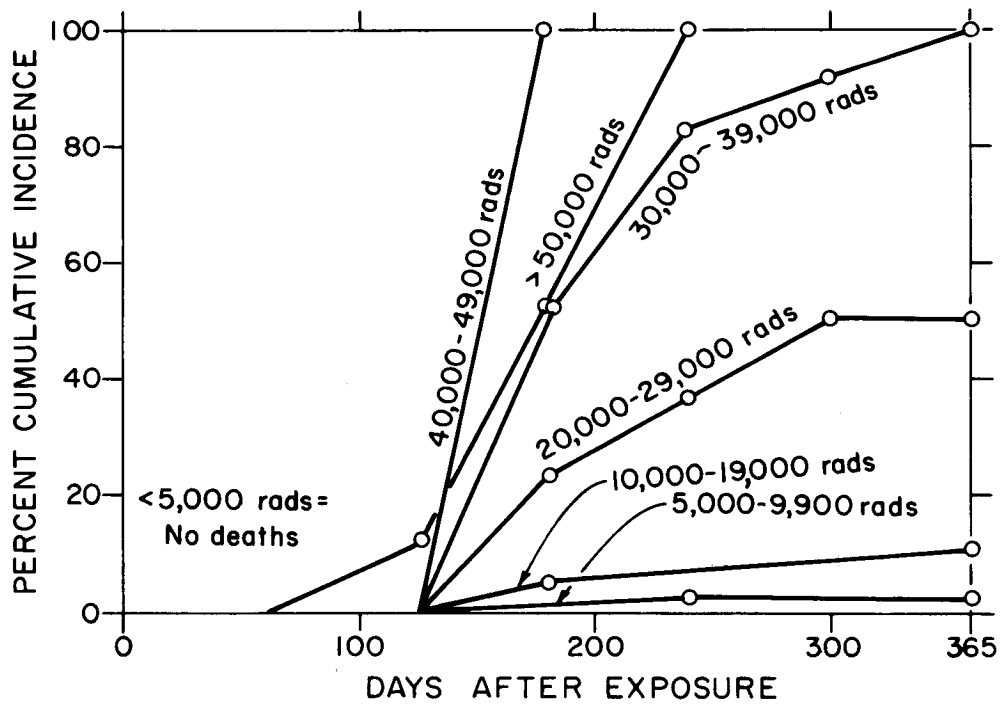


Figure 3. Cumulative incidence of deaths from radiation pneumonitis and/or pulmonary fibrosis in dogs after inhalation of  $^{91}\text{Y}$  in fused clay particles (doses to lung at 365 days after exposure).

Estimates of morbidity due to radiation pneumonitis can be determined from studies by Mauderly et al.<sup>38</sup> They found that 3 dogs exposed to  $^{90}\text{Y}$  in fused clay particles, which resulted in lung doses of 4900 to 5700 rads, developed radiation pneumonitis 2 to 3 months after exposure as evidenced by subclinical functional impairments. The defects were transient and could be determined only by dead space tolerance or treadmill exercise testing. All 3 dogs survived to 1 year after exposure. These results indicate that dogs with pulmonary doses of 5000 to 9900 rads (Figure 1) may well have had subclinical radiation pneumonitis even though they survived to 1 year after exposure. Therefore, the estimates of morbidity, from radiation pneumonitis for dogs in the 5000 to 9900 rad dose group may be considered 100%. No studies have been conducted on dogs with pulmonary doses appreciably smaller than 5000 rads.

There are scant quantitative data on which to compare the pulmonary response of man and the dog, however, some general statements can be made concerning predictions for man derived from animal derived data. Radiation pneumonitis in many species is generally qualitatively similar although there are certainly many minor variations in response. For example, the sequence of lesions in radiation pneumonitis and the recognition of early and late stages were initially derived from studies with rabbits.<sup>17</sup>

Also, various species require doses within a range of about 2 times each other to produce radiation pneumonitis. For example, the  $\text{LD}_{50/160-180}$  for thoracic irradiation in mice is 1170 to 1350 rads,<sup>21,27</sup> which is close to the effective dose needed to produce radiation pneumonitis in 50% of people exposed to 1050 rems.<sup>7</sup> The quantitative response of the dog to external thoracic irradiation is similar to that of mouse and man. Pulmonary radiation dose causing 50% death from radiation pneumonitis in dogs is from 1200 to 1775 rads.<sup>24,25</sup> Although the dose calculations are not exactly the same and the endpoints (clinical radiation pneumonitis vs. death from radiation pneumonitis) are not identical, the doses required to produce these endpoints do not vary by more than a factor of two. Thus, based on available data, the extrapolation of results from dog to man is reasonable and should fairly accurately predict the early effects of inhaled radionuclides in man.

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