UCD 472-505

RADIOACTIVE FALLOUT: An Overview of Internal Emitter Research in the Era of Atmospheric Nuclear Weapons Testing

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March, 1983

NOTICE

ACKNOWLEDGMENTS

Thanks are extended to Mrs. Susan Munn, who helped review the literature, to Mr. Charles Baty, who typed the manuscript, and to Dr. Leon Rosenblatt, who critically reviewed the report. Special gratitude goes out to Drs. Newell Stannard, Pat Durbin, Miriam Finkel, Leo Bustad, Roy Thompson, and Merril Eisenbud, who provided reference material and background information. This work was supported by the Department of Energy.

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I. INTRODUCTION

This report is a review of the literature on the radiobiology of internal emitters. Its purpose is to consider what has become known about the radiobiology of internally deposited radionuclides over the last four decades. Our primary emphasis is the progression of radiobiological information through the 1950s and early 1960s, when atmospheric testing of atomic weapons was occurring with increasing regularity.

Most of the over 280 references cited in this report are from the open literature, although use of technical reports was sometimes also needed. Our focus was on developing a reasonable, documented chronology of the evolution of knowledge about the radiobiology of fallout. We have used our scientific judgment about the significance of available information in distilling an enormous volume of literature into a report of this size.

We do not intend this report to be a complete survey of the subject. The scientific literature is replete with overviews of radiobiologic studies, and what has not been reviewed in the open literature has been reviewed in many documents, including those on nuclear reactor safety (US NRC, 1975), radiation risks (UNSCEAR, 1977, 1982; NAS, 1972, 1980), and radiation research in general (IRRC, 1980).

In this report, after a historical perspective (Chapter II), we address the general evolution of radiobiological research on internal emitters from qualitative studies on their radiotoxicity to quantitative assessments of the risk from exposures to them (Chapter III). Further, we look in general at important developments in the concern over fallout from nuclear weapons detonations through the era of atmospheric testing.

We also consider information on fission products that are biologically important (Chapter IV). Specifically, we discuss in detail isotopes of iodine, strontium, and cesium (Chapters V, VI, and VII, respectively). These radionuclides are components of radioactive fallout and are readily taken up by the body.

Finally, we also examine data for plutonium (Chapter VIII) and uranium (Chapter IX). These last two elements, not produced by fission but rather used in producing it, are generally consumed in the fission reaction. Those atoms that escape fission, however, can be dispersed and may present potential environmental and health hazards.

For each of the radionuclides discussed, we consider environmental pathways that are available for the eventual exposure to human populations and the metabolic pathways that determine the tissues at risk following exposure. We also consider the radiobiological effects of exposures given at high levels, and, when appropriate, the risks accompanying low-level exposures.

II. A HISTORICAL PERSPECTIVE

Considerable information on the metabolism and effects of fission-produced internal emitters was available in the 1940s. Most of it arose from work related to the development of atomic weapons (Smyth, 1946). Hamilton (1947) explained that research:

> During the early phases of the development of the Plutonium Project, it became apparent that one of the most serious problems to be encountered was the protection of personnel working in this field against the immense quantities of radiation and radioactive materials produced by the chain-reacting pile. The most important hazard that arises from the release of nuclear energy are radiations produced directly from fission and subsequently emitted by the resultant fission products and plutonium. The fission products can produce injury either as an external source of radiation or, if they gain entry into the body, by acting as an internal radioactive poison, quite analogous to radium poisoning. This latter consideration is a major concern, since the amounts required within the body to produce injurious effects are minute compared to the quantities necessary to induce damage by external beta and gamma irradiation ....
>
> The fission of uranium results in the production of thirty-four radioactive elements, extending from zinc to europium, and there have been identified nearly two hundred radioactive isotopes of this large number of elements that rise from fission. Since the possibility of entry of these fission products into the body had to be considered as one of the principal hazards to those working in the field of atomic energy, it was necessary to secure information as to

the absorption, distribution, retention, and excretion of these radioactive materials. In addition to evaluating the metabolic characteristics of these substances, it was necessary to duplicate as nearly as possible, with laboratory animals, the manner by which fission product poisoning might occur. This included a study of the behavior of these radioelements following their introduction into the body by the three major portals of entry, namely inhalation, oral ingestion, and through cuts and abrasions of the intact skin ....

No satisfactory estimates or predictions of the possible metabolic characteristics of most of the fission products could be made, since most of these substances are radioactive isotopes of elements concerning whose metabolic properties very little was known. In other words, there were no reliable data available that could make it possible in most instances to predict which of the fission products would be absorbed from the digestive tract and rapidly eliminated, once having gained entry into the body, and which ones might be selectively deposited and retained in some vital structure. Actually, there was only one fission product, radioiodine, that had received sufficient study with regard to its metabolic properties, prior to 1942, to permit a reasonable evaluation of the amount that could be tolerated within the body without producing damage. A second fission product, radiostrontium, had been studied before 1942, but not in sufficient detail to satisfy the requirements of the medical research program of the Plutonium Project. The nature of the metabolic characteristics of the other fission products at that date was essentially a completely unknown quality ....

In addition to the fission products, it was necessary to evaluate by similar tracer studies the potential dangers from plutonium poisoning. This element is radioactive and

> has a half-life only fifteen times greater than radium. In addition, the quantities to be isolated, purified, and used for a variety of purposes were considerable, to say the least. Later, several other of the heaviest elements, commonly called the actinide elements, which extend from actinium through curium (element 96) were included for study. These substances either arise directly in the chain-reacting pile or appear in certain phases of the atomic energy program and present potential health hazards because they all share the common property of radioactivity.

There was also information available on fallout from atomic weapon detonations. Livestock that were exposed to localized fallout from the Trinity Shot in New Mexico in July, 1945 showed effects of the exposure (beta burns on the skin) (Glasstone et al., 1950). Fallout occurring at more distant locations was also observed in August, 1945, in Indiana, when photographic film was fogged by radioactive contaminants in packaging materials (Webb, 1949). Research on fallout from Trinity continued for a number of years after the detonation (Larson, 1963).

Glasstone et al. (1950) discussed the effects of these weapons, briefly mentioning the potential of serious physiological hazard of radioactive fallout that deposits on the earth's surface in appreciable amounts. These authors also considered the problems of radioactive contamination of food and water, and tabulated fission products and their relative importance at varying times after fission. In addition, the biological significance of unfissioned uranium or plutonium released into the environment was also discussed.

Information on fission-produced internal emitters seems to have developed in three major phases. In the 1940s, studies related to the metabolism and

effects of radionuclides were performed. The impetus for this work was occupational safety. In addition, some medical work was also being done. In the 1950s and 1960s, the awareness of radioactive fallout changed the purpose of much work to addressing public safety. Much of the work was environmental in nature, which evolved into the discipline of radioecology. The first symposium on radionuclides in the environment was held in 1959 (Caldecott and Snyder, 1960), closely followed by a symposium on radioecology held in 1961 (Schultz and Klement, 1963).

In the 1960s and up to the present, work has continued related to the public safety from internal emitters, though the driving force evolved from contamination by nuclear weapons to the potential for contamination by nuclear reactors and related fuel cycle operations. Work also continued to address problems of occupational exposure. Unlike the research of the 1940s, which tended to emphasize immediate effects of high levels of exposure, the more contemporary work has emphasized the consequences of long-term exposures and latent health effects of low level exposures as well as the mechanisms of these effects. Radiation-induced cancer has been the significant end-point of most of the more recent research.

III. DEVELOPMENTS IN RADIOBIOLOGICAL RESEARCH

Radiobiological research on internally deposited fission products underwent a number of evolutionary changes from the 1940s to the present. These changes occurred in investigations on the health effects of these radionuclides and in attempts to estimate the risks that accompany irradiation. Studies on the environmental significance of radionuclides also changed, as prompted by the recognition of fission products in fallout as unwelcome companions of the testing of nuclear weapons.

Health Effects

Studies on the biological effects of internal emitters generally progressed from an initial production of radionuclides to metabolic studies on their distribution and excretion. From here, studies on the acute toxicity, elicited by exposures to large amounts of radioactivity, were next. Then, since most of the concern was for protection of the worker, chronic studies involving long-term exposures to lower levels of radioactivity were done to gain understanding about the late effects that might be produced. The prior experience with the late effects seen in the radium dial painters prompted long-term studies with other radionuclides in the 1940s, principally with bone seekers such as strontium-89, -90, and plutonium-239. In depth studies of these radionuclides began in the 1950s, when the Atomic Energy Commission established several beagle dog colonies around the country. Work continues to the present time.

For radioiodine, the pattern of research development in the 1940s was generally the same, though for a long time it remained fixed in the acute effects phase, since this was the desired end-point for the treatment of thyroid disorders. Only after the thyroid gland was shown to be relatively

radiosensitive and not radioresistant, which occurred in the 1950s when thyroid cancers were produced in animal models and when they were shown to be produced in children years after x-irradiation of the head and neck, was there more study of the late effects of radioiodine.

The significance of cesium-137 was not appreciated until the 1950s, when it was found in the environment. Although limited research on radiocesium was done in the 1940s, it went through the pattern of testing--metabolism, acute effects, late effects--later, and in a chronologically compacted time.

Risk Assessment

Acute responses to irradiation were fairly easy to describe and, probably, to predict, in that high enough doses would elicit acute effects, and lower ones would not. "Safe" exposures were at levels less than tolerance doses, that is, levels at which recovery would occur.

Assessment of radiation risk in the 1950s was in the context of thresholds, injury and repair, and lifeshortening. Blair (1962) discussed radiation injury in terms of acute reparable and irreparable injuries measured by life shortening. That low level radiation induced lifeshortening was primarily a carcinogenesis effect was not generally recognized (FRC, 1960). "Early" injury in exposed mammals was frequently measured by comparing pre- and post-exposure blood counts, a practice almost as widespread as the use of film badges for dosimetry.

For low-level exposures to pose risks for latent health effects was not consistent with the threshold, or tolerance, dose concept then in vogue. At that time genetic effects were thought to be without a threshold, or linear in response (NCRP, 1954), an opinion largely influenced by the early research on

fruit flies. Only later did the stochastic nature (e.g., cancer) of the response of somatic tissue to radiation become clear. Repairable injury (e.g. on spermatogenesis, leukocyte counts) was a functional phenomena and irreparable injury was an "accleration of aging" phenomenon that shortened lifespan.

With late effects such as bone cancers, the all-or-none principle described above became the all, none, or some principle. In experiments with groups of animals exposed to graded dosages of bone seekers, differences in numbers of cases of cancer and their times of occurrence were observed. Higher doses resulted in more tumors at earlier times than lower doses. Low enough doses did not result in effects before animals died of natural causes (Brues et al., 1947; Brues, 1949), thus leading to the concept of a "practical threshold" (Evans et al., 1972).

The shape of the dose-response curve for radiation-induced cancers became the subject of debate in the 1950s. Several scientists (Lewis, 1957; Court-Brown, 1958) espoused linearity as the proper way to express the relationship of dose and effect, citing a proportional increase in effect with increasing dose in irradiated human populations as evidence for their claim. Others (Mole, 1958; Finkel, 1958; Brues, 1958), who based their opinions more on animal data, considered a curvilinear dose-response relationship to be more appropriate.

The debate over the proper shape of the dose-response curve has continued to this time. This was demonstrated by the recent and controversy-ridden report of the Committee on the Biological Effects of Ionizing Radiation (NAS, 1980).

The words of Mole (1958) seem as fitting now as they were then written:

> Whatever the shape of the empirically determined curve, it is always possible that the shape of the curve changes at doses less than the lowest used. Even if there were several dose-levels at each of which the response was no different from the base-line control, it must be accepted that each of the measured responses has a statistical error. The possibility can never be denied that observations on a much larger scale would have shown responses really greater than the control. Thus the existence of a threshold can never be proved by an empirical dose-response curve. Equally, of course, for similar reasons the absence of a threshold can never be proved. Thus the existence or not of a threshold can be determined only on theoretical grounds.

Along with and because of the uncertainties of radiation effects, a risk philosophy had to be incorporated into the establishment of radiation protection hazards (Taylor, 1958). This philosophy was necessary because radiation standards, present for several decades already, were expressed in terms of "permissible" doses, which implied the acceptance of some small, but undefined (and undefinable) risk. Risks moved from being generally qualitative to being quantifiable (ICRP, 1966), and have been the subject of elaborate calculations, primarily with regard to safety from nuclear reactors (US NRC, 1975).

Recognition that radiation was hazardous resulted in the formation of several scientific advisory groups who made recommendations of limits for occupational and non-occupational exposures. These recommendations were issued in the form of periodic reports by: the International Commission on Radiological Protection (ICRP), founded in 1928; the National Council on Radiation Protection and Measurements (NCRP), forming in 1946 from an advisory

committee out of the National Bureau of Standards; the United Nations' Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), established in 1955; the National Academy of Sciences/National Research Council's (NAS/NRC) Committees on Biological Effects of Atomic Radiation (BEAR), which first published a report in 1956, and, later, the NAS/NRC's Committee on Biological Effects of Ionizing Radiation (BEIR).

The Federal Radiation Council (FRC) was formed in 1959 to provide federal policy on human radiation exposure. In 1970, this task was transferred to the Environmental Protection Agency (EPA), which also absorbed fission- and medical-related matters that had been under the Atomic Energy Commission and the Department of Health, Education and Welfare. The EPA continues to function with the same responsibilities, with interaction with the Nuclear Regulatory Commission, the Food and Drug Administration's Bureau of Radiological Health, and other agencies.

Environmental Radioactivity

At the same time radiobiological research on the effects of internal emitters was evolving, so, too, was environmental research developing. Most research in the 1940s was concerned with the work environment where man-made or technologically enhanced radioactivity would be encountered in much higher concentration than in the general environment.

In 1945, when the Trinity shot occurred, radioactive fallout was first produced locally (Glasstone et al., 1950). Fallout continued to be recognized as a contaminant of the environment thereafter, from testing in the Pacific in the late 1940s (Carter and Moghissi, 1977; Perkins and Thomas, 1980), but it appears that most concern was about the contamination of material exposed to the localized deposition of radioactive dust.

The more distant nature of fallout deposition was noticed in 1945, but not published until later (Webb, 1949). In this case, emphasis was on exposed photographic film rather than exposed human populations.

That fallout was present at distances far from the site of detonation was again demonstrated in the early 1950s in environmental samples (precipitation) that contained high levels of unnatural radioactivity (Meinke, 1951; Holter and Glasscock, 1952; Clark, 1954). Fallout occurring outside of the test sites, however, was not considered to create any immediate or long-range health hazard (AEC, 1953a).

A network of monitoring stations for fallout radioactivity was established in 1951 (Eisenbud, 1957). Fallout ^{90}Sr levels, from data from those stations, were published by Eisenbud and Harley (1953). The presence of fallout ^{131}I in thyroid glands was first published by Van Middlesworth (1954). The potential for health effects from these radionuclides, however, was not a cause for significant discussion in these early papers.

Although there was local worry about exposures from the Nevada test site in the early 1950s, serious concern about the health effects of radioactive fallout arose with the detonation of a larger weapon in 1954 (Anonymous, 1954). A detonation on March 1, 1954 in the Central Pacific resulted in fallout that necessitated the evacuation of 28 Americans and 236 native inhabitants from the Marshall Islands. Twenty-three fisherman on a Japanese trawler were also exposed to the fallout, and suffered significant medical effects. One of the fishermen died on September 23, 1954 (Arnold, 1954), from liver damage (Appendix VI, Conard et al., 1980). The Marshallese manifested early effects as well, and showed a number of late effects, many of them related to exposures of the thyroid gland. One person also died from acute myelogenous leukemia (Conard et al., 1975, 1980).

Concern about the toxicity of radioactive fallout from the detonation in March, 1954, resulted in a series of articles about fallout as a new peril for civil defense (Lapp, 1954, 1955a), fallout and goverment secrecy (Lapp, 1955b), the persistence of fallout and the problem of internal emitters (Lapp, 1955c), and global fallout (Lapp, 1955d). The Atomic Energy Commission reported on the effects of the March 1954 test in 1955 (AEC, 1955). Also in 1955, Congressional hearings were held to place on the public record factors about the effects of atomic weapons testing at the Nevada test site (US Congress, 1955).

By 1956, reports on the global distribution of fallout ^{131}I and ^{90}Sr from weapons tests were published (Van Middlesworth, 1956; Machta et al., 1956). By 1957, the correlation between weapons tests and ^{131}I in human and bovine thyroid glands was established, and the importance of cows' milk in human contamination was discussed (Comar et al., 1957). At about the same time, ^{137}Cs was shown to be in people (Miller and Marinelli, 1956). In 1957, Congressional hearings to bring together information on radioactive fallout were held (U. S. Congress, 1957). Further hearings were held in 1959 and 1963 (U. S. Congress, 1959, 1963).

The discipline of radioecology was firmly established in the early 1960s (Caldecott and Snyder, 1960; Schultz and Klement, 1963). Since that time it has become more sophisticated, with elaborate models of radionuclides in the environment used to predict exposures to human populations. Much of the information in these models, now used primarily for evaluating the environmental significance of various steps in the nuclear fuel cycle, had its origins in studies of weapons-related fallout.

There were many occurrences and investigations that took place during the era of atmospheric weapons testing. We have included what we consider important dates in this history of radioactive fallout in Table 1.

Table 1. Some Important Dates in the History of Radioactive Fallout.

Date	Event	Reference
1940s	Studies on metabolism and effects of internal emitters	Chaps. V-IX, this report
1945	Trinity shot, Alamogordo, New Mexico	Smyth, 1946
1945	Local fallout from Trinity	Glasstone et al., 1950
1945	Fallout from Trinity in Indiana	Webb, 1949
1946,48	Pacific testing	Carter and Moghissi, 1977
1946	Local fallout on ships from Pacific tests	Glasstone et al., 1950
1950s	Studies on metabolism and late effects of internal emitters	Chaps. V-IX, this report
1951	Testing begins at Nevada Test Site	Carter and Moghissi, 1977
1951,52, 1953	Fallout in precipitation in Michigan, Montana, and New York	Meinke, 1951; Holter and Glasscock, 1952; Clark, 1954
1953	Heavy fallout in Utah	AEC, 1953b
1953	Wide distribution of ^{90}Sr in fallout reported	Eisenbud and Harley, 1953
1954	Fallout on Marshallese from Pacific test	AEC, 1955
1954	Serious radiation effects in fallout-exposed Japanese fishermen	Arnold, 1954
1954	^{131}I in animal thyroid glands of animals distant from Nevada test site	Van Middlesworth, 1954
1955	Congressional hearings on fallout	US Congress, 1955
1956	^{137}Cs found in people	Miller and Marinelli, 1956
1957	Correlation shown between weapons tests and ^{131}I in thyroid glands; role of cows' milk in human exposures discussed	Comar et al., 1957
1957	Windscale reactor accident in England	Eisenbud, 1973

Table 1. Some Important Dates in the History of Radioactive Fallout. (continued)

1957	Congressional hearings on fallout	U. S. Congress, 1957
1957,58	Early papers and dose-response relationships published	Lewis, 1957; Court-Brown, 1958 Mole, 1958; Brues, 1958
1959	Symposium on radionuclides in environment	Caldecott and Snyder, 1960
1959	Congressional hearings on fallout	US Congress, 1959
1958-61	Moratorium on weapons testing	Carter and Moghissi, 1977
1960s	Studies on metabolism and late effects of internal emitters	Chaps. V-IX, this report
1961	Testing resumed	Carter and Moghissi, 1977
1961	National symposium on radioecology	Schultz and Klement, 1963
1963	Congressional hearings on fallout	US Congress, 1963
1963	Symposium on radioiodine	Bustad, 1963
1963	U.S., U.K., and U.S.S.R. end atmospheric testing	Carter and Moghissi, 1977
1960s-70s	French, Chinese continue atmospheric testing	Carter and Moghissi, 1977

In summary, the past four decades can be characterized according to the scientific emphasis occurring at that time. The characterizations, of course, are broad and general. In fact, research in almost all areas of internal emitter radiobiology was taking place in each of the decades.

The 1940s were a decade of discovery. The fission weapons were produced and along with their production, considerable new knowledge about the metabolism and effects of radionuclides was born. The application of radionuclides to medical procedures also showed great promise and resulted in much information.

In the 1950s, it became apparent that there were environmental and potential health consequences related to the weapons testing. An environmental awareness began to develop, as did concern about the long-term effects of continued exposure to low levels of radionuclides. As a result, larger studies were begun to address the biological significance of these exposures. These would continue through the next decades.

In the 1960s, environmental and public health awareness became more acute prior to the signing of the nuclear test ban treaty. Radioecological studies and models became more sophisticated. The long-term bioeffects studies continued.

In the 1970s, with the near absence of atmospheric testing, most of the radiobiologic research took on an orientation related to nuclear power generation, since this technology represented new sources of occupational and population exposures and environmental contamination. Concern was basically the same--the effects of long-term, low-level exposures. There was also concern about the likelihood of major reactor accidents and subsequent radiological impact.

The 1980s should see the completion of the long-term bioeffects studies begun decades earlier. Their results will lead, it is hoped, to an increased understanding of the relationship of radiation dose, effect, and time, and methods for the prediction of risks to people from exposure to internally deposited radionuclides.

IV. RADIONUCLIDES OF SIGNIFICANCE

Isotopes of iodine, strontium, and cesium have received the greatest attention as components of radioactive fallout. Although other radionuclides are fission products as well, few of them have the characteristics to make them as important biologically (Sternberg, 1968).

To be of radiobiological significance, a radionuclide released into the environment first must have a physical half-life of sufficient duration so that it will continue to be radioactive during the time required to enter into biological systems and to traverse food chains to reach the individual who consumes it. Iodine-131, with its 8-day half life, exists long enough to move through the atmosphere→vegetation→cow→milk→people pathway. Strontium-90 and cesium-137 have half-lives of 29 and 30 years, respectively, and can easily enter the same pathways for human exposure. Their longer lives also enable them to use other pathways as well, such as soil→vegetation→cow for ^{90}Sr, and vegetation→cow→meat for ^{137}Cs (Comar and Lengemann, 1967).

The significant radionuclide should also be able to be effectively assimilated into the body. Iodine-131 has easy access, because iodine is required for normal thyroid gland function and the body does not distinguish between isotopes of the element. Strontium-90 and cesium-137 can enter the body because they behave generally like calcium and potassium, respectively, which are important components of biological systems. It is the specific metabolism of each radionuclide that determines its potential for direct toxic effect. Other fission products tend not to have the ease of entry into the diet or into tissues that these three do.

Research on the radioecology and biological effects of other fission products has been done, though not on such an intense basis. For example, Hamilton (1967), in work on the Plutonium Project, studied the distribution

and excretion of a number of radionuclides, including barium-140, cerium-141 and -144, zirconium-95, ruthenium-103 and -106, and tellurium-127 and -129. Studies of ^{106}Ru metabolism were also done by Thompson et al. (1958) and Furchner et al. (1971). Considerable work was done on radiobiology of radiocerium (NCRP, 1978), not only because it is an abundant fission product with a 285-day half life, but also because ^{144}Ce is a beta-emitting bone seeker that provides a valuable tool for understanding the effects of bone seeking radionuclides (NCRP, 1978). Reviews of the radioecology of several radionuclides have been published, including ruthenium and rhodium (Auerbach and Olson, 1963), the rare earths (Palumbo, 1963), and zirconium (Held, 1963).

V. RADIOIODINE

Summary

Iodine-131 is the primary radioiodine that is of importance in radioactive fallout. It has an 8-day physical half-life and is a beta and gamma emitter. The thyroid gland is the principal target organ of ^{131}I.

The metabolism of iodine and effects of ^{131}I, especially for high doses, were known in the late 1940s as a result of medical uses of radioiodine. Hypothyroidism was the primary radioiodine exposure effect, while thyroid carcinogenesis came to be appreciated as a late effect of thyroid irradiation in the 1950s. Isotopes of iodine were known to be components of radioactive contamination from atomic weapons and nuclear facilities by 1950, and were reported to be in precipitation in the open literature in 1951 and in animal thyroids in 1954.

From the 1950s into the 1980s, radioiodines have been the subject of research, not only because of their role as a component of radioactive fallout, but also because of their position as potential environmental contaminants from nuclear reactors. Their use in medicine, as diagnostic and therapeutic tools, has led to an even greater understanding of their biological significance.

Environmental Pathways

A review of the literature indicates that little information on ^{131}I in the environment existed until the mid-1950s. Nevertheless, in the late 1940s there was concern about the hazard to animals grazing on land that was contaminated with radioactivity from airborne wastes from the production of nuclear materials. Out of this concern, experimental plans to evaluate the effects of ^{131}I in sheep were made in 1948 (Tornberg, 1964). In addition, by 1950

isotopes of iodine were recognized as contaminants of the environment following detonation of atomic weapons (Glasstone et al., 1950).

The earliest report in the open literature on ^{131}I in environmental samples appeared in 1951 when chemical separations were made on radioactivity in snow in Michigan (Meinke, 1951). In 1953, an assay of 10 sheep thyroids in Utah showed the presence of ^{131}I 2-3 weeks after an atomic detonation in Nevada (Wolff, 1957). In 1954, the radionuclide was shown to be in thyroid glands of cattle and sheep slaughtered in Memphis, TN, San Francisco, CA, and Boston, MA, but originating in other areas of the United States, including Kentucky and Florida (Van Middlesworth, 1954a). After his initial report, Van Middlesworth (1956) described the global nature of the distribution of fallout ^{131}I in cattle and sheep thyroids. Soon, Comar et al. (1957) demonstrated a correlation between increased concentrations of ^{131}I in thyroid glands in human and bovine thyroids with known atomic weapons testing. These authors also showed ingestion of ^{131}I to be of greater significance than inhalation for cows, and discussed the role of milk ingestion in the ^{131}I contamination of people.

At about the same time, Dunning (1956) published methods for the calculation of dose from inhaled ^{131}I and other, shorter-lived iodine isotopes for people and ingested ^{131}I for sheep; sample calculations were included that related to radioiodine exposures that had resulted from weapons tests in Nevada. The 1957 release of radioactivity from a reactor at Windscale in northwest England also resulted in opportunities for study of man-made radioactivity in the environment, particularly ^{131}I (Stewart and Crooks, 1958; Chamberlain and Dunster, 1958; Eisenbud, 1973).

Some 12 to 15 years after the time of peak fallout from the Nevada Test Site, a large number of children were examined for thyroid gland abnormalities

(Rallison et al., 1974). Two populations were examined, the first being children in Utah and Nevada who lived in areas exposed to fallout from testing in the 1950s, and the second, other children from the same states and from Arizona, who were considered unexposed. Tamplin and Fisher, whose 1966 report is cited by Rallison et al. (1974), retrospectively calculated average doses to all children in Utah between 1952 and 1955 to have been 46 rads (maximum dose = 120 rads). Later Mays, cited by the BEIR III report (NAS, 1980), estimated the average dose for exposed children to have been 120 rads, ranging from 30 to 240 rads. There was, however, no significant increase in thyroid neoplasia in exposed children when compared to the unexposed children. Benign thyroid neoplasms were found in 6 of 1,378 exposed subjects and in 10 of 3,453 unexposed controls. No malignancies were found in the exposed group while 2 were found in those who were not exposed (Rallison et al., 1974).

Iodine-131 was found to be present in urine samples of inhabitants of the Marshall Islands exposed to fallout in March, 1954 (Conard et al., 1975). At about the same time, in 1955, Van Middlesworth, using a scintillation detector for external monitoring of the thyroid, found detectable levels of ^{131}I in two people at the Nevada Test Site (Van Middlesworth, 1956). He also reported the presence of ^{131}I in human thyroids from autopsies. Soon afterwards, Comar et al. (1957) presented more human data on ^{131}I in thyroids from autopsies. Another major body of data on ^{131}I burdens in human thyroid glands resulted from measurements on thyroids made available at autopsy as well as from in vivo monitoring (Eisenbud et al., 1962). These later data were obtained in 1961, after the resumption of atmospheric weapons testing by the U.S.S.R.

In the mid-1950s, results of studies on the metabolism of radioiodine in lactation were being reported. The appearance in milk of ^{131}I after its

administration to a nursing woman (Miller and Weetch, 1955), to goats (Wright et al., 1955), and to cows (Comar and Wasserman, 1956; Lengemann and Comar, 1956) was shown. In the last case, the radioiodine work was part of a study designed to provide information about the secretion of fission products into milk. These studies in people and large animals, however, were not published until some time after the transfer of ^{131}I through milk was used as a method to irradiate nursing mice (Rugh, 1951).

After these early reports on the radiobiology of radioiodine, studies on a national and international scale continued. The primary pathway of ^{131}I to people was recognized as being atmosphere→vegetation→cow→milk→people, and predictive models for this and other pathways have been developed (Soldat, 1963; Ng and Thompson, 1966; US NRC, 1977). The prominence of the thyroids of children in the ^{131}I-milk pathway was recognized. A major symposium on radioiodine was held in 1963 (Bustad, 1964), in which were presented many papers on these and other topics.

Studies on the environmental aspects of radioiodine have continued to the present, not so much because of continued concern over short-term fallout from nuclear weapsons, but more so because of the potential for radioiodine releases from nuclear reactors. Investigations into the chemical nature of the radioiodine have been made to identify radioiodine species in nuclear reactors (Pelletier et al., 1978a, 1978b), and evaluations of other iodine isotopes, ^{129}I for example (Soldat, 1976), have been made.

Metabolic Pathways

The physiological role of iodine, that is, its concentration by the thyroid gland and its subsequent incorporation into hormones that are stored within the

gland or released to the body where they influence growth, development, and metabolism, has been understood for some time (Salter, 1940). Hence, when radioiodine became available in the late 1930s (Livingood and Seaborg, 1938), it found prompt utility among thyroidologists and physicians who used the iodine isotope to trace pathways of the element in the body first in rabbits (Hertz et al., 1938) and then in rats (Perlman et al., 1941). Much of the early use was related to diagnostic evaluation of patients with thyroid disease (Hamilton and Soley, 1940; Hertz et al., 1942; Hertz and Roberts, 1942a; Hamilton et al., 1943; Quimby and McCune, 1947; Soley and Miller, 1948; Werner et al., 1948; and Skanse, 1949).

The concentration of radioiodine by the thyroid in developing young was also studied. Thyroid glands were shown to take up ^{131}I in utero in the rat (Gorbman and Evans, 1941), the mouse (Speert et al., 1951), and the hamster (Hansborough and Seay, 1951), and prior to hatching in the chick (Hansborough and Kahn, 1951). The human fetal thyroid also was shown to concentrate radioiodine early in its development (Chapman et al., 1948a). Not only was the transfer of radioiodine across the placenta recognized, but so, too, was its movement across the mammary gland, as evidenced in studies on lactating and suckling mice (Rugh, 1951).

After these early reports, considerable information continued to be produced on the metabolism of ^{131}I, primarily because of the use of the radionuclide in medicine and in physiological and endocrinological studies. The widespread use of the radioiodine uptake test in diagnostic medicine resulted in increased understanding of how ^{131}I was handled by the thyroid and the body.

Thyroid uptakes of human neonates (2-3 days of age) were first done in the mid-1950s (Van Middlesworth, 1954b). Newborn infants were found to be hyper-thyroid-like, with regard to their ^{131}I uptakes, when compared to adults.

Radiobiological Effects

In the 1940s, there was already much information about the effects of high doses of radioiodine. Radioiodine was used therapeutically in the treatment of Graves' disease to reduce the amount of thyroid hormone produced by the hyperactive thyroid (Hertz and Roberts, 1942b, 1946; Chapman and Evans, 1946; Soly and Miller, 1948; Moe et al., 1950; Chapman et al., 1948b) and in the treatment of thyroid carcinoma (Seidlin et al., 1946; Keston et al., 1942; Frantz et al., 1944; Seidlin et al., 1949; Rawson et al., 1949; Trunnel et al., 1949; Dobyns and Maloof, 1951). Radioiodine was also used in the treatment of angina pectoris and congestive heart failure in patients who had normal thyroid function (Blumgart et al., 1948; Freedberg et al., 1950); the resultant hypothyroidism decreased cardiac function.

With the exception of the patients mentioned above who were treated for heart disease, most exposures of normal thyroid tissue to radioiodine were made in experimental animals. High doses were required to interfere with normal thyroid functions; therefore, the thyroid was considered to be fairly radioresistant (Warren, 1943). Exposures to sufficiently high doses of radioiodine impair the hormogenic capability of the thyroid, and can result in effects that are similar to those seen after thyroidectomy or as a result of thyroid disease involving loss of thyroid function. Hypothyroid individuals often manifest a number of conditions, including dry, cold, and coarse skin, coarse hair, a decrease in sweating, weakness, lethargy, constipation, weight gain, edema, and, in the very young, retarded growth. The effects of damaging doses of radioiodine were studied in a number of animal species, including chickens (Stanse, 1948; Winchester, 1949), rabbits and dogs (Hamilton, 1942; Hamilton and Lawrence, 1942), mice (Gorbman, 1947, 1950; Speert et al., 1951), and rats

(Findlay and LeBlond, 1948; Goldberg et al., 1950). These studies involved the administration of a single large dose of radioiodine.

The effects of chronic exposure to radioiodine in sheep were reported by Bustad et al. (1957a) and Marks et al. (1957). Exposures ranged from 0.15 to 1800 μCi ^{131}I per day for periods of a few months to 4 years. Corresponding total doses to the thyroids ranged from 400-800 rads to over 100,000 rads, at dose rates of 3.4 rads/week to 30,000 rads/week. At the lowest level (0.15 μCi/day) thyroids showed no damage, while those at the highest levels were ablated. Exposures at intermediate levels resulted in slight, moderate, or severe thyroidal effects, depending on the dosage, and the time of exposure. Although impairment of thyroid function was the effect of interest in this study, some thyroid adenomas and a fibrosarcoma were also reported (Bustad et al., 1957b; Marks and Bustad, 1963). Similar effects may be expected in euthyroid people after comparable doses. Exposures required for ablation of the human thyroid were found to be 30,000-40,000 rads (Goolden and Davey, 1963).

Thyroid Neoplasia

Although ^{131}I was being used in the treatment of thyroid cancer in the 1940s, there was apparently no work being done on the role of radioiodine in the production of thyroid cancer at that time. This is not to say that the possibility of the carcinogenic nature of radioiodine was being ignored, however. A 1946 editorial in the Journal of the American Medical Association (Anonymous, 1946) stated that

> The late development of cancer as a result of irradiation [by radioiodine], although perhaps unlikely, is certainly within the realm of possibility.

Nickson (1948), in discussing needs for protection for those working with radioiodine, pointed out the need for understanding the potential for cancer and other thyroidal effects that radioiodine possessed. Later, Trunnell (1949) warned

> The possibility of the development of neoplasms fifteen or twenty years after radioactive iodine therapy should preclude its use in all but elderly or otherwise bad risk patients.

Werner et al. (1949) also brought out the concern for subsequent thyroid cancer:

> It is feared by some that later malignancy may be induced in the thyroid as a result of the effects of a radioactive agent .... This ... radiation ... makes it likely that malignant degeneration in the gland may appear fifteen to twenty years hence.

When Goldberg and Chaikoff (1951) reported the production of thyroid tumors in rats given ^{131}I, they also emphasized the need for caution in using radioiodine in medicine.

In 1950, Duffy and Fitzgerald (1950) reported that several young patients with thyroid cancer had received prior irradiation. Later, Simpson et al. (1955) and Clark (1955) reported on the association between relatively low x-ray exposures and thyroid cancer in children. Subsequent studies, too numerous to reference in this report, but well represented by the long-term follow-ups of Winship and Rosvoll (1970), Hempelmann et al. (1975), and Modan et al. (1974), indicated that exposure of the thyroid gland to x-irradiation during infancy and

childhood increased the incidence of thyroid adenomas and cancer. Follow-up studies on hyperthyroid patients treated with large doses of ^{131}I also indicated that thyroid adenomas and carcinomas were produced (Dobyns et al., 1974).

The carcinogenic potential of ^{131}I was also noted in animal experiments. Goldberg and Chaikoff (1951) gave 400 μCi ^{131}I to 10 rats and found 2 thyroid tumors.

Doniach (1963) summarized the results of several studies done in the mid 1950s and early 1960s, in which the thyroid carcinogenesis of ^{131}I was evaluated and compared with that produced by x-irradiation. In that review, ^{131}I was considered to be 1/10 as effective as x-ray in the production of cancer, i.e. 10,000 rads from ^{131}I would produce in rats the same level of effects as 1000 rads from x-ray.

Differences in Radiobiologic Effectiveness. Observations of other thyroidal effects from diverse animal studies support the existence of differences in effectiveness of the two radiation exposures. McClellan et al. (1963), for example, compared the histopathologic changes in irradiated thyroids of sheep and estimated ^{131}I to be about 1/20 as effective as x-rays for the production of histologic effects. In mice, where the inhibition of goitrogenic stimulation was used as an index of radiation effect, ^{131}I was 1/4 to 1/2 as effective as x-rays (Walinder and Sjoden, 1971). Data from rats, using the same model as a test for effects, suggest ^{131}I to be about 1/8 as effective as x-irradiation (Grieg et al., 1970). Another study in rats, using thyroid tumorigenesis as the end-point, showed ^{131}I to be about 1/2 to 9/10 as effective as x-rays in the production of adenomas, but of equal effectiveness for the production of carcinomas (Lee et al., 1982). Unfortunately, animals in that study were killed ?

years after irradiation when 62 percent of them were still alive. Had the animals been allowed to live longer, the production of tumors may have changed, and the relative effectiveness of the two radiations may have been shown to be different.

Differences in effectiveness in the production of thyroid gland effects by various iodine isotopes have also been observed. In studies of mice whose thyroids were irradiated with ^{131}I, ^{132}I, or x-ray (Walinder et al., 1972), X-irradiation and ^{132}I (physical half-life = 2.2 hours) resulted in similar effects that were grater than those from ^{131}I. In rats, using the inhibition of goitrogenesis to compare the effectiveness of ^{131}I and ^{132}I, ^{131}I was shown to be only 1/9 as effective as ^{132}I (Book et al., 1980). Klassovskii et al. (1971), who compared the thyroidal effects of ^{131}I with mixtures of ^{131}I, ^{132}I, and ^{133}I (physical half-life = 21 hours) in rats, concluded that the histologic effects of ^{131}I were only 1/10 to 1/25 times as pronounced as those from the radioiodine mixture. Studies comparing ^{125}I (physical half life = 60 days) and ^{131}I indicate that up to 20 times more rads are required from ^{125}I than from ^{131}I for the same suppression of tracer uptake or inhibition of goitrogenesis (Gross et al., 1967; Grieg et al., 1970; Vickery and Williams, 1971).

Hence, it can be concluded that these radiations indeed have differences in their biologic effectiveness. The differences, apparent between x-irradiation and ^{131}I, and among radioiodines with different half-lives and emissions, can be considered to be related to the dose rate and the dose distribution of the irradiations. X-irradiation is given at high dose rates and results in uniform irradiation of the thyroid. Iodine-132, a short-lived radioiodine, irradiates at high dose rates, and since its emissions are fairly energetic, there is fairly uniform irradiation. Iodine-131, with its longer half-life irradiates at a

lower dose rate and in a spatially less uniform manner, though probably not to too great an extent in small rodent thyroids. Iodine-125, has an even lower dose rate, and, because of its emissions of lower energy, irradiates non-uniformly with higher doses to hormonogenic parts of thyroid follicular cells and lower doses to their nuclei (Grieg et al., 1970).

Following exposure to fallout from a thermonuclear test in the Pacific in 1954, the exposed population of the Marshall Islands exhibited a proportion of thyroid disorders, including neoplasia, much higher than would have been expected. The Marshallese, however, in addition to ^{131}I had also received total body gamma exposure and thyroid gland exposure to short-lived radioiodines ^{133}I-^{135}I (Conard et al., 1980). The short-lived radioiodines have not been studied for carcinogenesis, but other effects have indicated that their effectiveness should be greater than that of ^{131}I, as discussed above, that is, they act more like x-irradiation.

Iodine-129 (T_p = 16 million years) is another fission produced radioiodine. It appears to not have been considered an environmental or health risk until later in the nuclear age, when its significance as a problem of spent nuclear fuel processing and storage or disposal was recognized. Its importance in the environment as a contaminant of food items was reviewed by Soldat (1976) and Book et al. (1977). The toxicity of ^{129}I is limited, however, because of its very long half-life (and, therefore, low radioactivity per unit mass) and because the thyroid can contain only a finite quantity of iodine (Book, 1977, 1981).

Estimates of Thyroid Risk. Several attempts have been made to predict the risk of thyroid neoplasia from irradiation. Beach and Dolphin (1962), using data from several studies, described the thyroid response to dose as linear, corresponding to a rate of 1.7% thyroid malignancies per 500 rads to the thyroid, or 34 malignancies/10^6 persons/rad. Since the time at risk was taken to be 20 years, their annual risk for thyroid malignancies can be expressed as about 1.7/10^6 persons/rad/year. Hempelmann (1968), with data from other studies, predicted a risk for malignancies of 0 to 5.5 cases/10^6 persons/rad/year, and for thyroid nodules of 38-53 cases/10^6 persons/rad/year. Dolphin (1968), from other data, estimated the risk for thyroid cancer to be 100/10^6 persons/rad, or, considering the time at risk to be 20 years, 5 cases/10^6 persons/rad/year. The National Academy of Sciences BEIR Report (NAS, 1972) estimated the risk of thyroid cancer to be of the order of 1.6 to 9.3 cases/10^6 persons/rad/year. Later, the National Academy of Sciences (NAS, 1980) estimated the risk of thyroid cancer to be approximately 4 cases of thyroid carcinoma and 12 cases of thyroid adenoma/10^6/rad/year. In the Reactor Safety Study (US NRC, 1975), absolute risks for thyroid malignancies and nodules, based upon a large number of studies, were estimated to be 4.3 and 8.1 cases/10^6 persons/rem/year, respectively, or a total of 12.4 cases of thyroid neoplasia/10^6 persons/rem/year. For comparison, these numbers can be compared to an average annual incidence of thyroid cancer for both sexes, all ages and races combined, of 3.6 per 100,000 for locations represented in national surveys (NCI, 1975).

Since these estimates for thyroid neoplasia are primarily derived from external irradiation, estimates for ^{131}I risks should be lower to account for the differences in effectiveness of x-ray and ^{131}I, as discussed above.

The likelihood of hypothyroidism is low at low doses. Maxon et al. (1977) reviewed the medical literature and found that hypothyroidism was reported

following doses above 1000 rads for external irradiation and 20 rads following ^{131}I exposure. From the review of Maxon et al., the BEIR Committee concluded that the threshold for the induction of hypothyroidism was 2000 rads in external exposure and 5000 rads for ^{131}I (NAS, 1980).

Means of Protection

The thyroid gland's affinity for iodine not only makes it the target organ for radioiodine but also provides a means by which the thyroid may be protected from radioiodine. The administration of stable iodine suppresses the uptake of radioiodine by the thyroid by diluting the radioactive isotope and by invoking homeostatic mechanisms within the gland that reduce the amount of iodide taken up by the gland.

This so-called "blocking" ability of the thyroid gland was demonstrated soon after ^{131}I became available (Perlman et al., 1941), when rats were given ^{131}I with either 0.5 mg iodine as potassium iodide, 0.03 mg iodine, or no iodine, that is, carrier-free. Subsequent peak uptakes by thyroid glands were 2 percent and 7 percent for rats that received 0.5 or 0.03 mg iodine, respectively. Rats receiving only the tracer had peak uptakes of 65 percent.

The blocking ability of the thyroid has been the subject of many papers, including those by Adams and Bonnell (1962) and Blum and Eisenbud (1967). The National Council on Radiation Protection and Measurements (NCRP, 1977b) recommended the adequate blocking dose in cases of radioiodine exposures to be a daily dose of 130 milligrams of potassium iodide (and half that amount to infants under one year of age). Administration of the blocking agent was recommended to occur at thyroid doses of 10-30 rads or more. Data from a later study (Sternthal et al., 1980) suggested that thyroidal uptake can be suppressed

markedly by a single dose of 30 mg iodide and that suppression could be maintained with daily doses of at least 15 mg. Because there are a number of adverse conditions including thyroid abnormalities that may develop after exposure to large quantities of stable iodine, as discussed by the NCRP (1977) and Sternthal et al. (1980), care must be taken in its administration.

VI. RADIOSTRONTIUM

Summary

Strontium-90 is the important strontium isotope in radioactive fallout. It has a 29-year physical half-life and it and its short-lived yttrium-90 daughter emit beta particles. Strontium behaves like calcium; hence, bone is the principal site of ^{90}Sr concentration. Unlike the other fission products discussed herein, strontium has a long residence time and slow turnover rate once it is incorporated into bone mineral, characteristics that enhance its radiobiologic significance.

The metabolism of radiostrontium, its similarity to calcium, its concentration in bone and transfer to milk were all documented in the early 1940s. The effects were also implied in those papers that suggested its use in the treatment of bone cancers. The carcinogenic potential of radiostrontium was documented by the late 1940s, after having been determined in animal studies. Isotopes of strontium were known to be components of fallout by 1950, and reports of fallout ^{90}Sr appeared in the open literature in the early 1950s. Long-term studies on the effects of low levels of ^{90}Sr began (and continue) at several laboratories to investigate and better understand the late effects of this radionuclide on bone and bone marrow.

Environmental Pathways

Isotopes of strontium were identified by 1950 to be potential contributors to environmental radioactive contamination from the detonation of atomic weapons (Glasstone et al., 1950), and subsequently ^{90}Sr was documented in the open literature as a component of fallout (Eisenbud and Harley, 1953, 1956). Soon, the global nature of the fallout was discussed with regard to

world-wide meteorology (Machta et al., 1956). In addition, measurements of ^{90}Sr concentrations in foods and human tissues were made, and the potential hazard to people was considered (Libby, 1956; Eisenbud, 1957; Kulp et al., 1957; Langham, 1958).

Work in the early 1940s (Erf and Pecher, 1940) had reported the secretion of strontium into cows' milk. Some other aspects of environmental behavior of radiostrontium, namely, the uptake of the radionuclide by plant roots, had also been investigated in the 1940s (Jacobsen and Overstreet, 1947).

Studies on the transfer of ^{90}Sr and other fission products into milk were begun in the mid-1950s (Comar and Wasserman, 1956; Lengemann and Comar, 1956). Ingestion was considered to be the most significant route of human assimilation of ^{90}Sr (Langham, 1960), and dairy products were considered the primary source of ^{90}Sr in the diet (Russell, 1960). The transfer of ^{90}Sr from the atmosphere to diet to man was reviewed by a number of authors (e.g. Wasserman et al., 1965; Bennett, 1972).

Metabolic Pathways

Even though some investigations into the metabolism of strontium were done earlier (for instance, McCance and Widdowson, 1939), it was not until the availability of radioactive strontium (^{89}Sr) that its metabolism became well understood. Much of the experimental use of radiostrontium was as a substitute for calcium.

Early studies demonstrated the similarity of strontium and calcium in their metabolic pathways. Pecher (1941a,1941b) described the distribution and tissue uptake of injected ^{89}Sr and ^{45}Ca, showing skeletal uptake by the two radionuclides. After 24 hours, 58 percent of the administered ^{45}Ca was

in the skeleton, as was 33 percent of the ^{89}Sr. Pecher also noted the high yield and ease of counting of ^{89}Sr, compared to ^{45}Ca. Pecher and Pecher (1941) also demonstrated in mice the ability of radiostrontium to cross the placenta and the mammary gland in mice and concentrate in young bones. Erf and Pecher (1940), as mentioned above, collected milk from two cows injected with ^{89}Sr, and recovered 11 and 8% during the 4.5 days after injection.

Other studies included investigations into the biliary secretion of calcium and strontium (Greenberg and Troescher, 1942), the influence of growth hormone on strontium deposition (Marx and Reinhardt, 1942), and the effect of parathyroid extract on strontium metabolism (Tweedy, 1945).

Treadwell et al. (1942) performed metabolic studies of neoplasms of bone using ^{89}Sr, which was found to be taken up by growing bone and by osteogenic tumor tissues. Possible therapeutic use of radioactive strontium was mentioned (Treadwell et al., 1942) as a means of increasing radiation dose to affected areas, that is, as an adjunct to ongoing therapeutic methodologies.

The assimilation of a number of fission products and heavy elements, and their distribution and retention were studied in rats by Hamilton (1947). For ^{89}Sr and ^{90}Sr, he found that 5 to 60% of an oral dose was absorbed, that 65% accumulated in bone, and that they were exponentially eliminated with a half-time in the body of more than 200 days.

Copp et al. (1947) also investigated the metabolism of radioactive strontium, along with yttrium, cerium, and plutonium. Of these, only strontium was absorbed appreciably from the gastrointestinal tract. Absorption of strontium, furthermore, was 25 times as great in growing rats fed a low calcium diet as in adults with ample calcium in the diet. A deficiency in phosphorus caused a 3-fold decrease in strontium retention because of inhibition of bone

formation. Neither growth nor decreased dietary calcium or phosphorus had an effect on the metabolism of yttrium, cerium, and plutonium. Strontium was eliminated with a half time of 3-4 months, much more rapidly than the elimination of yttrium, cerium and plutonium which had half-times of 1-3 years. Work in rabbits also indicated that uptake of injected ^{89}Sr and ^{90}Sr by the skeleton was greater in young animals than in old ones, and was inversely related to calcium levels in the diet (Kidman et al., 1950).

The transfer of radiostrontium from the lung into the bloodstream was also investigated in rats (Abrams et al., 1946). Immediately after 30-min exposure to ^{89}Sr as $SrCl_2$, more than 50% of strontium that was deposited in the lungs had been removed from the lungs, and 25% was in the skeleton. The lung burden was reduced by half over the next 30 minutes, and after 8 hours, only 2.5% of the initial burden was in the lungs. Over 85% was skeletally deposited. Direct skeletal uptake of inhaled weapons fallout radiostrontium in test animals was demonstrated in 1952 and was found to be preferentially concentrated in growing bone (Smith et al., 1952).

Although the behavior of strontium was qualitatively similar to that of calcium, it was shown in experimental animals that the ratio of strontium to calcium in tissues was different from the ratio of the two elements in the diet. To better quantify and predict the differentiation in tissues or excreta, Comar et al. (1956) proposed the term "Strontium-Calcium Observed Ratio" (OR), where

$$OR_{\text{sample-precursor}} = \frac{\text{Sr/Ca of sample}}{\text{Sr/Ca of precursor}}$$

The OR denoted the individual tissues, excretions, or physiological processes involved in the preferential utilization of calcium over strontium, and when less than 1, expresses such a preference. For example, the $OR_{bone-diet}$ for rats on a commercial diet was 0.27. The OR did not imply action by the tissue causing the discrimination. Instead, to denote the physiological process of discrimination in a given tissue, the authors utilized the term "Strontium-Calcium Discrimination Factor" (DF). The product of the DFs equalled the OR.

That strontium was preferentially discriminated against by the placenta was found in beagle dogs (AEC Project No. 6, 1958). The $OR_{fetal\ bone-diet}$ was 0.31, based upon data from two pups, a value somewhat lower than the $OR_{adult\ bone-diet}$ of 0.4-0.5 of mature beagles (Della Rosa et al., 1972).

The metabolic studies of radiostrontium intensified when its potential toxicity as a component of radioactive fallout was recognized and studies on its effects began. The radiobiological significance of strontium metabolism was discussed in reviews (Thompson, 1960; Loutit, 1962; ICRP, 1972) and symposia (Lenihan et al., 1967; Goldman and Bustad, 1972).

Radiobiological Effects

The tumorigenic ability of radiostrontium was recognized in the 1940s. Strontium-89 was described as a "producer par excellence of bone tumors" by Brues et al. (1947), who reported that tumor development in over 3000 mice was approximately proportional to dose and to time, with a latent period that itself was related inversely to dose. Such a scheme was shown to fit data that were available for human radium dial painters. Besides bone tumors, aplastic anemia and myeloid metaplasia were common at necropsy (Brues et al., 1949).

The bone tumors that were produced were single and multiple, and, particularly in rats and rabbits, there were many instances of metastases. Doses ranging from 0.05 μCi/gm to 5.0 μCi/gm resulted in "considerable numbers" of tumors. Most of them (61%) appeared in long bones (Lisco et al., 1947).

Other work done at this time centered on the effects of ^{89}Sr on pregnancy and the transfer of the radionuclide from mother to young via the placenta and mammary gland (Finkel, 1947). Animals exposed to ^{89}Sr in utero or prior to weaning showed retarded growth, malformed long bones, anemia and bone cancers.

In a symposium on radiostrontium (Goldman and Bustad, 1972) effects of injected, ingested, or inhaled ^{90}Sr in beagle dogs were reported. Studies on ^{90}Sr-treated beagles began in 1947 at Argonne National Laboratory, and were subsequently expanded into several large programs at the the University of Utah, at the University of California at Davis, and at the Lovelace Foundation in Albuquerque. In these programs, the beagle dog remained the experimental subject of choice (Book, 1980). The most significant effects in animals given adequate exposures to ^{90}Sr have been tumors of bone, mostly osteosarcoma, and myeloproliferative disorders, which includes both neoplastic hematopoietic disease and preleukemic conditions.

All species that have received sufficient ^{90}Sr have developed osteosarcomas, including dogs (Pool et al., 1972, Dougherty et al., 1972; Finkel et al., 1972), monkeys (Casarett et al., 1962), pigs (Clarke et al., 1972), rabbits (Vaughan and Williamson, 1969), mice (Nilsson, 1972), and rats (Moskalev et al., 1969). Myeloproliferative disorders have been noted in dogs (Dungworth et al., 1970), pigs (Clarke et al., 1972), and rats (Moskalev et al., 1969). Mice developed lymphatic leukemia but not granulocytic leukemia (Nilsson, 1972).

Tumors arising adjacent to bone have been noted in several species treated with ^{90}Sr. In mice, squamous cell carcinomas were reported to originate in the hard palate and sebaceous gland of the external auditory meatus (Nilsson, 1972). Squamous cell carcinomas were also reported in the maxillary sinus in rats (Moskalev et al., 1972) and in the lining of internal and external ear in rabbits (Vaughan and Williamson, 1969). Squamous cell carcinomas of the gingiva have been found to be important later-occurring effects in beagles exposed to ^{90}Sr (by ingestion) from prior to birth until 18 months of age and observed for life (Parks et al., 1980). For the dogs, the gingival tumors probably reflect the results of continual irradiation from ^{90}Sr in teeth that is maintained at a high level, since teeth show a slower turnover of ^{90}Sr than does the rest of the skeleton (Della Rosa et al., 1964).

Fortunately, too few humans have been exposed to radiostrontium at high enough levels for the risk of neoplasia to be estimated. Based on radium dial painter risks, however, Mays and Lloyd (1972) estimated risks from ^{90}Sr. Their best estimates for the 50 yr risk to an individual for bone sarcoma from one rad were $(1 \pm 1) \times 10^{-6}$, using a linear model, and $(4 \pm 4) \times 10^{-10}$, using a dose-squared model. The current ICRP (1977) estimate of risk for ^{90}Sr-like radiation is 5×10^{-6} per rem. These numbers can be compared with a natural incidence of about 5×10^{-4}.

VII. RADIOCESIUM

Summary

Cesium-137 is the significant cesium isotope in radioactive fallout. It is a beta and gamma emitter with a 30-year physical half-life. Since it is similar to potassium in its metabolism, ^{137}Cs is distributed throughout the soft tissues of the body. Its relatively uniform distribution throughout soft tissues brings about a declining whole-body exposure that is relatively short-lived, since ^{137}Cs is not retained in the body for long periods of time. It easily moves through food chains and has been the subject of many radioecological investigations. Cesium-137 was not appreciated as a significant fallout dose component until it was found to be present in people in the mid-1950s.

Environmental Pathways

The first report of cesium-137 in people came after its presence was noted in measurements of whole-body radioactivity by gamma spectrometry (Miller and Marinelli, 1956). The persistence of ^{137}Cs in the human body despite its relatively short biological half-life was explained by continued exposure via the diet; ^{137}Cs was present in meat and milk powders. The presence of ^{137}Cs in people and in various foods and its relation to ^{40}K was reported by Anderson et al. (1957) who calculated that the significant contributors to dietary ^{137}Cs were dairy products. Dairy products and meat were considered to be the primary sources of fallout ^{137}Cs, while inhalation and ingestion of drinking water were said to contribute minimally to the ^{137}Cs body burden (Langham and Anderson, 1959).

The extent to which body burdens of ^{137}Cs reflect dietary input was best exemplified in two human populations who were at the end of the

environmental pathways for radiocesium: atmosphere→lichen→reindeer Laplander (Linden and Gustaffson, 1967) and atmosphere→lichen→caribou Eskimo (Hanson, 1967). In these populations, seasonal influences on dietary practices resulted in large fluctuations in ^{137}Cs burdens. Many other environmental aspects of ^{137}Cs were summarized by Davis (1963) and were addressed by others in a symposium on radiation ecology (Aberg and Hungate, 1967).

Metabolic pathways

In the 1940s, fission-produced radiocesium was administered to rats (Hamilton, 1947). Absorption from the gut was 100 percent; its distribution was throughout soft tissues, with 45 percent deposited in muscle, and it was retained in the rat with a half-time of 15 days. Inhaled radiocesium was readily absorbed from the lungs.

The metabolism of ^{137}Cs was studied later in rats and several farm animals by Hood and Comar (1953), who found a similar wide and fairly uniform distribution throughout the body. They also found that 0.2 to 3.5% of administered ^{137}Cs was transferred from pregnant rats to fetuses in late gestation (at days 17 to 21, respectively) with a fairly constant tissue concentration of 0.06% dose per gm regardless of fetal age. A dairy cow was shown to secrete 13% of an injected dose of ^{137}Cs into milk over a 30-day period. From an oral dose of ^{137}Cs, 10% was secreted into milk in 30 days.

The entrance of ^{137}Cs into animal tissues is primarily through the ingestion of contaminated foods. Absorption of cesium from the gut is close to 100% in monogastric animals (Richmond, 1958), but is generally only 50% to 80% in ruminants (McClellan et al., 1961; Wasserman et al., 1961). The reduced absorption, along with the high fecal-to-urinary ratio of excreted

^{137}Cs characteristically seen in ruminants (Hood and Comar, 1953), probably relates to the kind and greater bulk of their diet (Davis, 1963).

Cesium behaves in a manner that is physiologically somewhat analogous to potassium. Hence, cesium is distributed throughout soft tissues, and can expose those tissues with beta and gamma irradiations. Unlike the bone-seeking radiostrontium, however, retention is short (that is, elimination is rapid), with tissue exposure (and dose) declining with a half-period of about 2.5 to 5 months in people.

Because ^{137}Cs intake results in uniform exposure of all tissues, its significance as a hazard to the most sensitive tissue must be balanced by its distribution and dilution into all tissues. Cesium-137, like tritium, which also is uniformly distributed in the body, possesses the potential for genetic injury as well as carcinogenesis in sensitive tissues.

Radiobiologic Effects

Beginning in the 1960s, the long-term effects of ^{137}Cs were studied in beagles at Argonne National Laboratory, as reviewed by the NCRP (1977a). Sixty-five beagles in a lifetime study were given single intravenous injections of ^{137}Cs with dosages ranging from 1.65 to 4.31 mCi ^{137}Cs/kg, among their age groups. Destruction of bone marrow resulted in 25 deaths within 2 months after injection. Cancers were the main cause of death of the 40 dogs that survived acute effects (up to 12 years post-injection), and accumulated from 700 to 1600 rads. Cancers accounted for 20 deaths, and cancers were also found in tissues of other dogs dying from other causes. Neurofibrosarcoma, a tumor of the nerve sheath that is rare in dogs, was the most frequently occurring cancer, and was found in 8 of the 40 dogs.

Also mentioned in the NCRP Report (NCRP, 1977a) were 54 13- to 14-month-old beagles injected with ^{137}Cs and studied at the Inhalation Toxicology Research Institute. A later summary (ITRI, 1981) reported that 11 acute deaths were observed, and 20 of 32 dogs that survived acute effects died of cancers. Eleven were still alive. Dosages ranged from 0.9 to 4.0 mCi ^{137}Cs/kg and total doses ranged from 600 to 2200 rads.

VIII. PLUTONIUM

Summary

Plutonium-239 is a man-made alpha emitter with a 25,000 yr half life. For plutonium that reaches the blood, its target organs are bone and liver. Inhaled plutonium may affect the lung as well. Plutonium is an efficient carcinogen.

The metabolism of plutonium and its production of bone tumors were investigated in the 1940s. More elaborate and sophisticated studies on the biological significance were begun in the 1950s and 1960s and continue. Its effects on bone, liver, and lung have been demonstrated in a number of laboratory animal species.

Environmental Pathways

Most of the information on plutonium in the environment that evolved during the 1940s was related to monitoring environmental materials near nuclear installations (Stannard, 1973a). These investigations were centered primarily on aquatic environments and biota.

Alpha activity was found in animals trapped in the fallout zone of the 1945 Trinity shot several years after that detonation. The activity was assumed to be plutonium-239 (Olafson and Larson, 1963). By 1950, plutonium released to the environment from atomic weapons testing was recognized as presenting a serious potential for injury if inhaled or ingested, and calculations of hazards from world-wide contamination by plutonium were also made (Glasstone et al., 1950). Dogs and sheep intentionally exposed to the radioactive fallout from weapons tests in 1951 were found to have ^{239}Pu in their lungs (Smith et al., 1952).

In 1957, studies were undertaken on uptake by the body and retention after direct inhalation of plutonium in the radioactive cloud after detonation as well as after inhalation of plutonium resuspended by wind action following its deposition on the ground (Stannard, 1973a). Rats and dogs were exposed during passage of the radioactive cloud, while dogs, sheep and burros were exposed for a long post-event period of up to 160 days at several down-wind locations. The results indicated that dogs exposed to the cloud passage at the time of detonation had higher plutonium burdens than animals exposed to resuspended plutonium for long periods of time, even though the animals exposed to the passing cloud were not exposed to the highest airborne concentrations at ground level.

Because of concern about plutonium in the environment from atomic weapons and, later, the nuclear fuel cycle, considerable information has been published on its radioecology (Olafson and Larson, 1962; Stannard, 1973a; Healy, 1975; IAEA, 1976; Friedman, 1976; Hanson, 1980).

Plutonium has a low solubility in water and biological fluids and tends to be nonmotile in soils and other media. Hence, plutonium is much less likely to move through food chains to man than fission products discussed heretofore. Nonetheless, plutonium in the environment continues to be a timely topic, in view of its role in the end of the nuclear fuel cycle.

Metabolic Pathways

Because plutonium played a major role in atomic weaponry, considerable research on its metabolism and toxicology took place in the 1940s. Studies in rats on the distribution and excretion of plutonium in various chemical states were made following intravenous (Carritt et al., 1947) or intramuscular

injections (Scott et al., 1948), or after oral administration (Hamilton, 1947). From each mode of exposure, roughly two-thirds of the assimilated plutonium deposited in the skeleton, while the liver generally received the next highest concentration of the radionuclide.

Plutonium was found to be so poorly taken up from the gastrointestinal tract that only 0.007 per cent of an orally administered amount was absorbed. Of that which was absorbed, 65 percent was deposited in the skeleton. Removal from the skeleton was very slow (Hamilton, 1947).

Intravenously injected plutonium had its highest immediate concentration in liver and spleen. Later, it was translocated to bone (Brues et al, 1947).

The distribution and elimination of plutonium was also studied after rats were exposed to it by inhalation (Scott et al., 1949). After nose-only exposures of several minutes' duration, most of the radioactivity was in the head and lungs, but after 4 days, the lungs contained most of the residual activity. The lung concentration declined over the course of the 64-day study. After 64 days, 12 percent of the plutonium inhaled as plutonium nitrate was in bone, compared to 0.4 per cent of that inhaled as plutonium dioxide.

The metabolism of plutonium was also studied in 18 human subjects injected with tracer doses of ^{239}Pu in 1945 and 1946. As reviewed by Durbin (1972), bone and liver were shown to be the principal sites of plutonium deposition.

Plutonium metabolism in pregnant rats and mice was also studied (Finkel, 1947). A very small fraction of injected plutonium was found to move across the placenta.

Studies of factors influencing the metabolism and deposition in bone of several radionuclides, isotopes of plutonium, strontium, yttrium and cerium

were done in rats at about the same time (Copp et al., 1947). Unlike strontium, but like yttrium and cerium, plutonium showed behavior that was unaffected by the age of the rats under study or by calcium or phosphorus levels in the diet. This suggested that, while strontium followed the pathways of calcium metabolism, plutonium, yttrium, and cerium did not, and that they were deposited in the skeleton by other mechanisms.

A method of protection from plutonium toxicity was proposed by Copp et al. (1947), who suggested that where contamination had occured, the diet could be altered to dimineralize the skeleton. By then remineralizing the skeleton via dietary change, a protective layer of new bone would be laid down over the plutonium.

Subsequent studies in rats showed the uptake of chronic, orally administered plutonium to be 0.003% (Katz et al., 1955; Weeks et al., 1956). Uptake of plutonium given as a single dosage to pigs was 0.002% of the administered amount (Weeks et al., 1956).

In pigs the metabolism of plutonium after intravenous, intragastric, or intratracheal administration of plutonium(IV) nitrate was also studied. While liver and skeleton were the principal sites of plutonium deposition, the quantity absorbed depended on the mode of administration. Less than 1 percent of the administered Pu was in the skeleton and liver up to 2 years after intragastric administration or intratracheal dosing. After an intravenous dose, 50 to 77 percent was in skeleton and liver; in this case, however, the plutonium nitrate solution was buffered with citrate, which may have contributed to the difference (Bustad et al., 1962).

Stover et al. (1959; 1962; 1968) studied the long-term metabolism of plutonium in dogs whose skeletal and soft tissue retention of injected plutonium

was determined. The metabolism of inhaled plutonium also was studied in beagle dogs (Bair et al., 1962) indicating that not only its chemical form was important but, so too, was the particle size with which it was associated. That ^{239}Pu was not only retained in the lungs but also continued to accumulate in bronchial lymph nodes suggested that these organs may also be important targets for plutonium toxicity.

The metabolism of plutonium was reviewed by Langham (1959). More recent reviews include those by Vaughan et al. (1973) and Bair (1974).

Radiobiological Effects

The effects of plutonium-239 were noted inthe 1940s. Based on animal studies, "plutonism", as it was called, for high exposures was described as being similar to effects of acute whole body radiation. Results of acute exposures were presented by Bloom (1948) and Fink (1950). Plutonism for chronic exposure was seen to manifest itself with progressive liver damage and bone tumors (Brues et al., 1947). The majority of bone tumors produced by plutonium (62%) in mice, rats, and rabbits occurred in the spine (Lisco et al., 1947). Some aspects of the early toxicologic studies were reviewed by Stannard (1973b).

In the 1950s and later, the radiobiological effects of plutonium were studied in a variety of laboratory animal species, including mice, rats, rabbits, pigs, and dogs. Many aspects of plutonium toxicity were presented in various symposia (Thompson, 1962; Mays et al., 1969a; Stover and Jee, 1972; Healy, 1975; Jee, 1976; Wrenn, 1981). Other overviews were also published (Hodge et al., 1973; Bair et al., 1974; NAS, 1976), as were bibliographies (Thompson, 1976; Lisele et al., 1980).

The most significant effects of plutonium exposure are bone cancers, which have been produced in mice (Finkel, 1953, 1956; Finkel and Biskis, 1962) and dogs (Jee et al., 1962; Mays et al., 1969b) that were injected with plutonium. In dogs that inhaled ^{238}Pu (physical half-life = 88 years), bone cancers were also important causes of death, but some dogs also died of lung carcinoma and from pneumonitis and fibrosis (ITRI, 1980). Studies of dogs that inhaled ^{239}Pu, many of whom are still under study, showed radiation pneumonitis and fibrosis as important causes of death, with some incident lung cancers (ITRI, 1980). Many other investigators also reported bone cancers and lung cancers in a number of species exposed to plutonium, as reviewed by Bair (1974).

Other bone changes were noted in dogs (Taylor et al., 1962, 1972) and pigs (Clarke, 1962) injected with plutonium. Liver degeneration was noted in mice (Finkel and Biskis, 1962) and dogs (Taylor et al., 1973). Acute hematological changes were also noted in mice (Finkel and Biskis, 1962), pigs (Bustad et al, 1962), and dogs (Dougherty, 1973). Early lung changes (fibrosis, metaplasia) from inhaled plutonium in dogs were noted (Park et al., 1962).

The role of these and other animal studies in predicting risks to human populations have been discussed (Thompson et al., 1972; Bair, 1974; Thompson, 1975; Bair and Thomas, 1976). The animal data are particularly important since data from human exposures, it is hoped, will remain inadequate for the calculation of risks.

Generally risks for plutonium-induced bone cancer are derived from estimates for the radium dial painters (Mays and Lloyd, 1972; Rosenblatt et al., 1976; Rowland et al., 1978), and modified to account for the difference in the distribution in bone between radium and plutonium, the former being traditionally considered a volume seeker and the latter, a surface seeker (Marshall, 1969).

Recently, Thompson and Wachholz (1980) estimated the number of cancer deaths in the United States due to fallout plutonium. They calculated that as upper limits, a total of 125 deaths would occur, with 64 (51%) lung cancers, 27 (22%) bone cancers, and 34 (27%) liver cancers. They also noted, however, that the possibility of no cancer deaths from fallout plutonium was not precluded.

Plutonium has effective radiologic characteristics, yet it inefficiently moves through environmental and metabolic pathways. Hence, plutonium can be described as having a high toxicity, but a low hazard ranking.

IX. URANIUM

Summary

Naturally occurring, uranium has an exceedingly long half life and emits alpha particles. It is concentrated in kidney and bone. Uranium has been the subject of toxicological study for many years, and its nephrotoxic properties were known a century prior to work on its radiobiological significance. The chemical toxicity to the kidneys of natural uranium overrides any potential for radiobiologic toxicity. Only with high specific activity isotopes of uranium is the skeleton at risk for subsequent radiation-related cancer development.

Environmental Pathways

Uranium (^{238}U, ^{234}U, and ^{235}U) is naturally occurring and is distributed ubiquitously but variably throughout the earth's surface. It is present in water and in foods, so that small quantities are ingested daily. The NCRP (1975), from data of Welford and Baird (1967), reported an average daily intake of 0.9 picocuries of uranium. Approximately equal amounts (about 22 percent) of dietary uranium were derived from each of four food groups: cereals and grains; meat, fish, and eggs; green vegetables and fruits; and root vegetables. About 7 percent was from dairy products, and 2 percent was from drinking water. Inhalation was considered to be a very minor route of assimilation.

The dose rate to bone from natural uranium was calculated to be about 12 mrem/yr (NCRP, 1975). This value amounted to only about one-tenth of the total for skeletal tissues from naturally occurring radioactivity.

Any uranium that is released into the environment such as that which does not undergo fission in a nuclear weapon detonation would be restored to the

naturally occurring inventory of uranium. Its subsequent transfer to man can be expected to be like that of uranium in nature.

Metabolic Pathways and Effects

Uranium has a long history as a subject of toxicologic study. Hodge (1973), in reviewing the history of uranium poisoning from 1824 to 1942, cited over 350 references. Later research was reviewed by Yuile (1973), who discussed experimentation in animals, and by Hursh and Spoor (1973), who summarized data on people. Most of the early studies, and the later ones as well, for that matter, emphasized the nephrotoxic effects of natural uranium.

In general, hazards from uranium were considered to relate more to its chemical toxicity than to its radioactivity. This is because uranium-238, with a physical half life of 4.5×10^9 years, has a very low specific activity of about 0.33 microcuries per gram. However, there was concern that long-term exposures of sufficient duration, particularly enriched uranium, might pose a radiation hazard, such as that which occurred in the luminous dial industry with the radium dial painters (Martland and Humphries, 1929; Martland, 1931; Aub et al., 1952).

Work in the early 1940s (Tannenbaum et al., 1951) showed that tracer doses of uranium-233 as uranyl nitrate injected subcutaneously into mice and dogs were primarily in the skeleton one and two months afterwards, respectively. For mice, 67 percent of the total ^{233}U in the body was in bone, while 14 percent was in the kidney and 1 percent in the liver. For dogs, 90 percent of the total burden was in bone, 3 percent in kidneys, and 3 percent in liver. That bone and kidneys were the principal sites of uranium accumulation was also found by Neuman et al. (1948).

Even though most of the retained burden in mice and rats was in the skeleton, the total amount retained in the body was small (Tannenbaum et al., 1951). Less than 10 percent of the injected quantity of uranium remained in the body 1-2 months after the injection of non-toxic quantities. When the injected quantity of uranium was at a higher, toxic level, as much as 40 percent was retained. The destructive effects of uranium on the kidney (Barnett and Metcalf, 1949) were responsible for the altered pattern of uranium excretion in the latter group.

The toxicity of uranium compounds was studied in a number of animal species during the 1940s and later. Administration of uranium was by ingestion and inhalation as well as by other modes of exposure, and the duration of individual studies ranged from one month to two years (Voegtlin and Hodge, 1949 and 1953).

The significant target of natural uranium toxicity is the kidney. Even though there is long term retention of uranium by bone, administration of sufficient uranium to result in radiation effects would be difficult. This is because dosages of uranium that are even lower than what is required to produce skeletal effects would still be high enough to lead to toxic, fatal effects on the kidney (Bernard, 1958). It is the 4.5×10^{-9} yr half-life and the low specific activity of uranium-238 (about 0.3 microcuries per gram) that limit the amount of radioactivity that can be incorporated in the body. Even when natural uranium is enriched beyond the normal 0.7% ^{235}U (half-life = 7.0×10^{8} yrs), as is the case for uranium based atomic weapons (e.g., ~90+% ^{235}U) and uranium reactor fuel, the low specific activity of ~2 microcuries per gram for ^{235}U would limit the radiation exposure.

Skeletal effects can be expected to occur with high specific activity uranium isotope such as ^{233}U (half-life = 1.6 x 10^5 yrs; specific activity = 10 millicuries per gram) or ^{232}U (half-life = 72 yrs; specific activity = 37.7 curies per gram). Indeed, injection of each of these two uranium isotopes was shown to produce bone cancers in mice (Finkel, 1953). Natural uranium, however, showed no induction of bone tumors.

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