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April 1, 1996

Dr. Martin Steindler
United States Nuclear Regulatory Commission
Advisory Committee on Reactor Safeguards
Advisory Committee on Nuclear Waste
Washington, DC 20555

Dear Dr. Steindler,

Sorry that I had to rush off to catch an early flight, for no doubt the discussion that followed my departure was lively. Sometimes it is just not possible to do everything that you would like to do.

However, be that as it is, per our discussion during the break, enclosed is a preprint of my paper "Pathway to a Paradigm: The Linear Nonthreshold Dose-Response Model in Historical Context" which is scheduled to appear in the May issue of *Health Physics*. The published version will have some minor editorial type differences from the preprint, but essentially they are identical.

Expanding on my final comments at the meeting, let me again point out that the shape of the dose-response curve to ionizing radiation at low levels and for low dose rates is not known and is unlikely to be known with any degree of certainty in the foreseeable future. Thus the possibility of any particular dose-response curve, including hormesis or linear nonthreshold or quadratic with or without a threshold cannot be ruled out. Moreover, human radiation response can be evaluated in terms of many potential end points, and different end points are likely to have different dose-response curves. Indeed, it may be impossible to isolate the dose-response curve for one specific endpoint because of interferences from other endpoints and other causes. As noted in the enclosed preprint, the *overall* radiation response is likely to be Gompertzian, with the specific shape or slope of the toe of the curve unknown. It is not inappropriate or illogical to consider the existence of a real or effective threshold for specific low level radiation induced

Supported by a grant to Washington State University from the United States Department of Energy

effects. And, as is also pointed out in the paper, the assumption of linearity of response without threshold was chosen initially on the basis that was not only mathematically simple, but provided an *upper limit* to the risk of low level irradiation.

While there is a large body of evidence to support response curves other than the linear nonthreshold curve, given the above, it would seem prudent to proceed with some caution until more definitive and less equivocal understanding of the shape of the low dose response curve is obtained. My own view is that for now, radiation protection is best achieved by continuing to apply the linear nonthreshold extrapolation to low doses (but with a lower level cutoff), recognizing that in so doing the risks of low level radiation are likely to be considerably overestimated. Explicit in any linear extrapolation should be a lower limit or *de minimis* level below which exposure is ignored. Hence, by implication, risk at or below this *de minimis* level is effectively considered to be zero, whether applied to an individual or to a large population. At what point the *de minimis* level should be set, will depend upon who is setting the level, but in my opinion, given our current level of knowledge, somewhere between 10 and 1000 μSv (1-100 mrem) annually, would seem a suitable range of values. The upper end of the range would be applicable to occupational exposures, while the lower end, perhaps 100 μSv (10 mrem), would seem a suitable *de minimis* level for exposures of the general public. The above is entirely consistent with the discussion and recommendations of NCRP Report 121, with which I am in full accord.

I hope the enclosed preprint and discussion will be of interest and assistance to the ACRS and ACNW. Feel free to include this letter in the record of the meeting.

It was good seeing you again, and to participation in the efforts of the ACNW and ACRS.

Warmest regards,

Ronald L. Kathren
Professor of Health Physics, Director

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Enclosure

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PATHWAY TO A PARADIGM: THE LINEAR NONTHRESHOLD DOSE-RESPONSE MODEL IN HISTORICAL CONTEXT

The American Academy of Health Physics 1995 Radiology Centennial Hartman Oration

Ronald L. Kathren*

Abstract - This paper traces the evolution of the linear nonthreshold dose-response model and its acceptance as a paradigm in radiation protection practice and risk analysis. Deterministic effects such as skin burns and even deep tissue trauma were associated with excessive exposure to x-rays shortly after the discovery, and carcinogenicity was observed as early as 1902. Still, it was not until 1925 that the first protective limits were suggested. For three decades these limits were based on the concept of a tolerance dose which, if not exceeded, would result in no demonstrable harm to the individual and implicitly assumed a threshold dose below which radiation effects would be absent. After World War II, largely because of genetic concerns related to atmospheric weapons testing, radiation protection dose limits were expressed in terms of a risk based maximum permissible dose which clearly implied no threshold. The 1927 discovery by Muller of x-ray induced genetic mutations in fruit flies, linear with dose and with no apparent threshold, was an important underpinning of the standards. The linear nonthreshold dose-response model was originally used to provide an upper limit estimate of the risk, with zero being the lower limit, of low level irradiation since the dose-response curve could not be determined at low dose levels. Evidence to the contrary such as hormesis and the classic studies of the radium dial painters notwithstanding, the linear nonthreshold model gained greater acceptance and in the centennial year of the discovery of x-rays stands as a paradigm although serious questions are beginning to be raised regarding its general applicability. The work includes a brief digression describing the work of x-ray protection pioneer William Rollins, and concludes with a recommendation for application of a *de minimis* dose level in radiation protection.

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Introduction

It is but a few months short of a full century since Wilhelm Conrad Roentgen made a most insightful discovery, a discovery which has led to many changes in our understanding of the world and to numerous beneficial applications for mankind. As we look back over the century since this great discovery, we readily well recognize that the gift of x-rays is a two sided one, and that our noble profession of health physics exists because the benefits of that discovery cannot be realized without the payment of some price in the form of detriment. Indeed, it is precisely because of the two sided nature of this discovery that the profession of health physics has evolved.

A central aspect of the profession of health physics is to establish practical scientifically based radiation protection standards with the worthy aim of minimizing the detriment while at the same time enhancing the benefits derived from x-rays and other sources of ionizing and nonionizing radiation. For half a century than the professional lifetimes of virtually all current practitioners of health physics, the fundamental underpinning of these standards has been the linear nonthreshold dose-response model. Briefly articulated, the model states that any exposure to ionizing radiation, no matter how small, carries with it a commensurate risk of detriment (i.e. a fatal cancer or adverse genetic effect), with the risk being proportional to the dose accumulated. Professionally, although aware of other mathematical characterizations of dose-response, most of us engaged in the practice of health physics have known of nothing other than the linear nonthreshold model as the basis for the dose limits, risk evaluations, and others protective measures, at least insofar as the regulatory aspects of our work has been concerned. The model has assumed the status of a paradigm which, according to the dictionary, is synonymous with an ideal, a standard, a paragon or a touchstone.

The pathway to this paradigm will be the theme of this presentation. Thus, this paper will briefly review the scientific bases and supporting studies that led to the development and acceptance of the linear

nonthreshold model for low level radiation effects, emphasizing studies carried out in human populations. It will include consideration of observations and studies such as hormesis and the clear threshold for certain stochastic effects such as osteogenic sarcoma in the radium dial painters that do not support the linear nonthreshold model, as well as the plethora of studies that do. It concludes with a brief examination of the contemporary application of risk assessment in radiation protection practice and closes with the recommendation that to better fulfill the central goal of the profession of health physics, consideration should be given to incorporation of a *de minimis* basis or philosophy for operational radiation protection and for application to risk assessment of low level radiation effects.

In the Beginning: The First Decade

The pathway begins, as it necessarily must, with the twin discoveries of x-rays and radioactivity, made only a few months apart a few years before the close of the nineteenth century. In November 1895, German physicist Wilhelm Konrad Röntgen recognized that an energized evacuated Crookes tube was emitting a penetrating form of radiation and so discovered x-rays. The following March, French physicist Henri Becquerel observed the blackening of a photographic plate on which an ore of uranium had been placed and correctly deduced the existence of a penetrating form of radiation similar to x-rays.

Few discoveries have excited the world, both scientific and lay alike, as did the discoveries of x-rays and radioactivity, and a period of intensive study of these new phenomena began. Thus it was only a matter of weeks after the discovery by Röntgen that reports of deleterious biological effects attributable to the x-rays began to appear. The first of these appeared as brief news items describing eye irritation associated with the use of x-rays and fluorescent screens reported independently in two separate brief news items by two Americans, Thomas Alva Edison and William J. Morton in the March 5, 1896, issue of the British journal *Nature* (Edison 1896; Morton 1896) incorrectly attributing these effects to x-ray

exposure (Kathren 1962). About the same time, H. Marcuse, a German physician, associated injury to the skin -- dermatitis and loss of hair -- with exposure to x-rays in the first of what was to become a long inventory of articles in the medical and scientific literature describing what were clearly acute and hence deterministic effects manifested in the form of dermatitis, epilation, and erythema with deeper tissue trauma in the more extreme cases (Marcuse 1896).

Not surprisingly, the initial observations in humans as well as studies of the effects of x-rays (the great interest in radioactivity was to come a few years later after the publication of the doctoral dissertation of Mme. Curie in 1903) were related to deterministic effects. By the turn of the century, a scant five years after the discovery of x-rays, the fact that excessive exposure to x-rays would result in a variety of acute effects from high level exposure was by and large recognized and accepted by the scientific and medical community although a minority, including some prominent medical experts, remained unconvinced that skin burns and other acute deterministic effects observed in some patients were in fact attributable to their exposure to radiation, offering alternative explanations. But within another few years, virtually all accepted the incontrovertible fact, likely aided in this conclusion by a spate of successful malpractice lawsuits brought by those who had suffered such effects (Kathren 1962). Yet to be recognized and studied, however, were long term non-deterministic or stochastic effects or the effects of chronic low level exposure.

Interlude: William Rollins and the Origins of Health Physics

It is most fitting that this centennial celebration and the joint meeting of the American Academy of Health Physics, the Health Physics Society, and the American Association of Physicists in Medicine, is held in the city of Boston, for it is this city that was home to William Herbert Rollins. Rollins was born in Charlestown, Massachusetts, in 1852, and was raised in the Boston suburb of Lawrence where he apprenticed to local dentist for

three years before graduating in 1873 at the age of 21 from the Harvard University dental school. Subsequently, and while engaged in his practice of dentistry, Rollins also earned a medical degree from Harvard but never was to practice that profession.

An apparently shy and reticent man with a penchant for working with his hands, dentistry was more suited to Rollins. When he learned of x-rays, like so many others of the day, he quickly began his studies -- all personally and privately funded -- of this newly discovered form of radiant energy. Within months of the discovery, he devised a number of new applications and significant improvements to the primitive x-ray tubes of the day. His first publication, in July of 1896, described a 'cryptoscope' -- basically a fluoroscope for intraoral radiographic examinations, which innovatively featured leaded glass over the fluorescent screen which Rollins, some years later was to assert was designed to protect the eyes of the operator from radiation (Kathren 1964). His second publication, a month later, observed the value of x-rays in dentistry and described the intraoral use of celluloid films rather than glass plates for intraoral radiography (Rollins 1896). An interesting invention, described in 1899, was the 'Seehear', basically a combination of a fluoroscope and stethoscope which enabled the radiologist to hear the sounds from the heart and lungs as he was visualizing them.

From the beginnings of his investigations into the nature of x-rays, Rollins was apparently concerned with the potential hazards of x-rays and protection from same. He devised collimating diaphragms and leaded tube housings, perhaps as much to improve radiographic image quality as for protection, but it was clear that x-ray protection was an important aspect of his work. In 1901-2, he published a series of brief notes in the *Boston Medical and Surgical Journal* describing a series of straightforward experiments in which he exposed of guinea pigs to x-rays and observed the results. Primitive, crude, and, certainly by today's standards unsophisticated and perhaps even childlike in design and execution, these papers nonetheless rank as classics of radiation biology and radiation protection. The first was quite simply titled 'X-light Kills' (Rollins

1901a). In the terse and unpolished style that characterized his writing, Rollins used only 261 words the *Boston Medical and Surgical Journal* dated February 14, 1901 to describe an experiment in which he exposed two guinea pigs to x-rays two hours a day, noting how one died on the eighth day of the experiment and the other on the eleventh without external manifestation of trauma or pathology without manifestations of skin burns, heretofore always associated with excessive x-ray exposure, were not noted. This simple experiment was apparently the first in which it was shown that acute x-ray exposures could kill the higher forms of life. His reason for brevity was given in these sage words which have modern application as well, Rollins noting that ". . .
many details . . . are not given, remembering how many hours of sunlight have been lost through being obliged to read long papers." (Rollins 1901a). The brief article, however, included three protective precautions recommended to users of x-rays: radio-opaque glasses, shielded tube housings, and limiting exposure of the patient to the region of interest.

In the next issue of the *Journal,* Rollins (1901b) described the results of exposing a pregnant guinea pig to x-rays, noting the death of the fetus and expressing concern about exposing pregnant women for pelvimetry or routine x-ray examinations. Decades were to pass before routine radiography of pregnant women was halted, and then largely as a result of the classic epidemiologic investigation of Stewart and coworkers (1956) which linked x-rays *in utero* to leukemia in childhood. In a third note, Rollins described the lack of effects of his control animals and offered an ahead of his time suggestion based on his observations of the exposed animals, viz. that the demonstrated deep tissue effects that he had observed might prove valuable in treatment of inoperable cancers (Rollins 1901c), an application first attempted two years later by Chicago radiologist Nicholas Senn who favorably treated leukemia with splenic irradiation (Senn 1903).

A subsequent paper described still more studies with guinea pigs exposed to external x-ray fields, and included a brief history of the theories of x-ray burns. It also included tabulation of the daily weights of the exposed animals and controls, showing a drop for the former prior to their death,

and concluded with a lamented of the inability of Rollins to interest a pathologist in examining the tissues from his dead animals and the words ". . . it is hoped some clear-eyed observer will realize here is a new field where useful original work can be done." (Rollins 1902a) The final paper in the series summarized additional conclusions primarily related to x-ray therapy which he derived from his guinea pig experiments, and included the recommendation for protective purposes using only very soft x-rays for superficial therapy and maintaining a large tube to skin distance for deep therapy (Rollins 1902b).

Rollins contributions to x-ray protection alone were numerous and often decades ahead of their adoption. He was an early proponent of collimation and nonradiable x-ray tube housings and even designed a method of testing the efficacy of the latter, using time fogging of a photographic plate as a quantitative measure of leakage. He applied the general principles of protection derived from x-rays to radium (1902), recommended leaded goggles be worn by fluoroscopists (1902) and suggested reduction of patient exposure in fluoroscopy through the use of pulses or bursts of x-rays rather than a continuous beam (1903). By the time he privately published the compendium of his works entitled *Notes on X-Light* (Rollins preferred the term 'X-light' to x-rays or Roentgen rays feeling it was more descriptive and recognized the electromagnetic nature of the rays) in 1904, he had elucidated all of the fundamental principles of radiation protection, some of which would not be implemented for decades. His researches were all self financed, carried out as a hobby, and his numerous inventions and innovations were freely given to all without hinderance of patent or copyright or hint of monetary gain or personal acclaim. He was a devoted husband and left his entire estate to the Smithsonian for the establishment of the William and Herbert Rollins fund, after previously, and again with great prescience, donating land he owned near Wellfleet, Massachusetts, for the establishment of a wildlife preserve. This obscure Bostonian who flourished a century ago was a man of great character and ability. In this centennial year of the x-ray, he well deserves remembrance and recognition for his pioneering contributions to x-ray science and engineering generally, and especially to

health physics. It is he who truly merits the title of Father of Health Physics.

Toward Development of a Radiation Protection Philosophy: The Early Years

For the first three decades after the discovery of x-rays and radioactivity, there was no indication, let alone support, for the idea that biological response -- even a specific biological response -- to radiation was a linear function of dose. Recognition of the carcinogenic, and hence longer term effects, of radiation exposure was first made in 1902 by Frieben based on his observation of a carcinoma on the hand in a worker in a factory producing x-ray tubes (Frieben 1902). Over the next several years, reports of a number of x-ray induced malignancies, including fatalities, appeared in the literature, along with experimental studies with animals in which both skin carcinomas and sarcomas were induced by x-ray exposure. By 1911 at least 94 cases of apparent x-ray induced skin carcinoma in man were documented in the literature, and average of six per year since the discovery (Hesse 1911). By midcentury, only a total of 200 cases of x-ray induced skin carcinoma had been reported (Ellinger 1957), for an incidence rate of only 2.5 per year for the subsequent four decades despite considerably increased usage and opportunity for exposure. Protection practices clearly contributed to this improvement, although a part of the apparent slowing in cases may have come from decreased reporting since the phenomenon was no longer novel.

From his evaluation of these first 94 cases, Hesse (1911) found that the interval between exposure and the diagnosis or recognition of the skin carcinoma averaged nine years (range, 4 to 14 years), with the interval between an acute radiation induced dermatitis and diagnosis of the malignancy averaging 4 to 5 years (range, 1 to 11 years). This was a clear demonstration of the dependency of the latency period on dose, for the dose to those with dermatitis was likely greater than that to those who did not develop dermatitis, or in the latter cases the doses were fractionated. A few years later, the carcinogenic potential of chronic low level x-ray exposure was clearly stated by British physician Hector Colwell and his physicist colleague Sydney Russ in what may well have been the first text book of radiobiology (Colwell and Russ 1915, p. 283):

> "The significant fact, therefore, is that repeated small doses of soft X rays,when applied to human tissues, produce gradual changes therein, which may cause such tissues to develop malignant features."

However, well into the first century after the discovery of ionizing radiation the prevailing view regarding induction of malignancy by x-rays was that it was necessary for actual damage (as would be the case with high exposures producing acute effects) to occur in order to ultimately lead to malignancy. And, at least in the early years of the twentieth century, many subscribed to the premise that small doses of radiation might in fact be beneficial, some citing as justification the Arndt-Schulz Law. The Arndt-Schulz Law, which applied to drugs and served as an important underpinning of homeopathy, was formulated in the late nineteenth century prior to the discovery of x-rays and radioactivity and theorizes that small doses produce a stimulatory effect, while larger doses would produce increasingly deleterious effects. This is, of course, analogous to, if not an actual statement of, the more contemporary concept of radiation hormesis. The belief that small doses of radium or radium emanation (i.e. radon) was salutary was held by many reputable physicians through at least the first quarter of the twentieth century. It was, however, the observations of potential long term effects on the blood that greatly influenced radiation protection in those early decades following the discovery of x-rays and radioactivity. As early as 1911, a cause and effect relationship was postulated in four cases of lymphatic leukemia observed in radiologists (Von Jagie et al. reported in Colwell and Russ 1934, pp. 66ff). Minor blood changes, including leukopenia in radiologists, were described the following year, and, although such effects were not noted by all investigators, there was a growing awareness, perhaps subconscious to some extent, that continued low level irradiation at levels considered to be within the range of safety might produce adverse effects in the long term. This was buttressed by the deaths of a number of prominent radiation workers, including the redoubtable Marie Curie in 1934, from aplastic anemia and other causes attributable to their radiation exposure (Henshaw 1941). It was thus

effects on the blood -- deterministic effects specifically -- that served as the basis for early protection standards and for longer term sequelae of irradiation.

The Tolerance Dose and the Status of Radiation Protection Philosophy: 1925

The earliest considerations of radiation effects and protection were built on the principle that a certain specific level of radiation can be incurred by various tissues without apparent ill effect This in turn logically led to the concept of a 'tolerance dose'. More completely and precisely, the tolerance dose was considered to be that level of radiation to which an individual could be continuously exposed without demonstrable ill effect. Demonstrable ill effect or harm, of course, was considered in terms of what are now known as deterministic effects; risk (or more appropriately recognition of the hazard) was thus characterized in terms of a clinical manifestation of radiation effects such as a diminution in the circulating leukocyte count. The tolerance dose thus served as the basis for what was likely the first statement of a dose limit, determined as a fraction of the skin erythema dose, which was put forth by Arthur Mutscheller at the 1924 meeting of the American Roentgen Ray Society (Mutscheller 1925). It was a concept that served as the basis for radiation protection standards -- ie dose limits -- for the subsequent three decades.
In general, and as applied to early protection limits, the tolerance dose was based on a fraction of the so-called erythema dose, ie. the dose required to produce a perceptible reddening of the skin. Since the erythema dose is by no means an exact quantity, dependent as it is on radiation quality, dose rate, and the specific response of the individual, the tolerance dose was by no means an exact quantity. Mutscheller's original recommended level corresponds to a whole body dose of about 700 mSv/year and was derived from calculations of anticipated exposures in well run x-ray installations. Levels proposed by others within the next several years were, typically, roughly equivalent to a whole body equivalent dose in modern units of 250 to 500 mSv annually, an annual level considerably in excess of what is now considered as low dose in radiation protection practice.

There was considerable scientific and anecdotal support for the concept of tolerance dose. One of the few still living health physicists professionally active in the early days of the tolerance dose, Lauriston Taylor, in discussing efforts by three prominent early investigators independently working to establish a quantitative level for tolerance dose, observed " . . . no one of these people, or anybody else, claimed that they had ever detected any injury due to radiation at levels above this one-hundredth of an erythema dose per month" (Taylor 1980). There was, in fact, supporting evidence in the literature Barclay and Cox (1928) examined radiation risks to roentgenologists, making measurements under actual operating conditions.

They failed to detect any ill effect in either of the two workers they followed, one of whom they estimated was exposed to a daily dose of 0.007 unit skin dose (ie erythema dose) for six years, a dose rate 30 per cent lower than that proposed by Mutscheller, and equivalent to about 500 mSv annually in modern terms, over a time period of 6 years. Similar findings were reported by other investigators, buttressing the idea that low level effects did not occur. A major failing of these studies was that they involved only a few individuals, and were perhaps ingenuous in assuming that if effects were not seen in one or a few individuals exposed to relatively low level, such effects would be absent in all individuals so exposed.

The tolerance dose was thus effectively a statement of threshold in which was clearly implicit the idea of recovery (or repair) from any subclinical acute effects with denial of the possibility of long term low level effects. Such was the state of radiation risk philosophy a full three decades after the discovery of x-rays and radioactivity.

Watershed: H. J. Muller and the Fruit Flies

In 1927, American geneticist Herman J. Muller made a highly significant discovery which was to win for him a Nobel Prize and to exert perhaps the single most significant influence on radiation protection philosophy some

twenty years later, and for at least the next half century after that. In experiments with the fruit fly *Drosophila melanogaster*, Muller demonstrated that exposure to x-rays could result in the mutations, and that the mutation rate was linear with dose (Muller 1928). Muller's extraordinary observation of the mutagenicity of x-rays was quickly confirmed by Weinstein (1928) and shortly thereafter, mutations were induced in
plants by x-rays (Stadler 1928) and in somatic cells (Patterson 1928; Timofeev-Ressovsky 1929), lending support to the idea that x-ray induced mutations were generic and species independent. Studies in the 1930's established that the induced mutation rate was independent of dose rate, and, perhaps most significantly, that mutation was a single hit process with no threshold, and that the mutagenic effect of radiation is cumulative over a lifetime (Oliver 1932; Timofeev-Ressovsky, Zimmer and Delbruck 1935; Uphoff and Stern 1949). Moreover, of perhaps even greater significant than genetic mutations was the existence of x-ray induced somatic mutations which offered a plausible explanation for the carcinogenicity of ionizing radiations, and also was consistent with the long latency period associated with the production of cancer.

Radiation Protection Philosophy and Practice: 1925-1945

The two decades between 1925 and 1945 have been dubbed "The Era of Progress" and were a period when radiation protection emerged as a science in its own right (Kathren and Ziemer 1980). These years saw the formation of such protection oriented bodies as the International X-ray and Radium Protection Committee (1928), predecessor of the International Commission on Radiological Protection (ICRP), and the U.S. Advisory Committee on X-Ray and Radium Protection (1929), the direct forerunner of the modern National Council on Radiation Protection and Measurements (NCRP). During this 20 year span, these bodies, as well as the League of Nations, various national governments , and individual investigators were to promulgate radiation protection standards, all having as their underlying basis the concept of a tolerance dose.

In 1931, the American body put forth a tolerance dose of 0.2 R/day, and the international group did likewise in 1934. Subsequently, in 1936, the American body reduced its value to 0.1 R/day, largely as a result of changes in the assumptions and calculational method, further reducing the recommend maximum exposure level to 0.02 R/day in 1941, a level that corresponds almost exactly with the 50 mSv limit almost universally accepted for regulatory purposes today, more than a half century later. (Note: In the 1930's, dose was expressed in units of the roentgen, symbolized by R, which, for photon radiations, are roughly numerically equivalent to cSv). Also in 1931 the League of Nations, put forth a tolerance dose limit of 1 x 10^{-5} R/s, based on an exposure of 8 h per day 300 days per year, (Wintz and Rump 1931), which corresponds to about 860 mSv in modern terms. Significantly, and perhaps presciently, they noted that it was impossible to exactly determine a dose incapable of damaging cells, or ". . . exercising any stimulating action", and thus wrote in terms of a so-called harmless dose which would result in no effect detectable by clinical examination (Wintz and Rump 1931, p. 9), in effect leaving the door open at least a crack for effects determined or inferred from radioepidemiologic studies of human populations.

It was the Manhattan District of World War II that systematic and extensive study was made of radiobiological phenomena and to establishment of radiation protection criteria and standards. In large measure, the radiobiological studies in animals were devoted to deterministic effects, ie obvious clinical manifestations, with a major purpose being verification of the basic protection philosophy and criteria which were in turn based on the concept of tolerance dose (Cantril 1951; Nickson 1951). In some instances, results were quite unexpected and highly surprising. Lorenz and his coworkers (1954, 1955) observed that mice exposed to 0.11 R per day, approximately the accepted tolerance dose in the 1940's, outlived control animals, an observation that has never been satisfactorily explained. Clinical laboratory studies, carried out *en mass* on the workforce, failed to yield indications of potential long term low level effects (Jacobson and Marks 1951; Jacobson, Marks and Lorenz 1951) although clearly the population was not followed for a sufficiently long

period thus obviating the detection of possible long term effects from low level exposure.

At the conclusion of World War II, a half century after the discovery of x-rays and radioactivity, radiation protection philosophy was firmly grounded in the tolerance dose concept. To be sure, the concept of tolerance dose was not inconsistent with the idea of late or long term effects of irradiation, for indeed such effects had been demonstrated at least three to four decades previously, but only with what would today be considered high level doses. The generally prevailing belief underlying the tolerance dose was that there was a threshold dose that needed to be exceeded if any effects -- early or late -- were to occur. And, for many, implicit in the prevalent belief was the idea that complete recovery from radiation effects was possible, thereby precluding long term effects if the threshold level had not been reached.

However, the seeds of possible long term low dose effects had been sown by the work of Muller and other geneticists, already described briefly above, which raised serious questions regarding the existence of a threshold and the validity of the tolerance dose concept, and seemed to indicate biological response at low doses was both linear and time independent. This new idea, which would shape the direction of radiation effects research as well as radiation protection philosophy in the coming years.

The Groundwork is Laid: 1945-1970

After World War II, the pathway takes a significant turn away the from the tolerance to a new heading directly towards the linear nonthreshold dose-response model and becomes more of a two lane highway than the leisurely pleasant and relaxed country lane it once had been. In the late 1940's, scientific interest in the applicability of the linear nonthreshold model for somatic effects was kindled, and the model began to be applied in radiation protection risk assessment methodology. Usage was gradually refined over a period of perhaps fifteen or twenty years with special reference to the potential long term health effects from

atmospheric nuclear weapons testing. Regrettably, political or ideological considerations were not absent in the choice and refinement of the low dose-risk assessment model for this and other purposes, and sometimes took precedence over strictly scientific considerations.

To a great extent the choice of the linear nonthreshold model was dictated by its mathematical simplicity and its judicious or prudent representation of an upper limit for risk in the low dose region. Its principal scientific foundation lay in the studies of radiation induced genetic changes observed by Muller and others some two decades earlier in the fruit fly *Drosophila melanogaste* which were indicative of a nonthreshold linear response. The presumption was that what was likely the case for genetic effects also applied to somatic effects, and although somatic effects had only been observed at high doses, straight line extrapolation of the dose-response curve could be readily made down through the low dose domain to the origin.

Implicit in the early consideration of the linear nonthreshold extrapolation of the dose-response curve was the concept that the true risk in the region of extrapolation -- ie the low dose region where effect had not been observed -- would lie somewhere between zero and the upper limit, as defined by the location of the extrapolated line. This was not a denial of any other shape for the curve, nor even of the existence of a threshold. Rather the threshold -- zero response if you prefer -- was included in the range of values or effects from a given dose in the region of extrapolation. Perhaps what has in fact been forgotten or at least lost sight of over the years is that the original representation of the linear nonthreshold extrapolation of the dose-response curve into the low dose region in which there were no empirical data was actually couched in terms of a range of values or responses for any given dose, *with the extrapolated line itself providing the upper limit of the range of response at any given dose.*

Historically, the shift to the linear nonthreshold model and the refinement with respect to its interpretation came about relatively rapidly. In the fall of 1954, the NCRP put forth its new recommendations on permissible

dose from external sources of radiation in its Report No. 17, originally published as National Bureau of Standards Handbook 17 (NCRP 1954), and the British did likewise the following year. In place of the tolerance dose, Report No. 17 introduced the concept of the *maximum permissible dose* (MPD). Implicit in the MPD was the idea of acceptable risk, and hence a nonthreshold model, the basis for which were the observations of linearity in genetic mutations in *Drosophila melanogaster* which, for protection purposes, were assumed to also apply to somatic mutations. There was also unstated concern about genetic mutations as well, for during the approximately five year period that NCRP Report 17 was in preparation (1949-54), there were about 50 announced atmospheric weapons tests, and a growing realization of the potential genetic consequences of even small doses to large (ie in this case worldwide) populations.

Less than five years after the historic NCRP report, the first report of the United Nations Scientific Committee on the Effects of Radiation was published (UNSCEAR 1958). Some credence was given to the linear nonthreshold model, which was used along with a threshold model to make numerical estimates of effects. The UNSCEAR report included what is basically a brief summary of the state-of-the-art with respect to low level radiation effects, a statement that today, some four decades later, still rings true:

> "Present knowledge concerning long-term effects and their correlation with the amount of radiation received does not permit us to evaluate with any precision the possible consequence to man of exposure to low radiation levels. Many effects of radiation are delayed; often they cannot be distinguished from other agents; many will develop once a threshold dose has been exceeded;some may be cumulative and others not; and individuals in large populations, or particular groups such as children and foetuses may have special sensitivity. These facts render it very difficult to accumulate reliable information about the correlation between small doses

> and their effects either in individuals or in large populations." (UNSCEAR 1958, p. 42)

It is of interest to note that this statement clearly identified the existence of a threshold and further noted, in contradistinction to the current applications, that some effects may in fact not be cumulative.

With respect to leukemogenesis, which had already been unequivocally observed in the Japanese atomic bomb survivors, UNSCEAR concluded that both the threshold hypothesis model and the linear nonthreshold hypothesis corresponding to a single hit with no repair somatic mutation model had equal validity. This contention was disputed by the Committee on Pathologic Effects of Atomic Radiation of the National Academy of Sciences/National Research Council which straightforwardly stated that ". . . a considerable body of experimental evidence . . ." favored nonlinearity, and hence presumably a threshold, and urged that nonlinear relationships be given greater heed (NAS/NRC 1959). The following year, the short-lived U.S. Federal Radiation Council (FRC), which had been created only the year before, published its initial report in which it reiterated the original concept of the linear nonthreshold extrapolation, noting that the model merely provided the upper limit of risk for a given dose in the region of extrapolation (FRC 1960).

During this same time frame, the scientific questions were perhaps at once both illuminated and obscured by the extensive hearings of the Joint Committee on Atomic Energy of the U.S. Congress. The hearings focussed attention on the potential problems of low level long term radiation effects, and greatly influenced the thinking of both the scientific community and the general public. The Congressional hearings began in 1957 with an inquiry into the nature of radioactive fallout and its effects on people (JCAE 1957). The Committee heard testimony from scientific experts relating to both the linear nonthreshold hypothesis and threshold dose, as well as the concept of an acceptable level of exposure as expressed via the MPD. Although accepting proportionality for genetic effects, the bulk of the expert testimony did not favor a proportional -- ie linear nonthreshold hypothesis -- for low level long term somatic effects.

The Committee, while recognizing that the shape of the curve was not well known, concluded, among other things, that continued nuclear weapons testing in the atmosphere at the level of the previous five years represented a hazard to the population of the world, but left unresolved the question of whether there was in fact a threshold or 'safe' level for exposure, below which such effects as leukemia, bone cancer or life shortening would not occur.

An attempt was made by the Committee to answer that very question in its 1959 hearings (JCAE 1959). Again, the question remained unresolved, but the final Committee summary report, while pointing to the lack of experimental evidence regarding low level somatic effects and still equivocating with respect to the specific low level model that applied, quoted testimony by Karl Z. Morgan to the effect that only certain types of effects, including genetic mutations, leukemogenesis, and life shortening were without a threshold (JCAE 1959, summary volume p. 19). Also highly influential in the hearings and in the Committee's subsequent consideration of radiation protection standards was testimony by Edward B. Lewis, a biology professor at the California Institute of Technology, who made a strong case for the linear hypothesis as the basis for protection standards, and indeed conceptually put forth what is the current regulatory and radiation protection concept of As Low As Reasonably Achievable (ALARA) (JCAE 1960, pp. 404-407). Subsequently, throughout the 1960's, the JCAE considered the problems of worker protection standards and compensation, as well as revisiting fallout from weapons tests and carrying out hearings related to the radiological hazards associated with mining, moving subtly closer to a linear nonthreshold or proportionality hypothesis for low level long term effects with each succeeding series of hearings.

The next report of the UNSCEAR was issued in 1962. It, as well as subsequent reports in 1964 and 1972, reaffirmed its 1958 report and used the linear dose-response relationship to compute risks from various sources of radiation, offering as partial justification the argument of the mathematical simplicity and conservatism of the linear nonthreshold model (UNSCEAR 1962). The report (UNSCEAR 1962, p. 418) further noted

that the available data were insufficient to make absolute risk estimates. Again, in its 1964 and 1966 reports, UNSCEAR declared that the extrapolated linear curve marked the upper limit of the estimate of risk for a given dose, a concept also put forth by the ICRP in 1966 (UNSCEAR 1964; ICRP 1966).

To a considerable extent, concern over the low level long term effects of radiation led to the treaty banning atmospheric nuclear weapons in 1962. Optimistic plans for nuclear electric generation, however, aroused increasing concern regarding long term low level radiation effects. It was generally accepted within the scientific community that there was no threshold for genetic effects, even though such effects had never been demonstrated in human populations, including the survivors of the atomic bombings of Japan. However, there was still not common acceptance of the applicability of the linear nonthreshold dose response curve to somatic
mutations or effects. In 1964, the NAS/NRC, acting on a request from the FRC, established an advisory committee -- the so-called BEAR (Biological Effects of Atomic Radiation) Committee -- to look into problems related to radiation protection, including the shape of the low dose response curve. In an importr . departure from previous practice, this highly influential committee introduced the concept of regulation of populations doses based on genetic risk (and ultimately genetic dose) to future generations (NAS/NRC, 1972, p. 5).

The 1970's: The Pathway Turns into Superhighway

The change in direction that had begun after World War II continued, but at ever increasing speed. Indeed the pathway, to continue with the metaphor, was rapidly becoming a six lane superhighway, laden with high speed vehicles, each representative of a scientific or technical paper in the literature. The BEAR Committee subsequently gave way to the NAS/NRC Committee on the Biological Effects of Ionizing Radiations (BEIR) which issued its first report in 1972. This initial BEIR report, as do later BEIR reports, provides a comprehensive review of the literature relating to low level radiation effects and evaluation of risk assessment methodology to

the time of its publication. Although sidestepping the issue of the shape of the dose response curve at low doses, BEIR I nonetheless put forth absolute risk values for various nondeterministic (ie carcinogenic) effects derived primarily from linear extrapolation of the data for the Japanese atomic bomb survivors as well as other exposed groups which at the least, clearly implied there was no threshold with respect to low dose response (NAS/NRC 1972).

Another major shift to the linear nonthreshold dose-response model also took place in 1972. In that year, the U.S. Atomic Energy Commission AEC), forerunner of the current U.S. Nuclear Regulatory Commission (USNRC), incorporated the concept of 'as low as practicable' (now known as ALARA) into its regulations. Implicit in the ALARA concept is the linear nonthreshold dose-response. Thus, in perhaps the single year 1972, the situation had changed, and changed dramatically.

The 1970's also saw another major conceptual change with respect to radiation protection practice. In 1977, the ICRP adopted a new risk based system of radiation protection based on three considerations: justification of practices; optimization of doses; limitations of individual risks and presented this in its Publication 26 (ICRP 1977). In developing estimates of nondeterministic (stochastic was that term in use at that time, and basically referred to carcinogenic risk) risks to specific tissues, a number of tissue weighting factors were derived and these were then used to calculating a new dose quantity -- the effective dose equivalent. The effective dose equivalent was a weighted combination of doses to various parts of the body (such as organ doses from internal irradiation) with ' as to the whole body from external irradiation. The resultant single , nerical expression of effective dose equivalent expressed the total nondeterministic (ie stochastic) risk of radiation exposure -- partial body irradiation as well as whole body irradiation -- in terms of the equivalent risk of whole body irradiation (ICRP 1977). The system has been basically adopted, and refined and expanded upon not only by ICRP (ICRP 1977, 1978-80, 1990, 1991) but also by NCRP (1987) and various American regulatory bodies including the EPA (USEPA 1987), DOE (USDOE 1988) and USNRC (1991).

Although basically recommending the same permissible exposure limit of 50 mSv annually for occupational exposure, from the standpoint of applied radiation protection, the new ICRP system represented a sharp departure from past practice. In the United States in particular, contentious argument went on within the operational health physics community regarding the assignment of the entire 50 dose commitment from an intake of radioactivity to the year of intake, an idea particularly objectionable to some members of the health physics community who were involved with the protection aspects of long-lived bone seeking alpha emitters (eg Pu and Am isotopes). The basic problem, it seemed, lay not with the risk based concept *per se* but rather with the administrative problems of implementation of the new system, and, to some extent, resistance to change. More significantly, carcinogenesis was defined as a stochastic (now nondeterministic) effect, and the new system represented a complete departure from the concept of a threshold.

The fatal accident rate in so-called safe industries was introduced as a measure of acceptable risk. This was an important step in that it provided a perspective as well as a means of comparison of radiation risks with those associated with other human endeavor. The ICRP also defined and differentiated between stochastic and nonstochastic (now nondeterministic and deterministic) risks, and thus quite appropriately retained the threshold concept where it clearly applied, viz. to so-called nonstochastic risks such as radiation induced lenticular opacities and skin changes. It thus left open the door to applying the threshold concept to specific stochastic effects, if indicated by experimental data.

The Human Experience

While animal studies provide insights into possible long term low level effects of irradiation in humans, it is human epidemiologic and related studies that provide at least in theory the most relevant data regarding long term effects of low level radiation applicable to the setting of radiation protection standards. Indeed, despite significant limitations, radioepidemiologic studies have played a major role in the acceptance of

the linear nonthreshold paradigm. The nature and small size of the populations available, the existence of background levels of the effects being observed, and the vagaries of the dosimetry on which such studies are based are but three of the uncertainties in such studies that make it is intrinsically difficult to assess the shape of the dose response curve or the level of risk.

A major intrinsic limiting factor of radioepidemiologic studies relates to population size. In small study populations, there are likely to be few effects and the incidence of radiation induced effects may be overshadowed or swamped out by the natural frequency or incidence of whatever is chosen for study in the population. The ability to distinguish between the natural incidence and a radiation induced effect is a function of both size and dose, increasing exponentially as the dose is reduced. Thus, for effects that have a small likelihood of occurrence, the requisite population size may be prohibitively large if the dose is small. Radioepidemiologic studies of radiation workers have been particularly controversial and contentiously criticized, frequently on methodological grounds. However, the largest and most extensively studied cohort, the Japanese atomic bomb survivors, showed a clear and indisputable elevation in leukemia incidence peaking at 5-6 years post exposure, and elevated incidence of a number of solid tumors correlated with dose (Kato and Shimizu 1990), although it has been noted that at doses estimated to be in the range of 10 to 90 mSv, there was in fact a lower leukemia death rate among survivors (Kondo 1990).

Long term low level effects either documented or believed to occur in human populations include radiation induced leukemia and solid tumors, life shortening, and effects on the fetus. In addition, there is evidence for radiation hormesis, or stimulation, which may produce life lengthening or reduced incidence of disease including cancer, and possible adverse immunologic effects.

Leukemia has been perhaps the most widely studied nondeterministic effect and there is ample evidence both in humans and animals to make indisputable the conclusion that certain types of leukemia are in fact

radiation induced. However, the shape of the dose response curve or the resultant models for prediction of risk from low level exposure are as yet not well established (NAS/NRC 1990). Independent evaluation of approximately four dozen epidemiologic studies dating back to 1962 reveals equivocal results with respect to whether low dose or fractionated exposures do in fact carry significant leukemia risks, and certainly raise the question of whether the linear nonthreshold dose-response model is applicable to leukemogenesis. A recent case control study of persons exposed to weapons test fallout (Stevens 1990) was indicative of a possible low level leukemogenesis but other studies in populations exposed to fallout or diagnostic radiation have been negative or marginally positive (Gibson et al. 1972; Gunz and Atkinson 1964; Linos et al. 1980; Preston-Martin et al. 1989; Stewart et al. 1962). Studies in China comparing populations in high and low background areas have likewise failed to show an association between leukemia and low level exposure (Wei 1980), as have followup studies in patients treated for hyperthyroidism with radioiodine (Hoffman et al. 1982; Holm et al. 1991). On the other hand, other studies with protracted or low doses have at least implied a positive association (Davis et al. 1987; Spengler et al. 1983). Excess leukemia has been associated with exposure in radiologists or x-ray workers with high doses, but studies of persons with lower doses have not shown such an effect (Boice et al. 1991; Jablon and Miller 1978).

Studies of radiation workers in the nuclear industries would seem to offer the greatest promise of determining the shape of response curve at low doses, and specifically whether the linear nonthreshold hypothesis is valid. However, because only a small fraction of the cohort has recorded occupational exposures significantly greater than background, the statistical power of such studies is greatly reduced. Nonetheless it is significant to note that in only one study has a significant excess leukemia mortality in the workforce been observed. Combined analyses of the data from several studies have been carried out by several investigators and is currently under way by the International Agency for Research on Cancer. Again, results have not been unequivocal. For example, Gilbert et al. (1993)) obtained positive risk estimates from

their meta-analyses but the wide confidence intervals do not exclude the possibility of no risk, or define the shape of the low dose response curve. In their meta-analysis of seven studies, Wilkinson and Dreyer (1991) claimed evidence of elevated risk from leukemia, but again, this study has been criticized on methodological grounds (Gilbert 1992). In short, despite the large number of studies, the data are simply not adequate to characterize the shape of the dose response curve with exactitude. Moreover, the latency period is known to differ for different types of leukemia and appears to be dependent upon the age of irradiation NAS/NRC 1990).

Other studies of human populations have done little to clarify and define the shape of the low level dose-response curve. Although many, if not most, studies are consistent with the linear nonthreshold dose-response paradigm, none have provided unequivocal validation. Indeed, the studies of the radium dial painter provide compelling evidence to the contrary, at least for osteosarcomas, where Evans (1972) has shown clear evidence of a threshold. Thus, the evidence from both animal and human studies, if taken as a whole, is not clear cut and can be used to support a number of dose response curves for both mutagenesis and carcinogenesis in both humans and animals at low doses and dose rates. In general, however, the studies do not support a threshold model, although a notable exception appears to be osteogenic sarcoma for which there is clear evidence of a threshold in both humans and animals.

Further confounding and confusing the characterization of the low dose response curve have been reports of an apparent hormetic or beneficial stimulatory effect of low level radiation in humans. The basic premise underlying hormesis is similar conceptually to homeopathy, specifying that while large doses may be harmful, small doses are stimulatory and thus may lead to improved functioning of the immune system and to other beneficial effects. T. D. Luckey has documented a large and impressive body of literature -- much of it peer reviewed -- in support of the hormesis thesis, including apparently valid interpretations of human epidemiologic studies, including those of the Japanese atomic bomb survivors

(Luckey 1991). Certainly the reduced incidence of certain types of cancers in groups with low level radiation exposure, as has been reported in numerous radioepidemiology studies, can be cited as supporting evidence for hormesis, although an argument could also be made that these are simply statistical artifacts. A number of beneficial effects have been associated with low level exposure, including enhanced growth and development, resistance to infection and other immune system improvements, lowered incidence of cancer, and longer lifespan (Luckey 1983, 1991; Mine et al. 1990).

Although hormesis presents to some an attractive alternative to the conventional dose response evaluations of low level radiation effects, it has received scant attention in the conventional radiation risk evaluation process. Indeed, it is by and large ignored or even rejected out of hand as going against conventional wisdom by many otherwise independent radiation scientists. Certainly for some, hormesis -- the suggestion that low levels of radiation exposure may be beneficial -- is not a 'politically correct' viewpoint. However, recent publications of UNSCEAR provide new insights with respect to hormesis, which can be explained in terms of a cellular adaptive response mechanism to low levels of radiation (UNSCEAR 1993; 1994)

Contemporary Times (1980-1995)

The trailblazing groundwork put forth in ICRP Publication 26 was expanded upon by both the NCRP in its Report No. 91 (1987) and in ICRP Publication 60 (1990), which might be considered the second generation or direct descendent of the 1977 Publication 26. Both reports rely heavily on the emerging data and results from the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, and utilize the linear nonthreshold dose-response model as the basis for their recommendations. In addition to providing the bases for establishing a dose limit, Publication 60 put forth a new risk projection model and an in depth discussion of their proposed new approach to taking Relative Biological Effectiveness into account. A multiattribute approach was used by the ICRP in weighing risk, considering such factors as lifetime risk of fatality, loss of life expectancy, and both age related mortality and morbidity considerations for both fatal and nonfatal somatic and hereditable effects. Both the ICRP and NCRP put forth values and specific guidance for application of a Dose Rate Effectiveness Factor (DREF), applicable to low LET radiations and in large measure based on the time required to repair single strand breaks in DNA. The ICRP recommended application of the DREF at doses below 200 mGy or dose rates of less than 100 mGy per hour (ICRP 1991, p. 19).

Since the 1960's, there have been numerous reports of low level radiation effects in both humans and animals, and a complete or even near complete review or even listing of the literature is virtually impossible. Perhaps the most comprehensive review and evaluation of the scientific literature has been undertaken by the BEIR committee, but even that prestigious and expert group has not been unanimous in its interpretations or without disagreement. The so-called BEIR-III report, originally released in May 1979, was subsequently withdrawn and revised because of dissention among members of the Committee with respect to the shape of the dose response curve. When finally published in 1980, the BEIR III report included two 'minority' opinions as well as presenting the consensus of the rest of the Committee with respect to the shape of the dose response curve. The Committee by and large adopted the linear-quadratic model for

cancer induction; the two dissenting members took very different viewpoints, one adopting the linear model, the other a pure quadratic model (NAS/NRC 1980).

The BEIR III committee made a number of important observations in what was their final report. They observed that it was likely undeterminable whether dose rates at environmental levels, ie on the order of 100 mrad (1 mGy) per year, were detrimental to people, and further concluded that the available data did not support an increased risk of carcinogenesis at low dose rates from low LET radiations. The Committee also recognized that differing human genotypes as well as age differences may confer different degrees of risk with respect to carcinogenesis for a specific dose. The likelihood of a threshold for certain developmental effects from irradiation *in utero* was accepted based on a multitarget multi hit theory. And, with respect to genetic effects, although curvilinear models were examined, the BEIR Committee agreed that the linear nonthreshold model still provided the best fit to the observations of genetic effects, extrapolating these effects from animal studies.

The BEIR Committee has published two reports since the 1980 BEIR III. BEIR IV, published in 1988, was specific to the health risks of radon and other internally deposited radionuclides (NAS/NRC 1988). Although recognizing the importance of age, for mathematical simplicity the Committee chose a relative risk model to characterize radiation induced lung cancer for, unlike the absolute risk model, this model did not require a complex power function to take age into account and required few variables to characterize the observations of lung cancer in the miner cohort. Perhaps most significantly, the Committee made a number of specific suggestions for further epidemiologic and other studies that might more clearly reveal the shape of the long term low dose response curve.

The most recent report, BEIR V (NAS/NRC 1990), once again considered the broad topic of health effects from low level exposure to ionizing radiation. The Committee again noted the lack of human data to verify estimates of genetic effects, generally confirming previous estimates of

genetic risk in humans and the applicability of previous extrapolations from animal data There was, however, a change with respect to the calculation of somatic effects, which were determined with a linear no-threshold model modified in some cases for dose rate effects. Also introduced was the Dose Rate Effectiveness Factor (DREF) which modified or reduced the lifetime risk, perhaps by a factor of two or more, of a specific dose if delivered over a protracted period of weeks or longer.

The experiences of other learned bodies concerned with low level radiation risks, such as UNSCEAR and the ICRP, mirror to a great extent the BEIR Committee Together, the actions of these bodies have led to a more or less consistent radiation philosophy of the past two decades, one that is based on the principle that any exposure to ionizing radiation, however small, carries with it a commensurate risk of a long term effect, and that radiation exposures must therefore be kept as low as reasonably achievable below the numerical limits established as radiation protection standards.

To a great extent, the acceptance of this paradigm has been influenced by regulatory bodies and by the general public. The public has become increasingly fearful of radiation effects and demands ever increasing guarantees of safety and even zero risk. Unlike scientific bodies, which deliberate in private and among themselves, in the setting of standards for protection against radiation regulatory bodies must hold hearings and obtain public comment. Testimony and comments from the public are thus a driving force behind radiation protection regulations and standards, and have contributed greatly to the widespread current acceptance of the linear nonthreshold model, and the belief that this model is indeed be correct, and may even understate the risk of low level radiation exposure. So strongly held is this view that attempts by regulatory bodies to incorporate minimum levels -- so-called *de minimis*, below regulatory concern (BRC), or the negligible individual risk level (NIRL) of the NCRP have been abandoned. From the 1970's, risk evaluations of nuclear operations, and in particular nuclear waste disposal, have largely been based on the linear nonthreshold model and the assumption that any dose, no matter how small, carries with it some risk. Total risk is thus

estimated by summation of individual risks, and has been carried to the extend of including even a large number of vanishingly small individual risks in the computation. A strong case could be made for truncation of very small doses in such risk evaluations, but given the wide spectrum of opinion and belief with respect to low level long term radiation effects, even among the so-called radiation protection 'establishment', and despite nearly a century of experience with ionizing radiation, induction of long term effects such as cancer by low level exposures remains a controversial and often highly emotionally charged question which cannot be answered with any reasonable degree of certainty or scientific consensus.

Into the Second Century

As the first century following the discovery of x-rays and radioactivity draws to a close, the shape of the dose-response curve at low dose levels is still unknown but the linear nonthreshold dose-response model continues to serve as the basis for radiation protection standards and risk analysis as has been the case for about the past half century. Contemporary radiation protection practice is firmly and seemingly unswervingly based upon the linear nonthreshold model of long term low level risk, with effects at low doses determined largely from epidemiologic studies and extrapolation from high dose studies. The epidemiologic basis is less than solid; Land (1993), in a critique of the epidemiologic basis for the linear hypothesis, has clearly elucidated some of the significant problems associated with application of such studies to the problem, as has Gilbert (1991) in a review of low level external radiation studies. So too is the basis for extrapolations from high dose studies, which are sometimes done in total disregard of a clear and obvious threshold for the effect under consideration, the unequivocal threshold for osteosarcoma in the radium dial painters notwithstanding.

On the other hand, a number of recent papers indicate that the Chernobyl accident and other radiation releases in the Former Soviet Union are beginning to yield firm epidemiologic evidence of hitherto unreported and perhaps even unsuspected low level effects and much shorter latency periods for the development of cancers than heretofore suspected (Astakhova et al 1993., Kossenko and Degteva 1994). It is thus important to consider all observations of low level radiation effects in an appropriate perspective, without preconceptions, and to bear in mind that the linear nonthreshold hypothesis is just that -- hypothesis.

For the near term at least, the linear nonthreshold model for low level long term effects coupled with ALARA is likely to remain the current philosophy and practice in applied radiation protection. It is a conservative, mathematically simple, and satisfying philosophy and perhaps with even a touch of Occam's razor. Recently,

however, there has been increasing unrest in the radiation protection community as well as among other scientists with respect to the validity of the linear nonthreshold dose-response paradigm. In a provocative article, Peterson (1993) devised a tabular representation to characterize what he calls the distortion of the linear, nonthreshold dose-effect assumption, tracing it from an assumption in which every dose is postulated to have an associated risk of ill health, through various steps until the final one in which it is stated unequivocally that radiation has a linear dose response relationship and that all radiation exposure is unsafe.

Exhaustive studies and analyses by Cohen (1995) of the relationship between environmental radon concentrations and lung cancer have actually and consistently shown not only that the linear nonthreshold dose-response curve does not apply, but strongly suggest radiation hormesis. A recent Health Physics Society *Newsletter* (May 1995) exemplifies the concern and increasing frustration with the apparent obsequious application of the paradigm to radiation protection. And, in its 1994 report, UNSCEAR has devoted considerable attention to the possibility of a cellular adaptive response to low level radiation in humans, but notes that at present no conclusions can be drawn regarding its effects in human populations (UNSCEAR 1994).

While many observations of radiation effects are not inconsistent with linear extrapolation to low dose, there are a number of effects for which linear extrapolation is obviously inappropriate and incorrect. It is a preposterous and even arrogant denial of valid scientific observations to assume that the linear nonthreshold response is the only, or even the best, characterization of human response to low level radiation exposure. Clearly, some effects exhibit a threshold, as has been pointed out by Evans and his coworkers for osteogenic sarcoma in the dial painters (Evans 1972).

And, for others, there may be an effective threshold, determined by dose, dose rate, and other factors which determine the latency period. If the

latency period exceeds the life span, there is obviously no effect, and hence a threshold.

Recently Raabe (1994) has put forth three dimensional models of risk which lends strong and perhaps even conclusive support to the effective threshold concept put forth by Evans and his coworkers in 1972. His three dimensional analysis of dose-rate, time and response, suggest that there is no significant difference in the shape of dose response curves for radiation induced cancer, widely accepted as a stochastic (nonderministic) effect, and for radiation induced non-neoplastic tissue injury, a deterministic effect. Raabe's methodology clearly supports the concept of an effective threshold, and should be applied to other radiation effects to determine for which effective thresholds exist. Logically it would seem that if low level radiation effects, whether positive or negative, were significant in human populations, these would have been identified long before now. Human response to low level radiation exposure is clearly highly complex, and despite a plethora of scientific publications pertinent to the problem, the prescient statement from the UNSCEAR report of nearly four decades ago is still germane. The recent recommendations of the ICRP (1991) represent a reasonable and serious attempt to apply existing knowledge within the framework of a practical protection schema which can readily be adapted to incorporation of such factors as dose rate effectiveness (which is not single valued, but rather likely to be a smooth continuous function), LET, age dependency of a specific risk, and the expected variety of dose response curves for various specific effects into a single equation which could then be solved to obtain a dose for a predetermined acceptable risk level.

Human response to radiation exposure needs to include consideration of many factors such as latency period and dose rate whose influence on response is not well known. The data clearly show that the dose response curves for various endpoints are different. When taken as a whole, the sum total of all the various human responses to radiation exposure can be depicted quite well by the familiar Gompertzian or sigmoidal curve (Figure 1), which provides a rather satisfying characterization of human radiation response that fits quite well with our existing state of

knowledge. The Gompertzian model can readily be divided into two response functions, one representing the deterministic effects and the other the non-deterministic or stochastic effects. This portion of the curve can be drawn to include a threshold, or perhaps an effective or practical threshold, and can incorporate and accomodate a linear response as well.

The current schema propose no lower limit on dose, and thus would seem not only to fly in the face of practicality, but also appear incompatible with the principle of optimization and ALARA. Given the present state of knowledge, it is not unreasonable to apply the practical or effective threshold concept in low level radiation risk estmination and to incorporate this concept into regulatory and other radiation protection standards, as has been proposed for the past twenty or so years by a number of authors in terms of so-called *de minimis*, NIRL or BRC levels for regulatory purposes. Recognizing the danger of predictions, I nonetheless am convinced that early in the second century of x-rays and radioactivity such levels will become *de rigueur* in radiation protection practice, and that new models of low level radiation response, more in keeping with the scientific observations and the philosophy of optimization will be devised and applied to protection of people and the environment from the effects of radiation exposure. To do otherwise would be an abrogation of our responsibilities to the public and of our ethics as scientists.

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BIOLOGICAL EFFECTS OF LOW LEVEL EXPOSURES: DOSE-RESPONSE RELATIONSHIPS

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LEWIS PUBLISHERS
Boca Raton Ann Arbor London Tokyo

Library of Congress Cataloging-in-Publication

Biological effects of low level exposures : dose response relationships / editor, Edward J. Calabrese.
p. cm.
Includes bibliographical references and index.
1. Toxicology – Dose-response relationship – Congresses. 2. Chemicals – Dose-response relationship – Congresses. 3. Chemicals – Physiological effect – Congresses. 4. Low-level radiation – Dose-response relationship – Congresses. 5. Low-level radiation – Physiological effect – Congresses. I. Calabrese, Edward J., 1946–
[DNLM: 1. Dose-Response Relationship, Drug – congresses. 2. Dose-response Relationship, Radiation – congresses. 3. Adaptation, Physiological – drug effects – congresses. 4. Adaptation, Physiological – radiation effects – congresses. QV 38 B614244 1994]
RA1199.4.D66B55 1994
615.9 – dc20
DNLM/DLC 93-50076
ISBN 1-56670-093-0

Lewis Publishers is an imprint of CRC Press

No claim to original U.S. Government works
International Standard Book Number 1-56670-093-0
Library of Congress Card Number 93-50076
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

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REMARKS

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"Positive Health Effects of Low Level Radiation in Human Populations," M. Pollycove, Chapter 11 in "Biological Effects of Low Level Exposures: Dose-Response Relationships," pp. 171-187 (CALABRESE, E.J.)

as background information in an attachment to the meeting minutes of the US Nuclear Regulatory Commission's (USNRC) Advisory Committee on Nuclear Waste and the Advisory Committee on Reactor Safeguards on the subject of health effects of low-level radiation. These meeting minutes would be placed in the USNRC's Public Document Room.

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CHAPTER 11

Positive Health Effects of Low Level Radiation in Human Populations

Myron Pollycove, United States Nuclear Regulatory Commission, Washington, DC

Increased longevity and decreased cancer death rates have been observed in populations exposed to high natural background radiation and reported for several decades.[1-7] These observations contradict the radiation paradigm that all radiation, including that of natural background, is harmful in linear proportion to low level dose. Such observations have been considered by recognized radiation scientists to be spurious or inconclusive because of unreliable public health data or undetermined confounding factors such as pollution of air, water and food, smoking, income, education, medical care, population density, and other socioeconomic variables. Attempts to establish a threshold level below which radiation is not harmful have been negated by the great difficulty of obtaining accurate data on large human populations required to demonstrate the absence of very low risks of low-level radiation predicted by linear extrapolation of high-level radiation health effects. During the past four years, however, several epidemiologic studies have demonstrated that exposure to low or intermediate levels of radiation have apparently resulted in positive health effects.

Low Level Radiation of Nuclear Shipyard Workers

A ten-year study by the Johns Hopkins Department of Epidemiology, School of Public Health and Hygiene, of nuclear shipyard workers was concluded recently.[8] The Technical Advisory Panel (TAP), chaired by Arthur C. Upton, advised on the research and reviewed results. John Cameron, a member of the TAP, summarized the study and stated, "This study is probably the best evidence that low levels of ionizing radiation are without health hazard."

The results contradict the conclusions of the BEIR V report that small amounts of radiation have risk – the linear risk hypothesis.[9] The database

of almost 700,000 shipyard workers included almost 108,000 nuclear workers with exposures beginning in the 1960s until the end of 1981. Three study groups were selected: 33,352 non-nuclear workers (NNW), 10,462 nuclear workers with a working lifetime dose equivalent (DE) of less than 5mSv ($NW_{<5}$), and 28,542 nuclear workers with a DE greater than or equal to 5mSv ($NW_{>5}$). Five mSv (0.5rem) is approximately equal to the sea-level background radiation (340 mr/yr) one would receive in 1½ years. Deaths in each group were classified as due to: all causes, leukemia, lymphatic and hematopoietic cancers (LHC), mesothelioma, and lung cancer. The only cancer that showed a significantly increased incidence in the exposed groups as well as the NNW was the rare malignancy mesothelioma (36 deaths), a marker for asbestos exposure that is also associated with lung cancer. The data are summarized in Table 11.1.

The nuclear worker groups had a lower death rate from all causes, leukemia, and LHC than the non-nuclear workers. These apparently beneficial effects of low dose irradiation are consistent with the increased longevity and 15% lower mortality and cancer death rates seen in the seven western states with high natural background radiation averaging about 1m y per year above that of the other states.[1-3,7]

The non-nuclear workers' death rates exactly matched those of the external non-shipyard matched control population. This demonstrates absence of the external healthy worker effect ascribed to adequate income, better health care, and the presence of health sufficient to allow maintenance of a reliable work schedule. There remains the question of an internal healthy worker effect resulting from the possible selection of more active individuals to be nuclear workers. The $NW_{>5}$ group with the greater exposure had a death rate from all causes of 0.76 the standardized mortality rate (SMR),

Table 11.1. Health Effects of Low Level Radiation in Shipyard Workers

Cause of Death	$NW_{>5}$	$NW_{<5}$	NNW
All Causes	2,797	1,168	4,453
SMR	0.76	0.81	1.00
(95% C.I.)	(0.73, 0.79)	(0.76, 0.86)	(0.97, 1.03)
Leukemia	21	4	29
SMR	0.91	0.42	0.97
(95% C.I.)	(0.56, 1.39)	(0.11, 1.07)	(0.65, 1.39)
LHC[a]	50	13	84
SMR	0.82	0.53	1.1
(95% C.I.)	(0.61, 1.08)	(0.28, 0.91)	(0.88, 1.37)
Mesothelioma	18	8	10
SMR	5.49	6.14	2.54
(95% C.I.)	(3.03, 8.08)	(2.48, 11.33)	(1.16, 4.43)
Lung Cancer	237	98	306
SMR	1.07	1.11	1.15
(95% C.I.)	(0.94, 1.21)	(0.90, 1.35)	(1.02, 1.29)

[a]Lymphatic and Hematopoietic Cancers

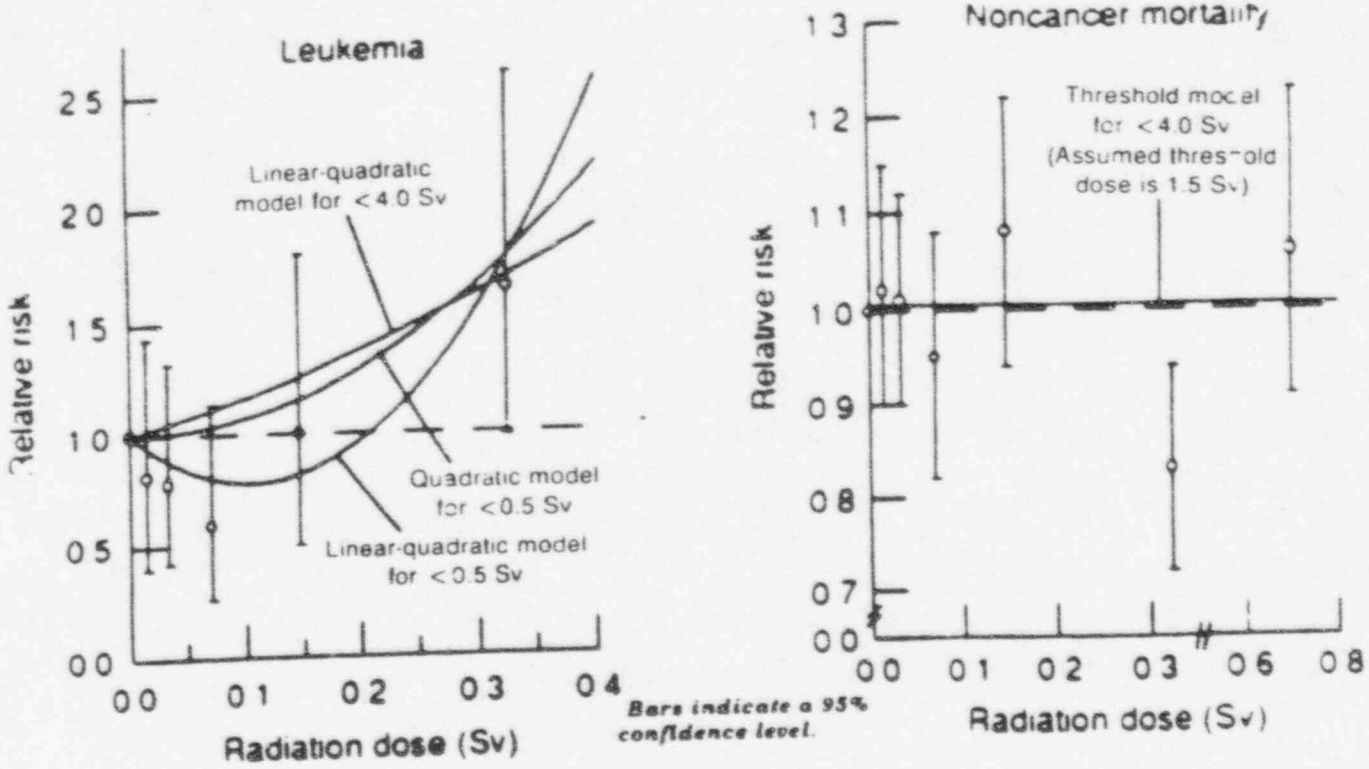
16 standard deviations below that of the non-nuclear worker group (NNW). The $NW_{<5}$ with lesser exposure had 0.81 SMR, about 8SD below the NNW. While a possible internal healthy worker effect could contribute to the lowered SMR of nuclear workers, comparison of the $NW_{>5}$ group with the $NW_{<5}$ group demonstrates that the group with the greater dose had the lower SMR with even greater statistical power. This provides very strong evidence that low levels of ionizing radiation are without health hazard.

Leukemia and Mortality of Atomic Bomb Survivors Exposed to Low Level Radiation

A recent article by Shimizu, et al.[10] concerning the effects of low level radiation in atomic bomb survivors concluded that analysis of dose response "in the less-than-0.5Sv region fails to indicate the presence of hormesis." They did not observe any significant decrease in the relative risks (RR) of (a) leukemia, (b) all cancers except leukemia, (c) lung cancer, (d) thyroid cancer, or (e) noncancer mortality. This conclusion is in agreement with the data shown for the three cancer groups (b,c,d), but appears inconsistent with the data presented for the RR of the leukemia and noncancer mortality groups.

The upper half of Figure 11.1 shows the data for these two groups as analyzed by the authors with a variety of models. The discussion of leukemia states that though the RR is less than 1 for the three groups with doses less than 0.1Sv, since all had $p > 0.10$ they did not differ statistically from unity and thus, were within the range of random variation. In clear contradiction to least square fits, the quadratic model for <0.5Sv was considered to better fit the data than the linear-quadratic model for <0.5Sv that demonstrated a RR of 0.78 at 0.11Sv. The lower half of Figure 11.1 shows analysis of the data with models that provide a better fit. The five data points for leukemia are fitted by an empirical polynomial function. The RR for the 0.010 to 0.019, 0.020 to 0.049, and 0.050 to 0.099 Sv dose categories appear consistently related to one another, not varying randomly. The RR of 0.6 plotted at 0.075Sv is 1.5SD less than 1($p < 0.15$). This study of atomic bomb survivors is in agreement with the decreased leukemia mortality seen in the nuclear shipyard worker study. In both studies the very low incidence of leukemia makes it difficult to obtain sufficient numbers for high statistical power.

Desired statistical power is present, however, for mortality rates. In the upper half of Figure 11.1 the RR data for noncancer mortality after low-level radiation are ignored and fitted with a threshold model derived from a prior study of survivors in the <4.0Sv high-level dose range, assuming the threshold dose is 1.5. Though the mortality RR of 0.83 in the 0.200 to 0.499 Sv dose category is 3.2 SD below 1 ($p = 0.001$) and is the most statistically significant data point of the entire study, nevertheless, this highly significant decreased RR is rejected with the statement, "The RRs for the sub-



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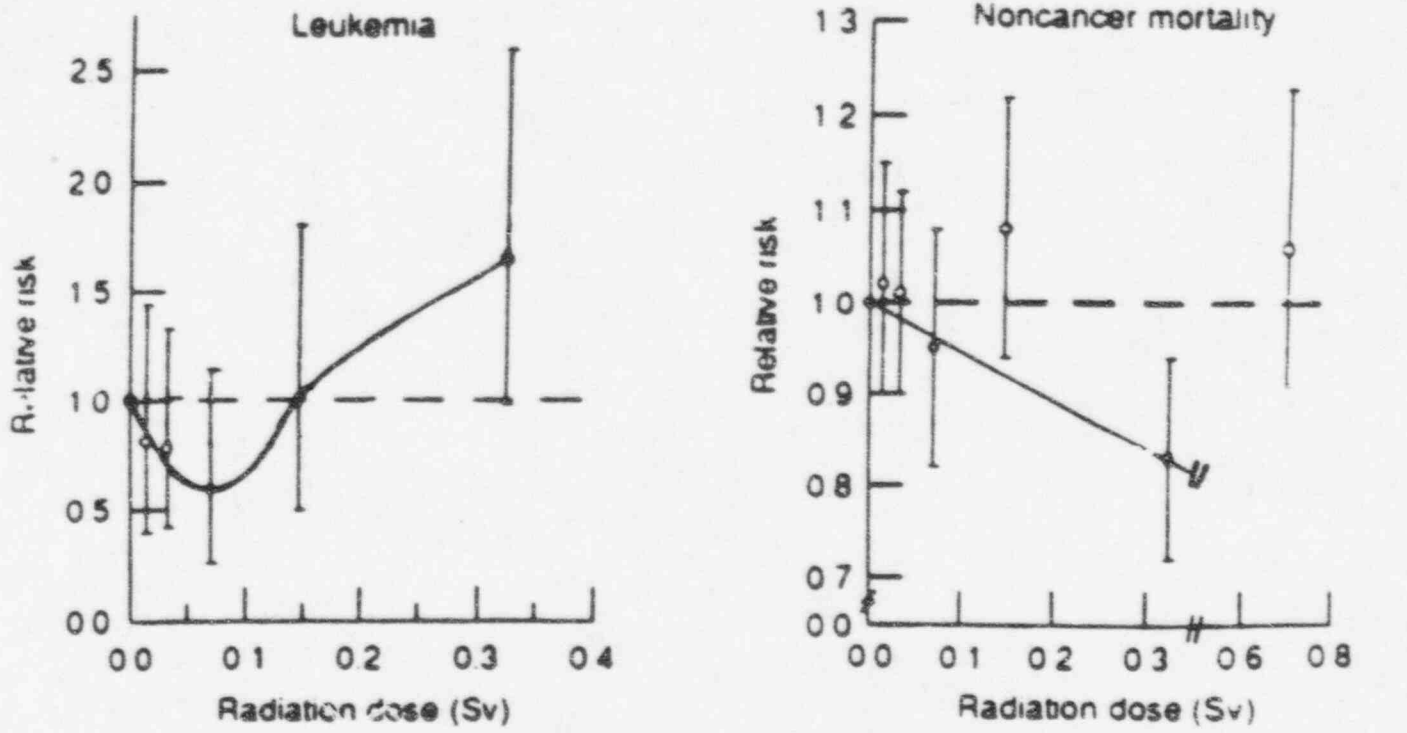

Figure 11.1. Dose-response analysis of atomic bomb survivors exposed to low-level radiation. The upper pair of relative risks of leukemia and noncancer mortality show the best fit models of the authors to their data. The lower pair of relative risks show the best fit models of the author of this review to their data.

groups within the low dose group (<0.5Sv) when compared with the 0-Sv group did not differ and were close to unity." If the only mathematical models used for analysis are those that a priori exclude a U-shaped dose-response relationship, it is not surprising that such analysis "fails to indicate the presence of hormesis." The lower half of Figure 11.1 fits a linear model down to, but no farther than, the noncancer mortality RR of 0.83. This decreased mortality risk associated with acute low-level radiation is consistent with the highly significant (-16SD and -8SD) decreased standardized mortality rates observed in prolonged very low level exposures of the nuclear groups of shipyard workers.[8]

Effect on Lifespan of Low-Intermediate Doses of Atomic Bomb Radiation

The above-mentioned decreased mortality risk reported by the US-Japan Radiation Effects Research Foundation (RERF) study of Hiroshima and Nagasaki is also consistent with the recent article on Nagasaki survivors from Nagasaki University and the Atomic Energy Research Institute, Kinki University, Japan. Mine et al. report upon the "apparently beneficial effect of low to intermediate doses of A-bomb radiation on human lifespan."[11] The decreased RR of noncancer male deaths to 0.65 ($p<0.05$) in the 0.50–0.99Gy dose range was to a large extent offset by the RR increase to 1.56 in cancer deaths (Table 11.2B). The male RR for total deaths in this dose range was 0.88 (Table 11.2A), with low statistical power ($p=0.34$). Fitting of a U-shaped dose-response relationship confirmed the significantly lower male RR for noncancerous diseases with maximum reduction to 0.76 ($p<0.02$) in the 1.00 to 1.49, average 1.08,Gy dose range (Table 11.2C). Female survivors, on the other hand, showed no significant change in RR of death from all causes until the 2.00 to 5.99Gy dose range was reached, in which there was a rise of the RR of both cancer deaths ($p<0.01$) and total deaths.

This significant difference in gender response to low and intermediate acute doses of radiation parallels the observations of Lorenz et al.[12] and Congdon[13] regarding comparison of the survival of male and female mice exposed to 0.0011Gy delivered in 8 hours daily from age 2 months to death. The longevity of irradiated male mice was significantly increased to 115% of irradiated controls (783 days vs 683 days). However, the longevity of female mice did not increase significantly above their control level of 803 days that was nearly matched by the extended lifespan of the irradiated male mice. Human populations also demonstrate that female longevity is greater than that of the male. These results suggest that low level irradiation of men and mice may stimulate a physiologic process in the male, relatively unenhanced in the female, that enables male longevity to approximate that of the female.

Table 11.2. Total Deaths and Relative Risks of Male and Female A-Bomb Survivors in Nagasaki During 1970–1988 Classified by T65 Dose

A. Initial numbers of subjects (1970), observed (*O*) and expected (*E*) numbers of total deaths and relative risk in 1970–1988 in Nagasaki among A-bomb survivors classified by T65D dose and sex.

T65D Dose (cGy)	Initial No. of Subjects		Total Deaths				Relative Risk (*O*:*E*)	
			Observed		Expected		All Causes	
	M	F	M	F	M	F	M	F
1–49	582	938	162	202	106·7	209	1·01	0·97
50–99	182	168	56	39	63·3	34·7	0·88	1·12
100–149	108	158	36	39	39·7	34·7	0·91	1·12
150–199	196	267	59	48	58·7	48	1·01	1·00
200–599	440	437	172	79	149·7	59·3	1·15	1·33

B. Observed (*O*) and expected (*E*) deaths in 1970–1988 in Nagasaki among A-bomb survivors classified by natural causes of death, sex and T65D dose.

Dose (cGy)	Number of Deaths from:			
	Non-Cancerous Diseases		Cancer	
	O	*O*:*E*	*O*	*O*:*E*
Males				
1–49	126	1·09	35	0·84
50–99	30	0·65	26	1·56
100–149	23	0·77	13	1·34
150–199	38	0·84	21	1·58
200–599	113	1·07	54	1·32
Females				
1–49	144	0·89	56	1·24
50–99	30	1·11	8	1·10
100–149	26	0·56	13	1·86
150–199	31	0·91	16	1·60
200–599	50	1·11	28	2·11

C. Calculated (*L*) values by the logistic function $p = 1/[1 + \exp\{-a - b_1(D - \langle D \rangle) - B_2(D - \langle D \rangle)^2 - cA\}]$ and observed (*O*) values for deaths from non-cancerous diseases in males in Nagasaki classified by T65D dose.

Dose (*D*) (cGy)	Number of Non-Cancer Deaths			
	Observed (*O*)	Corrected *O*:*E*	Calculated (*L*)	Corrected *L*:*E*
27 (1–49)	126	1·07	123	1·05
79 (50–99)	30	0·68	35·3	0·80
108 (100–149)	23	0·80	21·9	0·76
167 (150–199)	38	0·88	35·3	0·82
288 (200–599)	113	1·11	113·1	1·11

$\langle D \rangle = 130$; $a = -6{\cdot}14$ ($p < 0{\cdot}01$); $b_1 = 0{\cdot}29 \times 10^{-3}$ (p NS); $b_2 = 0{\cdot}213 \times 10^{-4}$ ($p < 0{\cdot}02$); $c = 0{\cdot}115$ ($p < 0{\cdot}01$).

NS = not significant.

Correlation of Lung Cancer Risk with Radon in Homes

The BEIR IV report [14] based upon a linear-no threshold extrapolation of the incidence of lung cancer in uranium mine workers exposed to high radon concentrations, predicts that the lifetime mortality risk of lung cancer is increased linearly by 10.8% per $pCiL^{-1}$. One $pCiL^{-1}$ approximates the world average[15] and is equivalent to 0.2 working-level-month (WLM).[16] The American Cancer Society projects for the United States 170,000 new cases of lung cancer in 1993.[17] Accordingly, prior continued home exposure of the population to one additional $pCiL^{-1}$ of radon would have produced 18,000 additional new cases of lung cancer in 1993. Five-year survival of treated lung cancer is only slightly more than 10%.[17] Relying upon the BEIR IV theoretical prediction, the Environmental Protection Agency (EPA) considers radon in the home to be the nation's leading health hazard.

However, there is no epidemiologic evidence to support the risks predicted by BEIR IV. To the contrary, epidemiologic studies in the United States,[18-20] Sweden,[21] Finland,[22] and China,[23] with increased radon concentrations up to 12 $pCiL^{-1}$, as well as in those areas below the average radon concentration of $1pCiL^{-1}$,[24-26] have all demonstrated a negative correlation of lung cancer with radon concentration. For a variety of reasons, these studies which contradict the linear-no threshold theory have been considered invalid by the National Academy of Sciences Committee on Biological Effects of Ionizing Radiation, National Council on Radiation Protection and Measurements, and the International Commission on Radiologic Protection. Criticisms have included poor statistical power, inadequate controls, and inadequate determination of the degree to which data have been altered by smoking and confounding factors such as numerous socioeconomic variables, geography, altitude, and climate. An extensive University of Pittsburgh National Survey of radon in homes was completed in 1992 that addresses these criticisms with excellent statistical power.

The University of Pittsburgh nationwide study based upon 272,000 measurements in the homes of 1217 counties was completed in 1992. This study and nine individual state studies were normalized to the EPA National Residential Radon Survey. The combined data set compiled from Pittsburgh, states, and EPA studies includes 1729 counties containing nearly 90% of the U.S. population. After deleting Arizona, California, and Florida, states with high retirement migration, and counties with incomplete data, 1601 counties remain included.[27] Figure 11.2 shows plots of mean age-adjusted lung cancer mortality rates (m) for white males (Figure 11.2a) and females (Figure 11.2c) vs mean radon levels (r) in homes of all counties within various ranges of r, along with the standard deviation of the mean, first and third quartiles, and the best linear fit to the data for individual counties, $m = 1a(1 + br)$. These mortality rates are corrected for smoking by use of Bureau of Census Population Surveys of smoking prevalence and BEIR IV risk estimates for smokers and nonsmokers, and are shown

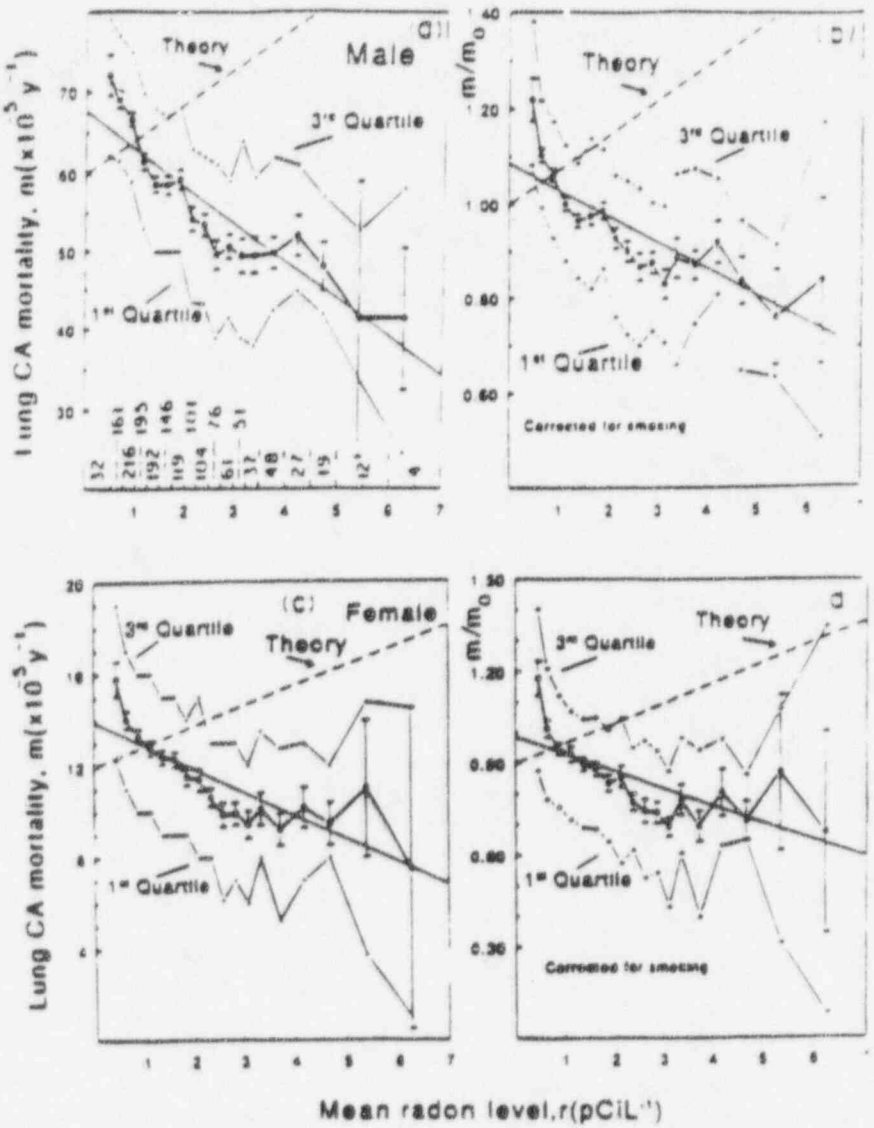

Figure 11.2. Lung cancer mortality rates in male (11.2a) and female (11.2c) residents vs mean radon level for 1601counties. Data points shown are average of ordinates for all counties within the range of r-values shown on the baseline of Figure 11.2a, the number of counties within that range is also shown there. Error bars are standard deviation of the mean, and the first and third quartiles of the distribution are also shown. Figure 11.1b, 1d are m/m_0 vs r which incorporate the effects of smoking prevalence. Theory lines are arbitrarily normalized lines increasing at a rate of $7.3\%/r_0$.

together with the best linear fit, $M = m/m_0 = A + Br$ in Figures 11.2(b) and 11.2(d). BEIR IV theory lines are normalized lines with slope B increasing mortality at a rate of 7.3%/pCiL^{-1}. After correction for variations in smoking frequency, there is a very strong tendency for lung cancer mortality to decrease with increasing mean radon level in homes, in sharp contrast to the increased mortality expected from the linear-no threshold theory. The discrepancy between theoretical and measured slopes is by 20 standard deviations. An earlier study based upon data for 965 counties furnished additional details of methodology and somewhat less steep negative slopes of m/m_0 vs r, with the discrepancy between theoretical and measured slopes by 7 standard deviations.[28]

Correction for the effects of smoking was made using the separate risk estimates for smokers and nonsmokers given by BEIR IV theory and estimations of the fraction(s) of the adult populations that smoke cigarettes in each county derived from Bureau of Census Surveys, with a correction factor for the fraction of the county population that lives in an urban area. The resultant slopes (B) in units of % per pCiL^{-1} are -7.3 ± 0.6 SD males and -8.3 ± 0.8 females, discrepant by 20 SD with the slope expected from BEIR IV theory, $B = +7.3$. Many other factors in addition to smoking are carefully analyzed to see whether any can explain this discrepancy. Pittsburgh radon measurements are consistent with EPA and state measurements. Potential problems concerning outliers and sampling issues are demonstrated to be absent. Uncertainties in lung cancer mortality rates (m) and smoking prevalence(S) are given elaborate consideration and shown to be unimportant causes of the discrepancy between theoretical and measured slopes.

A careful investigation was made of the possibility that one or more socioeconomic confounding factors other than smoking could correlate strongly and with opposite signs with both m and r. Those would introduce a strong negative correlation between m and r which would not be due to a direct causal relationship. The 54 socioeconomic variables (SEV) which are analyzed singly and in combination are listed in Table 11.3. The 54 values of B free of confounding by each SEV vary for males from -5.6 to -7.7, mean -6.9 ± 0.5, and for females from -5.4 to -9.1, mean -7.7 ± 0.8, and are quite close to values for the entire data set -7.3 and -8.3, respectively. Extensive statistical analysis of the possibility that some combination of SEV may act cooperatively to confound the m-r relationship concluded that the actual effect of confounding by combinations of SEV is to reduce the discrepancy between slopes by no more than 10%. Confounding by geography was also analyzed by considering the 34 states with at least 20 counties having known radon levels. The average of B-values is -6.1 for males and -7.2 for females; reductions in the discrepancy by 8.2% and 7.1%, respectively.

In addition to the 54 SEV and geography, also considered are the possible confounding physical features of altitude, average winter and summer temperatures, inches of precipitation, number of days per year with more than

Table 11.3. Socioeconomic Variables Used in the Analysis for Radon Radiation Lung Carcinogenesis in the Low Dose, Low Dose Rate Region

Population Characteristics	
PT–	total population
PD–	population/square mile
PI–	% pop. increase 1980–86
PU–	% in urban areas
PW–	% white
PS–	males/100 females
PE–	% age > 64y
PO–	% age > 74Y
PY–	% 5–17 years old
PN–	% born in state
PH–	persons/household
Vital and Health Statistics	
VS–	births/1000 pop.
VC–	% births to mothers < 20y
VD–	deaths/1000 pop.
VI–	infant deaths/1000 births
VM–	marriages/1000 pop.
VS–	divorces/1000 pop.
VP–	physicians/100,000 pop.
VH–	hospital beds/100,000 pop.
Social	
SS–	social sec. benefit/1000 pop.
SC–	crimes/100,000 pop.
SH–	% high school grad.
SU–	% college grad.
SE–	$/cap for education
Housing	
HO–	% owner occupied
HA–	% with >1 automobile
HV–	median value ($)
HN–	% < 8 years old
Economics	
EI–	$ per capita income
EH–	median household inc., $
EJ–	% persons below poverty level
EV–	% fam below poverty level
EU–	% unemployment
EW–	average salary, wage
EP–	$ per cap personal income
EM–	% earnings from manufact.
ER–	% earnings from retail trade
ES–	% earnings from services
EG–	% earnings from government
EF–	% earnings from farming
EA–	av. acres per farm
EL–	% mfg. firms > 100 emplys.
ED–	$/cap. sales–food stores
EC–	$/cap. sales–clothing
EX–	$/cap. sales–eating, drink
Government	
GF–	federal govt., $/cap
GL–	local govt., $/cap
GE–	% loc govt. expend.–educ.
GH–	% loc govt. expend.–health
GP–	% loc govt. expend.–police
GW–	% loc govt. expend.–welf
GR–	% loc govt. expend.–roads
GJ–	loc govt. empimt/10,000 Pop.
GV–	% vote for lead party, 1984

0.01 inch precipitation, average wind speed, and percent of time with sunshine as compared with the maximun. possible. Studies of these physical features concluded that none is an important confounding factor. The strong decrease in lung cancer mortality rates corrected for smoking frequency with increasing radon exposure is found in only the low altitude states or only the high altitude states; in only the warmest or only the coldest; in only the wettest or only the driest; etc. It is also found in only the states selected where the physical features are close to average. The BEIR IV theoretical prediction of lung cancer mortality from radon exposure corrected for smoking, $M = m/m_0 = A + Br$, does not take into account two recognized r-S correlations: (1) urban houses have 25% lower radon levels than rural houses and urban people smoke more frequently, and (2) houses of smokers have 10% lower radon levels than houses of nonsmokers. An extensive statistical study of the effects of these r-S correlations leads to the

conclusion that the BEIR IV prediction of B is reduced from +7.3 to +6.9, which contributes very little to decreasing the discrepancy with the large negative values of B, -7.3 and -8.3 obtained from the actual measured and reported data.

Linear-no threshold theories other than BEIR IV are considered which involve different treatments of smoking. Also considered is the "intensity of smoking." Analytic statistical study of these considerations lead to the conclusion that other theoretical predictions of B could reduce the discrepancy between 3% and 8%. The possibility that an unrecognized confounding factor could explain the discrepancy is recognized. However, the following properties are required of an unrecognized confounder that could resolve the discrepancy: (1) It must have a very strong correlation with lung cancer, comparable to that of cigarette smoking, but still be unrecognized; (2) It must have a very strong correlation of opposite sign with radon levels; (3) It must *not* be strongly correlated with any of the 54 socioeconomic variables (SEV); (4) It must be applicable in a wide variety of geographic areas and independent of altitude and climate. The first property alone requires of the unrecognized confounder that it must have increased by orders of magnitude since the beginning of this century, and have been much more important in males in the first half of the century, with effects on females rapidly catching up in recent years. The remaining properties impose additional requirements that are also most difficult to meet singly, while to satisfy the four simultaneously becomes incredible. These multiple restrictions upon an unknown confounder make it extremely improbable that one exists that would resolve the discrepancy.

These tests of the linear-no threshold theoretical prediction of lung cancer mortality induced by radon exposure, with the slope of the line determined by high dose exposures, demonstrate that the theory fails badly by gross overestimation of mortality in low dose, low dose rate range of radiation. A likely explanation is that stimulated biological defense mechanisms more than compensate for the radiation "insult" and are protective against cancer in a low dose, low dose rate range.

Breast Cancer in Women Exposed to Low Level Radiation

The Canadian study of fluoroscoped women includes 31,710 patients admitted to national sanitoriums between 1930 and 1952 and alive on January 1, 1950.[29] The results relate deaths from breast cancer between 1950 and 1980 that occurred 10 or more years after first exposure to fluoroscopic radiation. Fluoroscopic examination in Nova Scotia was performed AP (anterior-posterior), with the patient facing the fluoroscope. This position increased the breast dose to 50mGy per exposure compared to 2mGy per exposure in all the other provinces in which the examination was performed PA (posterior-anterior), with the patient's back against the fluoroscope. The standardized mortality rates from breast cancer for various dose ranges

is shown in Table 11.4 with the high dose, high dose rate data of Nova Scotia separated from the low dose rate data of the other provinces.

Linear and linear-quadratic dose-response models were compared with respect to data fit. The authors concluded "that the most appropriate form of dose response relation is a simple linear one, with different slopes for Nova Scotia and the other provinces." On the basis of this linear model, Table 11.5 predicts the lifetime excess risk of death from breast cancer after a single exposure to 1cGy, an amount approximately three times the average annual background radiation.

The epidemiologic data listed in Table 11.4 and the associated fitted models were not presented graphically. The omitted graph is shown in Figure 11.3, together with an empirical polynomial function fitted to the data. The linear model for 2mGy exposures discards the data at 0.15Gy and

Table 11.4. Canadian Study of the Incidence of Breast Cancer Following Fluoroscopic Examinations

Dose Gy	Standardized Rate Per 10^6 Person Years		
	Nova Scotia	Other Provinces	All Provinces
0–0.09	455.6 (131)	585.8 (288)	578.6 (301)
0.10–0.19		389.0 (29)	421.8 (32)
0.20–0.29		497.8 (24)	560.7 (26)
0.30–0.39	1709 (11)	630.5 (17)	650.8 (18)
0.40–0.69		632.1 (19)	610.0 (19)
0.70–0.99			1362 (13)
1.00–2.99	2060 (14)		1382 (17)
3.00–5.99	2811 (13)	873.1 (14)	2334 (14)
6.00–10.00	7582 (8)		8000 (9)
≥ 10.00	21.810 (12)		20.620 (13)

[a]The number of deaths is shown in parentheses. The calculations exclude the values for 10 years after the first exposure and have been standardized according to age at first exposure (10 to 14, 15 to 24, 25 to 34, and ≥ 35 years) and time since first exposure (10 to 14, 15 to 24, 25 to 34, and ≥ 35 years) to the distribution for the entire cohort.

Table 11.5. Predicted Lifetime Excess Risk of Death from Breast Cancer per Million Women after a Single Exposure to 1 cGy

Age at Exposure Yr.	Additive-Risk Model	Relative-Risk Model
10	125	108
20	95	89
30	67	55
40	42	27

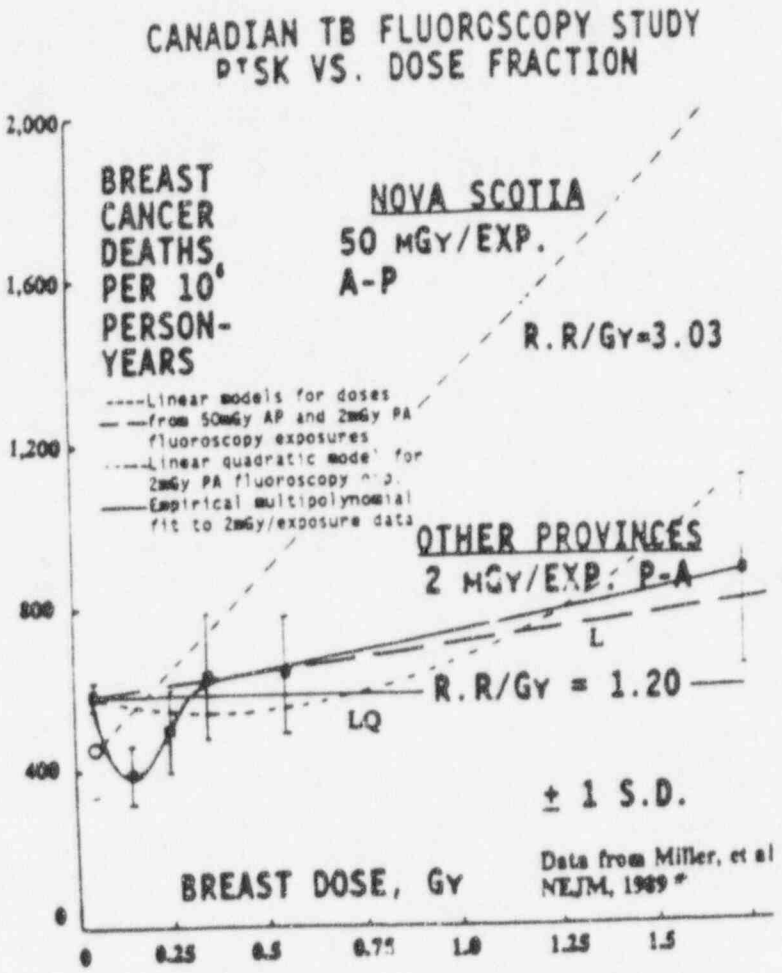

Figure 11.3. A graphic plot of the authors' data shown in Table 11.4. No graph was presented in their publication. The figure includes their "best fit" linear models, their linear quadratic model, and the best fit model of the author of this review to their data, an empirical polynomial function.

at 0.25Gy, the data with the best confidence limits. Compared to the controls receiving 0 to 0.09Gy, 0.15 Gy and 0.25 Gy demonstrate relative risks (RR) of 0.66 ($p < .01$) 0.85 ($p < .38$), respectively. While the RR of 0.85 is not statistically significant, it is consistent with the significant RR of 0.66 and the zero equivalent point of 0.31Gy indicated by the fitted polynomial function. For exposures above the zero equivalent point, the RR becomes positive after being negative in the range of 0 to 0.31 Gy. The decreased RR of breast cancer produced by low dose, low dose rate radiation were rejected a priori by the choice of mathematical models that extrapolate the

dose-risk relation from high dose exposures to low dose exposures. The risks associated with low dose exposures cannot be measured, the authors state "because the expected small excess of breast cancers would be obscured by the much higher background rate of breast cancer." Consequently, the unexpected was rejected since the possibility of a measurable decreased risk associated with low exposures appeared to be inconceivable. The highly significant decreased RR of 0.66 at 0.15Gy and the RR of 0.85 at 0.25Gy, both with the highest confidence limits of the entire study, are not shown graphically, not even discussed. Instead, the linear model for 0.002Gy exposures is used in Table 11.5 to predict the lifetime excess risk of death from breast cancer to be approximately 60 per million women after a single exposure to 1cGy at the age of 30. Nine hundred excess deaths from breast cancer are predicted theoretically from the exposure of one million women to 0.15Gy. However, the quantified low dose data predicts with better than 99% confidence limits that instead of causing 900 deaths, a dose of 0.15Gy would prevent 10,000 deaths in these million women.

Significant positive health effects associated with low level radiation have been demonstrated in a review of five epidemiologic studies: decreased mortality of nuclear shipyard workers, decreased noncancer mortality of atomic bomb survivors in both Hiroshima and Nagasaki and Nagasaki alone, decreased lung cancer mortality associated with increased radon exposure of the U.S. population, and decreased breast cancer mortality of women in Canada after having received multiple fluoroscopic examinations. The tendency to neglect or reject data that contradicts the linear-no threshold theory of radiation carcinogenesis is supported by confidence that chromosome aberration and gene mutation can be produced by a single particle of ionizing radiation and so initiate a malignancy. The number of such interactions with cell nuclei is both logically and demonstrably proportional to the dose. However, no consideration is given to biological defense mechanisms that could be stimulated further by low level increments of radiation above the background level. Such stimulated defense mechanisms could also decrease carcinogenesis by chemical and other non-ionizing agents as well as high level ionizing radiation. Multiple defense mechanisms at molecular, cellular, organ, and systemic levels involving enzymatic, hormonal, immunologic, and stress protein interactions are currently being demonstrated and confirmed by numerous investigators.[30-32] Recently a human radiation repair gene has been cloned and transfected into a mutant Chinese hamster with sensitivity to both ionizing radiation and certain alkylating agents resulting from defective repair of DNA strand breaks. These transfected mutants demonstrate overexpression of the human DNA repair minigene with repair capacity increased above that of the wild-type Chinese hamsters.[33]

Mounting reproducible evidence of the operation of various defense mechanisms and their stimulation by low dose ionizing radiation will provide further details of how biological defense mechanisms, nonoperative at

high doses, are stimulated and enhanced by low level radiation damage so as to overcorrect and predominate. These investigations have clarified why the negative health effects observed at high levels of radiation that effectively overwhelm these defense mechanisms c' inot be extrapolated to the low levels in which these stimulated defense mechanisms predominate with decreased cancer induction, decreased mortality, and other observed positive health effects.

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4. What Does the Nuclear Shipyard Worker Study Tell Us? *John Cameron (Univ of Wisconsin)*

The Nuclear Shipyard Workers Study[1] (NSWS) was designed to determine whether there was an excess risk of leukemia or other cancers associated with exposure to low levels of gamma radiation. The study was conducted at a cost of more than $10 million through a contract from the U.S. Department of Energy (DOE) to Matanoski at Johns Hopkins University, School of Hygiene and Public Health. The study was initiated in 1978. The study was completed in 1987. The results have never been published in the scientific literature. In 1991 the DOE made the 437-page study available to the public with a 2-page press release. In the debate on the health effects of low-level radiation, this study, which is perhaps the largest and best of its kind, with better dosimetry than most studies of large exposed populations, is largely ignored. It is fair to assume that if the result of this study had indicated a statistically significant 24% INCREASE in cancer mortality among the radiation-exposed shipyard workers, instead of a 24% DECREASE, there would have been extreme media and political and scientific attention (or perhaps even for a 2 to 4% statistically insignificant increase).

An NSWS technical advisory panel (TAP) chaired by Upton reviewed results and advised on the research. The author of this paper was a member of the TAP and of the NSWS Radiation Dosimetry Advisory Committee.

The study groups were selected from a database of almost 700 000 shipyard workers, including about 108 000 nuclear workers. The three study groups consisted of 28 542 nuclear workers with a working lifetime dose equivalent (DE) equal to or greater than 5 mSv (0.5 rem), referred to here as NW >5; 10 462 nuclear workers with a working lifetime DE <5 mSv, referred to here as NW < 5; and 33 352 nonnuclear workers, referred to as NNW. Five mSv is the amount of radiation a typical person receives from natural background radiation in ~20 months.

All three study groups were balanced in the initial sample to provide comparability on basic demographic characteristics to make between-group comparisons appropriate. The study included exposures received from the beginning of nuclear ship overhauls in the 1960s until the end of 1981.

Deaths in each of the groups were classified as due to all causes, leukemia, lymphatic and hematopoietic cancers (LHC), mesothelioma, and lung cancer. Mesothelioma was the only cancer that showed a significantly higher incidence for all groups. Mesothelioma deaths are considered a marker for asbestos exposure. There were only 36 mesothelioma deaths during the entire study of nearly a million person-years (in 70 730 workers).

Asbestos is also associated with lung cancer. The slightly higher incidence of lung cancer for all three groups compared to the general population may have been due to asbestos exposure.

Both nuclear worker groups had a lower death rate from leukemia and lymphatic and hematopoietic cancers than the nonnuclear group. All three groups had lower LHC death rates than the general population. Table I summarizes the data.

The most significant and surprising finding of the NSWS research was that the nuclear workers with the greatest radiation exposure, a cumulative lifetime occupational dose equivalent of 5 mSv or more, had a standardized mortality rate (SMR) of deaths from all causes of only 0.76 that for their age

TABLE I

Summary of Mortality, SMR, and 95% Confidence Interval for NW > 5, NW < 5, and NNW Shipyard Workers

RADIATION EXPOSURE:	NW>5	NW<5	NNW
CAUSE OF DEATH: N =	28,542	10,462	33,352
ALL CAUSES	2,797	1,168	4,453
SMR	0.76[a]	0.81[a]	1.00
(95% C.I.)	(0.73, 0.79)	(0.76, 0.86)	(0.97, 1.03)
LEUKEMIA	21	4	29
SMR	0.91	0.42	0.97
(95% C.I.)	(0.56, 1.39)	(0.11, 1.07)	(0.65, 1.39)
LHC[b]	50	13	84
SMR	0.82	0.53[a]	1.1
(95% C.I.)	(0.61, 1.08)	(0.28, 0.91)	(0.88, 1.37)
MESOTHELIOMA	18	8	10
SMR[c]	5.49[a]	6.14[a]	2.54
(95% C.I.)	(3.03, 8.08)	(2.48, 11.33)	(1.16, 4.43)
LUNG CANCER	237	98	306
SMR	1.07	1.11	1.15
(95% C.I.)	(0.94, 1.21)	(0.90, 1.35)	(1.02, 1.29)

[a]Statistically significant.
[b]Lymphatic and hematopoietic cancers.
[c]Associated with asbestos exposure.

and sex in the general population, while the nonnuclear workers had an SMR of 1.0. The standard deviation of the SMR was 0.015; i.e., the mortality rate for the nuclear workers was 16 standard deviations below that of the nonnuclear worker group[1].

The occupational exposure to the nuclear shipyard workers is comparable to the cumulated effective dose equivalent they received from natural radiation. Their total radiation, occupational plus natural, is comparable to natural radiation exposures in some parts of the world.

This study is probably the best scientific evidence, of many scientific data sources, to show that low levels of ionizing radiation exposure are without health hazard. The results clearly contradict the conclusions of BEIR that even small amounts of radiation have risk (in BEIR V and earlier reports), which have been largely based on the data from the Japanese atomic bomb survivors, who largely received their radiation exposures in very brief, high dose rate conditions and who are also now demonstrating that effective radiation health effects thresholds exist in the range of 20 to 200 rem.

1. "Health Effects of Low-Level Radiation in Shipyard Workers," U.S. Department of Energy Final Report (June 1991).

5. Residential Radon Exposure and Lung Cancer, *John S. Neuberger (University of Kansas Med Ctr)*

INTRODUCTION

Epidemiological studies of underground uranium and hard-rock miners, as well as animal experiments, indicate that the decay products of radon gas are a contributory cause of lung cancer. While one might expect that residential radon (progeny) exposure might be linked to an increase in lung cancer rates, sufficient evidence from residential studies is required to support this assumption. To date this evidence has not been definitive enough. There are differences in age, sex, dust exposure, and smoking between groups exposed in mines and in homes. A number of published studies have addressed this question[1]; a number of studies are under way.[2] The composite results from these studies may be useful in reducing the uncertainty. This paper summarizes and critiques results and discusses several methodological issues related to the studies.

METHODS

A literature review was undertaken and publications were classified according to exposure category, which included measured indoor air radon levels. Ongoing studies were ascertained from information provided by the International Agency for Research on Cancer,[3] project consultants, and radiation experts in all 50 U.S. state health departments. Current investigators provided detailed information on their studies. Published studies and ongoing protocols and questionnaires were translated into English, if necessary. Studies are included herein if they were case/control and included certain minimal information, including cigarette smoking, occupation, and measurements of indoor air radon.

RESULTS

Three published studies from Sweden all found a significant increase in risk for lung cancer from radon. On rural Oeland Island, an odds ratio (OR) of 5.1 [90% confidence interval (CI) = 1.4 to 18.5] was detected for exposures exceeding 150 Bq/m^3. In Stockholm, the equivalent risk was 1.7 (95% CI = 1.0 to 2.9). In a large study throughout Sweden, a significant increase in risk was seen for those smoking less than 10 cigarettes per day (relative risk = 3.7, 95% CI = 1.1 to 11.7). A small study in Maine found a significantly increased OR of 8.2 (95% CI = 2.1 to 31.7) for males under 65. One small study from Canada had an increased risk with radon (Port Hope), whereas a larger study did not (Winnipeg). Two reports were made of one study in New Jersey, which found a significant increase in risk with radon. For exposure to between 148 and 418 Bq/m^3, the OR_{adj} (adjusted OR) was 8.7 (90% CI = 1.3 to 57.8). A large study from Shenyang, China, found a nonsignificantly reduced risk as radon levels increased. No significant increase in risk with radon was found in studies conducted in Finland and Israel.

TABLE I

Odds Ratios of Published Studies and Number of Ongoing Studies of Residential Radon Exposure and Lung Cancer

Country	Odds Ratio	Number of Ongoing Studies
Sweden	**4.7**[a], 2.3, 1.8	0
U.S.	**8.2, 8.0**	8
Canada	2.4, 1.2	2
China	0.7	1
Finland	1.1	0
Israel	1.5	0
Other	-	Belgium 1, France 1, Germany 1, Hungary 1, Luxembourg 1, Russia 1, and United Kingdom 1.

[a]Statistically significant ($p \leq 0.05$ or ≤ 0.10) if in bold.

Out of ten published studies, six showed some evidence of a statistically significant increase in risk with radon (see Table I). Overall, for females the OR could fit into the range of 1.0 to 1.6. Problems with these studies included the use of 90% confidence intervals (instead of 95%), the large number of radon estimates, the lack of in-home mobility information, the lack of annual averages for radon readings, and the paucity of field quality assurance and quality control procedures for radon.

Ongoing studies are generally superior to the published studies in design. Many are obtaining 1-yr radon readings. A number are obtaining information on other risk factors for lung cancer. Results from these studies are crucially important. Meta-analyses have been suggested by some scientists; however, many studies lack comparability. Such analyses cannot supplant high-quality studies of adequate sample size.

1. J. NEUBERGER, "Residential Radon Exposure and Lung Cancer: An Overview of Published Studies," *Cancer Detect Prev.*, **15**, 435; **16**, 87 (1991).

2. J. S. NEUBERGER, "Residential Radon Exposure and Lung Cancer: An Overview of Ongoing Studies," *Health Phys.*, **63**, 503; **64**, 333 (1992).

3. *Directory of On-Going Research in Cancer Epidemiology*, IARC Scientific Publications No. 117, International Agency for Research on Cancer, Lyon, France (1992).

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News Flash

12:05 P.M. EDT March 6, 1996 by facsimile transmission to Forum Participants/Alternates, Federal Liaisons/Alternates

Health Physics Society Adopts Position re Low Doses of Radiation

Risks from Annual Doses Below 5 Rem Are Non-Existent or Too Small to Quantify

In the March 1996 issue of the Health Physics Society newsletter, the society published its position on how radiation risk should be expressed. The position, which is reprinted below, states in short that health risks should not be quantified for radiation doses exceeding background doses by less than 5 rem (5,000 millirem) per year or 10 rem during a lifetime. Because the health risks in this range are so small, only qualitative expressions of risk are appropriate, and the qualitative expressions should emphasize the "inability to detect any increased health detriment" from exposures at these levels.

Health Physics Society*
Position Statement

"Radiation Risk in Perspective"

Kenneth L. Mossman, Marvin Goldman, Frank Masse, William A. Mills, Keith J. Schiager, Richard J. Vetter

In accordance with current knowledge of radiation health risks, the Health Physics Society recommends against quantitative estimation of health risk below an individual dose of 5 rem in one year or a lifetime dose of 10 rem in addition to background radiation. Risk estimation in this dose range should be strictly qualitative accentuating a range of hypothetical health outcomes with an emphasis on the likely possibility of zero adverse health effects. The current philosophy of radiation protection is based on the assumption that any radiation dose, no matter how small, may result in human health effects, such as cancer and hereditary genetic damage. There is substantial and convincing scientific evidence for health risks at high dose. Below 10 rem (which includes occupational and environmental exposures), risk of health effects are either too small to be observed or are non-existent.

Current radiation protection standards and practices are based on the premise that any radiation dose, no matter how small, can result in detrimental health effects, such as cancer and genetic damage. Further, it is assumed that these effects are produced in direct proportion to the dose received, i.e., doubling the radiation dose results in a doubling of the effect. These two assumptions lead to a dose-response relationship, often referred to as the linear, no-threshold model, for estimating health effects at radiation dose levels of interest. There is, however, substantial scientific evidence that this model is an oversimplification of the dose-response relationship and results in an overestimation of health risks in the low dose range. Biological mechanisms including cellular repair of radiation injury, which are not accounted for by the linear, no-threshold model, reduce the likelihood of cancers and genetic effects

GUEST EDITORIAL

The Linear, No-Threshold Model in Radiation Protection: The HPS Response

Kenneth L. Mossman, HPS Scientific and Public Issues Committee

In this issue of the *Newsletter*, the Scientific and Public Issues Committee publishes the long-awaited Society position statement concerning the linear, no-threshold model (LN-T) in radiation protection. In recent months, the dialogue on the appropriateness of the LN-T model as a basis for establishing radiation protection standards and practices has reached the international arena. The Society's position should add a fresh perspective to the ongoing debate.

The Committee carefully considered the many viewpoints on the LN-T model, both pro and con, expressed in the *Newsletter*. Several Society members (David Gooden, Wade Patterson, Jim Tripodes, Al Tschaeche, and Gary Zeman) attended the Committee meeting 24 July 1995 in Boston during the HPS annual meeting and added significantly to the Committee's deliberations. Although many Committee members have been thinking about the LN-T problem for some time, Wade Patterson really got the ball rolling with a presentation to the HPS Board in January 1995 at the Charleston midyear meeting. Based on Wade's presentation, the Board charged the Scientific and Public Issues Committee with developing the position statement.

This position statement is based on the premise that there is substantial and convincing evidence for health risks at high dose; however, below 10 rem, risks of health effects either are too small to be observed or are non-existent. Accordingly, the Committee concluded that quantitative risk assessment below individual doses of 5 rem y^{-1} or 10 rem lifetime (above background) should be avoided because of insufficient epidemiological data to say anything about health risk. It became clear after several drafts, and after reading many letters in the *Newsletter* on the LN-T model, that the appropriateness of the LN-T model to predict risk at low doses is not the major question. The major question is: Should we be using *any* dose-response model to predict health risks at low dose? In the absence of epidemiological data in the low-dose region, and the need to extrapolate 2-3 orders of magnitude in dose (e.g., from direct observations of cancer at 30 rem to predicted numbers of cancers at an exposure limit for the general public of 100 mrem y^{-1}), is it appropriate to quantify risk?

The position statement recommends the use of qualitative expressions of risk below 5 rem in one year or 10 rem in a lifetime (above background). Clearly, there are many ways in which risk can be expressed qualitatively. For example, assume an individual receives a whole body dose of 10 mrem. The following is an appropriate qualitative expression of the risk:

The amount of radiation received is about 10 times lower than the allowable dose to individual members of the general public in one year. A radiation dose of this magnitude has not been associated with any adverse health effects and the risk is generally considered to be negligible.

Although the position statement does not specifically address the appropriateness of the LN-T model at low doses, national and international bodies such as NCRP and ICRP should be encouraged to further examine the issue. ■

Health Physics Society* Position Statement

"RADIATION RISK IN PERSPECTIVE"

Kenneth L. Mossman, Marvin Goldman, Frank Massé, William A. Mills, Keith J. Schiager, Richard J. Vetter

In accordance with current knowledge of radiation health risks, the Health Physics Society recommends against quantitative estimation of health risk below an individual dose of 5 rem[1] in one year or a lifetime dose of 10 rem in addition to background radiation. Risk estimation in this dose range should be strictly qualitative accentuating a range of hypothetical health outcomes with an emphasis on the likely possibility of zero adverse health effects. The current philosophy of radiation protection is based on the assumption that any radiation dose, no matter how small, may result in human health effects, such as cancer and hereditary genetic damage. There is substantial and convincing scientific evidence for health risks at high dose. Below 10 rem (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are non-existent.

Current radiation protection standards and practices are based on the premise that any radiation dose, no matter how small, can result in detrimental health effects, such as cancer and genetic damage. Further, it is assumed that these effects are produced in direct proportion to the dose received, i.e., doubling the radiation dose results in a doubling of the effect. These two assumptions lead to a dose-response relationship, often referred to as the linear, no-threshold model, for estimating health effects at radiation dose levels of interest. There is, however, substantial scientific evidence that this model is an oversimplification of the dose-response relationship and results in an overestimation of health risks in the low dose range. Biological mechanisms including cellular repair of radiation injury, which are not accounted for by the linear, no-threshold model, reduce the likelihood of cancers and genetic effects.

Radiogenic Health Effects Have Not Been Observed Below 10 Rem

Radiogenic health effects (primarily cancer) are observed in humans only at doses in excess of 10 rem delivered at high dose rates. Below this dose, estimation of adverse health effects is speculative. Risk estimates that are used to predict health effects in exposed individuals or populations are based on epidemiological studies of well-defined populations (e.g., the Japanese survivors of the atomic bombings in 1945 and medical patients) exposed to relatively high doses delivered at high dose rates. Epidemiological studies have not demonstrated adverse health effects in individuals exposed to small doses (less than 10 rem) delivered in a period of many years.

Limit Quantitative Risk Assessment to Doses at or Above 5 Rem per Year or 10 Rem Lifetime

In view of the above, the Society has concluded that estimates of risk should be limited to individuals receiving a dose of at least 5 rem in one year or a lifetime dose of at least 10 rem in addition to natural background. Below these doses, risk estimates should not be used; expressions of risk should only be qualitative emphasizing the inability to detect any increased health detriment (i.e., zero health effects is the most likely outcome).

Impact On Radiation Protection

Limiting the use of quantitative risk assessment, as described above, has the following implications for radiation protection:

(a) The possibility that health effects might occur at small doses should not be entirely discounted. Consequently, risk assessment at low doses should focus on establishing a range of health outcomes in the dose range of interest including the possibility of zero health effects.

(b) Collective dose (the sum of individual doses in an exposed population expressed as person-rem) remains a useful index for quantifying dose in large populations and in comparing the magnitude of exposures from different radiation sources. However, for a population in which all individuals receive lifetime doses of less than 10 rem above background, collective dose is a highly speculative and uncertain measure of risk and should not be quantified for the purposes of estimating population health risks.

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[1]The rem is the unit of effective dose. In international units, 1 rem = 0.01 sievert (Sv).

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*The Health Physics Society is a non-profit scientific organization dedicated exclusively to the protection of people and the environment from radiation. Since its formation in 1956, the Society has grown to more than 6,800 scientists, physicians, engineers, lawyers, and other professionals representing academia, industry, government, national laboratories, trade unions, and other organizations. The Society's objective is the protection of people and the environment from unnecessary exposure to radiation, and its concern is understanding, evaluating, and controlling the risks from radiation exposure relative to the benefits derived from the activities that produce the exposures. Official Position Statements are prepared and adopted in accordance with standard policies and procedures of the Society. The Society may be contacted at: 1313 Dolley Madison Blvd., Suite 402, McLean, VA 22101; Telephone: 703-790-1745; FAX: 703-790-2672; e-mail: hpsburkmgt@aol.com. ■

Reactions to HPS Position Paper

Risk Position Statement Endorsement Not Unanimous

C.E. Roessler, Ph.D., CHP
Member, HPS Board of Directors, 1993-96
Elysian, Minnesota

This is in regard to the HPS Position Statement "Radiation Risk in Perspective" that appeared in the March 1996 HPS *Newsletter*. The members of the Scientific and Public Issues (SPI) Committee should be acknowledged for the hard work and many hours that went into formulating a statement on this extremely important and highly controversial issue. However, I would like to emphasize a point for the readers who may not be familiar with the HPS position paper process in general and the background of this paper in particular.

The statement was developed and adopted by the SPI Committee (as identified on the author by-line) in accordance with the HPS Rule for the Committee. The statement was reviewed by the Board at several draft stages and was made available to the Board prior to release. However, the Board has not taken an official position. In informal discussion, there seemed to be majority concurrence but the statement does not have unanimous concurrence of the Board. ■

Response to Roessler Letter

Kenneth L. Mossman
SPI Committee
Scottsdale, Arizona

By Rule 7.1.24, HPS Board of Directors approval of an HPS Position Statement is not necessary. The rule simply requires that statements prepared by the Scientific and Public Issues Committee be transmitted to the Board prior to release to the membership (via publication in the *Newsletter*).

At an informal meeting of the Board held on Monday, 8 January 1996 President Mills discussed the position statement and asked for unofficial endorsement by the Board. Chuck Roessler's was the only negative vote. ■

Conflict in HPS Society Risk Position Paper

James E. Watson, Jr.
Chapel Hill, North Carolina

The Health Physics Society position statement titled "Radiation Risk in Perspective" was published in the March 1996 HPS *Newsletter*. This position statement correctly notes that there is evidence for health risks at high radiation doses, but at low doses risks of health effects are either too small to be observed or are non-existent. However, portions of the position statement imply that if health effects are not observed, they are non-existent. This ignores the possibility that health effects may have occurred, but were too small in number to be detected. The most conspicuous example of this is the statement that, "Below these doses (referring to 5 rem in one year or a lifetime dose of 10 rem), risk estimates should not be used; expressions of risk should only be qualitative emphasizing the inability to detect any increased health detriment (i.e., zero health effects is the most likely outcome)."

Even if non-zero health effects exist at low doses and if the number of effects is correctly estimated by extrapolation from data at high doses, many studies are not capable of detecting those effects. When effects are not detected, it is unknown whether or not they exist. To support a statement that "zero health effects is the most likely outcome" from exposure at low doses, it would be necessary to estimate the risk at those doses. This conflicts with the recommendation that risk estimates should not be used for low doses.

A later paragraph in the position statement is, in my opinion, more appropriate. It states that, "The possibility that health effects might occur at small doses should not be entirely discounted. Consequently, risk assessment at low doses should focus on establishing a range of health outcomes in the dose range of interest including the possibility of zero health effects." There is uncertainty regarding health effects at low doses, and that uncertainty should be stated. It is incorrect to imply that we are certain that health effects exist, or to imply that they do not exist because they were not detected. ■

Come now, and let us reason together.

— Isaiah 1:18

An EPA Response to Position Statement of the Health Physics Society: Radiation Risk in Perspective

Jerome Puskin, Ph.D.
Office of Radiation and Indoor Air, U.S. EPA

The Health Physics Society (HPS) position statement "Radiation Risk in Perspective" dismisses the traditional reliance in radiation protection on the linear, nonthreshold model and recommends that risks not be quantified at low doses. It is EPA's view that the HPS statement is seriously deficient in scientific justification, logical coherence, and clarity, and that the substance of the statement stands in sharp contradiction with recommendations from consensus committees established by NCRP, ICRP, UNSCEAR, and NAS. Implementation of the HPS recommendation would be unacceptable to exposed workers and members of the public and would effectively remove much of the basis for rational decision making about radiation protection.

The HPS paper states that, below 10 rem, risks of health effects are either too small to be observed or are non-existent. This neglects the epidemiological evidence for childhood cancer induction by *in utero* doses as low as 1-2 rem. For chronic dose rates of the order of natural background, direct evidence of human health effects from low dose irradiation is indeed lacking. Given statistical and other methodological limitations to epidemiology, this may always be the case. There is, nevertheless, strong circumstantial evidence that low-dose radiation can increase the risk of cancer and that the risk per unit dose at low doses and dose rates is not dramatically lower than what is observed in populations receiving an acute high dose exposure.

It is widely accepted that carcinogenesis is a multistage process in which a single cell gives rise to a tumor. Mutation of the cell's DNA is required in one or more of the steps leading to malignancy. Since cancer is a common disease, it is obvious that the background rate for each of these steps is not zero. It is therefore expected that any exposure increasing the rate of somatic mutations would increase the risk of cancer. There is compelling evidence that radiation is mutagenic down to the lowest doses. It appears that clusters of ionization generated by even a single electron track are capable of producing DNA damage that is not faithfully repaired with 100% efficiency (UNSCEAR 1993). The HPS committee fails to recognize that the existence of repair does not imply a threshold, or even a nonlinearity in the dose response at low doses.

It is reasonable to expect nonlinearity at sufficiently high doses and dose rates as the efficiency of repair decreases. However, human epidemiological data indicate approximate linearity in the dose response for solid tumors; consequently, there is no basis for expecting a large reduction in the risk per unit dose at lower doses in humans. An in-depth review of the influence of dose and dose rate on stochastic effects of radiation has been conducted by UNSCEAR, which concluded that the risk may be reduced by a "DDREF" factor for doses below 20 rad or dose rates below 0.01 rad min^{-1}, but that the DDREF in humans appears to be quite low: about 2 for leukemia and approximately 1 for most solid tumors (UNSCEAR 1993).

UNSCEAR has also recently reviewed the evidence pertaining to a possible beneficial effect of radiation at low doses (UNSCEAR 1994). Although the UNSCEAR committee found evidence for a protective effect ("adaptive response") of low-dose radiation in some cellular systems, likely resulting from induction of a DNA repair process, they found that: "[t]he presence of an adaptive response is not readily evident from the results of experiments in mammalian organisms in terms of reduced tumour induction. The low statistical power of the epidemiology studies also prevents a clear statement on the presence of an adaptive response in humans exposed to low doses." Thus, the significance of the adaptive response in cell preparations to human risk estimation is highly speculative. The UNSCEAR report states that "it would be premature to conclude that cellular adaptive responses could convey possible beneficial effects to the organism that would outweigh the detrimental effects of exposure."

Another incisive review of the low dose issue has been published by the NRPB (NRPB 1995). Their conclusions, cited below, are diametrically opposed to the HPS position:

> ...data relating to the role of gene mutations in tumorigenesis, the monoclonal origin of tumors, and the relationship between DNA damage repair, gene/chromosomal mutation and neoplasia are well established and broadly consistent with the thesis that, at low doses and low dose rates, the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold-like component. Whilst adaptive responses or other protective mechanisms may influence the risk of tumour development, they do not provide a sound basis for judgement that tumorigenic response at low doses and low dose rates of radiation is likely to have a non-linear component which might result in a dose threshold below which the risk may approach zero. These mechanistic studies, in addition to the epidemiological information, indicate that for radiation protection purposes there is little basis for arguing that low radiation doses (about 10 mGy) would have no associated cancer risk and that, in the present state of knowledge, it is ap-

propriate to assume an increasing risk with increasing dose.

The HPS position also suffers from imprecision in language and apparent internal inconsistencies. On the one hand, it recommends risks not be quantified at low doses; on the other, it acknowledges "[t]he possibility of health effects at small doses should not be entirely discounted..." and recommends that "risk assessment at low doses should focus on establishing a range of health outcomes in the dose range of interest including the possibility of zero health effects." It is unclear how one establishes such a range without quantifying the potential risk. Another point of confusion is that, in places, the HPS paper seems only to suggest that, because epidemiological studies lack power in the low dose region, we cannot confidently estimate risks there, but elsewhere it makes the somewhat ambiguous claim that, for low doses, "zero effects is the most likely outcome," which would seem to imply strong evidence for a threshold.

A major use of collective dose calculations is to provide a measure of benefits (from dose reduction measures) that can be weighed against costs. Dispensing with the collective dose measure would undermine the use of cost-benefit (ALARA) considerations in radiation protection. According to the HPS approach, a 9-rem lifetime dose to each of 100,000 people is no worse than the same dose to a single person. The NCRP recently published an evaluation of the collective dose issue (NCRP 1995) and drew conclusions opposite to those of the HPS. The NCRP recommended that all doses be included in collective dose calculations, *no matter how small*.

Included in a footnote to the HPS position is a brief statement of the organization's purpose:

> The Society's objective is the protection of people and the environment from unnecessary exposure to radiation, and its concern is understanding, evaluating, and controlling the risks from radiation exposure relative to the benefits derived from the activities that produce the exposures.

Unfortunately, "Radiation Risk in Perspective" represents an abandonment of these ideals in pursuit of an illusory objective of convincing the public that no risk can be attributed to low-dose radiation.

It is the EPA position that, so long as the uncertainties are properly assessed and communicated, quantitative risk estimates at low doses serve a legitimate role in deciding policy and in providing perspective for the public.

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United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 1994 Report to the General Assembly. United Nations, NY; 1994. ■

Observations Offered on Statement

Jerry J. Cohen
Walnut Creek, California

Regarding the HPS Position Statement on "Radiation Risk in Perspective" (March 1996 issue of HPS *Newsletter*), I would like to offer a few observations and questions. I believe the recommendation to limit risk assessment to doses above 5 rem in one year or a lifetime dose of 10 rem reflects sound science and logic.

Although the recommended practice would be in the best public interest, I somehow doubt that it will be warmly received by regulators or radiation advisory groups. However, the discussion on implications in the position statement falls short. Unless I am missing something, it seems that general acceptance of the recommendation and its implementation would constitute nothing less than a major upheaval in current radiation safety practice. Some questions related to the statement are:

1. What happens to ALARA? Current policy limits allowable doses to levels (below 5 rem y^{-1}) where, according to the position statement, risk assessment would be invalid. In ICRP guidance, dose optimization (ALARA) requires a consideration of collective dose and risk assessment. Should ALARA be abandoned? If not, how would it apply?
2. Predicted consequences of all currently proposed methods of radioactive waste disposal indicate doses far less than 5 rem in one year or a lifetime dose of 10 rem. Are societal concerns regarding radwaste disposal unwarranted?
3. Should clean-up efforts at contaminated sites be abandoned in cases where predicted dose consequences are well below levels where valid risk assessment could be performed?
4. In focusing on health consequences in the low-dose range, shouldn't we consider both positive and negative effects in addition to the possibility of zero effects? Given that we don't really know the nature and extent of these effects, how can the results of this consideration be applied in decision making? ■

Concerns Expressed About Position Statement

F. Owen Hoffman, Ph.D.
Oak Ridge, Tennessee
Iulian Apostoaei, M.S.
Oak Ridge, Tennessee

We would like to express our concerns about the recently issued Health Physics Society's Position Statement on "Radiation Risk in Perspective" (Mossman et al. 1996). Committee 1 of the International Commission on Radiological Protection (ICRP) has recently reviewed the current evidence for the shape of the dose-response relationship at low doses and unanimously concluded that the linear dose-response relationship continues to be assumed for purposes of radiation protection (Cox 1995). Using ICRP recommendations for the nominal probability coefficients for stochastic effects (ICRP 1991, Cox 1995), a 10 rem effective dose would be equivalent to a lifetime risk (detriment) between 3.7×10^{-3} and 1.5×10^{-2}. This is considerably higher than the 10^{-4} to 10^{-6} risk range typically assumed for the regulation of environmental carcinogens (Kocher and Hoffman 1991).

Furthermore, we do not agree with the assertion made in the Health Physics Society's Position Statement that radiogenic effects have not been observed below 10 rem effective dose. Ron et al. (1995) clearly show evidence of a statistically significant linear dose response relationship for thyroid cancer that holds for doses even below 10 rad to the thyroid. Using a quality factor of 1 (x-ray therapy) and a tissue weighting factor of 0.05 for the thyroid gland, this translates to an effective dose of 0.5 rem, which is considerably less than the asserted epidemiological threshold in the Health Physics Society's Position Statement. Five of the seven epidemiological studies considered in Ron et al. (1995) have a mean dose to the thyroid that is equivalent to an effective dose lower than 10 rem. For the case in which x-ray therapy is given to children suffering from tinea capitis, the mean thyroid dose was 9 rad (range 5 to 50 rad), or an effective dose of 0.45 rem (range 0.25 to 2.5 rem).

Finally, we would like to state our objection to the recommendation made in the Health Physics Society Position Statement that quantitative estimates of risk should not be extended below an effective dose of 5 rem per year or 10 rem in a lifetime because of the presence of high uncertainty about the shape of the dose-response model below the limits of epidemiological detection. We contend that as long as risk is suspected, it can be quantified provided that uncertainty in the risk estimates is also disclosed. In this case, the analysis should include all sources of uncertainty, including uncertainty in the dose-response model. This practice represents the state of the art in quantitative risk analysis (NRC 1994a and 1994b, NRC 1995, NCRP in press). The presence of uncertainty should never be used as a reason to preclude the calculation of risk unless the true risk is known to be zero with absolute certainty.

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■

Criticism of the HPS Position Statement "Radiation Risk in Perspective"

Paul S. Stansbury
Pasco, Washington

The "Radiation Risk in Perspective" Position Statement attempted to be brief and understandable to the lay reader, but it has serious flaws.

The first is its title. It is misleading. The paper is not about perspective, "the interrelation in which a subject or its parts are mentally viewed" (Webster's Ninth Collegiate). Instead it discusses "Limiting the use of quantitative risk assessment . . . "(fifth paragraph), quite a different subject.

Second, it incorrectly states that "[b]iological mechanisms . . . are not accounted for by the linear, no-threshold model." The NCRP specifically recommends a dose

rate effectiveness factor of two until more is known about "the complex process of multistage carcinogenesis" (NCRP 1993).

Last and most significantly, the Position Statement recommends that risk estimates of radiogenic health effects that are less than observable should not be used. Why not? We use information about a sample with radioactivity that is less than detectable, even negative. A mean of worker doses can be inferred from analysis of the results above the minimum detectable even if the mean itself would be undetectable. Such a measure is often useful in showing the success of ALARA efforts. When an expectation value describing the frequency of an on-off or yes-no event is less than 0.5, it is true that the most likely value is zero. It does not mean that such an expectation number has zero value.

The problem with expectation values describing low-level doses in a large population is their misuse in risk management decisions. For example, an expectation of 0.15 cancer deaths (3 person-Sv) is often viewed as "three times better" than an expectation of 0.45 (9 person-Sv). It is not always true that three times as much money should be spent to cause that threefold reduction. Smoke detectors caused 8 person-Sv in the U.S. in the 1980s (NCRP 1987). Would smoke detectors that cost three times as much but caused one third of the population dose be worth it? Of course not, but one better not ask public opinion, aided by the media, courts, and juries to make the decision. Often, it seems society wants to spend 30 times as much to reduce threefold an already low risk.

Using (or misusing) risk assessment values is where the HPS needs to make strong, clear, and scrupulously true statements. As much as I admire the individuals who put together the Position Statement, I have called some Board members about this one.

This letter expresses my own opinions and conclusions, and may or may not be the views of the U.S. Dept. Of Energy, the Pacific Northwest National Laboratory, or Battelle.

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Opposition to HPS Position Paper "Radiation Risk in Perspective"

Daniel J. Strom, Ph.D., CHP
Richland, Washington

The Health Physics Society's March 1996 *Newsletter* contains a Health Physics Society Position Statement "Radiation Risk in Perspective" (Mossman et al. 1996). I disagree with the Statement, and feel it will harm the credibility of the Health Physics Society (HPS) as a radiation protection organization.

The Statement does not distinguish between expectation values of risk in a population and health outcomes for individuals. The statement "zero health effects is the most likely outcome" is even true under the linear, no-threshold model for a *population* in which the collective dose leads to an expectation value of <0.5 cancer. The statement "zero health effects is the most likely outcome" is also true under the linear, no-threshold model for any *individual*. If one accepts a cancer risk of 5 percent per Sv, then to have an expected probability >0.5 for an individual cancer requires 10 Sv. If the Statement means that 'the most likely outcome of exposing each of the U.S. population of 263 million persons to 5 rem (above background) is zero health effects,' it should state that rather than implying it. I personally do not believe that depositing 900×10^6 joules of ionizing energy ($0.05\ J\ kg^{-1} \times 70\ kg \times 2.63 \times 10^8$) in a group of people will have the "most likely outcome of zero health effects." There *may be* zero health effects, but we do not base radiation protection on "maybe it's safe."

The Statement does not distinguish between science's ability to detect effects and whether there *are* effects. No one who has studied statistical inference, as applied to counting radiation events in a detector in the presence of background radiation, doubts that there can be radioactive material present in a sample that cannot be distinguished from background. The difficulty of detecting it increases as background increases. This understanding that 'something may be present but one can't detect it' is not applied to the minimum detection limits of epidemiology in the Statement, insofar as it does not distinguish between the conclusions that 'one won't be able to detect any adverse health effects' and 'there are no adverse health effects.' The former is true; the latter is unknown. There may be adverse health effects that will never be observable epidemiologically (NCRP 1995; Cox 1995). This doesn't mean that those health effects are not real, and

that efforts should not be made to avert them. Given the enormous background of cancer (over 30 percent of people get cancer and nearly 20 percent die of cancer; National Research Council 1990) and heritable ill-health (3.3 percent of live births have untow[illegible] outcomes with a genetic component; Brown and M[illegible]all 1993) in human populations, numbers of real adverse health effects that are significant from a public health standpoint may never be detectable, unless a unique signature for radiation-induced health effects is identified.

In th[illegible] context of the basis for current radiation protection standards, the statement "doubling the radiation dose results in a doubling of the effect" is simplistic and confusing, since it is neither true for deterministic effects nor for stochastic effects (cancer or heritable ill health). The statement is only true for the *probabilities* of stochastic effects in populations. The statement should read ". . . results in a doubling of the risk of the effect" or ". . . results in a doubling of the likelihood of the effect."

The statement "[b]iological mechanisms including cellular repair of radiation injury, which are not accounted for by the linear, no-threshold model, reduce the likelihood of cancers and genetic effects" is unsupported. I am unaware of evidence in the peer-reviewed scientific literature that repair reduces the likelihood of genetic effects *in humans*, the criterion th[illegible] is used in the next paragraph of the Statement. The dose- and dose rate-effectiveness factor (DDREF) is used in the linear, no-threshold model (for cancer) to account for repair (NCRP 1980).

The statement "[t]he possibility that health effects might occur at small doses should not be entirely discounted" implies to me that one can or should at least *partially* discount such a possibility. This simply does not follow from the preceding material in the Statement. The word "entirely" should be removed.

I am dismayed that the ideas of "prudent" and "conservative," which have been used in the face of uncertainty (that was acknowledged even in the Statement), seem to have been discarde[illegible] This contradicts recommendations of ICRP, NCRP, UNSCEAR, NAS BEIR Committees, and the United Kingdom's National Radiological Protection Board (Cox et al. 1995). I do not find that the Statement justifies its contradiction of the well-reasoned recommendations (supported by references) of those bodies.

For the above reasons, I personally do not support the HPS Position Statement "Radiation Risk in Perspective." More and more, it seems to me that some members of the HPS speak as if "radiation protection" means "protecting radiation's good name" rather than protecting humankind and the environment from the harmful effects of radiation. This Statement seems to have the tone of the former meaning.

I offer the following in place of the Statement:

1. Low doses of radiation (below 5 rem) are *very* unlikely to cause health effects in any single exposed individual. If received by every member of a large population, low doses of radiation may or may not increase the incidence of cancer and heritable ill health in such populations.
2. If such radiation-induced increases in incidence of cancer and heritable ill health do occur, they would not be observable in human populations by standard public health methods because these increases would be small when compared to the enormous natural incidence of these effects in the absence of additional radiation exposure.
3. Despite the fact that such possible increases in incidence of adverse health effects are not directly observable, the current state of knowledge cannot rule them out, and there are many reasons to believe that they do occur. Such non-observable effects may be real, large enough to be of concern, and of sufficient impact to justify some expenditure of public and private funds to minimize or manage their occurrence. Such expenditure is particularly justified when the radiation exposure is *imposed* on members of the public who neither control nor benefit from it, and for especially susceptible subgroups such as those with compromised immune systems.
4. In the face of the uncertainty about effects of low doses, those who hold the public trust for radiation protection choose to err on the side of safety by assuming that any increase of radiation dose brings an increase in likelihood of adverse health effects. This assumption is unlikely to underestimate radiation risks, and may well overestimate them. This assumption also leads to a philosophy of keeping doses as low as reasonably achievable (ALARA), keeping in mind the costs, feasibility, and social values associated with dose management.
5. Society should not squander resources, public or private, attempting to reduce radiation risks to zero. There are many opportunities to improve public and worker health that are more cost effective than some present and proposed radiation protection activities. The linear, no-threshold model should not be applied without a quantitative evaluation of the "reasonably" in "as low as reasonably achievable," which considers these other opportunities.

The opinions expressed here are entirely my own, and may or may not be the views of the U.S. Department of Energy, the Pacific Northwest National Laboratory, or Battelle.

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Objection to the "Radiation Risk in Perspective" Position Statement

Darryl Kaurin
Piscataway, New Jersey

I appreciate the tremendous effort, aptitude, and enthusiasm of the Scientific and Public Issues Committee in developing the "Radiation Risk in Perspective" Health Physics Society Position Statement. I have applauded previous position statements and the efforts by our leaders such as Kenneth Mossman for influencing the affairs of the national government in issues relating to radiation use and safety. I do, however, have very strong objections to the most recent Health Physics Society Position Statement.

That radiogenic health effects have not been seen in humans at doses below 5 rem is not true for the developing fetus (BEIR V, 1990, p.353). That low dose rates are much less effective than high dose rates is true in most cases, but Cardis et al. (1995) show that doses accumulated over the years in radiation workers result in leukemia (excluding CCL) risk estimates similar to those developed from the high dose rate A-Bomb survivor data.

Other objections to the statement include the following. While the position statement claims to avoid choosing between the Linear-No-Threshold model and an alternative in the "Guest Editorial," the statement effectively assigns a threshold of 5/10 rem per year/lifetime. The omission of ALARA implies a departure from use of the concept, or a threshold action limit for ALARA controls. Effective doses calculated using risk-based tissue radiation weighting factors given in ICRP-60 (1991) under the position statement should not be calculated unless doses are greater than 5/10 rem per year/lifetime. The statement implies repeatedly that health effects are negligible at low doses, since we can not measure the effects, which sounds more political than scientific.

It is my opinion that scientists should quantify and explain the natural order. Certainly, the risks at low doses are small, but they should be quantified and given statistical confidence intervals. To simply state that "since the effects cannot be measured, they are of no concern" does not help science and causes a loss of credibility with the public.

A large number of my colleagues have expressed similar reservations to the position statement. Since this statement should reflect the views of the society as a whole, I suggest that it be modified to address the concerns discussed.

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A Challenge to ICRP/NCRP Regarding the Linear Hypothesis

A. N. Tschaeche, CHP
Idaho Falls, Idaho

From all of the recent discussion about the Linear Hypothesis (LH), low-dose radiation risk, and regulatory requirements for ALARA, I think I perceive a pattern emerging. There are two camps into which most of those who have communicated about these subjects fall. One camp fully, and without reservation, supports the LH and all of its corollaries (ALARA and collective dose) for all purposes (e.g., standards setting, representing reality, legal maters, communicating with the public and legislators, developing risk numbers). I call that camp the "support camp" or "SC" for short. The other camp rejects the LH and its corollaries for any purpose. I call that camp the "reject camp" or "RC" for short. The recently pub-

lished HPS position paper on "Radiation Risk in Perspective" rejects the LH for developing risk numbers below 5 rem per year or 10 rem per lifetime. I might guess, if the HPS were pressed, it could extend that rejection to all other purposes.

The RCs reject the LH because there are data (Cohen, Evans, Muckerheide) that demonstrate its falsehood. In the scientific method, it only takes one piece of data to destroy a hypothesis or theory. The RCs fear the enormous cost with no measurable benefit of the regulatory application of ALARA and collective dose to environmental cleanup and decommissioning and decontamination work. They fear the public's perception that there is no dose without risk will result in the death of the nuclear industry.

The SCs believe in the LH because the existence of a threshold for low dose effects is not proven. The SCs fear unknown consequences if the LH goes away. For example, Strom queries: "What are the consequences if we're wrong (if we tell the public there are no risks from low doses)?" (HPS Newsletter, 1995). The ICRP and NCRP clearly do not want to even think about what would happen if their recommendations on standards for radiation protection should result in any harm to humans. In this thought, I agree.

However, their statement that there MAY be an effect has been corrupted into there IS an effect. The result is the public fears any radiation exposure, no matter how small. Why can't the ICRP/NCRP take the position that, until harm is demonstrated, doses of radiation below some agreed-on numerical value are safe and no resources need be expended to keep doses below that level? The opposite position (the one ICRP and NCRP take now) can never be demonstrated. Harm can be demonstrated. Which side should we be on at this point when we know much more about radiation effects than we did 50 years ago? And the ICRP/NCRP position has been corrupted so that the public fears even the tiniest dose?

I challenge the ICRP and NCRP to take everything into account, including the current public corruption of their recommendations leading to public fear of radiation and resulting legal and legislative obstruction of the beneficial use of radiation and radioactive material, the huge projected costs for decontamination, decommissioning, and waste disposal, the hormesis data, and the current information on cell repair and radiation stimulation effects, and revise their recommendations so that they cannot be corrupted and lead to public fear of low doses. I perceive that the ICRP and NCRP recommendations are one of the, if not THE, reason the nuclear industry is failing in the USA. Do not other members of the Health Physics Society agree? If so, we trust that the ICRP and NCRP members also agree and will take appropriate action to revise their recommendations.

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Editor's Note:

Some thoughts came to mind while I was diligently copy editing all of the correspondence regarding the linear no-threshold (LN-T) dose response model, the Society's "Radiation Risk in Perspective" Position Statement, and this *Newsletter* issue's comments on the Position Statement. Some people think that the controversy over the LN-T model falls into two camps. Al Tschaeche in his response to the Position Statement calls the camps SC (support camp) and RC (reject camp).

I keep thinking back to two recent *Newsletter* guest editorials. In the October 1995 issue, Steve Garry suggested that too much attention is being placed on the wrong issue—the linear, no-threshold theory at low doses instead of on the cost-effectiveness of environmental regulations. President-elect Rich Vetter in his December 1995 guest editorial said: ". . . the real issue is not the validity of the model but its application and social consequences."

Are they not on the right track? We will never have a risk-free world. It seems that the real issue is not whether the model is correct (we may never know that), but how it is applied and what the social consequences are of the application.

While risks of low-level radiation can be predicted with an LN-T model, many maintain that there is a practical threshold at which our resources are better spent dealing with other, more significant risks.

Perhaps this is the approach that the SPI Committee was trying to take in their recent Position Statement. However, the Statement has evoked a lot of concern over the recommendation that quantitative risk assessment should not be used below a certain level. It seems we still have two camps.

Is there a way to continue to expand on these ideas to bring everyone into the same camp?

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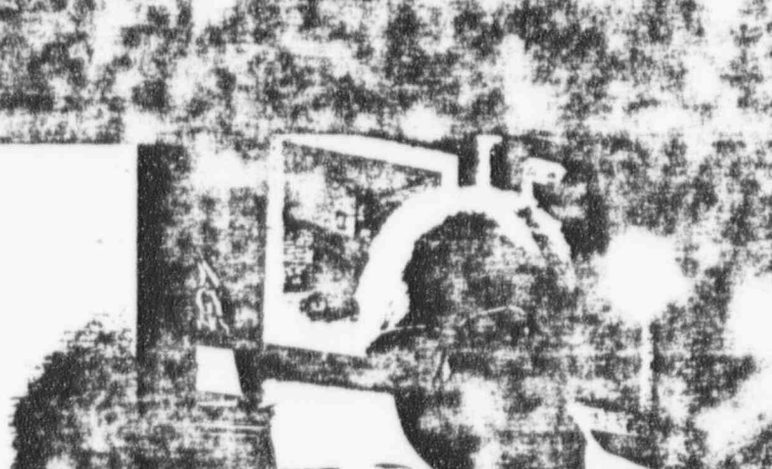
VOL. 7, NO. 6, JUNE 1996

THE RADIATION PROTECTION JOURNAL

The Official Journal of
the Health Physics Society



THE LINEAR NO-THRESHOLD MODEL: IS IT STILL VALID FOR THE PREDICTION OF DOSE-EFFECTS AND RISKS FROM LOW LEVEL RADIATION EXPOSURE?

PROCEEDINGS OF A CONFERENCE TO HONOR VICTOR BOND IN HIS 75TH YEAR

THE VALIDITY of the linear no-threshold model in radiation protection has been the subject of great debate in the scientific community. It is well known that a very high dose threshold exists for cancer induction with respect to radium deposited in bone, yet human data for other types of high and low LET exposures have not been as conclusive. For these reasons, experts from both sides of the issue were brought together to debate the current scientific basis for radiation protection using the linear no-threshold model.

The question of the validity of the linear no-threshold model in radiation protection has been a motivating force during a significant part of Dr. Bond's long and distinguished career. This conference was held in order to honor Dr. Bond's lifelong achievements and contributions to the scientific knowledge of radiation health effects and radiobiology.

MEETING PROGRAM

3 November 1994

8:30 A.M. **Greetings**—*N. P. Samios, Director, Brookhaven National Laboratory*
Objective of Conference—*E. P. Cronkite (BNL)*

I. Acute and Long-Term Effects of High and Low-Doses—*Chair, E. P. Cronkite (BNL)*

9:00 A.M. **Present System of Quantities and Units for Radiation Protection**—*W. Sinclair National Council on Radiation Protection, Bethesda, MD)*

9:30 A.M. **Whole-Body Radiation Effects on Human Beings—Prognosis Based on Severity of Organ Effects**—*T. M. Fliedner (University of Ulm, Germany)*

10:00 A.M. **Radioepidemiology of the A-Bomb Survivors**—*W. J. Schull (University of Texas, Houston, TX)*

10:30 A.M. *Coffee Break*

11:00 A.M. **Radioepidemiology of Occupational Groups (Naval Shipyards, Nuclear Power Employees, etc.)**—*G. Matanoski (Johns Hopkins University, Baltimore, MD)*

12:15 P.M. *Lunch*

II. Energy Deposition Events and Quantal Cell Responses—*Chair, R. Setlow (BNL)*

1:30 P.M. **Track Structure and Intracellular Organization**—*C. R. Geard (Columbia University, New York, NY)*

2:00 P.M. **The Role of Radiation in Multistep Carcinogenesis**—*J. Trosko (University of Michigan, Ann Arbor, MI)*

2:30 P.M. **Radiation Effects at Low Doses**—*R. J. M. Fry (Oak Ridge National Laboratory, TN)*

3:00 P.M. *Coffee Break*

3:30 P.M. **Quantization of Energy for Radiobiological Purposes**—*H. Rossi (Columbia University, New York, NY)*

4:00 P.M. **The Radiobiological Challenges Posed by Microdosimetry**—*A. Kellerer (Inst. Strahlenbiologie, Munich, Germany)*

4:30 P.M. **General Discussion**

5:15 P.M. **Adjourn**

4 November 1994

III. Microdosimetric Concepts and Their Impacts on Radiation Protection—*Chair, L. E. Feinendegen (BNL)*

9:00 A.M. **The Expression of Biologic Effects Through Microdosimetry**—*M. Varma (DOE)*

9:30 A.M. **Derivation of Hit Size Effectiveness Function (HSEF) for Diverse Biologic Effects**—*M. Zaider (Columbia University, New York, NY)*

10:00 A.M. **Assessing Biological Effects in Cells from Ionizing Radiation in Terms of Relative Local Effectiveness and RBE**—*L. E. Feinendegen (BNL)*

10:30 A.M. *Coffee Break*

11:00 A.M. **General Discussion**

11:30 A.M. *Lunch*

0017-9078/96/$3.00/0

Paper

EFFECTS OF LOW DOSES OF RADIATION

R. J. M. Fry*

Abstract—This is a brief review of what is known from experimental studies about the effects of low doses of radiation, and approaches that might improve risk estimates are discussed. The dose-response relationships for cancer induction by radiation vary markedly between tissues. The evidence suggests that 1) the induction of the initial events is dependent on the cell type because the size and/or the number of targets and how the cells handle the initial lesions differs between cell types; and 2) there are marked differences among tissues how initial lesions are expressed and proceed to overt cancer. The recent findings about adaptive responses are discussed in the context of what they contribute to our understanding about the response to irradiation. Lastly, the possibility of extending the approach of determining "The probability of causation," which Vic Bond played such an important role in establishing, is raised.

Health Phys. 70(6):823–827; 1996

Key words: cancer; risk estimates; dose; radiation effects

INTRODUCTION

It is an honor and a pleasure to be here to celebrate with you, Vic. I cherish the many years of friendship that we have had.

My charge is to talk about the effects of low doses. Some might equate that with being asked to give a reading from the Old Testament. An immense amount of time has been spent attempting to determine directly and to estimate indirectly the stochastic effects of low doses. However, the fires of controversy about the validity of the approaches still cause some heat, if little light. There is the complaint by some that the evidence does not support a no-threshold, linear dose-response relationship between dose and effect. By others it is stated that accurate risk estimates will be made only when we understand mechanisms. Perhaps with less sense than I should have at my age, I will attempt to review very briefly what we know from experimental studies about the effects of low doses, or, perhaps as importantly, what we do not know.

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(*Manuscript received* 29 *December* 1994; *revised manuscript received* 23 *August* 1995; *accepted* 20 *February* 1996)

0017-9078/96/$3.00/0

WHAT ARE LOW DOSES AND DOSE RATES?

With low doses and dose rates the effects of concern are the so-called stochastic effects: cancer and genetic effects. What is considered a low dose or low dose rate of low energy transfer (LET) radiation depends on the approach taken (see Rossi 1985). For example, if a low dose is defined as one in which only one track traverses a nucleus it would be less than about 0.2 mGy (UNSCEAR 1993).

The problem is that the size and number of targets for cancer induction are not known, but the evidence would suggest that they vary depending on the tissue and type of tumor. Of course, much of what this symposium is about is how to define the relevant interaction of energy and the biological target. From the point of view of radiation protection, there is the pragmatic question about the dose and dose rate at which a low dose and low dose-rate effectiveness factor (DDREF) should be applied. UNSCEAR (1993) concluded that a DDREF should be applied at a total dose of 200 mGy, independent of dose rate and at a dose rate of less than 0.1 mGy min^{-1}. These values were based on experimental animal studies. The value of 200 mGy is very much greater than the value based on the estimate of dose that would result in approximately a single track traversing a nucleus. The differences between tissues make it difficult and perhaps unwise to select single values. NCRP in Report 64 (NCRP 1980) suggested that a low dose was one between 0 and 200 mGy (20 rads) and a low dose rate was less than 50 mGy (5 rads) y^{-1}.

A single value for the dose rate at which the effect becomes dependent only on total dose and independent of dose rate can be obtained from investigations of life shortening. The findings of the most extensive such study is shown in Fig. 1. Up to about 250 mGy d^{-1} the mortality rate can be described by a slope 1 on a log-log plot (Sacher 1964; Grahn 1970). The "day" of irradiation lasted about 10 h, and on this basis the dose rate at which the slope of the mortality rate changed was about 0.4 mGy min^{-1}. It is assumed that irradiation throughout the life span did not affect the relationship of mortality rate to dose rate. The advantage of using life shortening is that it gives an integrated estimate of the effect of radiation on total cancer induction, and that is so because life shortening at low doses and dose rates can be accounted for by excess cancers.

In a comparable study on dogs exposed to dose rates ranging from 3.0 to 540 mGy d^{-1}, it was found that the

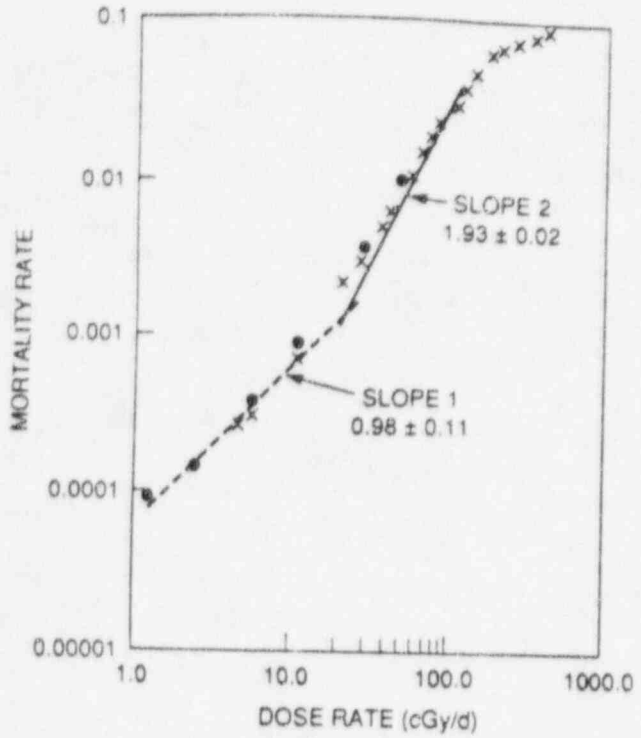

Fig. 1. Log-log plot of mortality rate based on mean after survival of mice exposed for about 10 hours per day at various dose rates to ^{60}Co gamma rays. Data come from Sacher (1964) and Grahn (1970).

slope of mortality rate as a function of dose rate was about 2 for non tumor deaths down to 3.0 mGy d^{-1}, whereas for tumor deaths the slope was 1. A high fraction of the tumor deaths were due to myeloproliferative disease. In these experiments the mortality rate was dependent on the accumulated total dose rather than the dose rate (Carnes and Fritz 1993).

It is much more difficult to suggest, based on animal experiments, a dose (single) at which a DDREF should be applied because of the very large differences among tissues. It can be seen in the panel on the right side of Fig. 2 that the dose-response curves for breast and lung cancer

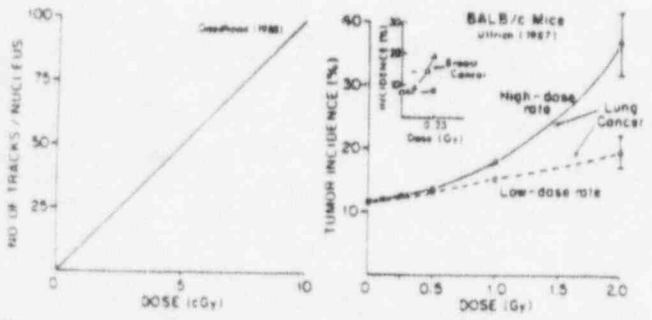

Fig. 2. Left panel: The number of tracks of low-LET radiation traversing a 8μm nucleus as a fraction of dose (Goodhead 1988). Right Panel: The incidence of breast cancer (upper curve) and lung cancer as a function of dose (Ullrich et al. 1987).

in mice are very different. It can be seen that in the case of lung cancer, at the lowest doses for which data for cancer incidence were obtained, there appears to be an initial slope that is linear up to at least 250 mGy, whereas in the case of breast cancer no such linear slope can be detected from the single dose-response curve. The lowest dose for which there are data for lung cancer is 100 mGy. The number of tracks per nucleus at a dose of 100 mGy of low-LET radiation is perhaps 100 or so (Goodhead 1988). If the initial linear slope reflects single track events, then the relevant target(s) is much smaller than the nucleus, which, of course, is reasonable. In the case of breast cancer, and based on the same assumptions, either the size of the target(s) is smaller than the nucleus but significantly larger than in the lung, or there is a difference in the number of targets. In the case of breast cancer, the very small linear component suggests a large sized or a large number of targets. In the case of lung cancer, the much larger linear component suggests a very small-sized target and/or a very small number of targets.

To speculate on whether these differences are consistent with what is known about the targets is difficult because there is so little information on either size or number of the relevant targets. It is not uninteresting that BRCA1 gene involved in some breast cancers is a large gene. In the case of tumors of the lung (Ullrich et al. 1987) and the liver (DiMajo et al. 1986), the alpha component is large. While the loci have not been mapped, the evidence suggests that about 85% of the resistance in mice for lung tumors is accounted for by one locus, *ptr* (pulmonary tumor resistance) (Bloom and Falconer 1964). Similarly, one locus, *Hcs*, accounts for 85% of the difference in susceptibility for liver carcinogenesis between a resistant and a susceptible mouse strain (Drinkwater and Ginsler 1986). There is the temptation to suggest that these results indicate the role of a so-called tumor suppressor gene (cell proliferation suppressor gene would be a more preferable term) in both these types of tumor.

If the targets for induction and their characterization are determined for the key tissues, the job of the modeler will be made a great deal easier and the models more credible. While it should be possible to estimate the target sizes from biophysical studies, the molecular biologists may win the race to do so.

DOSE-RESPONSE MODELS

The dose-response model used frequently for the induction of solid cancers is the so-called linear-quadratic model. If the model does hold for the induction of initial events in carcinogenesis then the effect per unit dose should be equivalent for 1) doses in the range of the linear component, 2) multiple fractions of doses in the range of the linear component, and 3) low-dose-rate exposures. If the model can be validated for the induction of solid cancers, as it was many years ago for chromosome aberrations, it would substantiate the use of low dose rate and multiple fractions for estimating the initial

slope of the dose-response curve and, therefore, estimates at low doses. A comparison of the effects of radiation given in single doses, multiple small fractions, and at low dose rates has been carried out for the induction of breast and lung cancer (Ullrich et al. 1987) and myeloid leukemia (discussed below).

The appropriateness of the linear-quadratic model is supported by the findings illustrated in Fig. 3. It can be seen that approximately the same initial slope for the incidence of myeloid leukemia in RFM male mice as a function of dose was found for small single doses, with fractions below about 200 mGy and at a dose rate of 50 mGy d^{-1}. These results are not surprising because a specific chromosomal translocation is involved in the induction of myeloid leukemia, and a curvilinear response would be expected for such chromosome aberrations. It is of interest that in the experiments of similar design carried out on the induction of breast and lung cancer, which apparently have very different dose-response relationships (Fig. 2), it was found that the effect per unit dose with low dose rate and small fractions dose was comparable. In the case of the lung, fractions of less than about 200 mGy resulted in a slope comparable to that for low dose rate exposures, but in the case of breast cancer the dose fraction had to be 20 mGy or less to obtain the same effect per unit dose as with a low dose rate.

These experiments suggest that the linear-quadratic model not only describes the initial events such as chromosome aberrations, but also the incidence of myeloid leukemia, breast, and lung cancer in mice. The results lend some promise that the effects of low doses can be estimated from data obtained at low dose rates and, more importantly, from data obtained from exposures to multiple small fractions. It is this latter exposure regimen that is of particular interest because it is characteristic of many industrial exposures. However, the total doses are low in most of the industrially-exposed populations which results in very imprecise estimates of risk. But there are some populations who have been exposed for medical reasons with multiple small fractions, for example the patients with TB, who were examined repeatedly by fluoroscopy. In these studies, the concentration was on the question of induction of breast cancer, and until recently no detailed study of the effects on the lung has been published, although Davis et al. (1989) did report an absence of lung cancer even with relatively high total doses from multiple fluoroscopic exposures. Howe (1992) has estimated the excess relative risks per Gy to be −0.019 for males and −0.12 for females in the Canadian TB patients.* The experimental data would predict that an effect of fractionation would be more likely to be detected in the case of induction of lung cancer than breast cancer, and that is what has been found in the epidemiological studies. The range of dose-response relationships found for induction of cancer by radiation in mice is huge, from threshold responses for skin cancer to linear or almost linear for breast cancer. This diversity should discourage generalizations.

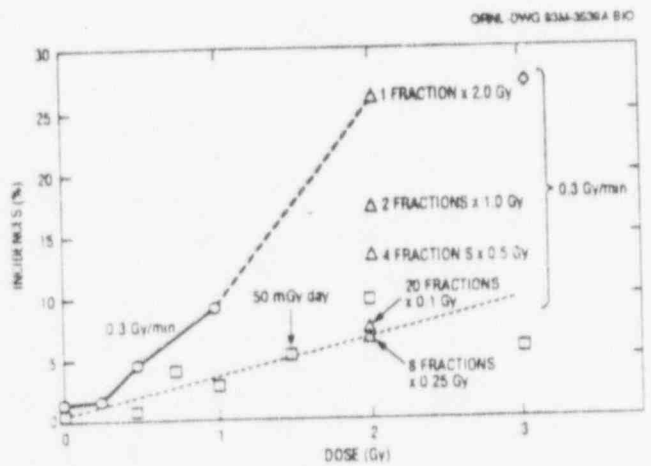

Fig. 3. The incidence of myeloid leukemia in RFM male mice exposed to single doses, 0–0.1 fraction of 2 Gy, 2 fractions of 1 Gy, 4 fractions of 0.5 Gy, 8 fractions of 0.25 Gy, 20 fractions of 0.1 Gy —, and, at 50 mGy d^{-1} □—□ 50 mGy d^{-1}.

ADAPTIVE RESPONSES

The fact that radiation has a stimulating effect on a number of biological processes, and that resistance can be induced, is far from new (for earlier references see Luckey 1980 and Joiner 1994 for review of more recent results). Under the name adaptive responses, rather than hormesis, there has been a surge of interest in the molecular, cellular, and genetic basis of radiosensitivity at low doses (Skov and Marples 1994). One aspect of these studies that stimulated interest in the question of induced repair is the evidence that the initial slopes of the survival curves of cells *in vitro* are steeper than previously detected. This finding is not accounted for by the presence of a hypersensitive subpopulation. The accepted explanation is that the initial steep slope of the survival curve changes to a less steep curve because of induced radioresistance. Sinclair (1993) has drawn attention to the effect of cell killing on the dose-response curve for the risk of cancer as a function of dose. It has become conventional to include a term that takes into account cell killing in the equation for the dose-response relationship of cancer induction as a function of dose. It should be noted that introduction of the cell killing term was based erroneously on experimental animal data. If the idea of a dose-dependent sensitivity with induced radioresistance is correct and applies to human cells *in vivo*, it may have relevance for estimates of risks at low doses. If the killing of cells at low doses has been underestimated, and if the assumption that reducing the number of cells at risk reduces the risk of cancer is correct, then the initial slopes of the dose-response curves for cancer induction may be less steep than estimated. As is often the case in

* In a recent publication (G. R. Howe, Radiat. Res. 142, 295–304 (1995)), the estimates of excess relative risk per Sievert based on a linear excess relative risk model were 0.02 (95% C.I. —0.01, 0.11 for males and −0.08 (95% C.I. —0.10–0.07) for females.

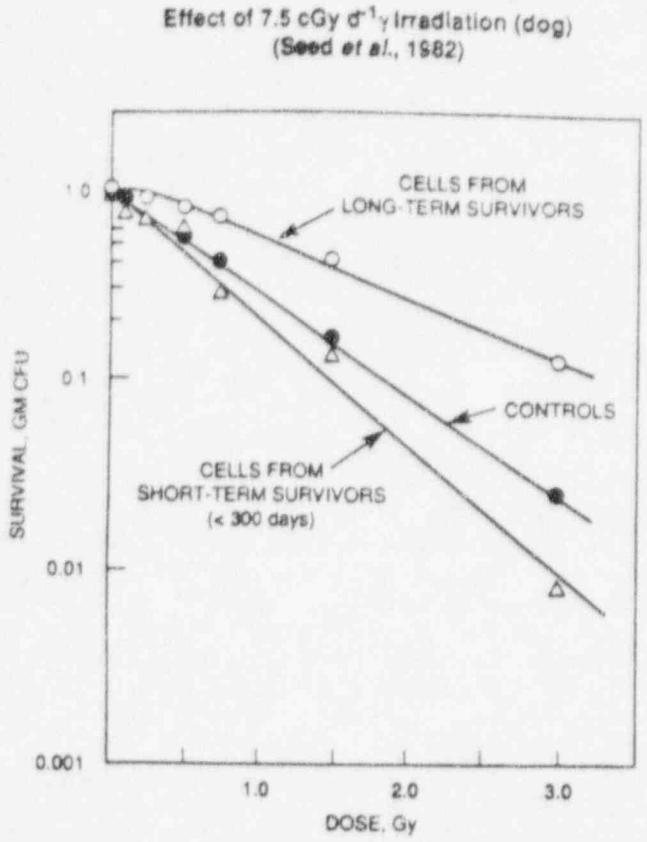

Fig. 4. The survival of GM-CFUs as a function of dose in beagles that have survived less than 300 d of exposure to 7.5 cGy per day gamma irradiation. △—△, and in those that survived considerably longer than 300 d of continuous exposure. ○—○, and in unirradiated controls. ●—● (adapted from Seed et al. 1982).

biology, there is the obverse of this coin. In dogs exposed to protracted gamma irradiation (Fig. 4), induced radioresistance of hematopoietic progenitor cells develops in only some of the animals (Seed et al. 1982). These dogs survive the damage to their hematopoietic system but only to die subsequently from radiation-induced myeloproliferative disease. Those not developing the radioresistance die of the effects of anemia. The apparent prevention of death from anemia due to induced resistance unfortunately increases the population at risk for the induction of leukemia at a later time.

The findings that priming doses that are small in size, and which are more effective when protracted, reduce chromosome aberrations, mutations, and neoplastic transformation *in vitro* may be part of the explanation of the reduction in the effects of radiation when it is protracted. In other words, protraction not only allows more repair because of the time between depositions of energy, but also more effective repair. Mitchel (1994) has shown that there is a higher rate of repair of DNA double strand breaks in cells given a protracted adapting dose.

The hope has been that the study of mechanisms would improve risk estimates. There have been wonderful discoveries about the genes involved in cancer, and the findings have reinforced the belief in multistage carcinogenesis. There are at least three important questions to be addressed. First, what is the influence of radiation on the stages after initiation? Second, are effects on so-called mutator genes central to the multistage process and the expression of initial events? Third, if the dose-response relationships for the initial events are linear-quadratic, why are the dose-response relationships for cancer induction in the atomic bomb survivors fitted best by a linear relationship? It is important to appreciate that such linear dose-response relationships do not mean that the slopes cannot be decreased when the dose rate of the exposure is reduced.

PROBABILITY OF CAUSATION

Lastly, remembering the central role that the honoree of this symposium, Vic Bond, played in developing the concept of the probability of causation, that is the probability that a particular malignancy may have been caused by a specified exposure to radiation, perhaps it is an appropriate occasion to address the possibilities of a new or revised probability of causation. The indicators that are used currently to estimate the likelihood of an association of exposure to radiation and the occurrence of a specific cancer are the dose and all of the factors, such as sex and age, that are taken into account in the risk estimates for each cancer site made by the NIH Committee (NIH 1985). The idea would be to add other indicators of exposure, especially mutations that are specific to radiation. To date, the only specific mutation that can be linked with a specific radiation is a mutation of *p53* induced by ultraviolet radiation (Brash et al. 1992). However, there have been a number of reports of "specific mutations" associated with alpha-particle irradiation. For example, Vähäkangas et al. (1992) and Taylor et al. (1994) have found "hotspots" in p53, but the mutations found by the two groups are not in the same exons. But there is some hope that mutations induced by specific chemicals can be distinguished from those caused by radiation. There are also quite different probabilities with regard to the cell type of certain tumors induced by different agents, for example in the lung (Land et al. 1993). Soon it may be possible to prepare a profile of a tumor that makes it possible to establish or eliminate that radiation caused a tumor with a greater degree of accuracy than previously. In the field of radiation studies, Vic Bond can look back with satisfaction that probability of causation was just one of his many different valuable contributions.

Acknowledgments—The research was sponsored by the Office of Health and Environmental Research and the Office of Epidemiology and Health Surveillance, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Lockheed Martin Energy Systems, Inc. It is a pleasure to acknowledge the help of C. Monday.

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Paper

CURRENT MISINTERPRETATIONS OF THE LINEAR NO-THRESHOLD HYPOTHESIS

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Abstract—Contrary to the "linear no-threshold hypothesis," which implies that "any amount, however small" of radiation energy is a serious cancer threat, it is shown here that only relatively quite large amounts of such energy can pose such a threat to a person or population. Key to doing this is to make a sharp distinction between the actual amount of the radiation agent imparted energy, ϵ, which must be expressed in units of joules, and the average concentration or density of energy, ϵ/m (i.e., absorbed dose), which is expressed in units of Gy. With any cellular system, e.g., in tissue culture, one can easily adjust the numbers of cells used at each dose point so that a clearly significant number of radiation-induced quantal responses (e.g., mutations, chromosome aberrations, malignant transformations, cell death), in the absorbed dose range of about 0.7 to 3 or more Gy, can be observed. However, if the number of cells is held constant as the absorbed dose is progressively reduced, a point is reached at which no significant excess is observable. This situation is frequently "remedied" by including more cells at that point, which, of course, can increase the number of malignant transformations sufficiently to render the excess statistically valid. However, because both axes are expressed in relative terms, the data point, despite having gained statistical significance, remains at the same location on the graph. This gives the false impression that no more of the agent energy was added or needed to achieve significance. However, if both coordinates are put in absolute terms, i.e., the actual number of quantal responses vs. imparted energy, and the same exercise of "improving the statistics" at low exposures is attempted, it then becomes evident that any point thus rendered significant must be relocated at a substantially higher energy point on the graph. This demonstrates unequivocally the fallacy in the proof of the "linear hypothesis" which is based on agent concentration response curves and not agent amount. It shows that the smaller the agent concentration (absorbed dose; ϵ/m), the larger the amount of radiation energy that must be added to the system in order to demonstrate a radiation-induced response. This suggests a minimum average energy requirement for production of a radiation-attributable cancer. It is concluded that the "linear hypothesis" should be abandoned as the cornerstone of radiation protection and practice.

Health Phys. 70(6):877–882; 1996

Key words: linear hypothesis; tissue sampling; radiation protection; cancer

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(*Manuscript received* 3 *February* 1995; *revised manuscript received* 10 *April* 1995; *accepted* 5 *February* 1996)

0017-9078/96/$3.00/0

INTRODUCTION

THE LINEAR no-threshold hypothesis, referred to henceforth as the "linear hypothesis," in essence holds that a) radiation effects produced with low level irradiation can be predicted quantitatively by linear "extrapolation" from effects produced with high level irradiation, and b) any amount of radiation, however small, is potentially harmful. This hypothesis is the core of present radiation protection policies, principles, and practices.

The purpose of the present communication is to challenge seriously the validity of the current approach to "proving" the correctness of the hypothesis and, thus, the validity of the hypothesis itself. It is further shown that radiation protection practices should be viewed and molded only in the framework of a public health problem, rather than as both a public health and a medical (individual) problem as is now done.

CONCEPTS, DEFINITIONS AND NOTATIONS

Key to understanding the main points to be made in this communication is to recognize the clear distinction that is being made between the actual amount of energy imparted to a biological subject, e.g., cell, organ, organisms, or population, and a related quantity, the mean energy concentration or density. The former is defined as the imparted energy, ϵ, in units of joules (ICRU 1993). The latter is the energy per unit mass, m, termed the absorbed dose, D, in units of Gy.

The symbols N_E, N_D and N_q, respectively, are used to refer to the number of subjects exposed; the number with at least one stochastically received hit (dose); and the number responding quantally, i.e., in an either-or fashion with no intermediate gradations. N_{ca}, the number of persons with cancer, is a particular example of N_q. A "hit" is an interaction between a single charged particle and an object, here of cellular or smaller dimensions, during which energy is transferred to the object. N_H refers to the total number of hits on all exposed subjects (cells) in an exposed population (Sondhaus et al., 1990). Linear proportionality in a "dose" response function implies that we are in a domain where the effects of all hits are acting independently. This generally occurs only with small exposures or with larger exposures at low rates, which, unless otherwise stated, pertains to all such functions presented here.

In general, it is recognized that 1) both cancers and genetic effects observed in a multicellular organ or organism are single cell in origin; 2) energy transfer from a radiation field is accomplished in the form of small, stochastically-delivered discrete packets of random size, the summation of which is ϵ; 3) the response and the physical insult presumed to be responsible for or related to the observed response, must, unless reasons are given for doing otherwise, be expressed on the same level of biological organization; and 4) the prime function of radiation protection is to estimate the number of excess cancers that will appear in an exposed population and to keep this number as low as is practicable, i.e., routine radiation protection lies in the province of public health and not medicine.

THE INADEQUACY OF THE PRESENT DOSE-RESPONSE RELATION

Fig. 1 shows the type of function frequently used to display the cancer data obtained from the atomic bomb survivors (Bond et al. 1991) and used extensively in connection with establishing radiation protection exposure limits. The population of public health interest here is all of the approximately 40,000 persons included in the eight data points shown on the graph, taken to represent all of the survivors in the two cities of Hiroshima and Nagasaki. The function is known, or is at least often assumed, to be linearly proportional. The coordinates are the same as those for medico-pharmacological-toxicological curves, which yield threshold, sigmoid shaped functions. No reason for this deviation has been advanced in the radiation protection or radioepidemiological literature.[‡]

Note that the absorbed dose D, ϵ/m, on the abscissa, because it is an intensive quantity, is not additive. Thus the values cannot be summed across different individual subjects, or groups of subjects, for the purpose of obtaining the total amount of physical insult transferred to the entire exposed and dosed population of interest. Therefore, the function in Fig. 1 is totally inadequate for public health purposes (in fact, the term "collective dose" is an oxymoron).

Nonetheless, the function in Fig. 1 has played a principal role in the conception of, and increasing attention paid to, the linear hypothesis. This despite the fact that the abscissa is the energy concentration, ϵ/m, rather than the actual amount of radiation energy, ϵ, demanded by the linear hypothesis. However, it is precisely this misuse of absorbed dose to represent the actual amount of radiation energy that, as will be shown below, has been largely responsible for the impression that one can "prove" that effects are demonstrable even in the lowest dose range of the linear function that constitutes the basis for the linear hypothesis.

A suitable extensive and therefore additive quantity, which can replace D in Fig. 1 and thereby render the function suitable for public health purposes, is the imparted energy, ϵ (Bond et al. 1991). Such a plot, in which ϵ is the independent variable, and which also is consistent with linearity, is shown in Fig. 2. The least squares fitted line shown includes the coordinates (0,0). Important is the fact that the inverse of the slope of the function, ϵ/N_{ca}, yields an estimate of the amount of energy required, on average, to produce one excess cancer in the exposed population. This value is nominally 3.0 kJ per individual cancer (Bond et al. 1991).

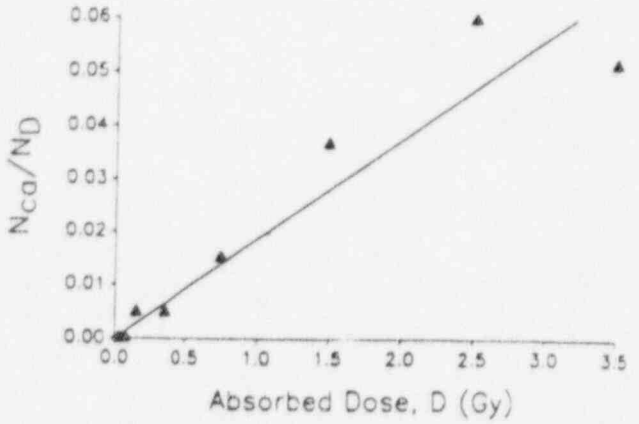

Fig. 1. The function now frequently used to represent the excess cancers in the atomic bomb survivors. The actual values, for solid tumors only, are taken from Bond et al. (1991).

A DECEPTIVE "PROOF" OF THE "LINEAR HYPOTHESIS"

Because the points on the function in Fig. 1 represent the actual cancer data on human subjects, they cannot be changed in order to test hypotheses. Therefore, the linear hypothesis is "proved" in surrogate single cell systems, using differing types of cells and endpoints (i.e.,

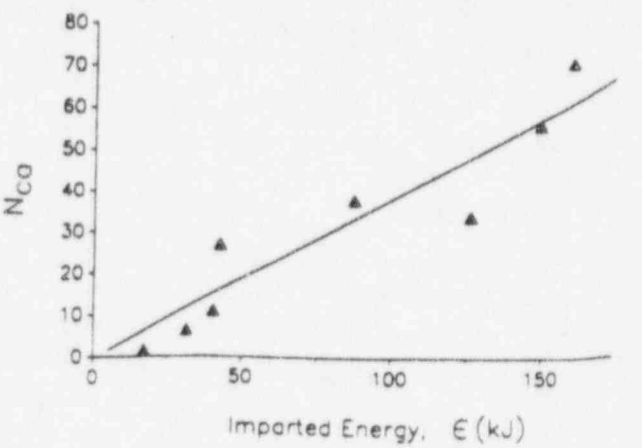

Fig. 2. The same data used in Fig. 1, plotted using the additive quantity imparted energy, ϵ, as the independent variable. The inverse of the slope shows that, on average, about 3 kJ of gamma radiation energy imparted to a population of human beings of mixed sexes and ages is required to cause one radiation-attributable cancer.

‡ For an explanation of the linearity, see Bond et al. (1995).

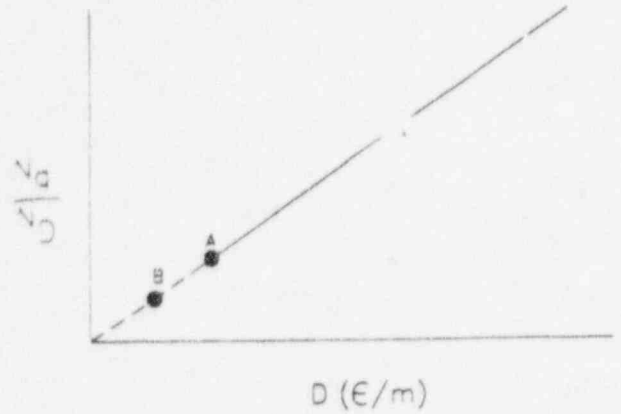

Fig. 3. A plot to illustrate the downward extrapolation process now utilized to "prove" the validity of the linear hypothesis. Point A represents the lowermost data point, using a number of person-simulating cells adequate to obtain statistically valid data points in the high-exposure region, at which such a valid point can be obtained. B represents any point in the dashed, linearly-"extrapolated" region, in which, using the same number of cells, statistically valid points can no longer be obtained.

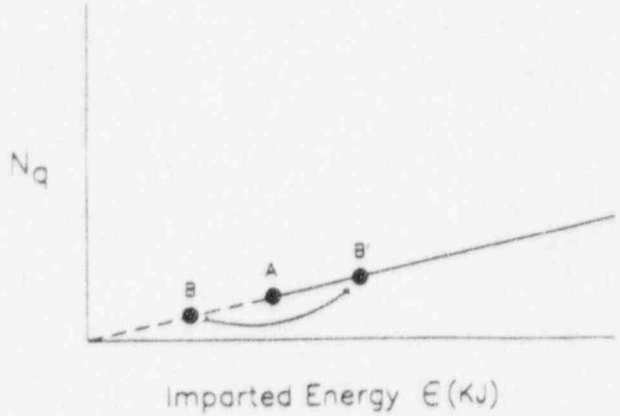

Fig. 4. The same plot as shown in Fig. 2, with the points A and B having similar meanings. However, because the independent variable is imparted energy, €, the fact that mass and thus energy had to be added to the system in order to render point B significant must now be overtly recognized. This is done by moving point B to a location above point A, e.g., to point B' on the graph.

principles can be examined, despite the enormous difference in the mass of the subjects). Such a surrogate cell system is depicted, schematically, in Fig. 3. At point A and above, a number of cells sufficiently large to ensure statistically significant values for quantal responses, N_q, have been used. Below this point linear extrapolation is performed as indicated by the dotted line (frequently, the procedure amounts to linear curve fitting, with no stated justifying model or theory, and includes the coordinates (0,0) obtained by subtracting out baseline values for N_q). B represents any point on the dashed line below point A, in the "extrapolated" region.

As is well known in physics and mathematics, "extrapolation" of a regression line beyond observed data points is frowned on and must be accompanied by good reasons. The justification provided at present for downward extrapolation is that points such as B on the function in Fig. 1 can be shown to be valid by repeating the experiment at point B, but now with a number of cells large enough to render the previously unreliable point B statistically significant. Thus, simply by "improving the statistics," one appears to be able to validate the hypothesis down to quite low energy concentrations, D.

Apparently overlooked is the fact that, when using more cells at point B, one is adding mass to the radiation field and thus energy to the cell system at that point. This results in a larger and thus significant value for N_q. However, this addition of energy is masked because of the normalization of all values of N_q to unit N_D, and all values of € to unit m i.e., all absolute values for mass are avoided. Thus, because proportionate amounts of both € and m are added, both N_q/N_D and €/m remain constant. This absence of any apparent change in the location of point B on function, attributable to the misuse of absorbed dose as an actual amount of energy, fosters the illusion that in violation of the first law of thermodynamics, one can obtain more N_q cells, which require energy to produce, with no requirement to add more energy to the system.

The error is made even more evident with the function shown in Fig. 4, which is derived from the same data used to construct Fig. 3. Because the abscissa is now the actual amount of energy transferred to the population, it is with this function that the linear hypothesis should be tested. Here again one can make the point B statistically significant by using more cells. However, because the abscissa is now the actual amount of energy, and the radiation quality remains constant, the point B in Fig. 4 must be moved from its present location to point A or higher. Thus, a constant large amount of radiation energy is required to cause an excess cancer, independent of the value of D.

The above analysis would appear to completely invalidate the method used to "prove" the linear hypothesis, and thus the hypothesis itself. One of the stronger points of the hypothesis is that it has appeared to be amendable to validation, and increasing efforts have been made to uncover more sensitive and more easily manageable cell systems that might permit one to "prove" its correctness by using smaller and smaller "amounts" (i.e., €/m), of radiation energy. Nonetheless, as shown above, however small €/m may be, a cancer can appear in an individual belonging to the dosed human population, only if the population is large enough so that at least 3 kJ of energy have been transferred to it (i.e., the value of €/m at any point does not at all equate to the actual amount of energy at that point, and certainly not necessarily to a small amount of radiation energy). Furthermore, because of the large baseline "normal" cancer incidence, there is no chance at all of detecting a significant excess number of cancers unless the [illegible] added is many times the 3 kJ level required to induce [illegible] cancer. Thus, on a function such as that shown in [illegible]

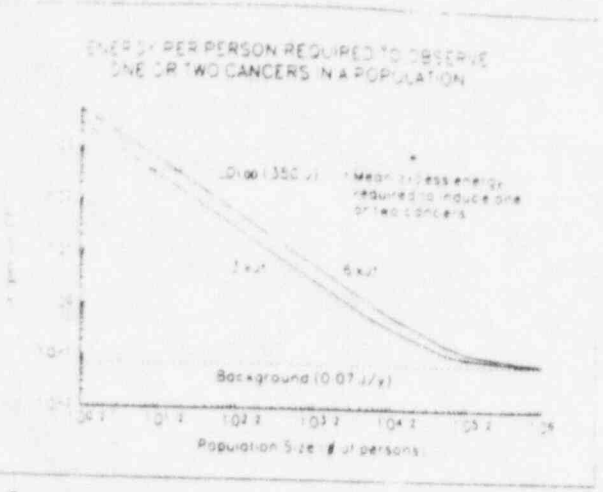

Fig. 5. A plot showing the results when 3 kJ of radiation energy is added to populations of different sizes. With small populations (including the extreme of one person), the 3 kJ are enough to be acutely lethal so that the question of a later-appearing cancer becomes academic. With very large populations, the energy per person becomes essentially that from background radiations. Thus the question of excess cancers again becomes academic.

the point B' would have to appear at a quite large value of ϵ.

Even though it has thus been shown (Fig. 5) that downward extrapolation is inadmissible, and even though more than the 3 kJ would be required for a statistically significant observation of excess cancers, a small probability of an induced cancer with a small amount of energy to the population cannot be ruled out. Thus, a distribution around the value of 3 kJ, with some (very small) probabilities existing at values of ϵ close to zero, would exist. Nonetheless, to answer the question of whether it is possible for truly small amounts of radiation energy to cause an (extremely rare) excess cancer in a person under any conditions, it would be much more useful and definitive to address the question principally from the biomedical standpoint alone, using disciplines such as molecular biology, cell biology, physiology, oncology, and immunology.

The above arguments also appear to have destroyed rather completely the interpretations of and impressions from the linear hypothesis that "low level" irradiation should be of major personal or public health concern, a factor that has induced an almost pathological fear of low level irradiation in a major segment of the general population. In fact, the above arguments appear to have reversed this completely. Rather than it being the rule that only a small amount of radiation energy is necessary to cause a cancer, on average a relatively enormous amount is required. In fact, the mean of 3 kJ required to induce 1 cancer in a population, if given to a "population" of 1 person, would be some 10 or more times greater than is required to kill a person acutely from non-cancer causes, even though delivered over a period of weeks or more.

The question arises as to why, on average, such a large amount of energy is necessary, when it is known that the amount of energy required to alter a biological molecule and thus presumably genes is, on average, approximately 35 ev. The answer lies in the fact that the vast bulk of individual cells and tissues is composed of "inert" materials such as water and hard bone. Also, of the enormous numbers of cells in the human body, only a small fraction is capable of developing into a still viable but clonogenic malignantly transformed cell. Thus, essentially all of the energy and resultant damage is collateral, in that it is deposited in "carcinogenically inert" material.

A single function that shows explicitly the meaning of the 3 kJ requirement for an expectation value of one cancer is shown in Fig. 5. This function demonstrates clearly that, even though one cancer is expected in the entire population, the average energy per person drops rapidly as the population size increases, until it reaches background level. It is meaningless, at this level and below, to discuss smaller amounts of energy per person. It also shows the reverse: i.e., as the population becomes small, the amount of energy per person required for the expectation of one cancer, rather than "however small," is so large as to be in the acutely lethal range.

PERSON-GY

The slope or "risk coefficient" derived from the function in Fig. 1 would be in terms of (N_{ca}/N_D)/Gy, or cancer probability ("risk") per unit agent concentration. However, the actual "risk coefficients" are reported as the slope of a different function (Fig. 6), in which the absolute or actual numbers of excess cancers observed is plotted as a function of person-Gy (Fig. 6 may well

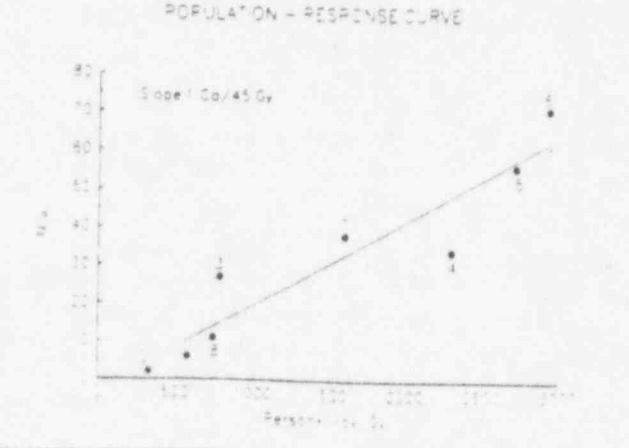

Fig. 6. A plot of the actual number of excess cancers as a function of person-Gy. Although the cancer data on the atomic bomb survivors is essentially always plotted in the form given in Fig. 1, the "risk coefficient" quoted, the actual number of (persons with) a cancer, per x number of person-Gy is actually the slope of the rarely, if ever before plotted function shown in this figure.

represent the first time that this function has been plotted, or at least presented). The slope is then (the actual number of excess) cancers per person-Gy.

The slopes of the two functions, for Figs. 1 and 6, then appear to be identical.[3] However, this change in function would appear to be a *de facto* recognition that, in public health of which radioepidemiology is a subdiscipline, it is necessary to take into account, as part of the independent variable, the number or mass of the persons dosed. However, the effort falls short because the units of the hybrid quantity on the abscissa are still ϵ/m and thus not additive. The solution lies in recognizing that the present system of radiation quantities and units, rooted in the toxicological model and early acute effects such as one appropriate for, e.g., cancer radiotherapy, is based on mass (e.g., gram-rad; kg-Gy; integral dose) and not on the number of individuals comprising that mass. Thus person-Gy, $N_D \times (\epsilon/m)$, is a proportional parameter of, and can readily be changed to the additive quantity, ϵ. Consequently person-Gy, rather than being simply an alternative way of plotting the function in Fig. 1, is rather an unsatisfactory way to represent the function shown in Fig. 2.

DISCUSSION AND CONCLUSIONS

From the above arguments and discussions, the following conclusions and recommendations appear to be justified:

1. Adherence to the linear hypothesis as the core of radiation protection theory, policy, and practice, at least in its present form, should be discontinued. The demonstration of the incorrectness of the way that the linear hypothesis is "verified," coupled with the not-unexpected finding that, with a weak carcinogen such as radiation energy, extraordinarily large amounts on average are required to produce even one excess cancer, even at the smallest value of D (ϵ/m), would appear to justify this change.
2. The proper independent variable for the linear hypothesis should be the amount of energy ϵ, rather than energy concentration D. However, with this change, apparent validation of the linear hypothesis by adding mass at low doses is not possible.
3. Current attempts to treat the low level irradiations encountered in radiation protection practice as both a medical and a public health problem should be discontinued. There are no biological indicators of an effect, or measure of the severity of that effect, which can permit a physician to estimate a probability that an exposed, non-cancer individual, will or will not develop a radiation-attributable cancer. A value of probability derived from a linear function with ϵ/m as the abscissa is most unlikely to coincide with the actual value for an individual, were it somehow to be ascertained medically. Thus radiation protection must be treated solely as a public health problem.
4. Rather than a collective value of physical insult to the population dosed, in terms of person-Gy or person sieverts, the actual number of expected cancers, for the defined population of interest, should be provided. It would then become evident how comparatively small is the public health problem posed by low level radiation, i.e., in the range of background or routine occupational amounts. For example, the estimated number of cancers induced per year, from all 111 operating power reactors in the United States, is no more than 10 and could be much less. This number can be put in perspective by comparing it to the some 600,000 or more new malignancies (excluding skin cancers), from all other causes, per year, in the U.S. (Ca-A Cancer Journal, 1990). The number of all excess cancers in the atomic bomb survivors is about 5 per year. Also, probabilities or risks can play no role in public health practice, i.e., probability or risk, *per se* has never injured or killed anyone. Only integer numbers actual observations of the number of quantal responders can be used.
5. It appears to be more sophistry than science, and reminiscent of the "angels on the head of a pin" debates, to argue about whether a small amount of radiation energy can cause an excess malignancy (which could be detected if it did occur). One excess cancer cannot affect significantly a public health problem of the magnitude of cancer.
6. The individual exposed, or potentially exposed to low level radiation should be apprised of the fact that radiation is a weak carcinogen, so that very large amounts of energy—more than 10 times that necessary to kill a person acutely—are required in order to yield an expectation value of one excess cancer in a dosed population (however small that population). The individual can be reassured by the above conclusions and their apparent verification, i.e., with low-level irradiation, the most extensive and detailed investigations have failed to reveal even one excess cancer. Therefore, the probability is vanishingly small, that a cancer will ever result from any given low level exposure of one individual. It is not possible at present to provide an exact prediction of cancer induction for an individual exposed to low level radiation.

It appears that the linear hypothesis has acted as a siren, in that it has lured those concerned into endless sophistic arguments that have turned out to be complete red herrings. In focusing attention so strongly on whether one person *might* get a cancer from a small amount of radiation, when the cancer could never be detected even if it were caused, it has blinded regulators completely to the fact that, on average, an individual requires relatively enormous amounts of energy from the weak carcinogen,

[3] Which they may or may not be, depending on the distribution representing the number of P-Gy, as a function of Gy. Although distribution was taken into account in constructing the function in Fig. 5, there is no evidence that this has been done previously [i.e., it apparently has been (wrongly) assumed that (N_{ϵ}-N_D/Gy and N_D-Gy) are not only the same conceptually, but always equal numerically].

radiation, to induce a cancer, the expression of which could never be observed.

Acknowledgements—This research was supported by the U.S. Department of Energy under Contract DE-AC02-76CH00016.

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3/24/96

FAX TO: John Larkins
CC TO: ACRS/ACNW Joint Subcommittee Members (JTL - please provide copies of this memo to the members)
Roxanne Summers
FROM: JCC
SUBJECT: 3/26/96 ACRS/ACNW Joint Subcommittee Meeting

Because of another commitment, I have decided to conserve your budget by not attending the 3/26/96 ACRS/ACNW Joint Subcommittee Meeting. Additionally, as a short timer on ACRS (my term ends on 5/30/96), I won't be around to participate in the on-going deliberations of low-level radiation health effects a subject dear to my heart. I have full confidence that the members of the Joint Subcommittee will come to an appropriate position on this issue without my presence at the meeting.

I have reviewed the impressive stack of paper on low-level radiation health effects that Roxanne put together for the meeting. I believe now, as I have believed for the 40+ years that I have been associated with the nuclear power industry, that the nuclear establishment has created an unwarranted fear of man-made ionizing radiation on the part of the general public with the "linear, no threshold" effects/dose hypothesis. This has resulted in a tremendous financial and health effects cost to society, not only with respect to the utilization of nuclear power, but in the use of all forms of nuclear technology.

There appears to be considerable technical bases for the March,1996 Health Physics Society's recommendation " ... against quantitative estimation of health risk below an individual dose of 5 rem in one year or a lifetime dose of 10 rem in addition to background radiation." However, the proponents of this position were given a number of clearly valid challenges by W.K Sinclair (See p 5 of Attachment 15 to Roxanne's memo). Of his several questions, I was particularly intrigued by his question regarding the usefulness of a threshold of a very low value of dose in actual radiation protection practice. I believe that we have an answer to this challenge as it concerns the regulation of nuclear power plants.

The last ¶ of Marv Goldman's comments (see Attachment 18 to Roxanne's memo) seem to me to be an especially cogent summary of where we are and where we should be going.

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"Let's stop debating what we believe and hope for, and put the linear no-threshold hypothesis to sound solid scientific scrutiny and objective testing. It's time for innovative research ! We need to do a complete review of the available data, and as well employ our newer molecular tools in unique research to better understand the radiation carcinogenisis process"

I don't believe that the NRC can change its regulatory approach (at least politically if not legally) until the NCRP (and the ICRP?) changes its radiation protection philosophy with respect to low doses of radiation. Attachment 24 to Roxanne's memo is a proposal to the NRC from the NCRP dated 2/10/95 (over a year ago) to produce a report entitled "Critical Evaluation of the Linear-No threshold Assumptions." The estimated cost of this three year study is $225k, a drop in the bucket relative to the RES budget. We need to know what action has been taken by the staff with regard to this proposal. It seems to me that this is an obvious first step in dealing with this issue, although I can imagine that there are staff people that might see this as a threat to their empires.

Finally, I believe that the Committees, either individually or jointly, should recommend to the Commission that the agency develop a proactive strategy to settle the question of the health effects of low level radiation exposure. This would be wholly consistent with this Commission's stated policy that NRC regulations should be risk informed.

BEIR VII "SCOPING STUDY"
Draft Work Scope
May 2, 1996

BACKGROUND

Since publication of the 1990 BEIR V Committee report, "Health Effects of Exposure to Low Levels of Ionizing Radiation," new information has become available ~~on the Japanese atomic bomb survivors and other~~ regarding cohorts exposed to ionizing radiation at low doses and dose rates. Studies at the molecular and cellular level have ~~pointed the way towards~~ contributed to a better understanding of carcinogenesis and may eventually lead to an improved basis for estimating radiation risks at low doses and dose rates. In addition, there is new information on the effects of low-level radiation in producing risk decrements of both mortality and cancer, and other non-cancer effects ~~other than cancer~~.

To be credible, it is critical that federal radiation protection measures and risk assessments be based on the best current science. Although the emergence of new epidemiological data and progress in understanding the biological basis for carcinogenesis is expected to continue in coming years, an ~~update~~ extension of BEIR V may be desirable at this time. Before proceeding with a full-scale National Academy (BEIR VII) review and analysis aimed at updating the existing state of understanding and quantification of risks from low dose, low-LET radiation, it would be advantageous to conduct a preliminary study that would examine the range of potential issues that could be addressed, along with an assessment of the usefulness of available sources of new information in order to define the most useful scope for BEIR VII.

PROPOSED PLAN OF ACTION

The Board on Radiation Effects Research will organize a small expert panel to investigate what issues a BEIR VII study might usefully address in depth. The scoping study should address each of the issues/areas outlined below and any others the panel deems relevant. In conducting its review, the panel should consider the current availability of data not evaluated by the BEIR V committee and the expectation of significant additional data during the period of the BEIR VII review. The panel should provide a final letter report that: (1) recommends which of these issues could profitably be addressed in depth in a BEIR VII study, (2) provides a basis for these recommendations, (3) lists primary sources of data that might be used, (4) assesses whether or not a detailed analysis of each issue could have a significant effect on the quantification or validity of radiation risk estimates, and (5) indicates what scientific disciplines would be required to adequately address each of them.

OUTLINE OF AREAS TO BE ADDRESSED IN SCOPING STUDY

In considering issues to be addressed in future BEIR studies, the panel should at least review the following:

1. Cancer risk estimatation at low doses

The form of the low dose response ~~below~~ in the dose range directly accessible to human epidemiological studies, including the evidence for or against linearity and thresholds ~~at or near background levels of exposure~~

Adjustments to organ-specific risk estimates at low dose rates, e.g. as expressed by a Dose Rate Effectiveness Factor (DREF)

Significance-or nonsignificance- of "hormetic effects," i.e., risk decrements in human populations resulting from enhanced prevention, repair, or removal of DNA damage in the exposed biosystem.[1] ~~(e.g., adaptive response, immune system stimulation) to the dose response for cancer induction~~

2. Numerical risk estimation

Alternative biologically based[2] models for projecting radiation-induced cancer risks in the U.S. population, for workers and the general population

Quantification of uncertainties in radiation risk estimates

Resolution of claimed inconsistencies in risk estimates derived from different epidemiological studies

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[1] UNSCEAR 1994 Annex B contains a discussion of various mechanisms for adaptive responses, such as, prevention by increased radical detoxification (page 205), repair by activated genes and their enzyme products (page 199), removal by apoptosis (pages 199, 208), and immune system changes (page 206).

[2] The following biologically based models include both the normal very high background of intrinsic metabolic mutations (2.4×10^8/cell/day) and the adaptive responses of the biosystem to radiation.

- A Cytodynamic Two-Stage Model that Predicts Radon Hormesis (Decreased, then Increased Lung-Cancer Risk vs. Exposure, Dr. Kenneth T. Bogen, Lawrence Livermore National Laboratory, University of California, February, 1996
- The meaning of the α-Term in the Dose-Risk Function for Late Radiation Effects, Ludwig E. Feinendegen, Medical Department, Brookhaven National Laboratory, Upton, NY, and US Department of Energy, Washington, DC

3. Existence of sensitive subgroups

Genetic predisposition to radiogenic cancer

Exposures to other agents that modify the effect of radiation (other than agents administered for this purpose)

Risks from prenatal exposures

In reviewing these and other issues, the sources of data considered should include (but not be limited to) the following:

- Japanese atomic bomb survivors data

  Cancer incidence and mortality data available subsequent to BEIR V analysis with emphasis on exposures at low doses and dose rates

  Dependence of risk on cancer site, age at exposure, age at observation, time since exposure, gender, city, and dose

  New dosimetric information, particularly pertaining to neutron doses at Hiroshima ~~on risk estimates applicable to elevated environmental exposures~~

  Evidence pertaining to possible low level radiatio induction of noncancer effects (mortality, genetic, teratological, cardiovascular, cataracts, etc.) ~~by radiation~~

- Other epidemiological low level data that has been cited as a basis for risk estimation at low levels of exposure

  Medically irradiated cohorts

  Populations exposed to chronic doses: (1) groups exposed in the former Soviet Union, (2) nuclear workers in the U.S. and other countries, and (3) other population groups for which studies have been reported (e.g., residents of high background areas).

  Evidence for carcinogenicity of I-131

- Laboratory studies pertaining to mechanisms of radiation carcinogenesis

  Occurrence of various types of DNA damage produced by radiation and intrinsic normal metabolism.

  Efficiency of biosystem in prevention, repair, and removal of DNA damage and its functional dependence on dose and dose rate

  Importance of specific gene changes caused by radiation or other agents in carcinogenesis

Influence of cell cycle on radiation-induced cellular changes and repair

In assessing what issues can be profitably addressed, the panel shall also consider recent reviews conducted by UNSCEAR, NRPB, ICRP, NCRP, and other organizations since the issuance of BEIR V. Should the panel recommend that it is not appropriate to evaluate specific issues at this time, the report should, if possible, indicate what additional data would be needed to make such an evaluation appropriate.

Proposal

To

U.S. Nuclear Regulatory Commission

to produce an NCRP report on the

Critical Evaluation of the Linear— No Threshold Assumption

April 1, 1995 to March 31, 1998

National Council on Radiation Protection and Measurements

7910 Woodmont Avenue, Suite 800

Bethesda, Maryland 20814

Contents

TECHNICAL PROPOSAL SUMMARY

Submitted by:	National Council on Radiation Protection and Measurements 7910 Woodmont Avenue, Suite 800 Bethesda, Maryland 20814
Type of Organization:	A non-government, not-for-profit, congressionally chartered, public service, scientific and educational organization
Principal Investigator:	Charles B. Meinhold, President National Council on Radiation Protection and Measurements 7910 Woodmont Avenue, Suite 800 Bethesda, Maryland 20814
Telephone:	(301) 657-2652
Cost:	$225,000, $75,000 per year for three years
Institutional Administrator:	W. Roger Ney
Institutional Financial Officer:	W. Roger Ney
Date of Submission:	February 10, 1995

Objective[1]

The objective is to make a critical scientific assessment of all biological studies of the effects of ionizing radiation, and radiobiological theory of effects, in the low-dose and dose-rate region, *e.g.*, less than approximately 200 mSv and 10 mSv h^{-1} and then to summarize these effects.

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[1]The NCRP is imminently qualified to perform this study as it has among its membership national experts in many fields to carry out its broad program in radiation protection and it can assemble the best scientific minds of national stature to serve on the committee to perform this assessment. In addition, the NCRP has the responsibility to meet the objectives of this study as given in its charter, see page seven. No other organization in the United States has this specific responsibility in its charter.

Rationale/Task[2]

Those responsible for establishing limits of radiation exposure for radiation protection purposes have assumed that at the low levels of dose relevant to radiation protection activities, the response of humans, as far as cancer induction or hereditary effects is concerned, is linear with no threshold. It has always been recognized, however, that this is an assumption and not a fact directly demonstrated by human epidemiological data nor uniformly supported by other biological data or theory.

Because the assumption of linearity plays such a vital role in our systems of radiation protection, both as a means of employing information available from human exposures at high doses and from a practical standpoint in facilitating exposure control, a critical examination of the scientific support, or lack thereof, for the assumption is warranted. The report to be prepared is aimed as such an examination.

The United Nations Sciertific Committee on the Effects of Atomic Radiation (UNSCEAR) has published two reports of particular relevance to this examination. Annex E of their 1993 report (UNSCEAR, 1993) reviews mechanisms of radiation carcinogenesis at low dose and low-dose rate. Their 1994 report (UNSCEAR, 1994) contains a section on low dose epidemiology and a section on adaptive response. These reports, particularly the 1994 report,

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[2] A study by the NCRP addressing this subject is timely in that there is considerable discussion taking place currently in the radiation protection community on adaptive response and radiation effects in general at low dose. This committee is not expected to specifically address risk estimates such as those derived from the survivors of Hiroshima and Nagasaki nor are they expected to specifically address the uncertainties in those estimates. However, the committee will perform a thorough assessment of the available information on radiation effects at low dose.

have raised questions of hormesis to the level of in-depth scientific analysis and will form an important aspect of the committee's reference material. The committee will also review the experimental data and the radiobiological theories of scientists who have varying opinions and theories on the response of biological systems to ionizing radiation in the low dose region.

It may be possible that definitive guidance on specific radiation protection assumptions at low dose could result, but a detailed exposition of what is known about the subject will, in and of itself, prove to be of major importance to all who have responsibilities that relate to radiation protection.

With the availability of funding, the NCRP will establish a scientific committee of national experts to conduct this assessment. It is anticipated that such a scientific committee would be comprised of recognized individuals with expertise in the scientific areas such as biophysics, genetics, DNA repair, experimental animal oncogenesis, dosimetry, radiation epidemiology, as well as operational radiation protection. It is anticipated that an additional 10 to 15 scientists with diverse opinion on the effects of ionizing radiation at low dose will be asked to present their views to the committee and to, therefore, serve as consultants to the committee. The consultants would not regularly attend meetings, but would most likely attend one meeting and have the opportunity to review the committee's report as it is developed. It may be effective to conduct a one or one and one-half day seminar where the consultants would be invited to present their views to the committee.

Such a committee would be expected to meet six to eight times during a three year period. The estimated cost of travel and secretariat support for such a committee is $75,000 annually. (A detailed budget will be provided on request).