BIOLOGICAL EFFECTS OF INHALED RADIONUCLIDES: SUMMARY OF ICRP REPORT 31

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A report on the biological effects of inhaled radionuclides was prepared by an International Commission on Radiological Protection Task Group charged with evaluating the hazards associated with inhalation of plutonium and other radionuclides.[1] The Task Group enumerated the biological responses, identified tissues and cells at risk, derived risk coefficients for inhaled radionuclides from animal experiments for comparison with human data, and determined an Equal Effectiveness Ratio for alpha emitters relative to beta-gamma emitters.

BIOLOGICAL EFFECTS

Since there are no human populations (other than uranium, fluorspar, and other miners who worked in mines containing high concentrations of radon decay products) that have shown health effects that can be associated with radionuclide inhalation, it was necessary for the Task Group to use data from animal experiments to describe the biological effects. Radionuclides deposited in the respiratory tract are either "insoluble" (not readily translocated to other tissues or excreted) or "relatively soluble" (more readily translocated to other tissues or excreted). Biological effects resulting from the inhalation of radionuclides depend upon the distribution and retention of these radionuclides in the body and upon the doses to the tissues irradiated.

Life-Span Shortening

The Task Group compared the mean or median survival time of animals exposed to radionuclides with those of appropriate controls. Only data from alpha-emitter experiments were used because of the paucity of beta-gamma emitter data. Figure1 shows the shortening of life span in animals that inhaled PuO_2. At deposition doses below about 0.01 μCi/g lung, the shortening of mean life span was less than about 10%. Several experimental groups had mean life spans greater than control groups. At doses above about 0.01 μCi/g lung, life-span shortening increased with dose. The dose causing a 50% reduction of mean life span was between 0.05 and 0.1 μCi/g lung. Similar results were obtained for soluble alpha emitters; the dose causing a 50% reduction of mean life span was about 0.1 μCi/g lung.

Pathologic and Clinical Responses

The shortening of life span following the inhalation of radionuclides was accompanied by and/or caused by certain pathologic changes, some of which were reflected in clinical signs and symptoms. Some of these effects appear to be nonstochastic, i.e., the degree of effect, rather than its occurrence, is a function of dose; examples are lymphocytopenia, respiratory insufficiency, pulmonary and lymph node fibrosis, and cellular metaplasia. Other effects, such as pulmonary and bone neoplasia, are stochastic since the probability of occurrence is related to dose. Since a full spectrum of doses has not been investigated for any inhaled radionuclide in any animal species, it is not possible

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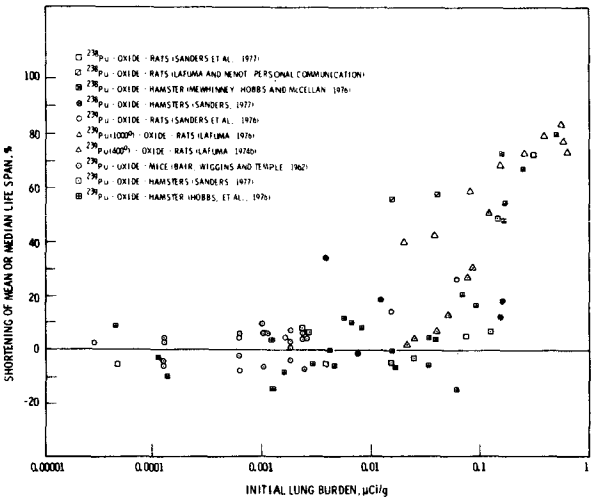

FIGURE 1. Shortening of Life Span by Inhaled PuO_2[a]

to know the lowest doses at which any biological effect *will occur* nor even the highest dose at which it *will not occur*. However, the available data were used to base judgments about the lowest dose range at which given nonstochastic effects are likely to be seen. For stochastic effects, such as death-causing neoplasia, estimates of the frequency of occurrence were developed.

Hematologic Effects. Hematologic effects occur after inhalation of radionuclides because of the irradiation of the hematopoietic tissue to which the radionuclides are translocated and deposited, and because of the direct irradiation of blood circulating in lungs, liver, and perhaps lymph nodes containing the radionuclide. Leukocytopenia was observed in animals after inhalation of soluble forms of alpha emitters or beta-gamma emitters. The most consistent hematologic response observed in dogs after inhalation of PuO_2 and insoluble beta-gamma emitters was lymphocytopenia. The Task Group concluded that lymphocytopenia is probably a nonstochastic effect, and that it probably can be detected after pulmonary deposition of ≥0.0005 µCi PuO_2/g lung. Much higher doses of inhaled insoluble beta-gamma emitters are required to cause a detectable lymphocytopenia, probably on the order of >0.01 µCi/g. Since both the magnitude and time of onset of lymphocytopenia are dose dependent, lymphocytopenia caused by these low doses would not occur until long after exposure to the radionuclide and might be marginally detectable.

Nonneoplastic Lesions. Respiratory insufficiency (characterized by increased respiratory rate, decreased arterial P_{O2} and increased P_{CO2} caused by diffuse fibrosis of the lungs) and alveolar edema may cause death within a month after inhalation of large amounts of alpha- or beta-gamma-emitting radionuclides. Death from respiratory insufficiency and fibrosis may also result after exposure to much lower doses and may occur in rodents after many months and in dogs after several years. Respiratory insufficiency is the major cause of death in those groups of animals that showed a greatly reduced mean life span, Figure 1.

The available data from several animal species indicate that respiratory insufficiency and possibly death resulting from extensive fibrosis in the lungs caused by radiation from inhaled radionuclides are nonstochastic processes and might be expected to occur after alveolar deposition of >0.01 µCi alpha emitters/g lung and of >0.5 µCi beta-

[a]See ICRP Publication 31 for references.

gamma emitters/g. If the retention times of the radionuclides in the lungs are short, larger quantities of the radionuclides would have to be deposited in the lungs to cause these lesions and early death.

Lymph nodes containing radionuclides may be severely damaged. The primary lesions are characterized by lymphadenitis and fibrosis with partial to complete depletion of germinal centers. Primary neoplasia does not appear to occur in lymph nodes of experimental animals that have inhaled alpha emitters or beta-gamma emitters. The dose-effect relationship for nonneoplastic lesions in the tracheobronchial lymph nodes is poorly known. Although lesions have been described in rodents, most of the dose-effect data from experiments with dogs suggest that fibrotic and/or atrophic lesions in the tracheobronchial lymph nodes are nonstochastic responses and that the dose at which these responses may be expected to begin to be observed is an alveolar deposition of about 0.001 μCi/g lung. This applies to insoluble alpha emitters such as $^{239}PuO_2$. In the case of more soluble alpha-emitting compounds, which are not as readily accumulated in the tracheobronchial lymph nodes as $^{239}PuO_2$, larger amount would be required to produce lymph node lesions. The dose of insoluble beta-gamma emitters required to produce such lesions is not known, but is probably greater than 0.05 μCi/g lung.

Neoplastic Lesions. Pulmonary neoplasia has been identified in miners of uranium and other substances as a consequence of inhaling alpha-emitting radon daughter radionuclides. Although pulmonary neoplasia has not been reported in human beings who have inhaled other radionuclides, such as the transuranic elements, it has been well demonstrated in experimental animals as a potential consequence of inhaling several different alpha-emitting and beta-gamma-emitting radionuclides.

In Figure 2 the incidences of lung cancer are plotted against the initial lung burdens of soluble alpha-emitting radionuclides. In rats, initial lung burdens above 0.001 μCi/g had an increasing probability of causing lung cancer. The low incidences at high doses reflected the shortened life spans due to deaths from causes other than neoplasia which prevented the full lung cancer potential from being expressed. At initial lung burdens below about 0.001 μCi/g, none of the experiments showed statistically significant increases in lung cancer, although several lung cancers occurred.

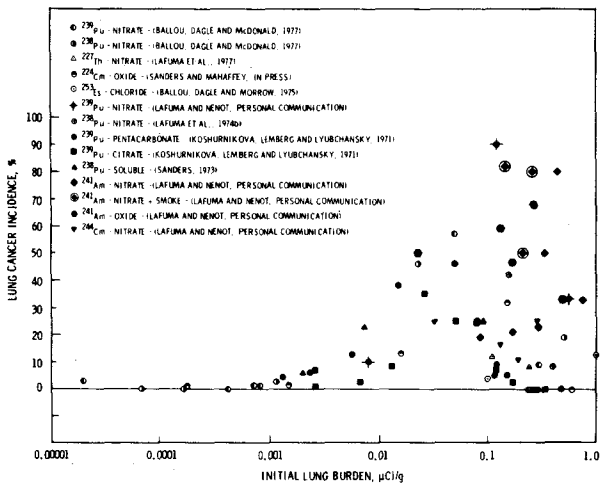

FIGURE 2. Relationship Between Incidence of Lung Cancer in Experimental Animals and Initial Lung Burdens of Inhaled, Relatively Soluble, Alpha-Emitting Radionuclides[a]

[a]See ICRP Publication 31 for references.

Like the data for relatively soluble alpha emitters, the lung cancer incidence for insoluble PuO_2 increased markedly at initial lung burdens above 0.001 μCi/g. Low-dose experiments are still in progress in which groups of dogs were exposed to initial lung burdens as low as 0.00003 μCi $^{239}PuO_2$/g lung and 0.000016 μCi $^{238}PuO_2$/g lung. In several experiments at different laboratories it was observed that hamsters were relatively insensitive to the induction of lung cancer. Thus, comparing species susceptibility to lung cancer caused by inhaled PuO_2 at the dose range where data exist (~0.01 μCi/g initial lung burden), beagle dogs were more sensitive than rats, which were more sensitive than mice, which were more sensitive than hamsters.

In studies of beta-gamma-emitting radionuclides deposited by inhalation or by intratracheal injection, initial lung burdens above 0.1 μCi/g led to increasing incidences of lung cancers. There are no data at lower doses.

While recognizing the possible shortcomings of using experimental animal cancer incidence data, the Task Group believed that, in the absence of a human data base, a quantitative descriptive model for radionuclide carcinogenesis in the lungs based on the animal data could be useful for risk assessment. Since a model could not be devised from hypotheses of the mechanism(s) of induction of cancer by inhaled radionuclides, the Task Group chose the logarithmic probit model usually employed in dose-response analysis and contrasted it with the linear model usually used to reflect conservatism. The incidence values for the linear regression model were weighted on a basis of the number of observations.

The original data for alpha emitters, uncorrected for control mortality, and the fitted functions (heavy solid lines) in Figure 3. suggest that insoluble alpha emitters were slightly more effective than soluble alpha emitters in causing pulmonary cancer in experimental animals.

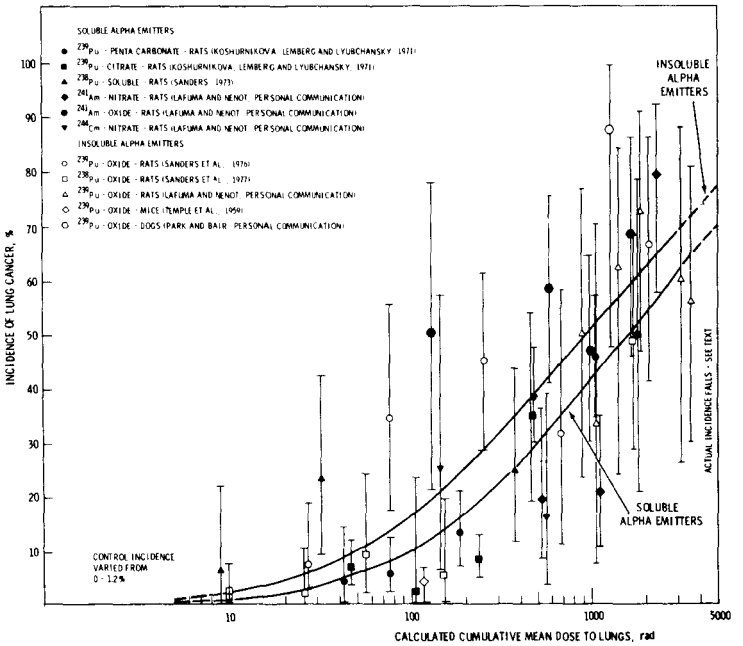

FIGURE 3. Relationship Between Incidence of Lung Cancer and Alpha Dose to Lungs from Inhaled Soluble and Insoluble Alpha Emitters; Probit Analysis[a]

[a]See ICRP Publication 31 for references.

Both the linear and probit models gave an adequate description of the alpha-emitter incidence results over the range of observed doses, Figure 4. However, the linear model used to describe the beta-gamma-emitter incidence data gave unrealistically high projected results at low or zero doses, Figure 5. Although the probit model gave more realistic values at low doses, the slope of the line was very shallow.

The improved Mantel-Bryan procedure also was used to obtain lung cancer risk estimates based on data from animal experiments. The Task Group compared these estimates with published estimates obtained by other methods (usually by linear extrapolations) from both experimental animal data and from limited human data, the latter mostly from external radiation exposures, Table 1.

The risk coefficients obtained by the Mantel-Bryan procedure and by extrapolating the fitted probit models are lower than those obtained from the fitted linear model and other published linear models using animal or human data. This means that for these experimental data, linear models yield a more conservative estimate of lung cancer risk than the other models. The applicability of these lung cancer risk coefficients to human beings who have inhaled or may inhale radionuclides is not known. However, the Task Group believed the risk estimates calculated from available animal data, summarized in Table 1, are supportive of the ICRP decision in Publication 26 (1978) to use a risk factor for the lungs of 2×10^{-3} Sv^{-1} (20×10^{-6} rem^{-1}).[2]

Comparison of the risk estimates obtained by analysis of all the alpha-emitter data, 25 and 36×10^{-6} rad^{-1}, with the risk estimate of 0.84×10^{-6} rad^{-1} for beta-gamma emitters gave an Equal Effectiveness Ratio of about 30 for inhaled alpha-emitting radionuclides. Thus, the experimental animal data tend to support the decision by the ICRP to change the recommended quality factor from 10 to 20 for alpha radiation (ICRP, 1977).[2]

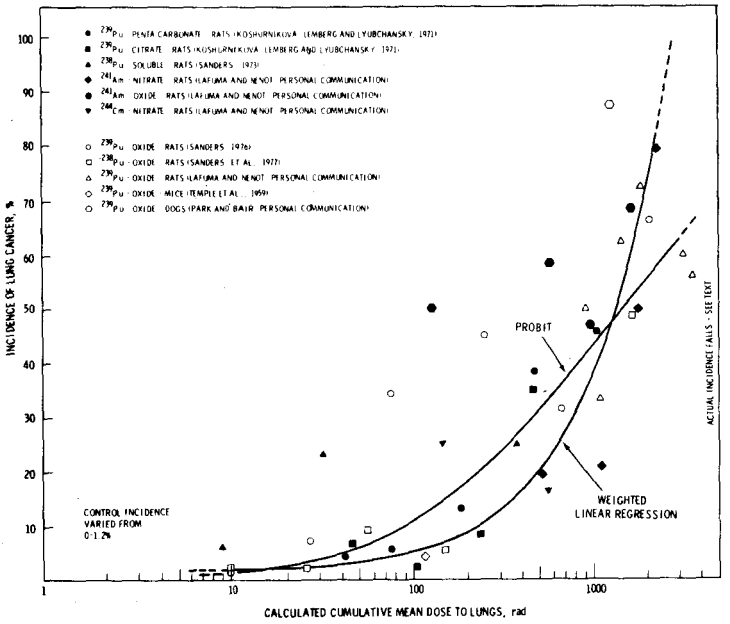

FIGURE 4. Comparison of Weighted Linear Regression and Probit Models as Descriptors of Alpha-Induced Animal Lung Cancer Data[a]

[a]See ICRP Publication 31 for references.

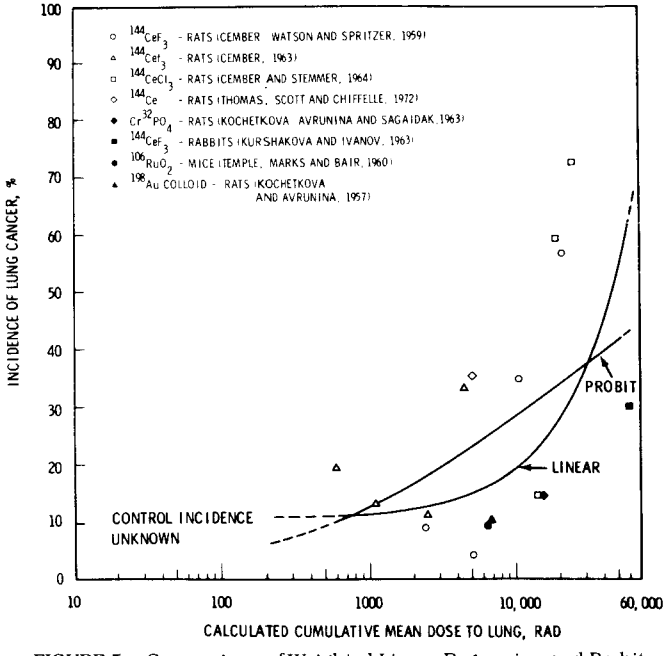

FIGURE 5. Comparison of Weighted Linear Regression and Probit Models as Descriptors of Beta-Gamma-Induced Animal Lung Cancer Data

Extrapulmonary Lesions. Various tumors in tissues other than those of the respiratory tract have been observed in animals after inhalation of alpha-emitting or beta-gamma-emitting radionuclides. These have occurred mostly in animals that have inhaled relatively soluble radionuclides which translocated from lungs to other tissues in the body. It is well documented that alpha-emitting radionuclides such as radium deposited in bone tissue can cause osteosarcomas in human beings as well as in experimental animals. Thus, bone neoplasia can be expected to be a potential consequence of inhaling alpha-emitting radionuclides if sufficient quantities are translocated to bone. In experimental animals, bone neoplasia has occurred at dose levels of about 0.01 μCi/g lung of inhaled soluble plutonium and other transuranic elements. Inhaled beta-gamma-emitting radionuclides such as ^{90}Sr and ^{144}Ce, which deposited in skeleton, also have been shown to cause skeletal neoplasia in experimental animals.

With the more highly transportable transuranic elements such as einsteinium, curium, and americium, the incidences of extrapulmonary and extraskeletal cancers were increased in experimental animals. These included kidney and bladder carcinomas and thoracic and abdominal lymphoreticulosarcomas. Although many of the inhaled radionuclides studied in experimental animals translocated to liver, relatively few liver cancers were reported. Since these usually occurred at long times after exposure it was concluded that liver cancer could be one of the predominate late consequences of inhaling radionuclides.

Numerous neoplasias were observed in the nasal cavities of animals that inhaled alpha emitters such as radon and uranium and beta-gamma emitters such as ^{91}Y, ^{144}Ce, and ^{90}Sr, probably as a result of continuous irradiation of the nasal epithelium

All of these neoplasias are associated with tissues and organs in which inhaled radionuclides are deposited or accumulated following translocation from the respiratory tract. However, the fact that a tissue accumulates radionuclides does not necessarily

TABLE 1. Summary of Risk Coefficients for Radiation-Induced Lung Cancer

Animal Species	Model	Risk Coefficients (cases of lung cancer per million animals or persons per rad) Insoluble	Soluble	all	Beta-Gamma Radiation	Reference [a]
Rodents and dogs	Improved Mantel-Byran	70	20	25	0.84	ICRP-31
Rodents and dogs	Probit	65	20	36	-	ICRP-31
Rodents and dogs	Linear	-	-	360	-	ICRP-31
Rats	Linear	1600	800	1250	-	Bair and Thomas, 1976
Dogs	Linear	-	-	600 [b]	-	Bair and Thomas, 1976
Man	Linear	-	-	400 [b]	20	Thorne and Vennart, 1976
Man	Linear	-	-	500 [b]	25	MRC, 1975
Man	Linear	-	-	200	-	Mays, 1976
Man	Linear	-	-	400 [b]	20	BIER, 1972
Man	Linear	-	-	200-800 [b]	10-40	UNSCEAR, 1972
Man	Linear	-	-	1000 [b]	25-50	UNSCEAR, 1977
Man	Linear	-	-	400 [b]	20	ICRP-26, 1977

[a] See ICRP Publication 31 for references.

[b] Values converted to rad from rem on basis of a Q factor of 20 for alpha radiation.

indicate a susceptibility to cancer induction. For example, the thoracic and, to a lesser extent, hepatic lymph nodes have been shown to accumulate concentrations of radionuclides that exceed by many times the concentrations retained in lungs or that occur in other tissues. This is especially true for insoluble compounds. Primary neoplasia of thoracic and hepatic lymphatic tissue has not been reported in any of the experiments with inhaled alpha- or beta-gamma-emitting radionuclides. In life-span studies with beagle dogs that inhaled $^{239}PuO_2$ or insoluble ^{144}Ce particles, metastases of primary lung cancers were found in thoracic lymph nodes, as were occasional lymphangiosarcomas and several hemangiosarcomas. There were no other lymph node cancers. Thus, lymph nodes in experimental animals appear to be much less susceptible to cancer induction than other tissues in which inhaled radionuclides are deposited or accumulated. Further, inhalation of radionuclides is not known to be related to the induction of lymph node tumors in any human being. These observations influenced the ICRP's decision to consider the lymph nodes with the lungs as one composite organ for radiation protection purposes.[3]

CELLS AND TISSUES AT RISK

High lung burdens of inhaled radionuclides result in profound structural and functional changes in which the pulmonary capillary endothelial cells are the most prominent cells at risk. Pulmonary carcinogenesis is the most serious effect of low doses of inhaled radionuclides. The cells at risk are the precursor cells and basal cell layers of the respiratory tract epithelia. The Task Group considered the possibility that certain types of neoplasia induced by inhalation of radioactive material could be related to the presumed cell(s) of origin, and the cell lines at risk, but recognized the types of neoplasias produced may also depend on the pattern of spontaneous tumor development in a given species and strain. For instance in uranium miners small cell carcinomas, associated with lower radiation exposures, and epidermoid carcinomas, associated with higher initial exposures, appeared to originate in the larger proximal bronchi. In animals after inhalation of radionuclides, adenocarcinomas and epidermoid carcinomas appeared to originate in peripheral regions of the lungs. If the types of neoplasia observed after inhalation of radionuclides do suggest the cell line at risk, basal cell layers and Kulchitsky cells of bronchial epithelia may be at risk in uranium miners who develop undifferentiated small cell and epidermoid carcinomas. For adenocarcinoma in experimental animals, the cells at risk appear to be bronchiolar and, possibly, type II pneumocytes or Clara cells.

The occurrence of hemangiomas in lungs of animals that have inhaled radioactive particles suggests that the endothelial cells of pulmonary capillaries are also at risk. At risk also are the cellular constituents of bronchial and tracheobronchial lymph nodes, which may accumulate large doses or radiation. These include the T and B lymphocytes, germinal center cells, plasma cell precursors, endothelial cells and possibly reticulum cells, histiocytes, fibroblasts, and other mesenchymal elements. Endosteal bone tissue, hematopoietic marrow, and liver and spleen tissue may also be at risk from radionuclides translocated from the lungs. Lymphocytes appear to be at high risk from inhaled radioactive particles because blood lymphocytopenia is among the earliest and most sensitive changes observed in experimental animals. Since inhaled radionuclide-induced lymph node tumors as well as lymphomas and leukemias have been very rare in animal experiments, nothing can be said about tissues and cells at risk for these types of neoplasia. The possibility of genetic damage to germ cells after inhalation of radionuclides was not excluded by the Task Group but was not addressed because of the lack of data.

HOT PARTICLES

The Task Group believed that knowledge about the behavior of inhaled alpha-emitter particles in the lungs and the interaction of alpha irradiation with cells is inadequate either to support or completely deny the hot particle theory concerning the induction of lung cancer. Animal experiments indicate that the lung cancer risk associated with inhaled plutonium particles in quantities that could be distributed in hot spots may be slightly greater than for more soluble and, therefore, more diffusely distributed alpha emitters. Other experiments with plutonium microspheres clearly showed that "diffuse"radiation sources in the lungs of hamsters were much more likely to cause both malignant and benign lung tumors than highly localized sources. The Task Group concluded that the risk of lung cancer from inhaled radioactive particles will be greatly overestimated if based on hot particle concepts.

OTHER FACTORS

The Task Group considered possible modification of the effects of radionuclides by inhalation of other potentially damaging agents. Only a few animal experiments have addressed the question of combined effects of inhaled radionuclides and air pollutants or smoking. Results of these few studies are inconclusive. Therefore, such factors had to be ignored in addressing the objectives of the report. However, it was stressed that the possibility that the effects of inhaled radionuclides could be greatly influenced by smoking, and air pollutants should not be ignored in protecting human beings from airborne radionuclides.

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