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RADIATION EXPOSURE OF URANIUM MINERS

A report of an Advisory Committee from the Division of Medical Sciences: National Academy of Sciences—National Research Council—National Academy of Engineering
Washington, D.C.

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FEDERAL RADIATION COUNCIL
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PREFACE

A special subcommittee of the National Academy of Sciences—National Research Council Advisory Committee to the Federal Radiation Council was appointed at the request of the Council staff to prepare this report on "Radiation Exposure of Uranium Miners." The report includes information available through July 1968 and is based on contributions of individual subcommittee members, a meeting of the subcommittee on May 2, 1968, a meeting of the full committee on June 25, 1968, and subsequent correspondence. The members acted as individuals, not as representatives of their organizations.

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Radiation Exposure of Uranium Miners

SECTION I. INTRODUCTION

1.1 Increasing attention has been given, within recent years, to observations that extended exposure in some uranium mines is associated with an increase in lung cancer. Upon approval by the Federal Radiation Council (FRC), its staff carried out a study on the radiation hazards associated with the underground mining of uranium ore. A preliminary draft of the staff report was prepared for use in hearings on "Radiation Exposure of Uranium Miners" held by the Joint Committee on Atomic Energy during the summer of 1967. The FRC staff report, Report 8 Revised, "Guidance for the Control of Radiation Hazards in Uranium Mining" (*1*), was issued in September 1967. The published two-part record and summary analysis of the hearings (*2*) and the FRC staff report constitute a most comprehensive collection of relevant data and viewpoints. The broad objectives were to determine whether uranium miners were being protected by adequate standards and to ascertain how low an exposure would be necessary to insure a proper level of safety for the miners. This necessarily led to considerations of risk versus benefit and to examination of the scientific basis for estimating the magnitude of risk associated with low levels of exposure.

1.2 It was apparent that the subject was most complex and that divergent viewpoints were held on many important issues.

1.3 Accordingly, it was intended that an interpretative report be prepared by persons competent in related areas of radiobiology, but not necessarily having intimate connection with specific aspects of uranium mining. This report has three major objectives: (a) evaluation of the degree of reliability that can be assigned to conclusions from present data, (b) indication of urgent problems that need to be answered to provide adequate reliability for future conclusions, and (c) clarification of the best possible basis for decisions that have to be made now before completely adequate information becomes available. There is included only such factual material as is necessary for understanding of the viewpoints presented. Reference can be made to previously mentioned reports for additional details.

SECTION II. GENERAL CONSIDERATIONS IN ESTABLISHMENT OF GUIDANCE

A. Background

2.1 It has been known for centuries that numerous miners who worked for several years in mines in which pitchblende was present developed fatal pulmonary disease. This was recognized particularly in Schneeberg in the Erz Mountains in Saxony, and in Joachimsthal on the Bohemian side. The possibility was put forth first in the 1920's that lung diseases, particularly carcinoma, might be associated with high levels of radon in the mines. This thesis was further developed in the thirties and forties, and now there seems to be little question that inhalation of the mine air played an etiologic role in the development of cancer.

2.2 Epidemiologic studies during the 1950's on men working in uranium mines in the United States also indicated an increased incidence of lung carcinoma. Additional studies have confirmed this and have suggested an additive and perhaps synergistic effect between exposure in the mines and cigarette smoking. There thus seems to be no question that extended exposure in some uranium mines is associated with an increase in lung cancer. There is further evidence that the incidence may be correlated with the product of the length of time worked and the average concentration of radon and its daughter products during that time. There is no absolute proof that exposure to radiation is in fact the etiologic factor in the development of lung carcinoma under these circumstances; however, few, if any, would question the high probability that radiation exposure does play a definitive role.

B. The Problem of Guidance

2.3 A specific problem at hand is to decide on the most objective approach to determining the limits of exposure for uranium miners independently of any considerations of actual values that a given approach might yield. Many philosophies exist with respect to what should be the "allowable" exposure for any noxious agent. Broadly speaking, they range from the thesis of "zero" exposure and hence zero additional effect, to various figures for exposure that are presumed to result in some definite but "tolerable" increase in the probability of occurrence of harm. Short of barring all exposure and thus reducing the risk to zero, all philosophies, however lax or rigid they may be, involve implicitly or explicitly an evaluation of the degree of risk as a function of exposure to or dose from the noxious agent. The problem, then, is essentially to decide whether an objective basis can be found for evaluation of dose-effect relationships with respect to the uranium miners.

C. Approaches

2.4 There are two fundamental approaches to the problem—the "empiric," based on epidemiologic data, and the "theoretical," based on hypothesis and calculation.

2.5 With respect to the empiric approach, studies conducted in the United States have resulted in the accrual of a large amount of data on the incidence of lung carcinoma in uranium miners (*1*, *2*). Estimates of the degree of

exposure, expressed in WLM,[1] have been made for such persons, even though physical measurements on which to base the estimates were not available in a large proportion of the cases. On the basis of these estimates, however, an attempt has been made to construct an exposure-effect curve (ref. (*1*), p. 22). By appropriate curve fitting, one can attempt to determine the nature of the exposure-effect relationship and can, in principle, then extrapolate to determine some exposure level that will result in some acceptable degree of risk.

2.6 The analogy to this approach is found in the use of human data on radium-dial painters and others who received radium internally, in establishing the present maximum permissible body burden (MPBB) for radium of 0.1 μCi total body burden. Epidemiologic studies on the persons so exposed to radium were conducted, and disease and mortality associated with the radium exposure were evaluated. Estimates of radium body burden were made. The primary data for establishment of the MPBB lie in the curve of degree of effect in human beings versus body burden of radium in microcuries (2*A*). The introduction of a suitable safety factor led to the 0.1 μCi MPBB, which is still extant and which is the prime standard for setting the MPBB for bone seekers. It should be noted that although large numbers of calculations of absorbed dose in rads and of dose equivalent in rem from the radium body burdens have been made, such calculations are not necessary for and are not used in establishing the body burden of 0.1 μCi of radium. The primary approach is to use dose-effect data from human beings, with dose in terms of μCi of radium.

2.7 The second approach (theoretical), which is in principle completely distinct from the first, involves the establishment of hypothetical dose-effect relationship; that is, the establishment of some exposure expressed in quantities of dose equivalent (units of rem), which will result in some presumably acceptable but unspecified increased individual risk. An acceptable risk to a person implies a high probability of escaping injury altogether. A variety of hypothetical dose-effect relationships can be invoked, but the one most commonly used is the "linear no-threshold" hypothesis because it is felt to be the "safest." In principle, one could establish an excess incidence of effect or increased individual risk that is deemed to be acceptable and determine the corresponding exposure in rem, on the basis of the hypothetical dose-effect relationship chosen. Actually, what appears to be more common is simply the establishment of an exposure (usually exposure rate), expressed in rem, with no incidence figures attached. With respect to the lung, a dose-equivalent rate of 15 rem/year is established (see pp. 642 and 643 of Part 1 of the hearing *(2)*). It must be emphasized that the 15 rem per year is not based on direct evidence (in the human being or in animals) that any ill effects or any particular degree of risk would be associated with this exposure rate. The number represents a "best estimate," arrived at in the absence of data on actual dose-effect relationships. It should also be emphasized that the 15 rem per year is a value for dose-equivalent rate averaged over some macroscopic tissue volume; no cumulative total dose equivalent that will result in an "acceptable" level of damage is given.

2.8 Once the "allowable" dose to the assumed critical tissues is established, it is necessary to calculate the exposure in terms of radioactivity in the mine atmosphere that would lead to this dose-equivalent rate. A number of assumptions are involved in the calculations, including:

(a) the value for the RBE (relative biologic effectiveness) for alpha emitters, for car-

[1] Working Level (WL): A level of concentration or burden of radioactivity in a given air environment. Related to environments containing radon and daughter products of radon, a WL is represented by any combination of short-lived radon daughters in 1 liter of air that will result in the emission of 1.3×10^5 MeV (million electron volts) of potential alpha energy from the radioactive decay of the radon daughters. This numerical value is derived from the alpha energy released by the total decay of the short-lived radon daughter products at radioactive equilibrium with 100 picocuries of radon-222 per liter of air.

Working Level Month (WLM): A unit of radiation exposure obtained from working in an environment of 1 WL for 1 month (170 hrs.). (For example, 12 months at 1 WL = 12 WLM; 12 months at 0.3 WL = 3.6 WLM.) Most standards provide a further restriction on exposure, that no quarter of the work year shall involve greater than half the permissible annual total; for example, in the first case above, 6 WLM; in the second, 1.9 WLM. The designation CWLM is often used to represent Cumulative Working Level Months.

cinoma of the human lung (this value is not known and must be estimated);

(b) the "critical tissue" in which the tumor is formed (it is not certain in what tissue or in what portions of the lung these tumors arise);

(c) the effect of nonuniform dose distribution (the degree of influence of "hot spots," as contrasted to an "average" tissue or organ dose, is unknown but may well be important);

(d) the model that describes the kinetics of cell proliferation in the presumed critical tissue, commonly taken to be the bronchial epithelium (available models vary widely, and the dose and dose-rate to tissues are highly dependent on the model selected); and

(e) the amount of radioactivity deposited per unit time in the presumed critical tissue, for a given level of radioactivity in the atmosphere of the mine.

2.9 Both broad approaches, the empiric and the theoretical, involve many errors and assumptions. In an effort to decide whether one has merit over the other, the following broad principles are offered.

(a) It is best, whenever possible, to work from actual dose-effect data relating to the organ and exposure conditions of interest.

(b) It is better, whenever possible, to apply available data on human beings than on animals.

(c) If data on the human being are not available, or are felt to be so scanty and poor as to be essentially unusable, then dose-effect relationships established for animals should be used, if available.

(d) The use of hypotheses of dose-effect relationships and necessary calculations to arrive at exposure levels should be reserved for situations in which the human or animal data are such that the relative error in the empiric approach is definitely greater.

2.10 In regard to the uranium miners, data on exposed human beings are available. The precedent exists, as already described for radium, for using epidemiologic data of this nature in establishing guidance. It is necessary to attempt to assess the relative error involved in the two approaches. With the empiric approach, as indicated, the error is large. It is possible, however, to place limits of error on the dose-effect relationship obtained (one can obtain a curve to describe the dose-effect relationship simply by obtaining a least-square fit of the data); alternatively, one can attempt to impress on the data a curve that fits some hypothesis. The theoretical approach also carries potentially large errors, to many of which no limits of error can be assigned. The largest uncertainty lies in the assumption that 15 rem per year will lead to some degree of effect that will be acceptable. There is no way of putting limits of error on this assupmtion because it is an "educated guess." The second largest assumption, again with no limits of error, involves the amount of radioactivity deposited in the critical tissue per unit of exposure to radiation in the atmosphere. Other sources of error include the particular lung model adopted, the effect of nonuniform exposure, translocation of radioactivity, and uncertainty as to the critical tissue.

2.11 We are thus faced with two approaches, each with a large uncertainty. The degree of error can be assessed in the empiric approach; it is essentially unassessable in the theoretical approach. Also, with the theoretical approach, a long chain of potentially large and unassessable errors are involved, which are multiplicative. In the absence of an absolute assessment of the degree of error in each approach, it is not possible to decide objectively, on the basis of degree of error, which approach is the more objective. It is clear, however, that there is no compelling reason to use the theoretical approach on the basis of relative probable error. For the future, errors in the empiric approach may be reduced by the availability of more data on effects, but the errors may also be increased because of reductions in the levels of exposure that have gone into effect. Nevertheless, there are strong reasons at present for using and improving the empiric approach in

arriving at guidance for exposure of uranium miners.

2.12 The above conclusion is in no way intended to discourage efforts to calculate dose or to downgrade the importance of understanding and quantitating dose-response relationships in radiobiology and in radiation protection. On the contrary, every effort should be made to improve dosimetry, so that more meaningful calculations can be made. Eventually, the theoretical approach may provide better understanding of the various factors involved and permit generalizations to other exposure situations.

2.13 Regardless of approach, it is necessary to inquire into the reliability of estimates of the dose and of the effect produced. As a starting point, it is usually assumed that the estimation of radioactivity in the ambient atmosphere bears a constant relationship to the radiation exposure. Further refinement and understanding come from consideration of physical and physiologic processes in the lung, although, with present information, it is doubtful that such considerations contribute practically to quantitation of radiation dosage. The status in regard to both atmospheric measurements and lung processes is presented in section III. The effects are discussed in sections V and VI.

SECTION III. THE WORKING LEVEL CONCEPT

A. General

3.1 The Working Level [1] refers to a concentration level or burden of short-lived radon daughter products in a given air environment, and present epidemiologic data are based on the Working Level Months (WLM) as the unit of radiation exposure in the dose-effect relationship. It is evident that the Working Level was designed to represent the radiation exposure potential of uranium mines in the face of a variety of nonequilibrium conditions. It is unsatisfactory for two reasons. First, there are inherent difficulties in sampling methods and instrumentation; this is by no means unique to uranium mines nor to the Working Level concept, but occurs with all types of air-sampling programs. There are partial remedies based on proper decisions, such as those concerning the type and number of samplers and the number and duration of samples taken. Second, the Working Level, conceptually and in practice, gives no recognition to the relative contributions of the various radon decay products to the radiation dose and, in particular, fails to recognize the "free-ion" fraction. There is an appropriate and apparently successful instrument-development program underway in both area and personnel dosimeters; thus, much of the instrumental inadequacy soon may be eliminated.

3.2 Assuming that the problems other than instrumental can and will be overcome, we might reasonably expect that the Working Level measurements in combination with information about the worker's activity, respiratory physiology, and associated environmental factors can be amalgamated into a reasonable estimate of exposure in the future.

B. Methods and Measurement

3.3 Measurements of radon and airborne daughters are still being made by the methods described in Public Health Service Publication 494. This document originally appeared in 1957 and was submitted to the hearings (*2*) in 1967 as representing contemporary procedure. The methods are time-tested and satisfactory in competent hands, and there seems no reason to question the figures obtained by using them.

3.4 Some field measurements of radon concentration have been made with scintillation detectors, but these probably do not have the accuracy of the laboratory assays.

3.5 A sample for the radon daughter determination is obtained by pulling a known volume of air through a filter paper, which is subsequently assayed in the laboratory. The laboratory assays can be expected to have the usual random error distribution, above and below the true value, but this may not be the case for the sample collection. Most of the operational uncertainties will tend to reduce the amount of material collected, and hence lead to an underestimate of the airborne activity. If representative samples are to be obtained, the field personnel must be well trained.

3.6 Monitoring efforts have properly concentrated on radon daughters, because they are responsible for the greatest proportion of

[1] See footnote 1, p. 3.

the airborne hazard. Some 1,200 mines are under surveillance, in which about 12,000 determinations of radon daughters have been made over a 10-year period. This averages to about one sample per mine per year, but the distribution is far from uniform. In some mines where disturbingly high concentrations were found, series of closely spaced measurements may have been made as corrective measures were instituted. In some mines, no measurements have been made.

3.7 Uranium mines may be classified by a variety of characteristics, such as depth, degree of wetness, rock porosity, and character and extent of ore bodies. Correlations of these characteristics with measured values of airborne radioactivity permit an estimate of activity levels in unmeasured mines. Experienced workers have more confidence in these estimates than most outsiders would anticipate.

3.8 Exposure values assigned to the period before 1956 are highly unreliable, being based almost entirely on estimates rather than measurements of concentrations. The sampling frequency increased with time, but some of the 1956–1960 values may nevertheless be in error by an order of magnitude. Values for the period after 1960 are the most reliable, but even here many of the Working Level values reported are only estimates, no measurements having been made.

3.9 There is some uncertainty in the average Working Level values even in mines in which a number of measurements have been made. Each assay depends of necessity on a spot sample, representative only of the conditions existing at the time and place of sampling. The usefulness of spot samples in estimating average exposure levels has been evaluated (*3*) and found to be acceptable, if not ideal. Errors in the techniques of sampling and of field assay methods have been estimated to be less than 10 percent under favorable conditions (*4*). The conditions can vary widely with the nature of mine operations, such as blasting, ventilation, and amount of ore uncovered. The mine air may be almost free of dust and fumes, so that the radon daughters, created as individual nuclei, may exist in an essentially gaseous state for an appreciable period. However, Diesel engines may be running, producing soot particles that serve as condensation nuclei, hydrocarbon residues of various sorts, and carbon dioxide. The variable concentrations of these chemical contaminants introduce both physical and biologic uncertainties.

3.10 The physical uncertainties have been demonstrated by the finding of different particle size distributions and lung depositions between an operating and a quiescent mine environment. Virtually nothing is known about any additive or synergistic effect of radiation and other common mine contaminants, such as arsenic, copper, germanium, lead, and zinc. Concentrations of these elements are detectable but are probably too low to be of biologic significance. Opinions on this point are by no means unanimous.

3.11 The problem of determining an individual uranium miner's radiation exposure is complicated by the fact that official mine records do not necessarily show his actual job assignment. Only the miner himself, and to a lesser extent his immediate supervisor, know the areas in which he has worked. Another problem is possible exposure from previous mining experience. Retrospective information of this type is of dubious validity.

3.12 The latent period for tumor induction makes the early values of exposure and dose particularly important. It is unfortunate that, of the present data on uranium miners, these important early exposure values are the least reliable.

3.13 In addition to uncertainty in the physical measurements, there are great variabilities in the actual radiation dosage as delivered to the critical tissues, depending mainly upon physiologic and physical processes in the lung. These are discussed below.

C. The "Free-Ion" Controversy

3.14 In the evaluation of Working Levels, the concentration of free ions (RaA) is a key issue because of its presumably important contribution to the radiation dose and dose rate received by the bronchial tree. The controversy over what values to use for the free ion-fraction seems unresolvable at present and probably will remain so, in view of the wide range of free ion values reported in mine atmospheres. One possible solution to the problem is, of course, to avoid trying to settle on a "universal" value and, instead, to use measured values for each circumstance.

3.15 The deposition characteristics of free ions on small molecular aggregates of the radon decay products within the human respiratory tract have been studied by several investigators. (*5–10*).The average desposition value appears to be about 35 percent. Recent data obtained at the Beaverlodge mines by personnel from the NYO Health and Safety Laboratories (*11*) give a mean deposition value of 38 percent, with a standard deviation of about 15 percent. With large tidal volumes (>1 liter), the total deposition for radon decay products generally exceeded 50 percent. Investigators at the Health and Safety Laboratories have also measured the nasal deposition of free ions; their reported values generally exceed 60 percent, and average about 65 percent. The widely accepted value of about 25 percent nasal deposition for free ions, obtained experimentally by Chamberlain and Dyson (*12*), is lower than diffusion theory predicts, and lower than that determined in other studies with aerosols of comparable diffusivity. Increasing the free ion deposition in the nasal passages will correspondingly reduce tracheobronchial dose estimations.

3.16 A variety of papers (*5, 8, 11, 13, 14*) indicates that in uranium mine atmospheres the alpha activity derived from radon decay products is associated exclusively with particles below 0.5 μm in diameter. In most instances, the major part of the activity appears to be on particles well below 0.1 μm. Mine atmospheres, however, have quite different aerosol distributions; commonly, the mine aerosol has a mass median diameter greater than 1 μm and a count median diameter less than 0.5 μm. There is no evidence that the alpha activity is distributed on the mine (vector) aerosol distribution in a predictable way. Estimates of the surface area distribution (based on geometric configuration of particles and not specific surface-area measurements), for example, fail to give an activity distribution corresponding to actual measurements. It is probable, therefore, that the activity is distributed more closely to the numerical distribution.

3.17 The Task Group Report on Lung Dynamics (*15*) dealt with this general topic in a limited way. It suggested, among other things, that the nasal efficiency is increasing for particles below 0.01 μm and that the graphic representations of size-deposition used in the report were not designed to handle aerosols composed primarily of such minute particles. In fact, the Task Group considered the whole area as a special problem. A second Task Group was later organized under ICRP Committee 2 to investigate this problem in detail. There has been no formal report from this group.

D. Lung Models

3.18 It now appears technically feasible to obtain suitable air-sampling information for assessment of exposure conditions in uranium mines. To evaluate this information more directly in terms of hazard potential to the worker, some knowledge of the intermediate processes is necessary. One approach is to draw on the established physical-chemical properties of the atmospheric contaminants and apply them to a physiologic and anatomic model of the respiratory system. The development of a lung model not only provides for expressing air-sampling information in terms of dose to the tissue, but also divides the relationship into its components. The significance of individual factors is thereby subject to assessment,

and the possibility of modifying these factors is brought into focus; in addition, recognition is given to areas for which information is lacking, uncertain, or controversial.

3.19 Several models have been developed specifically for the radon daughter problem; those of special merit have come from Altshuler and coworkers (*16*), Jacobi (*17*), Thomas (*18*), and Haque and Collinson (*19*). These epitomize the degree of sophistication currently possible, and it is considered that they cannot be improved on, in principle, to any important extent. There are, however, small but significant differences among these models, and these have rather important effects on the ultimate estimation of dose. One of the more significant distinctions has already been discussed; that is, the daughter ratios and the amount of free ions assumed present in the exposure. Other important distinctions include the anatomic dimensions of the bronchial tree, the thickness of the mucous and the bronchial cell layers, the presence or absence of effective mucociliary clearance, and the presumed deposition pattern. It is not productive to study these models and decide that this or that assumption is more likely correct, because these investigators have all drawn their ideas and assigned values from a body of information that lacks consistency and completeness. Perhaps in a few instances it would be possible to state preferences because of new information or information that might not have been known to the persons involved. Still, when the various models are used with the same kind of Working Level assumptions, they tend to give approximately the same kind of dose estimate to the bronchial tree; that is, they range within a factor of about 6, and this includes the effect of assuming that different areas of the bronchial tree receive the greater dose.

3.20 The effective half-life of radon daughter products was estimated, using several of the lung models, on the assumption of a 15-minute exposure. The theoretical elimination curves from the foregoing models predict an effective half-life around 15 to 18 minutes. Experimentally determined effective half-lives for radon decay products in the lungs have been found to average 37 minutes in subjects studied by external counting methods after inhalation exposures to mine atmospheres (*9*). This half-time value essentially corresponds to that of radium-C decay.

3.21 Although the data are limited, clearance measurements for radon decay products generally give effective half-times somewhat longer than those obtained in other human studies of tracheobronchial clearance using radioactively labeled aerosols (*20*), This is probably due to a more peripheral deposition pattern for the smaller particles serving as a vector for the radon decay products; in addition, there is a possibility that, after deposition, the radionuclei rapidly dissociate from the aerosol particles (*21*) and later experience adsorption to and absorption by the bronchial epithelial cells. Whatever the explanation, there now seems to be ample information to substantiate the view that radon decay products (radium-A to radium-C) undergo negligible biologic clearance from the human bronchial tree.

3.22 In summary, existing lung models and dosimetry use different assumptions, but starting with a relatively uniform exposure basis (a similar ratio of daughter products and percentage of free ions), they give an exposure equivalent estimate of about 7 $\pm$ 5 rad per WLM (*1, 2, 18, 19, 22*).

E. Correlation of Bone Levels

3.23 A novel approach to the exposure-radiation dose relationship in uranium miners has been undertaken by Black and coworkers (*22*). They attempted to correlate the bone levels of lead-210 with estimated exposures (WLM). A key assumption in their development depends on the relation between the lung burden of lead-210 and the amount redistributed to bone; this apparently varies from about 10 percent to 65 percent. Black and coworkers selected 22.5 percent, and obtained approxi-

mately the same rad dose to the bronchial tissue per Working Level Month as is determinable by the various lung models, viz., about 2 rads. There are still large uncertainties involved in this interesting approach that require further substantiation.

F. Quality Factors

3.24 The published literature gives no adequate basis for assigning a quality factor for alpha particles where lung carcinoma is concerned.

SECTION IV. DOSE-EFFECT RELATIONSHIPS

A. Considerations of Carcinogenic Mechanisms in General

4.1 To derive meaningful conclusions from the sparse data on uranium miners and to use experience from the clinical radium data, it is necessary to understand some of the general aspects of: (a) carcinogenic mechanisms, (b) time patterns of cancer induction, (c) wasted radiation, and (d) shapes of dose-effect curves, particularly in regard to thresholds and the linear hypothesis (*2, 23*).

4.2 Cancers caused by radiation cannot be pathologically distinguished from the same types of cancers resulting from other causes. They can be distinguished only statistically with respect to their incidence in irradiated populations, compared with control populations.

4.3 None of the many types of changes that radiation can cause in cells or tissues is specific or unique for radiation. These types of changes can be caused by a variety of agents or conditions, including many of those known or suspected to be carcinogenic or to promote carcinogenesis. Some of the effects of radiation seem to be additive to carcinogenic or promoting effects of other agents and conditions.

4.4 The precise mechanisms of carcinogenesis are not known completely. Available information indicates that most, if not all, types of cancer develop as a result of multistage or multievent mechanisms, including: (a) initiating celluar events that change the cells of origin of the potential cancer in a manner (chromosomal or other organelle aberrations, mutations) that confers on them neoplastic potential, and (b) promotional events, in which further changes in cells or in local or systemic environment act on the potentiated cells to change them or permit or stimulate them to proliferate as cancer cells. The precise number and nature of the cellular and environmental events for any type of cancer are not known.

4.5 Carcinogenic mechanisms can involve events occurring at any time from the prezygotic stage to the time of cancer appearance. They can involve: (a)a prezygotic (inherited) cell mutations, which can spread during development to all kinds of cells; (b) postzygotic somatic-cell mutations acquired throughout life; (c) viral factors; and (d) changes in systemic factors (depressed immune competence, hormonal imbalances) and in local tissue (disorganization and damage), which result from the many pathologic or inherent processes that occur with time. These latter include the changes in cells and tissues caused by a variety of endogenous and exogenous carcinogenic initiating and promoting agents. The incidence of lung cancer, for example, tends to increase with advancing age.

4.6 Radiation can cause all the changes required to induce cancer; however, it may be only one of the causes. Even small doses of radiation can cause cellular changes, including chromosomal aberrations and cell mutations, some of which have been implicated as initiating cellular events in carcinogenesis. In large doses, radiation can, in addition, cause tissue disorganization and physiologic changes that are essential or contributory to carcinogenesis. Although there is as yet no consensus as to the mechanism of radiation-induced carcinogenesis, the following have been sug-

gested: (a) production of ions and inorganic radicals with hydrogen peroxide formation in aqueous systems, (b) direct production of somatic mutations that predispose to the development of cancer, and (c) activation of oncogenic viruses (although virus-induced cancers have not yet been found to occur in man). With regard to the first hypothesis, it has been suggested that a number of organic peroxides have carcinogenic properties, and that peroxides in general may act by catalyzing the depolymerization of DNA and RNA.

4.7 As already implied, lung cancer is apparently preceded by considerable local tissue damage and disorganization. The experimental induction of lung cancer by irradiation of normal animal lung requires large radiation doses, but the required doses are reduced if local tissue damage and disorganization are caused by other means. In addition to radiation, other factors may play a role in the etiology of lung cancer in uranium miners, including: (a) cigarette smoking, (b) Diesel exhaust fumes, (c) uranium ore dust, (d) upper respiratory and viral infections, (e) nitrogen oxides derived from explosives, and (f) hydrocarbon mists from oil-lubricated pneumatic drills.

4.8 The relative contribution of any particular radiation exposure to the induction of a particular cancer and the radiation dose required to induce the cancer in a person (individual dose threshold) depend on the extent to which the rest of the carcinogenic mechanism will have been completed by changes caused by factors other than the exposure in question. Obviously, the age or life expectancy of the person at the time of exposure in relation to the required time for induction and development of the cancer is one of the determining factors in the individual dose threshold or susceptibility to radiation induction of the cancer. In this regard, there is ample experimental evidence, at least for cancers that increase in incidence with age, that the time between irradiation and the appearance of radiation-induced cancer increases as dose decreases.

4.9 The effect of a radiation exposure in radiation carcinogenesis in a population may be either (a) to cause earlier induction and development of cancers (temporal advancement) in persons who would have had the cancers eventually without the exposure, or (b) to cause cancers (absolute induction) in persons who would not have had the cancers otherwise. The yield of cancers in any given period after exposure will be determined by which of these processes or what combination of them applies among the cancer cases, and by any changes in survival time caused by the exposure. The difference between temporal advancement of cancer and absolute induction of cancer by radiation exposure involves all grades of contributions of radiation to the total mechanism of the cancer. The difference between the two, at least on a statistical basis, cannot be fully appreciated without thorough determination of the differences in total lifetime incidence, as well as in the age-adjusted incidences between exposed and control groups.

4.10 Most of the available radiation information on man, and even much of the available information on experimental animals, is limited to a period after exposure that is considerably shorter than the survival time of the groups studied. Therefore, the total lifetime incidence of cancer can be estimated only by extrapolation that involves assumptions concerning the future incidence of cancer in both the exposed and the control groups.

B. Considerations of Radiation Dose Threshold in General

4.11 It is the distribution of the individual dose thresholds for a cancer in a population that determines the shape and intercept of a dose-effect curve.

4.12 The term "threshold dose" has real meaning only in terms of the radiation effect in an individual. If a population is being considered, it has meaning only in terms of the radiation effect in the most susceptible individual in that population; that is, the one with the lowest dose threshold for the effect.

4.13 Theoretically, there is a finite probability that exposure to the smallest quantity

of ionizing radiation can cause a change in a cell—for example, a point mutation—that can contribute a part of the complex mechanism of carcinogenesis in a tissue. Whether this cellular change results in the induction of a cancer—that is, in a "no-threshold" individual—depends on whether the balance of the mechanism is provided by other means.

4.14 The more heterogeneous the population, with respect to factors influencing individual susceptibility or dose threshold for a radiation-induced cancer, the greater the probability of inclusion of individuals in whom the smallest amounts of radiation exposure could complete the required carcinogenic mechanism.

4.15 On logical or theoretical grounds, it is erroneous to assume the existence of an absolute threshold dose for cancer of any kind in all populations of any size or character. It is reasonable to assume that no absolute dose threshold exists for radiation induction of a cancer in a highly heterogeneous population of great or unlimited size, even though the probability of a "no-threshold" individual is very low, and even though some samples of the population may show an observable or high threshold ("practical threshold").

4.16 The "practical threshold" dose is the largest dose that has been observed to be ineffective for causing an increased incidence of effect (persons with the cancer of interest) in the samples of the population that have been studied for this effect. The "practical threshold" may differ between different samples of a population according to differences in distribution of individual thresholds (and ages) at the lower exposure levels.

4.17 Different tissues (for example, lung and bone), in addition to their inherent differences in susceptibility to carcinogenesis (including radiation carcinogenesis), may differ also in the extent to which they are subjected to exogenous carcinogenic or damaging, cancer-promoting agents and conditions. This factor, among others, may result in differences in dose-effect relationships between tissues, and should be considered in any attempt to relate one tissue to another in this respect.

C. The Relevant Dose in Protracted Irradiation

4.18 With protracted, nonuniform exposure of tissue to alpha particles, there is uncertainty, not only as to the tissue component-dose that is relevant to carcinogenesis, but also as to the portion of the total accumulated exposure that effectively contributed to the induction of the cancer.

4.19 For each subject it takes a certain amount of time to accumulate the exposure (induction dose) required to ensure that cancer will be induced and appear within his remaining life span. After the induction dose has been accumulated, it takes some time (latent period) for the cancer to appear. In protracted irradiation, some of the total accumulated dose is "wasted" and irrelevant, as far as the induction of a cancer is concerned. Some of the dose in excess of the minimal induction dose conceivably may shorten the latent period to some extent by substituting for other contributing factors that would have occurred eventually.

4.20 When the individuals of an exposed population receive the protracted exposure at greatly different rates, a particular induction dose takes longer to accumulate at a low-dose rate than at a high-dose rate. This longer time would be taken at the expense of time available for the latent period even if dose rate did not influence the required size of the induction dose. However, because the available evidence indicates that dose rate does influence the carcinogenic effect, the required induction doses may be larger at the lower dose rates and take still more time to accumulate.

D. Dose-Effect Relationships—General

4.21 For cancer induced by local exposure of the tissue of origin of the cancer, there is, in general, an increase in incidence and a reduced latent period with increasing dose within a certain dose range. With further increasing dose, there may be a decline in the rate of increase in incidence. This decline at high-dose levels is represented first by a plateau in the dose-effect curve at peak incidence levels, and then by a fall in the curve at still higher dose levels. This fall in the curve at the highest dose

levels has been attributed to degrees of tissue destruction that eliminate cancer induction in some persons. Fractionation of such large doses (in the declining incidence range) can increase the incidence, presumably by reduction of the excessive tissue damage, but fractionation of a dose in the range of rapidly rising incidence may reduce the incidence.

4.22 For present purposes, several kinds of dose-response relationship should be considered. An observed dose-response relationship may be either linear or curvilinear (quadratic, sigmoid), and in either case with or without a well-defined threshold (practical).

4.23 A curvilinear relationship between dose and the probability of cancer induction would be expected for cancers, such as lung cancer, that depend greatly on localized tissue damage, which itself is characterized by a curvilinear dose-effect relationship with threshold. However, even under these circumstances, a linear relationship is possible in a group in which there is a range of individual thresholds distributed in a manner permitting a linear relationship.

4.24 On the basis of the above considerations and the limitations of dose-effect studies of radiation carcinogenesis at the lower dose levels, it must be expected that even an observed dose-effect curve with an apparently high- "practical" threshold may have in reality a poorly defined threshold or none at all at lower dose levels, owing to the presence of a small proportion of low-threshold individuals. This lower threshold may be represented by a long, low tail of the curve preceding the point of more rapid rise in the vicinity of the "practical" threshold point. The length and position of this tail and its relative practical importance would depend on the distribution of individual thresholds in one or another population, and this distribution can be skewed in various ways by variable influences.

4.25 As a basis for protective measures, an arbitrary decision may be made that the probable tail in this theoretical quasi-threshold curve represents so few individuals as to be regarded as negligible.

E. Dose-Effect Relationships—Assumptions

4.26 In the absence of data on cancer incidence related to low doses or dose rates of radiation, the extent to which such exposure has a carcinogenic effect and the shape of any dose-effect curve are matters of speculation and hypothesis, regardless of the observed shape of the dose-effect curve for larger or more intense doses. This becomes more true as the dose range to which the observed dose-effect relationship is limited or for which it is valid becomes higher.

4.27 The establishment of a well-defined dose-effect curve on the basis of a wide range of doses and dose rates is helpful in the arbitrary selection of a "practical" threshold or in the selection of a curve and its shape for extrapolation to lower levels of exposures for which there are no concrete data. Nevertheless, the relationship at the low-dose or dose-rate levels is still hypothetical and involves great assumptions concerning the dose-effect relationship, the carcinogenic mechanisms operating, the dose-rate dependence, the distribution of individual dose thresholds, and the latent period for the manifestation of the effect. When relationships (often based on the linear hypothesis) are used for purposes of radiation protection it is necessary to discourage the acceptance of such procedures as scientific dogma. There should be explicit qualification of the scientific validity of the arbitrary assumptions involved.

4.28 In the present state of data on man, which involve nonuniform exposure of tissue and individuals of heterogeneous groups, often with differences in dose rates, it is necessary for a particular risk estimate to select a single value of a quantity that characterizes the exposure of a group or subgroup, even though such a value may be of limited significance or accuracy. Mean accumulated tissue dose (or exposure) for the individual and for groups of individuals is the only criterion that can be used practically to estimate risks of cancer in such populations until adequate knowledge of more relevant criteria becomes available. Fur-

thermore, when the dose rate is not uniform and its influence in the exposed group is not known, it must be ignored until more adequate data are available. The linear hypothesis is the only one that normally permits the use of mean dose or exposure as the significant dose factor under conditions of nonuniform exposure and exposure rate in an individual and among individuals, and that permits the neglecting of dose rate. The use of a nonlinear dose-effect relationship requires consideration of the individual dose and dose rate, and the distribution of doses and dose rates for purposes of estimating risk or setting dose limits.

4.29 If the slope (rate of increase in incidence with increasing dose) to be used for linear extrapolation to low-dose levels is obtained from observed dose-effect data that happen to be in the most rapidly rising segment of the total curve, it is likely that the risk per unit dose at the low-dose levels will represent an upper limit. However, if the slope for linear extrapolation is obtained from observed data that happen to be in the high-dose range of the dose-effect curve, where the doses exceed the maximum effective induction dose (plateau of constant incidence with increasing dose) or where the doses are associated with a decline below the peak incidence found at lower doses, the risk per unit dose at lower dose levels may be underestimated. In any case, such estimates of risk are reliable only in the range of observed dose-effect data from which they were validly derived and only under the associated conditions of the exposure and the exposed.

4.30 The presently available data on lung cancer and exposure to radon daughter products (expressed as Cumulative Working Level Months) in uranium miners do not permit reliable quantitative description of the exposure-effect relationship, or even identification of the general shape of the curve, because of: (a) uncertainties as to exposure and exposure rate, (b) limitations on numbers and followup time, and (c) inability to separate out the effects of combined factors, such as cumulative exposure, exposure rate, age at exposure, minimal and exposure-related latent periods, relevant induction exposure, and exposure to other agents. Therefore, it is not possible at present to select from these data a reasonably reliable or valid exposure-effect relationship for extrapolation to low-exposure levels on the basis of an arbitrary assumption of a hypothesis, linear or otherwise.

SECTION V. PATHOLOGY

5.1 The most noteworthy feature of the pathology of lung cancer in the uranium miners of the study group is the great preponderance of the small-cell undifferentiated tumors in the higher exposure categories, as reported by Saccomanno and others (*24*); details are tabulated in reference (*2*) pp. 1062–1067. With estimated exposures of less than 360 WLM, two of 11 neoplasms were of the undifferentiated type. This cannot be stated to be in excess of the expected incidence of this tumor type. With estimated exposure levels of 360 WLM or more, small-cell undifferentiated tumors accounted for 60 to 70 percent, whereas tumors of this type usually constitute 20 to 30 percent of all malignant bronchogenic neoplasms in males.

5.2 The small-cell undifferentiated type is known to have predominated in the lung cancers among the cobalt miners of Schneeberg and Joachimsthal in fact, it is understandable from morphologic similarities that these tumors were first considered to be lymphosarcomas and not identified as carcinomas until the late 1920's (*25*). It must be recognized, with the methods currently available, that it is not possible to determine whether any given lung cancer was caused by ionizing radiation. Thus, the etiologic role of ionizing radiation in the genesis of lung cancer of uranium miners at high exposure must be accepted as a high probability, on the basis primarily of epidemiologic evidence with suggestive support from histologic evidence. Among the miners of the Schneeberg district, it was not until after 1928 that evidence was presented that radioactivity of the ores was the principal etiologic factor (*26*, *27*). Hueper (*28*) has summarized data relating ionizing radiation to the pathogenesis of pulmonary tumors. Koelsch (*29*) reported, of 469 deaths among the miners of this district from 1875 to 1912, that 276 were due to pulmonary carcinoma. This extremely high mortality from cancer of the lung, first noted by Harting and Hesse (*30*) in 1879, suggests the existence of a special environmental factor or factors different from those of the general experience of the ordinary miner.

5.3 It has been established that the American uranium miners likewise have a mortality from lung cancer clearly in excess of that reported among other miners in the United States (*31*). Epidemiologic evidence of the etiologic role of radiation, rather than other possible factors, is summarized by Wagoner (*32*) and by Cooper (*33*), and is further discussed in relation to presumed exposure in section VI of this report.

5.4 The question of the possible potentiating or cocarcinogenic action of two or more agents in the development of pulmonary carcinoma may be raised. An excellent example in animal pathology is represented by the experiments of Kotin and Wiseley (*34*). They found that squamous metaplasia and invasive and metastasizing squamous carcinoma developed in C–57 black mice only if the animals were exposed to both mouse-adapted influenza virus and an aerosol of ozonized gasoline ("artificial smog"). Only acinar atypical proliferation was observed if either agent was used alone. This study has special significance, in that spontaneous squamous cancers are exceedingly rare in rodents, and a cocarcinogenic effect of viral and chemical agents was demonstrated.

5.5 In man, the relation of interstitial pneumonia, honeycombing, and atypical epithelial proliferation to cancer of the lung has been studied in considerable detail (*35*). It is of note that all the patients in the honeycombing-carcinoma group were male, and also that all the patients from whom a smoking history had been obtained were cigarette smokers. In the case of the cancer patients without a background of honeycombing, at least 16 percent were nonsmokers. It is known that the honeycombing itself is not necessarily associated with smoking. These observations suggest the possibility of some potentiating effect that is related to the combination of widespread pulmonary scarring with associated epithelial hyperplasia, and exposure to cigarette smoke. Selikoff, Hammond, and Churg (*36*) have recently reported a similar relationship between exposure to asbestos, smoking, and neoplasia. Of 87 nonsmokers in a group of 370 asbestos workers, none died of bronchogenic carcinoma during the study period, but of 283 of the workmen with a history of regular cigarette smoking, 24 died of bronchogenic carcinoma, although only three were expected to die of this disease.

5.6 There is evidence that pulmonary fibrosis and atypical proliferation are relatively frequent in uranium miners (as in other miners) in comparison with the general population (*32*). Exposure to ionizing radiation superimposed on such chronic pulmonary disease might have a potentiating effect in relation to development of bronchogenic carcinoma. This general relationship requires further study, and specifically the nature and extent of noncancerous (possibly precancerous?) pulmonary disease in the miners should be investigated in a systematic and detailed manner.

5.7 Also to be considered is the possible cocarcinogenic action of smoking and exposure to radon and its daughters. This hypothesis is supported primarily by epidemiologic evidence presented in section VI. It is evident, however, that there is a large excess of respiratory tract cancers among uranium miners, even when account has been taken of variability associated with age, smoking, and other factors (*37*). As emphasized by Kreyberg (*38*), epidermoid carcinomas, rather than small-cell undifferentiated neoplasms, predominate among cigarette smokers in general.

5.8 A number of features of the natural history of the respiratory tract neoplasms associated with uranium mining may have relevance to pathogenesis, as well as etiology. Most of the tumors in these miners appear to originate in major bronchi, as is typical of the dominant small-cell undifferentiated type. The idea that such tumors are derived from reserve cells that are relatively deeply placed in the epithelial lining (*39*) is a hypothesis without firm foundation, and it must be admitted that the histogenesis is essentially unknown. Localization in the large bronchi may be related to the occurrence there of a cell type that is particularly sensitive to some factor associated with uranium mining, or possibly to maximal effective concentration of a responsible factor or factors in this distribution. The complexity and unresolved state of the problems relating ionizing radiation exposure to tissue dosage are considered particularly in section III of this report.

5.9 Cytologic examination of sputum has been suggested as a method of surveillance whereby precancerous lesions might be detected in uranium miners, as in other "high-risk" groups (*40*). Further exploration of this method under carefully controlled conditions, using the "blind" reading technique in correlation with long-term followup of patients, is needed to establish its validity.

5.10 Some conclusions that may be drawn at this time are:

(a) The reported dominance of small-cell undifferentiated bronchogenic carcinomas among uranium miners, especially in consideration of epidemiologic data, strongly suggests that radiation may be the most important determining factor in the excessive prevalence of lung cancer among uranium miners at the higher exposure levels. Reexamination of the pathologic material by a second experienced panel of experts is in progress and

should provide valuable information and interpretation (*34A*).

(b) Granting the strong possibility of the cocarcinogenic effect of cigarette smoking, and perhaps also fibrosing pulmonary disease, the preeminence of the radiation factor is likely for the same reason; that is, predominance of the small-cell type.

(c) The following subjects are worthy of investigation as problems in pathology, as well as epidemiology:

(1) the nature of fibrosing pulmonary disease in these miners, with attention to intensity and duration of exposure in the mines, and

(2) sputum cytology as a clue to the development of precancerous lesions in the lung, as well as to diagnosis of manifest cancer.

(d) There is also a need for accurate information regarding the radiobiology of the lung exposed to inhaled radioactive gases of particles in relation to:

(1) the effects of the radioactive materials as a function of the physical decay process;

(2) pulmonary dynamics in terms of the transport or persistence of the radioactive materials in the various possible distributions within the lung; and

(3) the cellular response of the lung itself.

SECTION VI. EPIDEMIOLOGY

6.1 Epidemiologic data on man must constitute the final court of appeal on questions of risks to man associated with environmental exposures. Despite uncertainties in dose categorization for uranium miners and despite the relatively small populations involved, epidemiologic data have been developed that have considerable bearing on two issues of primary concern:

(a) Is there a cause-effect relationship at 100 to 400 CWLM?

(b) Is there a synergistic effect on cigarette smoking on the production of lung cancer in uranium miners?

A. The Question of a Cause-Effect Relationship at 100 to 400 CWLM

6.2 We should separate this issue into two questions:

(a) Is there a statistical association between lung cancer and exposures at 100 to 400 CWLM?

(b) If so, is radiation the principal causative agent?

6.3 There have been several epidemiologic studies of lung cancer and other causes of death in uranium miners in Europe, in hard-rock metal miners in the United States and elsewhere, and in coal miners; however, none of these studies can be said to cast any light on the specific question posed here. In regard to the hard-rock metal miners, the variety of the associated exposures, which include radon, makes it difficult to assign causal roles to any particular item or combination of items. In regard to the coal miners, the data from different countries are conflicting and information on radon and other exposures is lacking. The U.S. Public Health Service study of U.S. uranium miners is the only study in which information on levels of exposure makes it at all feasible to attempt a description of the relationship between lung cancer rates and cumulative exposure to radon daughter products. It is also the only relevant study in which histories of cigarette smoking have been obtained. Unless otherwise specified, the data quoted in the following paragraphs are taken from the most recent report of the U.S.P.H.S. study (*41*).

6.4 In the U.S. Public Health Service study the data for white underground uranium miners who died from January 1950 through September 1967 show a statistically significant excess of deaths ascribed to lung cancer in each of the three categories of estimated cumulated exposures under 840 CWLM (ref. (*41*), also table 1 in app.). For all exposures less than 840 CWLM, 7.2 deaths were expected, on the basis of the death rates for the general white male population of the mining area, and 25 were observed. This excess is most unlikely to be due to chance ($p < 0.01$). In the exposure category of 120 to 359 CWLM, 2.4 deaths were expected and 10 were observed ($p < 0.01$).

6.5 For the three exposure categories over 840 CWLM, the most recent data continue to show the consistent and marked increase in lung cancer risk with increasing exposure that was observed earlier. This provides strong evidence for the hypothesis that radiation is

a major causal factor in lung cancer at these exposure levels.

6.6 A trend toward increasing risk with increasing exposure is not seen in the three exposure categories under 840 CWLM; indeed, the relative excess of observed over expected is lowest in the 360 to 839 CWLM category. There are, however, several reasons why it is difficult to demonstrate the presence or absence of a trend at these levels:

(a) Numbers are small and random fluctuations may be important. Variations on only one or two deaths in any of these categories would produce changes in their relative positions on a scale of risk.

(b) Measurements of exposure levels in the mines and estimates of the cumulative individual exposures may not be sufficiently accurate to discriminate among the three categories.

(c) Prior experience in hard-rock mines also involving exposure to radon daughters (not included in the computation of CWLM) will naturally become of relatively greater significance when the exposure from uranium mining is small. Thus, seven of the eight lung cancer cases in the < 120 CWLM category had prior hard-rock mining experience of between 7 and 30 years. In the two other categories (120 to 359 CWLM and 360 to 839 CWLM), however, one half of the lung cancer patients had prior hard-rock mining experience of 2 years or less. If attention is restricted to miners without prior hard-rock experience, there were in the three exposure categories under 840 CWLM, 3.1 expected lung cancer deaths and six observed. Among miners with less than 10 years of prior hard-rock experience, there were, in the same exposure categories, 1.6 expected and eight observed lung cancer deaths. The impression is strong that prior hard-rock mining experience complicates the dose-response relationship in the lower exposure catagories, but it is unlikely to explain the overall excess of lung cancer cases in these categories.

6.7 Uranium miners appear to be somewhat heavier smokers than the general male population of the United States, but not sufficiently so to introduce substantial changes in the expected number of lung cancer cases. Smoking habits of the men in the low-exposure categories are similar to those in the high-exposure categories, and the excess cases in the low-exposure categories cannot be explained by any peculiarity of smoking patterns.

6.8 The question of accuracy of statement of cause of death on death certificates has been carefully reviewed by the U.S. Public Health Service. The data quoted above refer to tables that include only cases in which lung cancer is certified as the underlying cause of death. The restriction to cases in which the cancer was certified as the underlying cause was imposed because this is the basis for the cause-specific mortality rates in the general population from which expected numbers were derived. Not all the cases included in the latest mortality analysis have yet been reviewed histologically; however, in a review by the U.S. Public Health Service of 34 cases included in an earlier analysis based on the same criteria, 28 cases were confirmed as primary lung cancer, and only two were considered not to be primary lung cancer. Available material was inadequate for diagnosis in the other four cases (ref. (*2*), p. 1265). Several cases of lung cancer in addition to those used in the mortality analysis are known in the study population. The estimates of risk given in the U.S. Public Health Service data are minimal estimates, in this respect.

6.9 The biggest source of uncertainty in interpreting the data from the U.S. Public Health Service study, particularly in the low-exposure categories, is the accuracy of allocation to categories of exposure. This problem has been referred to earlier in the report. As time passes, more and more experience will be gained during periods when exposure levels have been more accurately recorded, and, correspondingly, interpretations will be more firmly based. Meanwhile, the possibility of errors in exposure estimates does not warrant the rejection of inferences from what, taken at face value, is a rather impressive accumulation of cases

in the low exposure categories. The errors involved in omission of exposures attributable to prior hard-rock mining have been referred to in paragraph 6.5. With respect to errors in assignment of exposures during the uranium mining experience, it does not appear that there has been any differential bias in assignment to exposure categories of miners who subsequently developed lung cancer.

6.10 The question of whether the increased risk seen at approximately 100 to 400 CWLM is due to exposure to radon daughter products is complex. In favor of the hypothesis that radon daughters are a contributing factor is the evidence that these grants are primarily responsible for the lung cancer observed at high-exposure levels. On the principle of parsimony, in this instance by assuming that the same relationship holds for the lower exposure levels, it seems reasonable to attribute at least part of the observed increase at 100 to 400 CWLM to the radon daughters. However, the lack of demonstrated increase in risk with increasing exposure at the lower exposure levels calls for caution in accepting this hypothesis. The possibility that other factors associated with uranium mining, or with mining in general, account for all or part of the increase cannot be excluded.

6.11 It should be noted that the data are compatible with a variety of dose-response curves, and theoretical dose-response relationships cannot be used to argue for or against causal association in the 100 to 400 CWLM exposure category. The observations do not support the hypothesis of a threshold in this range of exposure or higher.

6.12 In summary, it is concluded that there is a statistically significant increase in the lung cancer risk for miners with 100 to 400 CWLM exposure that cannot be explained by any known artifact of the data. The question of whether radiation exposures of this level induce cancer must still be considered open. In the opinion of the committee, the hypothesis is favored that radiation exposure at least contributed to the excess lung cancer observed in the miners in the approximately 100 to 400 CWLM category. This conclusion may require revision when more definitive data become available on such matters as:

(a) the measurement of CWLM from all mining experiences, not only that attributable to exposure in uranium mines;

(b) histologic confirmation of the types of lung cancer seen at the various levels of exposure;

(c) the identification of other, possibly relevant exposures experienced by uranium miners; and

(d) the use of various comparison groups, including miners with minimal radiation exposure.

B. Synergistic Effect of Cigarette Smoking and Uranium Mining

6.13 Although available data are relatively sparse, there is a distinct suggestion in them that cigarette smokers among the uranium miners are particularly susceptible to lung cancer. Two pieces of evidence support this suggestion.

6.14 Among the white underground miners in the U.S. Public Health Service study group, 78 percent were smokers and 22 percent nonsmokers. Sixty of the 62 deaths from lung cancer to date have occurred in smokers. The number of lung cancer deaths expected on the basis of general population rates was 10.1. Given a relative risk of 10 for smokers vis-a-vis nonsmokers, these expected deaths would have broken down as 0.3 in nonsmokers and 9.8 in smokers. The deaths in excess of 10.1—that is, 51.9 deaths—are the deaths attributable to uranium mining. If these deaths occurred independently of smoking, we would expect to find them distributed by smoking habits in the same proportion as the mining population; that is, 22 percent of them, or 11.4 deaths, would have been in nonsmokers. The occurrence of only two deaths in nonsmokers is not likely to be due to chance ($p < 0.01$).

6.15 Among 761 nonwhite, mostly American Indian, underground uranium miners in

the U.S. Public Health Service study, 1.3 deaths from lung cancer were expected and only two were observed, one in a smoker. Although there are alternative explanations, this observation is explicable in terms of a synergistic effect of cigarette smoking and uranium mining, inasmuch as 82 percent of the person-years at risk of the nonwhite group were referable to nonsmokers.

SECTION VII. CONCLUSIONS

7.1 At this time, the empiric approach using epidemiologic data represents the best basis for establishment of guidance for exposure of uranium miners. This approach at present necessarily assumes that the cumulated exposure to radon and its daughter products, based on measurement or estimate of mine air and expressed in Working Level Months (WLM), bears a constant relationship to the radiation dose to the critical tissue.

7.2 Uncertainties in regard to estimations of Working Levels and of absorbed dose to tissue can be considered in two categories: (a) physical measurements of mine air, and (b) physical and physiologic processes in the lung.

7.3 In regard to the physical measurements, it is considered that exposure values assigned to the period before 1956 are highly unreliable, being based almost entirely on estimates, rather than measurements of concentrations. The sampling frequency thereafter increased with time, but even so some of the 1956–1960 values may be in error by an order of magnitude. Values for the period after 1960 are the most reliable, but nevertheless many of the Working Level values reported are only estimates, no measurements having been made. It is unfortunate that the early values are so unreliable, because the latent period for tumor induction makes these early values of exposure and dose particularly important.

7.4 Improvement in physical measurements may soon be expected. Assuming that other problems can be overcome, we may expect that measurements, in combination with information about the worker's activity, respiratory physiology, and associated environmental factors can be used to provide a reasonable estimate of exposure or body burden.

7.5 Although our present capabilities for estimating the actual dose-equivalent to lung tissue cannot be used for guidance purposes, studies of this problem should be continued and expanded to provide future understanding. The primary information needs concern: (a) the proportions of free ions, (b) more basic data with which to improve lung models, (c) the critical tissue, and (d) the quality factor for the radiation.

7.6 The presently available data on exposure to radon and its daughter products and the mortality rate from lung cancer do not permit reliable quantitative description of the exposure-effect relationship or identification of the general shape of the curve. The primary deficiencies in the data are: (a) uncertainties as to exposure and exposure rate, (b) limitations in number and followup time, and (c) unknown interrelationships of combined factors, such as cumulated exposure, exposure rate, age at exposure, minimal and exposure-related latent periods, relevant induction exposure, "wasted" exposure, and cancer-promoting effects of other agents and conditions. These deficiencies could be remedied at least in part by epidemiologic studies of properly chosen comparison groups.

7.7 The reported dominance of small-cell undifferentiated bronchogenic carcinomas among uranium miners exposed at the higher levels suggest the importance of the radiation factor, granted the strong possibility of the cocarcinogenic effect of cigarette smoking and perhaps also of fibrosing pulmonary disease.

7.8 Recognizing the unreliability of present data on uranium miners, but accepting them at face value with a realization that decisions must be taken before completely adequate scientific evidence is available, the committee draws the following conclusions:

(a) There appears to be a causal association between lung cancer and exposures of approximately 1,000 CWLM and higher.

(b) There is a statistically significant increase in the lung cancer risk for miners with approximately 100 to 400 CWLM exposure that cannot be explained by any known artifact of the data.

(c) The hypothesis is favored, pending more definitive data, that radiation exposure at least contributed to the excess lung cancer observed in the miners in the 100 to 400 CWLM category.

7.9 Existing data strongly suggest that cigarette smokers among the uranium miners are particularly susceptible to lung cancer.

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APPENDIX

Table 1 gives the expected and observed respiratory cancer deaths in relation to estimated cumulative exposure to airborne radiation and years of uranium mining for white underground miners followed from 1950 through September 1967. There are 62 cases of respiratory cancer in 3,414 white miners, representing 35,439 patient-years. The method of assigning patient years and calculations of expected deaths are described in sections 3.11 and 3.12 of FRC Report 8 (*1*). The groupings for estimated cumulative exposure in WLM of <120, 120 to 359, 360 to 839, 840 to 1,799, 1,800 to 3,719, and >3,720 were used in earlier reports to yield approximately equal numbers of person-years in the first four categories as shown in table 6, FRC Report 8 (*1*), with 16,964 person-years.

Table 2 is a complete listing of cases of respiratory cancer and cancer deaths in this population. The cases are listed in order of increasing estimated WLM. Cases 1 to 49 are the earlier cases listed in FRC Report 8 Preliminary (*2*). Cases 50 to 78 have been added since that report. Cases identified by an asterisk have not been used in the calculations of table 1. Certain cases are included even though respiratory cancer was not listed on the death certificates as a cause of death, since there was laboratory evidence of lung cancer. Also, some persons with lung cancer did not die prior to September 30, 1967, the cut-off time for these analyses.

These data were made available through the generous cooperation of Dr. F. E. Lundin, Jr., of the U.S. Public Health Service.

TABLE 1. ***Expected and observed respiratory cancer deaths in relation to estimated cumulative exposure to airborne radiation and years after start of uranium mining—white underground miners, 1950–September 1967 inclusive (41)***

Estimated cumulative exposure, WLM	Person-years at risk[a]	Years after onset of underground uranium mining							
		<5		5–9		≥10		Total	
		Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
≤120	10,325	0.69	1	1.05	2	0.77	*5	2.51	*8
120–359	9,554	.43	1	.99	3	.97	*6	2.39	*10
360–839	7,368	.21	0	.72	1	1.34	*6	2.27	b7
840–1,799	5,107	.07	0	.35	b3	1.28	*8	1.70	*11
1,800–3,719	2,406	.01	0	.10	0	.84	*17	.95	*17
>3,720	679	.00	0	.03	*3	.21	*6	.24	*9
Total	35,439	1.41	2	3.42	*12	5.41	*48	10.06	*62

[a] By estimated WLM to the month at risk or through 1963, whichever was earlier.
[b] Significant at 5-percent level.
[c] Significant at 1-percent level.

TABLE 2. ***Description of respiratory cancer cases and deaths among study groups of underground uranium miners, 1950–September 1967 inclusive, listed in order of increasing estimated WLM***

Cigarette smoking habits			Underlying cause of death (from death certificate)	List number[a]	Year of death	Age at death, years	Years hard-rock mining[b]	Months worked underground	Time span of exposure	Range of estimated WL	Estimated WLM	Methods of diagnosis and comments
Case	Packs per day	Years smoking										
			White Subjects									
52	1	30	Metastatic carcinoma; primary probable bronchogenic, left lung.	162	1966	48	16	1	1960	5	5	Not available.
51	1	53	Carcinoma, bronchogenic	162	1966	71	24	36	1954–1957	1	36	Autopsy.
2	1	20	Carcinoma, right lung	163	1965	48	08	8	1950–1951	5	37	X-ray; biopsy; autopsy.
3	1	35	Undifferentiated carcinoma, bronchus, left upper lobe.	162	1965	56	31	25	1954–1960	0.2–1	38	X-ray; autopsy.
1*	1	36	Squamous cell carcinoma	191	1962	57	03	7	1951	7	49	X-ray; biopsy; sputum; autopsy. Clinical data clear as to bronchogenic origin, but "lung" was omitted from death certificate.
4	1	36	Squamous cell brochogenic carcinoma.	162	1958	55	07	6	1955	10	60	X-ray; autopsy.
50	1	50	Carcinoma of the lung	163	1965	65	30	13	1957–1958	5	65	X-ray; pleural fluid cytology.
54	1	38	Carcinomatosis, lung	163	1967	59	12	33	1954–1961	1–4	85	Not available.
53	1	27	Bronchogenic carcinoma	162	1966	44	00	24	1954–1963	1–6	116	Pneumonectomy; autopsy.
6	1½	40	Epidermoid carcinoma of lung	163	1962	54	19	7	1949–1956	6–20	123	X-ray; biopsy; autopsy.
5	1	34	Squamous carcinoma, lung	163	1965	53	00	5	1952–1953	7–41	138	X-ray; biopsy.
10	2½	60	Carcinoma of lung	163	1964	71	00	12	1953–1957	10–15	165	X-ray; bronchoscopy; sputum; autopsy.
58	1	31	Undifferentiated squamous cell carcinoma.	163	1966	45	02	9	1957–1958	10–25	165	Autopsy.
59*	1½	50	Carcinoma of the lung	163	1967	62	00	28	1937–1960	5–10	192	Autopsy.
7	1	47	Bronchogenic carcinoma	162	1964	65	02	69	1948–1961	1–5	203	Not known.
57	1½	43	Carcinoma, right lung, with metastases.	163	1966	58	17	36	1957–1960	4–15	241	Not available.
56	1	49	Carcinoma of lung	163	1962	64	26	65	1956–1962	2–6	260	X-ray; sputum; bronchoscopy; biopsy.
8	0	0	Carcinoma of lung	163	1965	57	14	36	1949–1962	0.6–21	269	X-ray; biopsy; autopsy.
9	1	17	Oat cell carcinoma right lung	162	1962	66	07	52	1952–1961	0.2–16	283	X-ray; sputum; biopsy; autopsy. Stopped cigarettes 28 years before death.

TABLE 2. *Description of respiratory cancer cases and deaths among study group of underground uranium miners, 1950–September 1967 inclusive, listed in order of increasing estimated WLM*—Continued

Case	Cigarette smoking habits: Packs per day	Cigarette smoking habits: Years smoking	Underlying cause of death (from death certificate)	List number [a]	Year of death	Age at death, years	Years hard-rock mining [b]	Months worked underground	Time span of exposure	Range of estimated WL	Estimated WLM	Methods of diagnosis and comments
55	1	25	Metastatic bronchogenic carcinoma.	162	1960	42	01	12	1959–1960	4–36	287	X-ray; biopsy; autopsy.
62*	1½	34	Subdural hematoma	936	1967	53	04	57	1952–1961	1–15	429	Autopsy. Other significant condition listed on death certificate: Carcinoma of right lower lobe of lung with metastasis to liver.
14	1	54	Carcinoma of lung	163	1963	73	00	51	1950–1957	4–20	494	X-ray; sputum; biopsy; autopsy.
63	1	32	Carcinoma, squamous cell, right lung.	163	1967	47	06	43	1954–1963	5–20	511	Autopsy.
60	1	29	Adenocarcinoma, lung	163	1965	49	19	84	1956–1963	2–19	564	X-ray; sputum; autopsy.
64*	1	28	Carcinoma of lung with extensive metastases within the abdomen.	163	1967	62	18	60	1957–1962	4–15	589	Autopsy.
16	1	43	Carcinoma, lung	163	1965	59	11	135	1952–1963	1–19	593	X-ray; autopsy.
12	1	26	Primary sarcoma of mediastinum.	164	1964	46	01	39	1954–1958	5–50	605	X-ray; biopsy. Tumor removed 4 years prior to death, but death was really a complication of surgery.
13	1	54	Bronchogenic carcinoma	162	1963	69	00	100	1951–1960	0.2–21	699	X-ray; biopsy.
61	1½	8	Carcinoma of the lung	163	1966	56	00	24	1953–1963	1–100	831	Autopsy. Stopped smoking 14 years before death.
23	1½	34	Bronchogenic carcinoma	162	1961	54	00	60	1954–1959	5–30	866	X-ray; sputum; autopsy.
22	1	36	Pulmonary malignancy	162	1965	51	00	60	1955–1960	4–25	886	X-ray; autopsy.
66	1	51	Carcinoma, right lung	163	1966	66	00	100	1952–1963	3–21	924	Autopsy.
66	1	51	Carcinoma, right lung	163	1966	66	00	100	1952–1963	3–21	924	Autopsy.
20	1	47	Disseminated bronchogenic carcinoma.	162	1965	62	01	30	1940–1959	25–55	940	X-ray; biopsy; autopsy.
25	1	34	Carcinoma, right lung	163	1960	50	12	76	1951–1959	2–40	1,017	X-ray; bronchoscopy; biopsy.
68*	½	20	ALIVE				00	67	1952–1958	1–35	1,032	Lung cancer diagnosed 7–67, age 59. Stopped smoking 8 years earlier.
21	1½	40	Bronchogenic carcinoma	162	1965	58	00	135	1947–1963	0.3–36	1,075	X-ray; autopsy.
24	1	37	Bronchogenic cancer	162	1963	59	00	105	1952–1963	0.5–25	1,082	X-ray; sputum.
65*	1	39	Metastatic carcinoma of lung	165	1966	60	25	116	1950–1960	1–35	1,170	Not available.
27*	1	38	Cancer of adrenal gland	195	1960	47	00	64	1953–1959	5–58	1,174	X-ray; biopsy; sputum; autopsy.
69*	1½	37	ALIVE				09	175	1940–1963	1–21	1,239	Lung cancer diagnosed 8–67, age 51.
15	2½	22	Carcinoma of lung	163	1965	57	02	92	1952–1963	0.3–100	1,367	X-ray; autopsy.
17	1	34	Cancer of lung	163	1964	53	00	104	1939–1963	0.1–25	1,557	X-ray; biopsy; autopsy.
67	1	42	Carcinoma, lung, oat cell with mediastinal metastases.	162	1966	49	04	47	1959–1963	3–108	1,574	Autopsy.
18	1	35	Carcinoma, lung	163	1964	51	00	187	1945–1963	1–69	1,791	X-ray; sputum; autopsy.
26	1	35	Cancer of lung	163	1966	49	08	142	1952–1964	1–42	1,904	X-ray; bronchoscopy; autopsy.
19	1	37	Carcinoma, lung	163	1963	47	00	221	1940–1963	1–10	1,944	X-ray; sputum; autopsy.
29	½	17	Carcinoma, lung	163	1956	51	16	78	1940–1953	5–50	1,995	X-rays; autopsy.
33	1½	26	Probable primary carcinoma of lung.	162	1963	45	07	153	1941–1962	4–25	2,055	X-ray; autopsy.
32	1	29	Bronchogenic carcinoma	162	1964	45	00	88	1940–1958	2–32	2,124	X-ray; biopsy.
71	0	0	Bronchogenic carcinoma	162	1966	65	00	155	1947–1963	1–50	2,180	Autopsy.
73	½	45	Squamous cell carcinoma, lung	163	1967	60	00	180	1936–1962	0.3–40	2,363	Autopsy.
30	1½	35	Oat cell bronchogenic carcinoma.	162	1962	47	11	138	1936–1962	5–25	2,369	X-rays; sputum; autopsy.

TABLE 2. ***Description of respiratory cancer cases and deaths among study group of underground uranium miners, 1950–September 1967 inclusive, listed in order of increasing estimated WLM*—Continued**

Case	Cigarette smoking habits: Packs per day	Cigarette smoking habits: Years smoking	Underlying cause of death (from death certificate)	List number [a]	Year of death	Age at death, years	Years hard-rock mining [b]	Months worked underground	Time span of exposure	Range of estimated WL	Estimated WLM	Methods of diagnosis and comments
37*	1	44	Cancer of lung	165	1961	60	00	121	1949–1959	3–31	2,406	X-ray; biopsy; sputum; autopsy.
31	1	30	Carcinoma, lung	163	1963	48	00	151	1937–1959	3–55	2,492	X-rays; autopsy.
74	2	38	Bronchogenic carcinoma	162	1967	54	13	104	1954–1963	3–50	2,662	Autopsy.
34	1	33	Oat cell carcinoma, left lung	162	1961	56	00	122	1944–1960	0.4–42	2,864	X-ray; biopsy; autopsy.
70	1	28	Pulmonary carcinoma, undifferentiated.	163	1966	46	00	153	1947–1963	2–56	2,900	Autopsy.
36	1	16	Oat cell carcinoma of lung	162	1965	51	00	177	1948–1963	2–31	2,914	X-ray; sputum; autopsy. Pathology diagnosis changed from oat cell to epidermoid at autopsy.
35	1	44	Bronchogenic carcinoma	162	1963	62	07	116	1940–1962	0.8–44	2,919	X-ray; autopsy.
72	1	35	Carcinoma, left lung with metastases (mature squamous cell).	163	1966	54	01	164	1940–1962	2–53	2,933	Autopsy.
44	1	38	Carcinoma of bronchus	162	1965	55	04	150	1940–1958	10–100	3,390	X-ray; autopsy.
75*	1½	42	Not available	n.a.	1968	59	04	113	1949–1961	1–170	3,560	Not available.
39	1	30	Carcinoma, left lung	163	1957	50	05	125	1941–1953	30	3,672	X-rays; autopsy.
28	1	24	Adenocarcinoma of lung	163	1956	48	00	131	1940–1955	0.6–50	4,175	Bronchoscopy; biopsy; x-rays. "Adenocarcinama" was not reported by pathologist.
48	1	40	Bronchogenic carcinoma	162	1966	58	23	165	1950–1963	2–56	4,235	X-ray; biopsy; autopsy.
43	1	26	Bronchogenic carcinoma right lung.	162	1960	45	00	156	1944–1960	3–230	4,237	X-rays; sputum; autopsy.
41	1	20	Carcinoma, right lung	163	1965	49	00	136	1939–1963	2–60	4,363	X-ray; autopsy.
45	1	38	Carcinoma, lung	163	1963	55	00	80	1954–1962	5–150	4,984	X-ray; biopsy; autopsy.
42	1	26	Cancer of lung	163	1958	43	08	105	1949–1958	10–230	5,187	X-ray; bronchoscopy; autopsy.
38*	0	0	Pancreatic cancer	157	1955	62	02	228	1925–1949	10–30	5,640	X-ray; autopsy. Widespread metastasis at autopsy.
46	½	32	Carcinoma, lung	163	1959	54	00	78	1951–1957	15–100	5,845	Autopsy.
47	1	43	Anaplastic bronchogenic carcinoma.	162	1964	58	00	102	1950–1958	15–100	6,875	X-ray; biopsy; autopsy.
49	1	34	Adenocarcinoma of lung	163	1965	51	00	111	1950–1960	15–100	6,935	X-ray; sputum; biopsy.
						Nonwhite Subjects						
78	1	29	Carcinoma of lung	163	1967	48	07	44	1951–1957	2–35	684	Not available.
77*	0	0	Bronchopneumonia, Emphysema.	527	1965	54	00	143	1950–1962	1–36	1,168	Autopsy. Other significant condition listed on death certificate: Tumor, unspecified, left lung.
76	0	0	Carcinoma of lung	163	1965	56	00	153	1950–1963	0.4–36	1,276	Not available.

[a] Sixth Revision of International Lists.

[b] Before onset of underground uranium mining.

*Indicates cases which were not in mortality analysis (1950–September 1967 inclusive).