Inconsistencies and Open Questions Regarding Low-Dose Health Effects of Ionizing Radiation

Wolfgang Köhnlein, Münster, Rudi H. Nussbaum, Portland

Abstract

The effects on human health of exposures to ionizing radiation at low doses have long been the subject of dispute. In this paper we focus on „open questions" regarding the health effects of low dose exposures that require further investigations. Seemingly contradictory findings of radiation health effects have been reported for the same exposed population or inconsistent estimates of radiation risks were found when different populations and exposure conditions were compared.

Such discrepancies may be indicative: (1) of differences in sensitivities among the applied methods of epidemiological analysis or (2) of significant discrepancies in health consequences following comparable total exposures of different populations under varying conditions.

We focus first on inconsistencies and contradictions in presentations of the „state of knowledge" by different authoritative experts. Subsequently, we review studies that found positive associations between exposure and risks in dose ranges where traditional notions generalized primarily from high dose studies of A bomb survivors or exposed animals would have predicted negligible effects. One persistent notion in many reviews of low dose effects is the hypothesis of reduced biological effectiveness of fractionated low dose exposures, compared to that of the same acute dose. This assumption is not supported by data on human populations.

From studies of populations that live in contaminated areas, more and more evidence is accumulating on unusual rates of various diseases, other than radiation induced malignancies, health effects that are suspected to be associated with relatively low levels of internal exposures originating from radioactive fallout.

Such effects include congenital defects, neo natal mortality, stillbirths and possibly genetically transmitted disease. A range of open questions challenges physicians and radiation experts to test imaginative hypotheses about induction of disease by radiation with novel research strategies.

I INTRODUCTION

I.1 Low dose radiation health effects: defining the „state of knowledge"

The „state of knowledge" of health effects from low dose exposures to ionizing radiation has recently been reviewed in extensive reports by three prestigeous national and international commissions of scientific and medical experts with partially overlapping membership, known by their acronyms UNSCEAR [89], BEIR V [4] and ICRP [39]. Publication of these reports was followed by a number of summaries in scientific journals, authored by recognized radiation experts, that purport to present a „scientific consensus" of low dose effects in a more accessible format for health professionals. A critical comparison between various presentations of „accepted views", however, reveals inconsistencies, in both categories, that of „established facts" and that of „unsettled questions" [28].

I.2 Inconsistencies and open questions

In 1990 the BEIR V Committee (composed of 17 experts on radiation epidemiology, bio effects, and risk estimation) issued a 400+ pages report [4] which serves as a widely quoted and prestigeous review of low dose radiation health effects. In the body of this report, the Committee acknowledges some critical areas of uncertainty and controversy, particularly with regard to estimates of radiogenic risk pertaining to anthropogenic increases in low dose exposures above unavoidable natural background levels, both occupational and environmental. Obviously, such estimates are of the greatest importance to guidelines for the protection of public health. Yet, within the BEIR V report, we find inconsistencies between the Committee's conclusions, as stated on different pages (see sec. I.2.1 below). Moreover, few of these obviously unresolved questions found their way into the most widely quoted Executive Summary. Subsequent authoritative overviews in scientific journals have not only glossed over some of these inconsistencies in the BEIR V report, but they also present different views of what constitute „well established" and „unproven" aspects of low dose health effects. We will highlight some of these inconsistencies by quoting or paraphrasing statements from the BEIR V report and comparing them with assertions on the same topics from three subsequent journal reviews, all citing BEIR V as a major source. Editorial comments, reflecting on the citations, have been placed in square brackets. In our discussions, „low doses" means the dose range well below 50 cGy.

We will select five controversial issues in the debate about protracted low dose exposures, to illustrate our point.

I.2.1 BEIR V [4]

A. Shape of a dose effect curve for cancer induction

In several places of its report, the BEIR V Committee concurs with the large team of scientists at the Radiation Effects Research Foundation in Hiroshima, Japan, which has collected and analyzed the Life Span Study (LSS) of A bomb survivors for decades: after a one time (acute) exposure, a linear, non threshold relation between excess mortality from cancers, except leukemia, and dose gives an excellent fit to the 1950 1985 LSS data, if restricted to doses below 200 cGy. However, BEIR V „recognizes that its risk estimates become more uncertain when applied to very low doses" and the Committee concedes rather obliquely that „departures from a linear model at low doses, however, could either increase or decrease the risk per unit dose" (p.6).

B. Dose rate effectiveness factor (DREF) at low doses (see sec. II.1)

In its report, the BEIR V Committee states: „For low LET radiation [low linear energy transfer, such as from beta and gamma radiation] , accumulation of the same [total] dose over weeks or months, however, is expected to reduce the lifetime risk appreciably, possibly by a factor 2 or more" (p.6) Such a downward correction for linearly extrapolated risk values is called DREF (Dose Rate Effectiveness Factor).

On the next page (p.7), however, we read: „While experiments with laboratory animals indicate that the carcinogenic effectiveness per Gy of low LET radiation is generally reduced at low doses and low dose rates, epidemiological data on the carcinogenic effects of low LET radiation are restricted largely to the effects of exposures at high dose rates. Continued research is needed, therefore, to quantify the extent to which carcinogenic effectiveness of low LET radiation may be reduced by fractionation or protraction of exposure".

For decades, findings from animal experiments at high and very high doses have given support to the speculation that the human dose effect relation for cancer induction is strongly concave if low dose exposures are accumulated over extended time periods (dose fractionation). Such a relation implies a practically zero effect threshold at doses of the order of natural background irradiation and a significantly smaller risk per unit dose at lower than at higher doses.

Fifteen pages later, the Committee states: „There are scant human data that allow an estimate of the dose rate effectiveness factor (DREF)“ (p.22).

Then, in a subsequent section the report picks up the same topic:

„Since the risk models were derived primarily from data on acute exposures ..., the application of these models to continuous low dose rate exposures requires consideration of the dose rate effectiveness factor (DREF) .... For the leukemia data, a linear extrapolation indicates that the lifetime risks per unit bone marrow dose may be half as large for continuous low dose rate as for instantaneous high dose rate. For most other cancers in the LSS, the quadratic contribution is nearly zero, and the estimated DREFs are near unity. Nevertheless, the committee judged that some account should be taken of dose rate effects and in Chapter 1 suggests a range of DREFs that may be applicable“ (p.171 4).

C. Biological effectiveness of X rays versus gamma rays

Referring to work by a previous authoritative radiation commission, the International Commission on Radiation Units and Measurement [38] (ICRU), BEIR V states:

„Most human exposures to low LET ionizing radiation are to X rays, while the A bomb survivors received low LET radiation in the form of high energy gamma rays. These are reported to be only half as effective as ortho voltage X rays. While that is not the conclusion of this Committee, which did not consider this question in detail, it could be argued that since the risk estimates that are presented in this report are derived chiefly (or exclusively) from the Japanese experience they should be doubled as they may be applied to medical, industrial, or other X ray exposures“ (p.218).

The physical basis for such a possible effect is the roughly four fold higher ionization density in tissue by medical X rays than that by high energy gamma rays [42].

D. Role of free radicals in tumorigenesis by ionizing radiation

„To the extent that the effects of radiation are mediated by free radicals, which can also mediate the effects of promoting agents, sequential exposures to radiation may serve to promote tumorigenesis through mechanisms similar to those of chemical promoting agents“ (p.139)

The report gives, however, no further consideration to the question, whether radiogenic free radical production, in particular, at low doses and low dose rates could link protracted low level exposures to various diseases or immune depression, known to be promoted by these highly reactive chemical species [30].

E. Radiation hormesis

On p. 383 the report states:

„Although 'beneficial' effects of radiation have been alleged on the basis of reduced mortality in high background areas in the United States, analyses that include an adjustment for altitude indicate no ‚beneficial‘ effects.... This apparently ‚beneficial‘ effect of radiation may, in fact, be an example of confounding ....“

I.2.2 „State of knowledge“ summaries after BEIR V

The first of the three summaries discussed below was published in a journal for public health professionals by members of the BEIR V Committee [91]. Hence its statements conform largely with the BEIR V report, except for some significant omissions. The other two summaries [33, 52] show deviations, as well as omissions, compared to the BEIR V report. They have been di-

Upton et al. [91]	Hendee [33]	Little [52]
	A: Shape of dose effect curve	
The non threshold dose incidence hypothesis, first supported by the association between childhood leukemia and pre natal diagnostic x irradiation at doses comparable to natural background, has been extended to other malignancies, as well as to genetically significant mutations. Data on teratogenic effects (e.g. small brain size or severe mental retardation) are also compatible with a nonthreshold linear dose effect curve.	The linear model furnishes the most conservative (i.e. highest) risk estimates for exposures to low doses of radiation, even though evidence establishing the linear model as the correct relationship is still relatively inconclusive.	Induction of mutations in human cells is a no threshold linear function of dose, independent of dose rate. The dose response for induction of breast cancer is linear without threshold. While there are several epidemiological studies that have purported to show carcinogenic or leukemogenic effects of irradiation in the dose range below 10 cGy, there are no theoretical reasons, nor are there supporting animal data, or low dose A bomb survivor data in the range 1 - 9 cGy suggesting that there should be a convex upward dose relation, that would be required to observe a rapidly rising cancer incidence at very low doses, close to natural background.
	B: Doserate effectiveness	
In the absence of adequate human data on the carcinogenicity of protracted low LET irradiation, the BEIR V Committee was unable to specify the extent to which their projections may overestimate the risks of a dose of radiation that is accumulated over long periods of time.	Suggests, [somewhat obliquely] that a DREF of 2.25 (from a 1980 BEIR report) should be applied to the BEIR V risks. [No specific justification is given, other than that it would reduce risks closer to earlier estimates.]	The dose rate effect for induction of specific gene mutations in human cells may be significantly less than that observed in rodent cells. Nevertheless, when the experimental data are considered along with limited epiidemiologic data, a DREF of 2has been recommended for chronic exposures. However, little or no decrease in risk was observed for induction of breast cancer, when the dose was received in a protracted manner, as opposed to a single brief exposure.

C: X-rays versus Gamma-rays		
[Not mentioned]	[X ray exposures of most medical workers far below protection guidelines are discussed, but no mention of a possibly higher biological effectiveness of X rays, compared to gamma rays on which the guidelines are based.]	[Not mentioned]
D: Free radicals		
[Not mentioned]	[Not mentioned]	Ionization results in the production of free radicals that are extremely reactive and may lead to permanent damage of affected molecules.
E: Radiation hormesis		
Although several studies have found that the rates of cancer and other diseases vary inversely with natural background radiation levels, which some investigators have interpreted as evidence of beneficial („hormetic") effects of low level irradiation, the relationship does not persist after the effects of altitude and other confounding variables have been adequately controlled.	[Not mentioned]	A lack of correlation between cancer incidence and background radiation was observed in different studies. Low dose epidemiologic studies in populations of limited size must be carefully controlled, and are often prone to bias by confounding factors.

rected to physicians and radiologists in general. Quotes or paraphrases from these reviews have been keyed to the topics A to E, as defined above, for convenient comparison.

The usefulness of reviewing „unanswered questions after BEIR V" for the purpose of identifying new directions for investigations, was recently recognized by other researchers in the field [34].

The present contribution is predicated on the premise that a special focus on unrefuted positive associations of very low dose exposures with health effects that are inconsistent with long held notions, will suggest unorthodox hypotheses. Testing these will require investigations in yet insufficiently explored areas that are likely to reveal a greater than expected complexity of interactions between low dose radiation exposures, other environmental toxics and disease.

Because of their dominance in shaping prevalent notions about the effects of radiation, we briefly review the findings from the A bomb survivor study, with particular emphasis on low dose effects. In subsequent sections we summarize a selection of studies that are pertinent to our above stated premise.

II THE FOLLOW UP STUDY OF A BOMB SURVIVORS (Acute Exposures)

II.1 Evolution of Official Low Dose Radiation Risk Estimates

Officially adopted radiation risk estimates about health effects of radiation at low doses have been based primarily on extrapolations from the continuing follow up study of about 90,000 inhabitants of Hiroshima and Nagasaki who had survived the first five years after the physical and social devastation caused by the atomic bombs. Until the mid 1970s cancer mortalities among survivors with exposures below 100 cGy had not shown statistically significant excesses above Japanese national averages, in contrast to findings at higher exposures. Growing demands for occupational and general radiation protection standards lead national and international radiation regulatory commissions to resort to models for downward extrapolation to reasonable levels of occupational exposure from the well established high dose observations. By implicitly postulating the existence of a universally valid dose effect relation, the ICRP [37] UNSCEAR [89] and BEIR III [3] reports in the late seventies, all concluded either explicitly or implicitly that linear, no threshold extrapolation from high dose A bomb survivor mortalities would in fact overestimate low dose radiogenic risks. For fractionated low dose exposures „dose rate effectiveness factors" (DREF's) of at least a factor 2, were recommended.

However, microdosimetric analyses have shown, that at decreasing doses, the concept of dose rate looses its meaning entirely because of the discrete nature of the radiation - cell interaction: the smallest possible effect must be caused by a single cell traversal [2, 26].

More recently, official evaluations of cancer risk from ionizing radiation have undergone significant upward revisions compared to those published about a decade earlier [4, 39, 89].

For the non leukemia A bomb data, RERF analysts found that a DREF value much above one for acute low dose exposures is not consistent with the updated data [60, 61, 92]. Yet, disregarding the new evidence, the conclusions by UNSCEAR [89], BEIR V [4], and ICRP [39] retained their previous recommendations to reduce estimates of radiogenic risks, based on a linear dose effect model, for protracted low dose exposures by DREF corrections of at least a factor of two (see above).

II.2 A bomb Survivor Study as Universal Standard

The interpretations of A bomb survivors' cancer mortality or incidence statistics by scientists at the Radiation Effects Research Foundation (RERF) in Hiroshima and other official commissions, have become the authoritative standard to which all findings from epidemiological studies on other exposed populations, such as nuclear workers, have been compared. In particular, studies that found substantially higher radiogenic risks at low doses and low dose rates than those officially adopted [96] have been labeled „renegade" by some recognized radiation experts and have been imputed to be in error by others [67, 83, 97]. Rather than questioning the comparability of incongruent studies, some epidemiologists invoke bias of unknown origin in the occupational data in order to set aside their own findings, if they differ from those derived from LSS statistics [24]. Almost no attention has been given to evidence in the RERF data that these discrepancies might reflect unrecognized intrinsic incommensurabilities in health profiles and age distributions, between the LSS cohort and a worker population quite apart from the vastly different characteristics of irradiation [77, 78]. Adopting the LSS findings as a universal standard also implies the untested hypothesis that a single dose effect relationship can describe all conditions of exposure [96].

II.3 Direct Evaluation of Incremental Excess Cancer Risk from Mortalities Among the Lowest Dose Subcohorts

Linear extrapolation models used by BEIR V and RERF to predict low dose risk values can be checked by a straightforward analysis of mortality data, limited to the lowest dose sub cohorts. The methods used in all official analyses of A bomb mortality data have weighted the resulting risk values toward those observed in the medium to high dose range [62]. Recently, two groups of researchers published independent analyses that were restricted to cancer mortalities among the A bomb survivors who had been exposed to less than 50 or 100 cGy [26, 50, 56]. These low dose sub cohorts include about 80% of the entire LSS cohort. Using the 1950 1985 follow up data [71], and combining new DS86 sub cohorts from both cities, these authors have shown statistically significant ($p < 0.01$) excess mortalities (for cancers except leukemia) for the combined „6-19 cGy" sub cohort (mean colon dose 10.9 cGy) compared to the combined „0-5 cGy" sub cohort (mean colon dose 0.7 cGy) (Fig. 1). The „0 - 5 cGy" dose group was chosen for comparison, rather than RERF's „zero" dose group, since the combined sub cohort includes survivors, nominally unexposed to the radiation flash from the explosions, as well as an unknown fraction who at that distance from the epicenter were affected by fallout exposures [59]. This additional dose is not reflected in DS86 estimates of individual doses. Other uncertainties have arisen recently in regard to the contributions of neutrons to individual doses of survivors, especially affecting the low dose sub cohorts who were located at large distances from the explosions [63, 80, 81]. For the lowest dose DS86 sub cohorts, we can thus expect that upward corrections in mean doses will have to be made, with the greatest correction to the lowest mean doses, decreasing rapidly with increasing DS86 mean dose.

A graphical display of cancer mortality versus mean dose elucidates more directly the relevant dose response association than the usual display of relative risk versus dose. Weighted linear regression analysis over the dose ranges listed in Table I and displayed in Fig. 1, yields a higher slope for mortality versus dose (or incremental risk per unit dose) for the dose range „0-19 cGy" than for the dose range „6-99 cGy". While statistically only weakly significant, the 1950-1985 survivor mortality data for the low dose range, suggest that the incremental excess cancer risk per cGy for single exposures may be greater below 20 cGy, than in the medium dose range 20 - 100 cGy, for which our estimate of excess lifetime risk (9 ± 1) per 10^4 p-cGy (Figure 1 and Table I) is consistent with the value of about 12 per 104 p cGy published by RERF analysts [71] or the value of about 7 per 10^4 p-cGy from BEIR V [4]. To check our conjecture and possible bias from using aggregate mortalities, one of RERF's chief statisticians applied a more extensive model for fitting excess relative risk that includes stratification for city, sex, age at exposure and follow up period. For the mortality data below 100 cGy, he found improvement in the fit for excess relative risk proportional to the square root of dose (convex curve) compared to a linear dose dependence [Donald A. Pierce, private communication 1991]. Unfortunately, updated mortality data for 1950-1990, have yet to be published by RERF. Non uniform upward corrections to sub cohort mean doses due to unaccounted for fallout or neutron doses might well augment the convex shape of the dose effect relation. In this context, it is noteworthy, that RERF analysts, studying the issue of a hypothesized threshold and the shape of the dose response curve for leukemia (acute lymphocytic leukemia or ALL and chronic myeloid leukemia or CML) among the LSS cohort at very low doses, found a better fit of the data to a non threshold convex dose effect relation (logarithmic with dose) than to a linear one with a hypothesized 5 cGy threshold [12].

II.4 Summary of low dose effects from the A bomb survivor study

Findings from the A bomb survivor follow up studies (DS86, 1950-1985 follow up) which contradict the validity of applying a DREF to low dose exposures:

* (1) both the A bomb survivor cancer mortality (1950 1985) and incidence data (1950-1987) fail to suggest the existence of a threshold for cancer induction down to very low doses [17, 72, 92].

* (2) doses less than 5 cGy and probably as low as 1.6 cGy have been associated with excess cases of leukemia (ALL and CML) among A bomb survivors [12, 85]. Carter [12], found a better fit of the data to a non threshold convex dose effect relation (logarithmic with dose) than to a linear one with a hypothesized 5 cGy threshold ($p = 0.056$).

* (3) doses in the range from less than one to a few cGy have been associated with brain damage in pre natally exposed children of A bomb survivors [70].

* (4) mortality for solid cancers in the „6-19" cGy dose group (mean colon dose 10.9 cGy) is significantly higher ($p < 0.01$) than it is in the „0-5" cGy dose group (mean colon dose 0.7 cGy), and there is a suggestion for a convex dose relation. (section II.3)

III EFFECTS FROM OCCUPATIONAL EXPOSURES (Protracted Exposures)

III.1 Critical evaluation of government sponsored nuclear worker studies

So far, practically all epidemiological studies of nuclear worker populations in the industrialized world have been funded and overseen directly or indirectly by government agencies that have promoted military and civilian nuclear technologies. Historically, production interests in nuclear installations have competed directly with concerns for the protection of workers or public health.

The impact of this situation on the quality of radiation epidemiological research has been amply demonstrated by a critical review of 124 U.S. and British government studies undertaken by a task force of twelve independent physicians and epidemiologists assembled and sponsored by Physicians for Social Responsibility. Their eye-opening report concludes that:

(1) „The Department of Energy's (DOE) (and its predecessor agencies') epidemiology program is seriously flawed ...

(2) There appear to be major inaccuracies, and serious questions as to consistency and reliability in the measurements of the radiation exposures.

(3) The nearly exclusive focus on mortality studies ... eliminates from consideration virtually all cancers which may be related to radiation exposure but which will not or have not yet caused death, and thus severely limits our knowledge of the health consequences of low level ionizing radiation exposure. ...

(4) ... the problems and flaws evident in many investigations are precisely those which tend to produce false negative results." [20].

A large number of the mortality studies under review found no statistically significant association between cancer induction and low dose radiation exposures. Most of them extended over limited follow up periods, too short to observe long latencies. Also, when workers' mortalities are being compared to national rates, the findings are biased toward lower risk for all causes of death among radiation workers (healthy worker effect).

Nevertheless, in a few of the reviewed studies and in some that have been published more recently, significant increases in specific types of cancer were found, for example prostatic cancer [5, 35], multiple myeloma, lymphatic and hemapoetic neoplasms, and bladder cancer [74], leukemia [95], multiple myeloma [21, 23, 24], and lung cancer [15, 66]. These positive findings have either been dismissed as due to unknown causes or chance by the authors or they have been ignored in revisions of radiation protection standards [55].

However, there is no reasonable justification for ignoring findings of positive associations of radiogenic risk with exposure on the basis of their smaller number or because of disagreeing with inconclusive or negative findings, unless specific substantial errors in the analysis can be shown. Mutually inconsistent epidemiological findings are likely indicators of essential differences in sensitivity to detecting small dose related excess mortalities at low exposures which depend critically on the choice of case and control populations, on the dependability of dose records over long periods of time, as well as on adequate statistical controls for a variety of selection effects associated with mortality rates [73].

In evaluating the significance of a particular health study, the uncertainties and ambiguities in epidemiological methods must be considered (see table III). For example, a recent published international study using large-scale pooling of cancer mortalities from UK, U.S., and Canadian nuclear installations by Cardis et al. [11] based on a methodology similar to that used before by Gilbert et al. [23, 24] finds a negative assiciation of dose with cancer mortality (except for leukemia). While presented as „the most precise direct radiogenic risk estimates“ on the formal basis of its statistical power, the critical reader will realize that these data originate from widely diverse work environments using non-uniform techniques and methods for dose monitoring and recording. Moreover, incomplete control for heterogeneous confounding variables across different worker populations, including the effect of age on susceptibility, can reduce significantly the sensitivity for a test of low-dose health effects [20, 79]. The Cardis et al. study is a prime example, illustrating that statistically defined „high power“ per se does not protect an epidemiological study from an inconclusive or flawed result.

III. 2 Worker studies showing low-dose radiation effects.

In contrast, two major U.S. studies did establish statistically significant excess cancer mortalities at mean exposures far below allowable yearly exposures, both among Hanford (1944 -1986) [46] and Oak Ridge workers (1943 -1984) [32, 64, 96]. Comparable results were found in a British study [6]. The risk values obtained from these studies are more than an order of magnitude larger than the official values (see Table II), flatly contradicting the claims of international radiation commissions that radiogenic risks per unit dose are lower for low-dose exposure spread over long periods of time (low dose rates) than equivalent acute exposures. No wonder the above findings were met by rejection and heated debates [64, 67, 83, 97].

Meanwhile, the U.S. Department of Energy (DOE) in a new promotional publication seems to have taken account of the above findings in its statement on radiation and human health. The DOE states: „In general, the risk of adverse health effects are higher when exposure is spread over a long period than when the same dose is received at one time“ [90].

III. 3 Do mutually inconsistent epidemiological study results neutralize each other?

There is no reasonable justification for ignoring „aberrant“ findings unless specific substantial errors in the analysis can be shown. Mutually inconsistent epidemiological findings can often be explained by the investigators' choices of different criteria for data selection, or by using divergent methods of statistical controls for confounding variables. Specific methodological decisions are likely to determine a study's statistical sensitivity as to whether or not the existence of a dose-related excess cancer mortality at low exposures can be established. Such choices include allowances for individual variations in susceptibility (e.g., due to age at exposure) and cancer latencies, controlling for selection effects within different groups of the workingforce and other socio-economic confounders affecting baseline mortality rates [20, 47]. For low-dose exposures, an equally important source of systematic bias, likely to reduce a study´s sensitivity, are ambiguities in recorded occupational doses at or just below detection limits of radiation monitors over decades of employment and improvements in monitor technology [79, 98].

For discussions of other relevant occupational radiations studies, including those dealing with airline flight and medical x-ray personal, we can refer to pervious reviews [57, 58]. For these groups, elevated cancer risks and chromsome aberrations have been linked conclusively to low-dose radiadion exposure. Much debate continues about postulated genetic effects of paternal exposures, initiated by the findings of leukemia and lymphoma clusters among young people near the Sellafield nuclear plant in West Cumbria, Great Britain.

Subsequent mutually inconsistent findings from epidemiological studies around nuclear installations, or contrasting clinical reports among populations affected by fallout, highlight one of the most crucial open questions regarding long term health consequences of continuing radioactive contamination of the biosphere. The authors recognize the serious problems in estimating internal doses, yet without considering the biologically more damaging exposures from internally lodged radioisotopes, compared to those from external sources, the issue cannot be resolved. Research in this area will be decisive in advancing our knowledge.

III. 4 Higher risks per unit dose for medical x-rays, compared to risk estimates from A-Bomb gamma rays

The biological effects of nuclear radiation in tissue depend in a complicated manner on the density of ionizations and chemical bond breaking capacities of primary radiation and secondary electrons along their paths. These processes are determined by the nature of the primary radiation and they become more concentrated at lower and lower energies. Alpha particles and neutrons produce much more highly concentrated damage in tissue than high energy electrons or photons. A thorough nontechnical discussion of various biological interactions of ionizing radiation with living tissue can be found in [26]:(chapter 19).

A 1986 report by a joint task force from two official international radiation commissions presented radiobiological evidence that at the same (relative low) dose, 250 kVp medical x-rays are about twice as biologically effective as high-energy gamma rays [38]. A more recent publication on the biological effectivenes of A-bomb neutrons also includes information about relative biological effectiveness (RBE) of x-rays versus gamma-rays. Using the frequency of induced chromosome aberrations in human blood lymphocytes in vitro as the indicator, and comparing 250 kVp x-rays with Co-60 gamma rays at varying doses, the x-rays were about 2,7 times as effective as Co-60 gamma [16].

A-bomb gamma rays with considerably higher mean energies in the 3-6 MeV range are still less biologically effective than the lower energy Co-60 emission as recently demonstrated by Straume in a review surveying the relevant literatur [81] and shown in figure 2. This means that the radiological risks per dose for exposures to 250 kVp x-rays and even softer x-rays in the case of mammography (less than 30 kVp) at low doses are between 4 to 5 times higher than A-bomb gamma rays. It is surprising that this warning has been omitted from the summaries of known effects from low-dose exposures to soft x-rays in influential medical publications.

Most of the man made radiation exposure of general populations in industrialized countries result from application of medical x-rays [4, 39]. Thus, a medical exposure risk value four to five times greater than that assumed by radiation protection commissions and used as guidelines by radiologists, call for revisions in standard patient risk versus benefit analyses for radiological procedures.

IV CONCLUSIONS AND DISCUSSION

A number of findings reviewed in the previous sections are at variance with the summaries of the „state of knowledge" (sec. I), which have been primarily based on official interpretations of the A bomb survivor follow up study (sec. II). Neither the fetal hypersensitivity to radiation [8, 9, 25, 31, 43, 44, 48, 49, 99], nor an increase in susceptibility for cancer induction for an aging population [14, 22, 96] are part of the accepted notions on radiation effects at low doses. Nor does this body of assumptions link low dose exposures resulting from radioactive fallout (either from nuclear testing or from reactor accidents) to any of the observed congenital effects like infant mortality [53, 68, 69, 94] rare childhood cancers [29] and low birthweight [27]. When levels of fallout contamination over large areas of the globe became known, local authorities everywhere, referring to the pronouncements by official national and international radiation regulatory commissions, reassured the populations under their jurisdiction that their levels of exposure would be much too low to cause any adverse health effects. In the light of the new evidence, sadly, these statements have now lost their credibility.

Also, on the basis of the foregoing summaries of studies, we draw the following conclusions regarding the five issues selected in sec. I.2.1. as having been controversial:

A. Dose effect Relation at Very Low Doses

While the A bomb survivor mortality data 1950 1985 yield a non threshold linear dose effect relation for cancers (other than leukemia) down to about 20 cGy with a suggestion of an increased excess relative risk in the lowest dose range, the most recently published cancer incidence statistics 1950 1987 [17] show a statistically strong non threshold linear acute dose effect relation for all solid tumors down to the 1 10 cSv organ dose range with an excess relative risk about 40 % larger than that derived from the mortality data. Some of the epidemiological studies of protracted occupational exposures with life time accumulated doses under 50 cSv and mean doses of the order of natural background find excess risks per unit dose for cancers substantially in excess of those predicted by linear extrapolation from the LSS mortality or the incidence data. This apparent discrepancy in initial slope of the dose effect curve could be due to bias from selection effects [77, 78], uncertainties in dose assignments in the LSS cohort, or the accumulated occupational doses [45, 83]. However, we like to emphasize that the hypothesis of a universal dose effect relation, which would require consistency of risk over such widely different population characteristics and conditions of radiation exposures, remains unproven.

B. Presumed Reduced Biological Effectiveness of Ionizing Radiation (DREF)

The occupational exposure studies reviewed in [57, 58], the pre natal X ray and external background exposure studies [31, 49], as well as the studies related to airborne radioactive emissions [53, 69, 94] are all inconsistent with the hypothesis of reduced biological effectiveness of ionizing radiation at protracted irradiation (I.2.1B).

C. Enhanced Biological Effectiveness of Medical X rays, Relative to High Energy Gamma Rays

This extremely important question in terms of its implications for public health has only been touched upon in the BEIR V report by referring to a 1986 review by the International Commission on Radiation Units and Measurement [38], but without in depth discussion. BEIR V [4] suggests, however, that the radiation risk estimates as derived from the acute gamma ray exposures of the Japanese survivors which form the basis for all radiation protection guidelines may underestimate these risks by a factor of two for medical, industrial or other low energy x ray exposures. In the three reviews of the current state of knowledge of radiation effects, cited in sec. I.2.2, especially directed toward physicians, this topic is not even listed among the open questions, implying that the generally accepted risk values (derived from the A bomb studies) are applicable to all medical exposures as well. Yet, there are well documented findings [86, 87] of twice as large a mutational effect in Tradescantia for 250 kVp x rays compared to Cs 137 gamma rays and factors between 2,7 and 5 for the induction of chromosomal damage are found when comparing soft x-rays with A-bomb gamma-rays. [16, 82]. There is a physical basis for expecting such a difference in biological effectiveness [26]. The significance of these radio biological findings for human exposures is an unsettled question with broad ramifications for radiation protection.

D. Free Radicals, Low Dose Exposures and Health

Except for mentioning the possible creation of free radicals by ionizing radiation in the BEIR V report (sec.I.2.1 D) and by one of the reviews cited (sec. I.2.2 D), the possibility that this interaction could provide a strongly non linear alternative biological mechanism [76] to the well known direct mutational interactions of radiation with human cell nuclei in the induction of disease in particular, at very low doses has not become part of the discussions of low dose radiation effects, in spite of a burgeoning literature linking free radicals to a wide spectrum of diseases, as well as suggesting possible treatments [30].

E. The Radiation Hormesis Hypothesis

All of the low dose studies of radiation effects in human populations reviewed above are inconsistent with hypothesized long term cancer reducing effects of such exposures in excess of unavoidable natural background of human populations (hormesis) (sec. IV.A.2). One can only speculate about the continued „popularity" of this conjecture among some groups of radiation experts.

Suggestions for New Research

By comparing statements about the above listed five aspects in different authoritative presentations of „known" health effects of low dose exposures, and by focusing on inconsistencies or selective omissions, we have identified unsettled questions in the mainstream „state of knowledge". However, the identification of unsettled questions can be extended by reviewing findings from a number of unrefuted studies on populations other than the LSS cohort of A bomb survivors, that are inconsistent with traditional notions and, therefore, have been rejected, ignored or glossed over in purportedly comprehensive reviews of the field. These inconsistencies raise a range of additional questions about the limitations of currently accepted concepts.

Finally, in the aftermath of the widespread fallout from the explosion of the Chernobyl reactor in the former Soviet Union, there are suspected associations of disease with radiation exposures that have barely been reported in the scientific literature. An additional relevant summary of observed health effects as a consequence of the Chernobyl nuclear explosion, presented at an International Workshop on the Impact of the Environment on Reproductive Health (30 September - 4 October 1991), Copenhagen, Denmark) can be found in [51]. While an international team of radiation experts invited by the Soviet government and financed by the IAEA confirmed an increased rate of a variety of health problems, but dismissed any possible association with radiation exposure [36, 65]. In the mean time ten years after the accident almost 1000 thyroid cancers in children exposed in 1986 have been confirmed in the heavy contaminated areas as reported recently at an International Congress in Berlin [40]. Many severe health problems other than cancer are seen in the cohorte of the liquidators and in the normal population [58]. Very recently an increase in germline mutation at human minisatellite loci has been reported and found to have a positive correlation with levels of radioactive contamination [18]. High levels of genetic changes in rodents living near the destroyed nuclear reactor have been observed. The base pair substitution rates for mitochondrial cytochrome b gene are hundreds of times greater than those typically found in mitochondria of vertebrates [1]. These findings are not in accord with the state of knowledge as documented in authoritative reports [33, 52, 91] (8,9,10). In the United States, only a handful of government funded health studies have been initiated among populations („downwinders") that have been at risk for internal exposures by various pathways as a result of radioactive releases into the environment from weapons production and testing facilities, in some instances possibly in synergism with chemical exposures. These populations at risk include large groups of civilians and tens of thousands of military personnel, who had been stationed at nuclear sites or who were involved with nuclear bomb tests. Some official epidemiological studies on these populations were admittedly „defensive" in nature [75] (0), responding to pressures by affected populations for material compensation. On the other hand, an increasing number of well researched investigative reports and small scale health surveys, organized by members of the affected populations themselves [7, 10, 13, 19, 41, 93] document the existence of clusters of cancers and similar patterns of other serious health problems among downwinders near various nuclear sites. An increasing body of verifiable observations, not matched by reasonable alternative explanations by scientific bodies, presents a challenge to public health agencies to commence large scale unified health surveys and to radiation experts to extend their research strategies into insufficiently investigated interactions of radiation with human health. There is an urgent need for the formulation of novel guiding questions that need to be translated into testable hypotheses.

Table I
1950 - 1985 Radiogenic cancer risk and projected lifetime excess risks per 10^4 person-cGy.[a]

Subcohort Dosimetry	Dose range [cGy]	Dose groups used in analysis[b]	1950-1985 Excess risk per 10^4 p-cGy	Estimated life-time risk[c] per 10^4 p-cGy
All cancers exept leukemia				
Colon dose	0-49	0,-5,-9,-19,-49	5.0±1.5	18.1±4.9
	0-19	0-5,-19	9.1±1.4	33±5
	6-99	6-19,-49,-99	2.8±0.3	9.3±1.1

a Table I adopted from refs. [50, 56].
b dose ranges in adjacent cSv intervals: -5=1-5; -9=6-9; -19=10-19, etc., except for the dose groups 0 and -5 combined, indicated by 0-5.
c a detailed discussion of this estimation is given in refs. 28, 29. The errors shown are standard errors.

Table III
Choises and variables to be considered that affect the sensitivity of epidemiological studies to find health affects os low-dose radiation exposure in the presence of confounding factors

- data selection (exclusions)
- heterogeneities in health profiles (selection effects)
- recognition of significant controlling variables
- stratification of variables
- variations of susceptibility with age at exposure
- variations in latency periods
- socio-economic factors affecting base-line mortality or morbidity
- ambiguities in assigning exposure levels
- distinguishing between external and internal exposure

Table II
Selected radiogenic cancer risk estimates for exposures at low doses, acute or protracted

Exposure conditions					Excess cancer risk per 10^4 p-cGy†	
Reference	Dose Range cGy	Dose Rate	Applicable Population	Applicable Follow-up	Observed Risk	Lifetime (estim.)
Nussbaum -Köhnlein [56]	1 - 11	Acute Bomb Gamma	~ 90.000 A-bomb survivors	1950-1985	9.1	33
same	11 - 69	Acute Bomb Gamma	same	1950-1985	2.8	9.3
Gofman [26]	0 - 5	Acute Bomb Gamma	same	1950-1985	5	30
same	0 - 5	Acute Bomb Gamma	recalculated for U.S. population	1950-1985	-	26
Gilman, Knox, Stewart, Kneale [25]	< 0.5	Acute X-ray pre-natal	~ 24.000 British children who died of cancer	age 0-15 years	13 (mortality)	n.a.
Bithell, Stiller [8]	< 0.5	Acute X-ray pre-natal	same as above	age 0-15 years	17.5 (incidence)	n.a.
Modan et al. [54] [0]	1.6 mean to breast	Acute X-rays	~ 11.000 Israeli children, age 5-9 years	23-37 years after exposure	relative risk# > 12 for breast cancer	n.a.
Mancuso, Stewart, Kneale [46]	2.2 mean (~ equal to back-ground)	low rate	~ 28.000 nuclear workers Hanford (WA)	1944-1986 deaths	Working Life Risk 85 for all workers > 440 for exposures after age 58	
Wing et al. [96]	1.7 mean < 5 for 68 %	low rate	~ 8.000 nuclear workers Oak Ridge (TN)	1943-1984 deaths	Working Life Risk ~ 110 average for all workers, all ages	
Beral et al. [5]	0.8 mean	low rate	~ 23.000 British nuclear workers	1951-1982 ~ 19 Y mean follow-up	Working Life Risk ~ 165 average for all workers, all ages	

† e.g. for a lifetime excess cancer risk of 30 per 10^4 person-cGy: exposing 15,000 people to an average accumulated dose of 10 cGy (100 mGy) will on average lead to [(30 cancers)/10^4 p-cGy]($1.5x10^4x10$ p-cGy) = 450 extra radiogenic cancer deaths over the lifetime of these 15.000 people.

this means that exposed children have a 12-fold risk for developing breast cancer as adults than unexposed controls.

Table II continued

Range of estimated lifetime risk values for protracted low-dose exposures of normal populations by international radiation commissions$			
UNSCEAR (1988)	2 - 5	fatal cancers per 10^4 p-cGy	ref. [88]
BEIR V (1990)	4	fatal cancers per 10^4 p-cGy	ref. [4]
ICRP (1990)	5	fatal cancers per 10^4 p-cGy	ref. [39]

$ including recommended Dose Rate Effectiveness Factore of two, not supported by human studies [26, 58]

Fig. 2
Biological effectiveness of low-LET radiation
The data are the low-dose linear slopes of the linear-quadratic dose response curves for chromosome dicentrics induced in vitro in human lymphocytes exposed to the radiation indicated and evaluated at the first division [82].

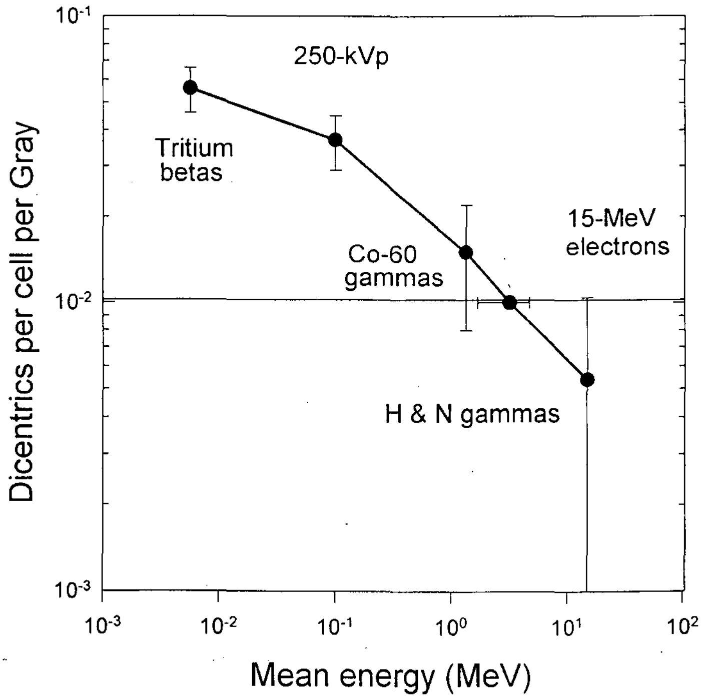
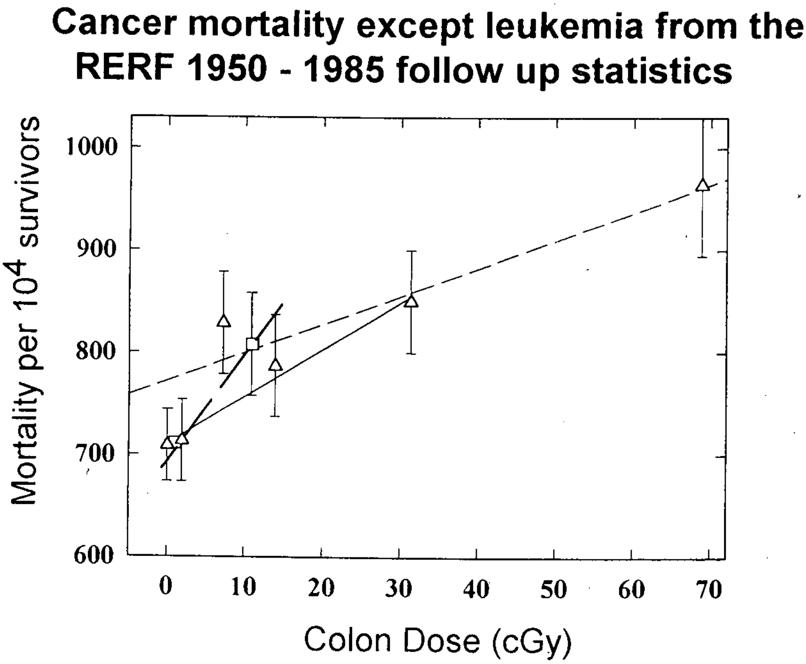


Fig. 1

1950 - 1985 LSS mortality from all cancers except leukemia

Cumulative mortalitiy per 10^4 survivors for the lowest six DS 86 colon dose sub cohorts 0, 1-5, 6-9, 10-19, 20-49, 50-99 cGy [triangles] and for the two combined 0-5 (mean dose 0.7) and 6-19 (mean dose 10.9) cGy sub cohorts [squares] versus mean colon dose (cGy). Standard error bars are shown. The increase in mortalities between the 0-5 and 6-19 cGy sub cohorts is statistically significant ($p < 0.01$). The solid line is an error weighted linear fit to the five [triangle] data points below 40 cGy mean dose (line 1, Table I). The two dashed lines are weighted linear fits to (1) the two data points for the combined 0-5 and 6-19 cGy dose groups [two squares] (line 2, Table I) and (2) the three data points for the dosegroups 6-19, 20-49, and 50-99 cGy with mean doses above 10 cGy [one square and two triangles] (line 3, Table I), respectively. The slopes of the three lines correspond to the three values of excess risk per 10^4 person cGy listed in Table I. Data from ref. 71.



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