Title

BEIR IV. THE EFFECTS ON POPULATIONS OF EXPOSURE TO INTERNALLY DEPOSITED ALPHA-EMITTING RADIONUCLIDES: 1987. HEALTH RISKS OF RADON AND OTHER INTERNALLY DEPOSITED ALPHA-EMITTERS

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Publication Date

1987-09-01

LBL-24173
UC-48

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Health Risks of Radon and Other Internally Deposited Alpha-Emitters

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September 1987

Donner

Biology & Medicine Division

Prepared for the U.S. Department of Energy under Contract DE-AC03-76SF00098

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BEIR IV

Committee on the Biological Effects of Ionizing Radiations

Board on Radiation Effects Research

Commission on Life Sciences, National Research Council

A Report to the International Commission on Radiological Protection

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September 1987

This work is supported in part by the U.S. Department of Energy under Contract No. DE-AC03-76SF00098 and in part by the U.S. Environmental Protection Agency, The U.S. Regulatory Commission, National Academy of Sciences-National Research Council.

Introduction

The BEIR-IV Report addresses demonstrated and potential health effects in human populations exposed to internally deposited alpha-emitting radionuclides and their decay products. Emphasis has been placed primarily on the carcinogenic effects in humans, and where possible, quantitatve risk estimates for cancer induction are presented. The largest part of the Report concentrates on the health outcomes due to exposure to radon and its progeny, primarily because of a need for a comprehensive characterization of the lung cancer risk associated with exposure to radon and its short-lived daughters in indoor domestic environments. The Report also addresses health effects due to exposure to other groups of radionuclides and their progeny that emit alpha particles, viz., the isotopes of polonium, radium, thorium, uranium, and the transuranic elements.

Alpha-emitting radionuclides and their daughter products may be absorbed into the tissues of the body following inhalation or ingestion, through wounds in the skin, or after injections and instillations for diagnostic or therapeutic medical applications, and irradiate adjacent cells, tissues and organs. Laboratory animal experiments and human studies demonstrate that radiation effects depend not only on the physical properties of the emitted radiations, but also on the physical and chemical characteristics of the radionuclides, which contol their deposition, transport, metabolism, excretion, and reutilization within the body. Radiation health effects in humans include cancer induction, genetic disease, teratogenesis (induction of developmental abnormalities), and degenerative changes. The most important target tissues for

cancer induction and degenerative changes are the respiratory tract, bone, liver, and the reticuloendothelial system.

Lung cancer risk is derived from the epidemiological surveys of underground miners who breathe high levels of radon-222 progeny; risk estimates based on dosimetric models of the respiratory tract are complex, and values are based largely on the location of the target cells in the bronchial epithelium, the physiological processes involved in the variable dosimetry, and uncertainties introduced by numerous confounding risk factors, such as smoking. The risk of bone sarcomas is derived from the United States radium dial painters who ingested radium-226 and radium-228 and from German patients who received radium-224 for therapeutic purposes. The risk of head sinus carcinomas is obtained from the United States radium dial painters; the radon-222 gas and its progeny accumulated in the sinuses and mastoid air cells in workers with increased body burdens of radium-226. The human data on liver cancer risk come mainly from Thorotrast patients who received colloidal thorium-232 dioxide and its progeny during medical procedures. Interpretation of these studies is complicated by the potential physical and chemical effects of the colloidal material, although laboratory animal experiments suggest that nonradiation factors of Thorotrast are not important in liver tumor induction. All of these epidemiological surveys are presently in progress, none is completed, and the person-years of follow-up are still relatively small, so that the lifetime carcinogenic risks of alpha-radiation exposure remain uncertain. And finally, sufficient human data are not available for assessing the late health effects of the transuranic elements, e.g., plutonium-239, and here it has been necessary to estimate risks from these internally deposited alpha-emitters in humans by simplified mathematical and dosimetric models or from comparison of effects with other radionuclides, where both direct experimental observation in

laboratory animals and knowledge of radiation effects in humans are available. Complications arise in evaluating such comparisons because of such factors as different time patterns of deposition and resorption of the various radionuclides, e.g., radium vs. plutonium in bone.

This Report attempts to respond to a broad range of scientific questions that impact current public health issues; not all of these questions can be addressed adequately with currently available information. There is considerable variation in the amount of data from epidemiologic studies of human populations and from experimental animal investigations that are available for each radionuclide. For certain of the alpha-emitting radionuclides, such as radon and its daughters, radium and thorium, human epidemiological data are available. For others, however, such as the transuranic elements, some useful information is available on humans; accordingly, dependence must be placed on extensive experiments with animals. As in all experimental studies with animals, the extent to which the information and conclusions can be extrapolated to humans and the confidence that can be placed on such an extrapolation remain uncertain. Where human data are available, wherever possible the Committee has relied on its own analyses using current epidemiological methods to address these problems rather than relying solely on published information. The Committee has also explored statistical methods for analysis of interspecies comparisons of the risks from different radionuclides where useful animal data are available and the human data are limited. The Committee recognizes the uncertainties inherent in such animal-to-human extrapolation; nevertheless, the Committee believes the methodology introduced helps provide for more detailed comparisons as additional data from epidemiologic and animal studies become available.

Radon

The evaluation of the lung cancer risk from radon and its progeny has been the most challenging task of the Committee. Numerous studies of underground miners exposed to radon daughters in the air of mines have shown an increased risk of lung cancer in comparison with nonexposed populations. Laboratory animals exposed to radon daughters also develop lung cancer. There is abundant epidemiological and experimental data to establish the carcinogenicity of radon progeny. These observations are of considerable importance because uranium, from which radon and its progeny arise, is ubiquitous in the earth's crust, and radon in indoor environments can reach relatively high levels. Nevertheless, while the carcinogenicity of radon daughters is established and the hazards of high levels of exposure during mining is well recognized, the risks of exposure to lower levels of radon progeny have not yet been precisely characterized. However, risk estimates of the health effects of lower levels of exposure are needed to address the potential health effects of radon and radon daughters in homes and to determine acceptable levels of exposure in occupational environments.

Two approaches are currently being used to characterize the lung cancer risks of radon daughter exposure: mathematical representations of the respiratory tract that model radiation doses to target cells and epidemiological investigation of exposed populations, mainly underground miners. The dosimetric approach used by other investigators and committees provides an estimate of lung cancer risk of radon daughter exposure that is based specifically on modelling the dose to target cells. A number of different dosimetric models have thus far been developed; all require certain relevant assumptions, some not subject to direct verification, concerning the deposition of radon daughters in the respiratory tract and the type, nature and location

of the target cells for cancer induction. Accordingly, the Committee chose not to use dosimetric models for calculating the lung cancer risk estimates in this Report. The results of such dose-effect models were used to extrapolate lung cancer risk coefficients derived from the epidemiological studies of occupational exposure of the underground miners to the general population in indoor environments. However, the lung cancer risk estimates for radon daughter exposure derived by the Committee in this Report are based solely on the epidemiological evidence.

The Committee turned to the available epidemiological data because the studies of radon daughter exposed miners provided a direct assessment of human health effects. While each of the investigations has limitations, the approach of a combined analysis of major data sets permitted a comprehensive assessment of the health risks of radon daughter exposure and of factors influencing the risk of exposure. In analyzing the data, the Committee used a descriptive analytical approach rather than using statistical methods based on conceptual models of carcinogenesis or radiation (dose-reponse) effects.

The Committee obtained data from four of the principal studies of radon-exposed miners (the Ontario uranium miners, the Saskatchewan uranium miners, the Swedish metal miners, and the Colorado Plateau uranium miners) and developed risk models for lung cancer from its own analyses.

In the Committee's model, viz., a modified linear dose-effect relationship, although simple in its mathematical formulation, the excess relative risk after a 5 y lag period varies with time since exposure rather than remaining constant and depends on age at risk; the expression, therefore, is a departure from most previous risk models which have assumed that the relative risk is constant over both age and time. In the Committee's relative risk model, radon exposures more distant in time have a somewhat lesser impact on the age-specific excess

relative risk than more recent exposures. Moreover, the age-specific excess relative risk is higher for younger persons and declines at older ages. The Committee's analysis did not assume a priori that analysis based on the relative risk was necessarily more appropriate than alternatives, such as the absolute risk. However, an absolute risk model would have involved a complex power function of age. The relative risk form adopted by the Committee provides a simpler description of observed lung cancer risks rin the miner cohorts; it requires fewer variables than would an absolute risk form.

Recognition that radon and its daughter products may accumulate to high levels in homes has led to concern about the potential lung cancer risk resulting from indoor domestic exposure. While such risks can be estimated with the current model for excess relative risks, it must be recognized that the Committee's model is based on data from occupational exposure and underground miners' mortality experience. Several assumptions are required to apply risk estimates from an occupational setting to the indoor domestic environment. Accordingly, the Committee assumed (1) that the epidemiological findings in the underground miners could be extended across the entire lifespan, (2) that cigarette smoking and exposure to radon daughters interact multiplicatively, (3) that exposure to radon progeny increases the risk of lung cancer proportionally to the sex-specific ambient risk of lung cancer, and (4) that a WLM yields an equivalent dose to the respiratory tract and to the bronchial epithelium in both occupational and environmental settings. This last assumption was a qualitative decision by the Committee. The Committee concluded that additional data on ventilation rates and aerosol characteristics in mines and homes are needed to address quantitatively the comparative dosimetry of radon daughters in the occupational and environmental settings.

Based on the estimates of excess relative risks per WLM of exposure to

radon progeny derived from analysis of the four miner cohorts, and the assumptions outlined, the Committee projected lung cancer risks for United States males and females. The Committee's risk projections estimate lifetime risks, ratios of lifetime risk, average lifespans, and average years of life lost for various exposure rates and durations of exposure. Tables are provided in the Report for estimating risks conditional on survival and exposure to a particular age and for smokers and nonsmokers of either sex. For projecting lifetime effects due to radon exposure, the Committee used the 1980-1984 United States mortality rates as referent rates, and a five-year lag period. In all of these cases, most of the absolute increase in risk occurs to smokers for whom the risk of lung cancer is ten or more times greater than for nonsmokers.

Comparisons of estimates of the lifetime risk of lung cancer mortality due to a lifetime exposure to radon progeny in terms of WLM and alpha-particle dose to the target cells of the bronchial epithelium--excess deaths per million persons exposed--made by this and other scientific committees appear in this table. Although the present Report uses much information not available for the earlier reports, the differences mainly reflect differences in assumptions made and the models used by the various committees--the present Committee developed risk models for lung cancer mortality from its own analyses of the epidemiological studies.

Study	Excess Lung Cancer Deaths/10^6 Person-WLM
1987 BEIR IV	350
1984 NCRP (1)	130
1981 ICRP (5)	150-450
1980 BEIR III (7)	730
1977 UNSCEAR (9)	200-450

The BEIR IV Committee's modified relative risk model differs from the others in that it incorporates a dependence of the relative risk of lung cancer mortality on both time since exposure and age at risk. This model was derived from a formal statistical analysis of primary data from four of the most complete epidemiological studies of underground miners.

The uncertainties that affect the estimates of the lung cancer risk due to exposure to radon progeny given in this Report must be considered by users. These uncertainties include (1) random and possibly systematic errors in the original data on exposure and lung cancer analyzed by the Committee, (2) inappropriate statistical models for analysis or mispecification of the components of the models, (3) sampling variation, and (4) incorrect description of the interaction between radon daughter exposure and cigarette-smoking. (5) In addition, the actual computed lifetime risk and expected life shortening depend on the age-specific disease rates of the referent population, in our examples the 1980-1984 United States population mortality rates. Projections based on a different referent population would be expected to differ, although the ratio of lifetime risks and years of life lost to ambient values may be more stable across populations.

Review of the literature and the Committee's own analyses of the relevant data did not lead to a conclusive description of the interaction between radon daughters and cigarette smoking for the induction of lung cancer. Several data sets were analyzed, and while the Committee chose a multiplicative interaction on a relative risk scale for its risk projections, it recognizes that a submultiplicative model is also consistent with the data analyzed. However, neither additive nor subadditive models appear consistent with the available data.

A few exploratory epidemiological investigations of the lung cancer risk associated with radon daughter exposure in homes have been carried out, but the study populations have been small and the results inconclusive. The Committee judged these exploratory studies to be inadequate for the purposes of risk estimation. For this reason, the Committee's risk projections for the general population are based on the studies of miners. The Committee concluded that estimates of lung cancer risks from studies on miners can be used to estimate the potential lung cancer risk from elevated levels of indoor radon; however, the estimates derived are uncertain. The Committee has provided estimates of the effects of indoor exposure to radon in homes while recognizing that differences between mining and domestic environments and the interaction between smoking and exposure to radon progeny remain incompletely resolved.

Polonium

In laboratory animal experiments the relative toxicity of polonium-210 is a function of time and radiation dose. At high doses, it is much more toxic than uranium, plutonium, radium, or the transplutonic elements. Because of its shorter half-life, toxicity at longer times and lower doses, it is comparable to plutonium-239, i.e., about five times as effective as radium-226; at very low doses and very long times, its effectiveness approaches that of radium-226.

Experimental studies in humans and accidental exposures indicate metabolism in the human body is similar to that found in laboratory studies in animals. Only a few cases of effects in humans due directly to exposure to polonium-210 have been documented, and thus estimates of carcinogenic risk from exposure to polonium cannot be ascertained directly. Estimates for lung cancer risk from radon in mines can be used to infer risk of short-lived polonium isotopes; liver cancer risk can be inferred from experience with the Thorotrast

cases, and risk for the longer half-life isotopes can be approximated from organ specific risks for high-LET radiation. For example, applying risk estimates for radon-222 for the short-lived polonium isotopes and for plutonium-239 for the longer-lived polonium isotopes, on this basis, very approximate lifetime risks of lung cancer mortality may be estimated. Liver risks would be similar, but the bone cancer risk would be considerably less.

Radium

The main sources of information on the health effects of radium deposited in human tissues are the United States cohorts with occupational exposure (mostly dial painters and radium chemists) and medical exposures to radium-226 and radium-228, and the German patients given repeated injections of radium-224, primarily for treatment of ankylosing spondylitis in adult life and tuberculosis in childhood. Malignant effects are almost exclusively the induction of skeletal tumors and to carcinomas arising in the paranasal sinuses and mastoid air cells. The evidence for induction of leukemia is weak except at dose levels far in excess of occupational, environmental or therapeutic exposures encountered during the past 50 y.

The dose-response data for bone sarcomas are characterized by low-dose regions of zero observed risk. A variety of dose-response relationships are consistent with the human data within the higher dose range for cohorts in whom bone tumors have occurred, the lifetime risk for radium-224 is estimated to be about 200×10^{-4} person-Gy average skeletal dose for children and adults when a linear function is assumed for the dose-response relationship and taking into account the apparent increase of risk with dose protraction. Tumors are distributed over time, their frequency diminishing with a half-life of about 5 y after a minimum latent period of 4 y.

For radium-226 and radium-228 bone sarcoma induction, various dose-response functions provide statistically acceptable fits to the data. Within the higher range of exposures where tumors have been observed to occur, these functions predict approximately the same risk for a given exposure. Below this range, where there have been no tumors observed, the functions differ considerably for some exposure levels. The cancer risk coefficient is estimated to be approximately 2×10^{-4} person-year-Gy.

Bone sarcomas have appeared 7 y after first exposure and continued to appear throughout life. The appearance time increases with decreasing dose and dose rate and characterizes a practical threshold of about 0.8 Gy average skeletal dose below which the chance of developing bone cancer from radium-226 and radium-228 during the normal lifetime is extremely small and possibly zero.

Carcinomas in the paranasal sinuses and mastoid air cells are observed following exposure to radium-226 or to radium-226 in combination with radium-228, but have not yet been observed among persons exposed to radium-224. The tumors occurred as early as 19 y after exposure and continue to occur throughout life. In the dose range where tumors have been observed to occur the linear risk coefficient is approximately 16×10^{-4} person-year-Gy average skeletal dose from radium-226 (minimum latency period of 10 y). Causation is thought to be partly associated with the generation of radon-222 by radium-226 decay with subsequent irradiation of the sinus and mastoid epithelial tissues by radon-222 and its progeny.

Thorium

Epidemiological surveys of Thorotrast patients are in progress in Germany, Denmark and Portugal; additional studies are being carried out in Japan and the United States. Approximately 4,000 patients are being followed.

The late effects of Thorotrast incorporated in the body are primarily the induction of liver cancers and bone sarcomas and myeloproliferative disorders, including leukemias. These appear in excess, notably liver cancer, in all epidemiological studies.

Risk estimates for thorium-232-induced liver cancer, bone cancer and leukemia have been calculated; these come from the epidemiological surveys of the Thorotrast patients who were injected with colloidal thorium-232 dioxide and its progeny. For liver cancer, a lifetime linear risk coefficient is estimated to be about 260-300 x 10^{-4} person-Gy (average dose of alpha radiation to the liver), with a 20 y minimum latent period. For bone sarcoma, the lifetime linear risk coefficient is estimated to be about 55-120 x 10^{-4} person-Gy (average dose to the skeleton without bone marrow), and a 5 y minimum latent interval. For leukemia, a lifetime linear risk coefficient of 50-60 x 10^{-4} person-Gy is estimated with a 10 y minimum latent interval.

Uranium

Uranium compounds may induce detrimental health effects due to both chemical toxicity or alpha-radiation damage. Animal experiments demonstrate a specific toxic effect of natural and depleted uranium on the kidney, but with little evidence of toxic effects on other organs, chemical toxicity results in renal damage; the renal tubules are affected, and chemical complexing leads to cell death and renal insufficiency. Uranium compounds have produced lung fibrosis and lung cancer in primates, dogs, and rodents, due to alpha-particle irradiation of bone and of the lung, respectively.

Epidemiological surveys of uranium miners and millers occupationally exposed chronically to dusts containing relatively high concentrations of

natural uranium compounds have not demonstrated serious renal disease nor increased rates of malignant tumors. No association has been demonstrated between the effects of chronic uranium dust and mortality, nor has there been an association established in humans exposed to low-specific-activity uranium for renal disease, nonmalignant respiratory disease, leukemia or bone cancer. However, these epidemiological studies had limited statistical power and there were confounding risk factors that obscured the interpretations of an association with alpha radiation during chronic exposure to uranium.

Experiments in animals using high-specific-activity uranium suggest that the most probable carcinogenic effect expected in humans would be an increase in bone sarcomas. Estimates of the effects of human population exposures to natural uranium indicate that a small excess of bone sarcomas could result. For a linear dose-response relationship, ingestion of soluble uranium isotopes in water or food at a constant daily rate of 1 pCi/d could be associated with a lifetime risk of 1.5 excess bone sarcomas per million persons; the incidence of spontaneously-occurring bone sarcomas in the United States is about 750 per million.

Transuranic Elements

Human exposures to the transuranic elements primarily involve occupationally exposed workers in nuclear facilities. The United States Transuranium Registry and other studies involving several thousand workers who have been accidently exposed, predominately to low levels of transuranic elements, have shown that plutonium tends to concentrate in the tracheobronchial lymph nodes with smaller amounts in the lung, liver, and bone. The most extensive epidemiological study of plutonium workers found that mortality experience for the entire cohort was less than expected based on

United States mortality rates. The human data and the alpha-radiation dosimetry are, at present, alone inadequate to provide direct calculation of cancer risk coefficients in the radiosensitive organs and tissues.

Currently, human cancer risk estimates may be derived from studies of human populations exposed to other alpha-emitting radionuclides. For lung cancer the lifetime risk estimate is approximately 700 x 10^{-4} person-Gy, based on the estimates for radon-222 and its progeny; this value is about one-third greater than those derived from studies of plutonium in dogs. The Committee has applied a Bayesian components of variance model to 15 different data sets for bone sarcoma induction in humans and laboratory animals. This analysis yields, for plutonium deposition in human bone, a lifetime risk estimate of 80-1100 x 10^{-4} person-Gy. This is based on human radium and animal transuranic and radium data, and is consistent with estimates based solely on radium-224 data in human beings. For liver cancer, the lifetime risk is approximately 300 x 10^{-4} person-Gy, based on the human Thorotrast data. In applying these cancer risk estimates to the transuranic radionuclides, their origin and the data on which they are based and the uncertainties associated with their calculation, must be considered.

Genetic Effects

The genetic effects of an average United States population exposure of the gonads to 0.01 Gy of low-LET radiation per 30-y reproductive generation (0.33 mGy/y) has been estimated in the 1980 BEIR III Report. Estimates based on the current incidence of hereditary disorders and on the relative mutation risk are the increases expected in the different classes of genetic disorders among 1 million liveborn people whose ancestors had received this increased radiation exposure. This information was combined with RBE values for alpha irradiation

derived from plutonium-239 experiments in mice, specifically an RBE for mutations of 2.5, and for chromosomal aberrations of 15, relative to x- and gamma rays. Numerical estimates of incidence of three classes of genetic effect over a 150-y span (5 generations) were made for continuous average population gonadal exposure to 0.33 mGy/y. For a stable population of about 1 million persons, nearly 200 dominant, X-linked, and translocation genetic effects would accumulate over 150 y.

What May We Conclude?

The Committee found it necessary, based on time and resources available, to narrow the scope of its charge, to examine only those alpha-emitting radionuclides known to induce health effects in exposed human populations, and to concentrate its efforts on specific areas in each case. The Committee's focus and efforts were strongly influenced by the need to address the health effects of inhaled radon progeny because of the concern of lung cancer risk due to increased levels of indoor radon. Where epidemiological surveys were available, e.g., radon, radium and thorium, analysis of human data was preferred to laboratory animal data, e.g., polonium, uranium and the transuranic elements, for quantitative human risk estimation. The constraints of time precluded: (1) detailed reviews of the scientific literature, (2) thorough examination or application of all relevant mathematical, metabolic and dosimetric models presently being developed, or the development of new models for each radionuclide and each tissue; (3) analysis of the wide range of laboratory animal experiments for estimation of human risk coefficients; and (4) characterization of indoor radon levels in the United States or analysis of the relevant but limited epidemiological data for estimation of lung cancer risk in the general population. Accordingly, the Committee has attempted to

limit the scope of its Report primarily to those areas of current societal concern, e.g., the health outcomes of inhaled radon progeny.

As in the case of the 1980 BEIR-III Report, the current Committee cautions that the risk estimates derived from the epidemiological and the experimental animal data should not be considered as precise numerical values. All are derived from analyses of incomplete data and involve numerous uncertainties. It is expected that these risk estimates will change as new information and methods for analysis become available. And lastly, the Committee assumes no responsibility to recommend regulatory limits, or to address cost-benefit issues involving the radionuclides of concern. Such issues are beyond the scope of the task and the expertise of this Committee.

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