REPORT ON THE RECENTLY-UPDATED STUDY OF CANCER MORTALITY IN THE A-BOMB SURVIVORS: INSIGHTS FOR RADIATION PROTECTION.

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The *Radiation Effects Research Foundation* (RERF) in Hiroshima has recently released an updated study of cancer mortality in the *Life Span Study* (LSS) cohort of survivors of the atomic bombings at Hiroshima and Nagasaki (1). (The LSS is believed to contain about one-half of the total number of survivors who were within 2.5 km of the hypocentre.) The update has considerably more statistical power than previous studies because of five more years of follow-up (1986-1990 inclusive) and because of adding 10,536 survivors for whom DS86 dose estimates recently became available ("Version 3"). Together these add about 550,000 person-years of follow-up compared to the previous report, which covered mortality to the end of 1985. Moreover, about 25% of the excess solid cancer deaths have occurred in these last five years of follow-up.

The cohort now has 86,572 subjects for whom dose estimation (a prerequisite for epidemiological studies) has been done. There are 50,113 members with estimated doses greater than 0.005 sievert; the mean dose for this subset is 0.20 Sv. These were mostly persons within 2.5 km of the bombings in Hiroshima or Nagasaki, and who still lived in the cities in 1950. The remainder of the LSS represents 36,459 people with doses estimated to be <0.005 Sv. These constitute a comparison group; they were age- and sex-matched to the "exposed" subset. They were selected from survivors within 2.5-10 km of the hypocentre.

Since the LSS is the most important source of information about the risk of induced cancer in humans following acute radiation exposures, this paper first summarizes this important new information. This is a keystone of radiation risk assessment and therefore of our radiation protection history; one cannot make sense of the current controversy concerning "linearity" without understanding what this data says and doesn't say. This communication then moves into a discussion of what implications there may be from this updated information, in the context of current debates about whether the "linear-no threshold" model is an appropriate one for radiation protection use. Note that this "use" may be distinct from the question of whether the linear-no threshold [LNT] model accurately reflects actual levels of risk at low doses, including the specific question of whether or not it might be possible to demonstrate that there is a dose below which no actual excess risk exists which is emerging as a contentious, even emotive, issue within the health physics and radiation protection communities.

EXCESS CANCER RATES & THE QUESTION OF LINEARITY

Radiation-risk estimates in the LSS are based on a relatively small number of extra cancers. There have been a total of 421 excess cancer deaths during the period 1950-1990. Of these estimated 421 excess cancers, 334 were solid tumors and 87 were leukemia.

The basis for these numbers can be summarized as follows. In the overall LSS cohort ("zero" plus "exposed"), a total of 7827 deaths from cancer were observed versus 7406 expected (difference = 421) . For solid cancers, there were 7578 observed deaths versus 7244 expected (difference = 334), and 249 observed deaths from leukemia versus 162 expected (difference = 87). It becomes a bit more complicated (but more instructive overall) when we examine the corresponding numbers for the "zero" and "exposed" subsets separately. In the period 1950-1990, there were 4741 cancer deaths in the > 0.005 Sv group and 3086 in the "zero" (< 0.005 Sv) group (remember that there are different numbers of persons in the two sub-sets). The "zero" group had 3013 observed solid cancer deaths (versus 3055 expected, for a small but non-significant deficit of 42) and 73 observed deaths from leukemia (versus 64 expected, for a difference of +9); both of these deviations are within the range statistically expected for a risk of zero. The "exposed" group had 4565 observed deaths from solid cancer (4189 expected, for a difference of 376) and 176 observed deaths from leukemia (98 expected, for a difference of 78).

One useful way to explain the level of risk is the "**attributable risk**"--the fraction of the total cancer deaths which can be ascribed to radiation among those with a non-zero dose. The attributable fraction for solid tumors in the LSS is 0.08 (i.e., 8%).

While most of the excess leukemia has already occurred, arising mostly within the first fifteen years following exposure, for solid cancers the excess absolute risk has increased in proportion to the natural, age-specific risk. That is, the data do appear to follow the "constant relative risk" model used to project the likely total number of excess cancers which will arise (it is this projected total which is the basis for our radiation risk coefficients, not the number which have occurred to date.)

Of the cohort, 56% overall were still alive at the end of the period covered by this analysis. The survivorship value obviously depends strongly on age ATB ('at time of bomb'). Cohort survival ranges from 94% for those 0-9 ATB to 16% for those 40-49 ATB (1% for those 50+ ATB). Since a large proportion of those exposed as adults has died, there is thus little uncertainty about projecting their lifetime risk.

However, uncertainty does remain about how best to project, beyond the current follow-up, the lifetime risk of those exposed as children. Different risk projection models give lifetime excess risk estimates which range from essentially the same as for persons exposed at age 30, to a risk which is 1.8-times as large. Continued follow-up of the LSS is important to decrease the uncertainty remaining with respect to this group.

The proper context for this number of "421 excess cancer deaths" needs to be understood. It should not be taken as representing the total number of cancer deaths to date in the "population of A-bomb survivors". This is because the LSS cohort includes only about half of the "exposed" group, and even then, only for the [approximately] 80% for whom doses have been assigned. A proper estimate of the total cancer deaths to 1990 attributable to the detonations would therefore be approximately 1050.

RADIATION RISK COEFFICIENTS FOR INDUCED FATAL SOLID CANCERS

There is **no statistically significant non-linearity in the range 0-3 Sv** for excess solid cancers. (Above 3 Sv, the slope decreases somewhat; this may reflect cell-killing). The excess absolute risk (EAR) per sievert for solid cancers, for persons exposed at age 30, is estimated as 0.10 for males [10% per Sv] and 0.14 [14% per Sv] for females. The risks for someone exposed at age 50 are about one-third the preceding.

Models which were linear in dose raised to a coefficient k were used to provide an assessment of linearity as a "fit" to the data. The authors reported that models with $k < 1$ generally provided a worse fit than a linear ($k = 1$) model.

This absence of statistically significant non-linearity led them to quote risk over the whole range of exposures in terms of risk per Sv.

DOES RISK DIFFER IN WOMEN AND MEN?

These differences (above) between men and women in radiation risk coefficients are not statistically significant. The prevalent view that women are decidedly more at risk than men for a given radiation exposure is partly an artifact of the *relative risk* data presentation method employed previously by RERF and others. I'll use present numbers to illustrate this. The actual excess relative risk (ERR) per Sv for women in this study is about twice the value for men. In evaluating this, it must be borne in mind that this is offset considerably by their lower natural rate of cancer mortality (in the specific population which constitutes the LSS cohort). In Japan the natural age-specific cancer rates for women are lower than for men: the lifetime background risk for a person of age 30 of dying from cancer is about 21% for women and about 29% for men. The excess absolute risk (EAR) is obtained by

multiplying the ERR by the natural background rates. When this is done, the ERR ratio for men:women of 2:1 collapses to an EAR ratio of 1.4:1.

Additionally, the higher EAR for women is not attributable mainly to sex-and site-specific cancers like those of the breast, uterus and ovary, despite a widely-held impression that this is so. The major single contributor to the difference in fact is stomach cancer. In Japan stomach cancer is quite common; it has an environmental cause, being related to diet and lifestyle.

Rates of stomach cancer in North America are markedly lower. In such a "risk transfer" analysis, the contribution to EAR of radiogenic stomach cancer would diminish; this would decrease the sex-related difference in Canada, say, compared to Japan.

But what may be more important is that the natural rates of fatal cancer are approximately equivalent in Canada between the two sexes, whereas in Japan the rates for females overall are (as mentioned) about two-thirds that for men. Given the higher ERR/Sv values for women from the RERF analysis, taking this component into account would tend to increase the differences (EAR) in ostensible radiogenic cancer risk between men and women in Canada compared to Japan. Legal imperatives of "equality between the sexes" aside, we may not be able to count forever on hiding behind the thin defence of saying that these differences are not statistically significant. The issue certainly merits further examination.

REMEMBER THE DDREF

This is a suitable time to remind the reader in a simple way of the broader context for these values. These EAR values may appear to be high compared to the values you are familiar with in the work situation. This is because the A-bomb survivor population received the radiation dose that placed them at risk in a single exposure, virtually instantaneously. What we know as the DDREF (*dose and dose-rate effectiveness factor*) has not been applied and does not apply to the LSS cohort.

For estimating the risk of radiation exposure received in the way it is in the occupational situation (that is, when a human population is exposed to relatively low doses of sparsely ionizing radiation delivered over a long time), a DDREF is applied in recognition of the lower effectiveness of low dose-rate exposure in causing radiogenic cancer—essentially recognizing the non-linearity of response. (The evidence supporting this comes from a vast array of radiobiological data on animals, cells and even human beings.) The DDREF is applied as a *divisor* to the EAR estimates. The ICRP recommends use of a value of two for DDREF. An EAR of 0.10 per Sv from acute exposure (for example, from this RERF update) essentially would become an estimated EAR of 0.05 per Sv for low dose, low dose rate exposure in radiation protection. This latter is the familiar "5% per Sv" population risk estimate for exposure over a lifetime. For a population of nuclear workers, a value of "4% per Sv" is currently considered to be appropriate for purposes of decisions about risk management. It is less than "5% per Sv" chiefly because the years 0-18 are absent from occupational exposure, and the lifetime risk is therefore lower.

LEUKEMIA

The excess lifetime risk for leukemia at 1 Sv is about 0.015 for males and 0.008 for females, for exposure at either 10 or 30 years of age. For exposure at age 50, the leukemia risk is about two-thirds the preceding.

The reason why the leukemia risks are quoted **at** 1 Sv as opposed to "per Sv" is that a different equation (the linear-quadratic equation) best fits the leukemia data. The non-linear fit is such that for leukemia, the risks estimated for 0.1 Sv are about one-twentieth those for 1 Sv. (In other words, one-tenth the dose gives a two-fold lower risk than expected by strict proportionality to the risk at 1 Sv). This is equivalent to a dose and dose-rate effectiveness factor of two, but is not a DDREF as such.

Remember that these risk coefficients hold only in a statistical sense, for the "average" of a population. The risk coefficients don't necessarily apply to any particular individual. This caveat holds for both leukemia and for solid cancers.

SHOULD FORMAL RADIATION RISK COEFFICIENTS FOR ACUTE, SINGLE EXPOSURES BE REVISED UPWARDS?

Prima facie, these results may seem to call for a possible upwards revision of the formal ICRP radiation risk coefficients. The immediately apparent reason is that the summed risks (solid cancers plus leukemias) add up to 0.115 per Sv (11.5% per Sv) for males and 0.148 per Sv (14.8% per Sv) for exposure at age 30. The 'mean' of the EAR for men and women at age 30 would be slightly greater than 13% per Sv, which is above the "10% per Sv" reference value for risks to the general population (i.e., 5% per Sv multiplied in this case, to "uncorrect" for the DDREF of 2). But settling on a risk coefficient for the general population includes issues of risk transferability and other considerations; it is not so simple as taking the bare A-bomb survivor risk values.

However, the best values for the LSS cohort may be even higher. There exist other longer-term impacts which also favor upwards revision.

"Misclassification errors" are one. An appreciable proportion of cancer deaths are known in general to be misclassified as non-cancer deaths on death certificates; a much smaller proportion of non-cancer deaths are misclassified as cancer deaths. The relative differences are greater than the approximately 1:3 ratio of deaths from cancer versus "all other causes": an earlier study within the LSS found these misclassification rates to be 20% and 3%, respectively. A correction for misclassification errors would increase the EAR by a factor of about 1.16 (2). The values reported here do not have this correction applied.

Dosimetric considerations are another factor. The coefficient of variation in individual dose estimates is about 35%. This imprecision is not randomness (which statistical methods allow for) but rather systematic bias. This bias is in the direction that results in underestimation of risk. If allowances were made for these systematic dose errors, the cancer risk estimates would increase by a factor of about 1.1 (3).

THE STUDY PROVIDES NO EVIDENCE FOR A THRESHOLD

That there is no statistically significant non-linearity for solid cancers (there is for the case of induced leukemias, as has been mentioned—the induction fits a linear-quadratic model better) has already been remarked. A stronger statement is warranted, according to the authors: **the new data do not provide any evidence to support a contention that there is a threshold below which no excess risk exists.** The uncertainty in the lower dose categories has in fact been decreased since the last analysis (which covered up to 1985).

In fact, if there is any departure at all from linearity at low doses, the new data indicate that the risk per Sv may be greater in the very low dose categories. The estimated values for risk per Sv in the three lowest dose categories range from 2- to 7-times greater than the value (an ERR of 0.37 per Sv)estimated using the entire 0-3 Sv range of data (Table 1).

Table 1
Estimated values for ERR per sievert in the lowest dose categories (1)

Dose category (Sv)	ERR per Sv (±standard error)
0.005-0.02	2.6 ± 2.1
0.02-0.05	1.6 ± 0.90
0.05-0.10	0.60 ± 0.40
0.10-0.20	0.43 ± 0.25
0.20-0.50	0.38 ± 0.13
(0-3 Sv; overall range)	**(0.37)**

The numbers for ERR per Sv in the lowest dose categories, showing non-linearity in the "concave upwards" direction up to seven times greater than the value averaged over the entire 0-3 Sv range of data, are statistically significant, though just barely so.

This result should be treated with some considerable caution. On the one hand, it seems to support a conclusion that there exists a greater relative risk for low dose exposure. On the other hand, other more prosaic explanations are likely. The most plausible is that a differential exists between near and distant survivors in respect to their likelihood of cancer being actually recorded on the death certificate as a cause of death. This sort of bias could occur, for example, because of the heightened scrutiny given to the LSS cohort.

The RERF has indirect evidence that this is so. Tumor registry incidence data is supported by more accurate diagnostic criteria than is the case for certification of cancer as a cause of death.. The degree of non-linearity in the lowest dose categories is much smaller than above when cancer incidence is assessed.

RISK IN HIROSHIMA CONTINUES TO BE APPARENTLY GREATER

Higher estimated radiation risks persist for Hiroshima compared to Nagasaki. (The city differences have in fact increased since the last report. One possible explanation relates to differences between the two cities in mean age at exposure: this is about 3.6 years greater for Hiroshima than for Nagasaki survivors. This factor may not entirely be corrected for.) There is a seductive notion that this is because the dose estimates for Hiroshima are too low. The idea that the cities could be brought into line by increasing the neutron component at Hiroshima has received considerable attention. Correction factors have been estimated, based on recent neutron activation analyses; these have values of about 0.75 at 650m, 1.0 at 750m, 2.0 at 1000m and 10 at 1600m (4). On the face of it, increasing the neutron component of the dose should have a major effect, reducing the estimated risk per Sv. This arises because neutrons are given a radiation weighting factor, or w_r, of 10. A change in the neutron component of dose thus is amplified in terms of equivalent dose. If the total equivalent dose that gives rise to the fatal cancers in Hiroshima is increased, it follows that the estimated risk per unit dose decreases.

If the neutron dose was increased, it is argued, this would decrease the risk estimates for Hiroshima specifically, and bring them more into line with the estimates from the Nagasaki survivors. (This is basically merely an argument for consistency, and assumes that rates for the two cities should be the same. This may not be a valid presumption. The populations in the two cities might differ in susceptibility factors, including possibly genetic ones.)

A lot of confusion exists in regard to the likely effects of possible revisions. Extravagant claims have been made. It may not be true that a revision of the dose estimates for neutrons will result in a dramatic decrease in radiation risk

coefficients. These correction factors apply only to the neutron component of the dose, and the crucial question is where they come into play. What really counts is where the LSS members who impact on risk assessment were located in this slant range, and what their present neutron component of dose is estimated to be in DS86. The most important data in the LSS dose-response analysis comes from the range of doses received by persons located in the slant range between 1000-1200m ATB (at time of bomb). For such persons, the present DS86 estimates the neutron component of their dose as about 1½%. Even if this was adjusted upwards by 2-3-fold (remember that a radiation weighting factor, or w_r, of 10 is applied), the authors feel that the net effect at most would be for the risk estimates for solid cancer in Hiroshima to decrease by only about 15%, according to the authors of the present RERF update. If they are correct, this is a modest change, and would serve only to counteract some of the other factors mentioned as suggesting that the LSS risk estimates should be even higher.

WHAT IS THE LOWEST DOSE AT WHICH THERE IS A STATISTICALLY SIGNIFICANT RISK?

The **"lowest dose at which there is a statistically significant excess risk"** has been a much-used (and abused) number. A good case can be made that this value is now rightfully some **50 millisieverts or so**. This is a substantial reduction.

Some explanation is useful to clarify what this now means. The previous update of the LSS cohort had indicated statistically significant excess cancer mortality only for doses above 200 mSv. This was the lower bound of the dose category for which the rate in the "exposed" population was significantly higher than in the "control" population, in the LSS. There was a lot of confusion about just what this result meant. At doses lower than this, there has been an unfortunate tendency to imply that that this means that no risk exists. This results from a misunderstanding of the data and of "statistical power". **The absence of a finding is not** at all the same thing as **a finding of absence**. Clear clues existed in the earlier data that the absence of statistical significance below 200 mSv likely reflected merely statistical limitations: the point estimates of risk in the lower dose categories were generally positive and showed a trend of increasing as dose increased (5).

This "lowest dose at which there is a statistically significant excess risk" was established in this updated analysis in a different way than before. The authors feel that the former approach of testing for significance in arbitrary dose categories was inappropriate. Their approach in this updated analysis was to **determine the minimum dose d_m for which a statistically significant dose response exists when analysis was restricted to the range $[0, d_m]$. This d_m is 0.05 Sv (50 mSv).** In other words, a statistically significant trend of radiation effect is seen when data inside the interval from zero dose to 50 mSv is considered on its own. The authors state that "The range $d < 0.05$ [Sv] for a significant effect is substantially less than has been reported previously." This may be debated; the conclusion depends strongly on the aptness of the "control" group.

A POSSIBLE IMMEDIATE 'ADJUSTMENT' FOR RADIATION PROTECTION?

So how might LSS Report 12 impact on how we do radiation protection? I feel that the results for acute exposure do warrant immediate attention in one aspect. For radiation protection purposes, the so-called *dose and dose-rate effectiveness factor* has been assumed to apply if the total dose is 200 mSv or less, *whatever the dose rate* (6). (There is additionally a conclusion that the DDREF may be applied, for the purposes of assessing the risk of tumor induction in man, if the dose rate is below 0.1 mGy min^{-1} (when averaged over about an hour), *whatever the total dose*, but this aspect does not concern us in the present discussion.)

The present RERF results indicate that a dose below 200 mSv, at least given as a single, prompt exposure, may carry with it more actual risk than the present ICRP risk coefficients imply. It would be prudent to assume that single, acute exposures of 50 mSv and quite possibly lower can carry the full-blown (non-DDREF-applied) risk level. **The assumption that low doses *per se* have the "lower" risk coefficient may not be tenable if the exposure is received at high dose rate.** What this says for radiation protection practice is simply that we have to be more cautious than before about the possible risks associated with fairly large individual acute doses.

The important global insight is that dose rate (which includes dose fractionation) is emerging as a more important parameter than dose is, in lessening the ultimate consequences of exposure.

SO THE JAPANESE A-BOMB SURVIVOR RESULTS LOOK LINEAR—SO WHAT?

It seems highly reasonable to me that we concede--*in the case of acute exposures*-- that "linearity" indeed holds for solid tumors, and to lower levels of total dose than has generally been appreciated. So what? I think proponents of arguments that the risks at low doses are overestimated are in a sense barking up the wrong tree by attacking the concept of linearity *per se*.

The cancer mortality experience in the Japanese cohort is not the real issue in occupational radiation protection. It is merely a guide—and only a guide--to help us make sound and scientifically defensible decisions. The real issue is assessing the likely level of risk for workplace exposures. Our debate concerns chronic exposures, and by "chronic" I include fractionated acute exposures. Even if the risk coefficients from the LSS may indeed be somewhat larger than we have supposed, they are still a large remove from the risk we need to evaluate. Judgments about the roles of dose (and dose fractionation) versus dose-rate are needed to fill the gap. The uncertainty in radiation protection relates to the value for the DDREF--and indeed, whether any single value is appropriate.

There really are two issues here. One problem relates to the cost-effectiveness of regulations. The point here is that even **if linearity should be correct, regulations aimed at achieving "improved" radiation protection may not at all be cost-effective**, especially when compared with regulations for other substances and other risks to life. If this is the problem, I urge people to address this directly, as opposed to obliquely via an attack on the concept of linearity *per se*. I think we will all gain, and the societal debate will gain, if we separate out the social from the scientific aspects. This issue is social.

The second issue is the scientific one. Here I feel we have a duty to assess the issues strictly scientifically, and to go beyond a "balance-of-probabilities" argument. I think our regulators will rightfully insist on this, and I am certain the greater Canadian constituency will.

I consider the problem here to be that we are trying to prove that low dose exposures are not dangerous, and that this is really an impossible task to prove. The reason for this is two-fold: radiation really is a relatively poor carcinogen, and the occupational doses are too low for any effect to be detectable. The best we can hope for is to obtain data that doesn't show that a significantly-enhanced risk exists. **This is not "proof of no effect"—it is merely "no proof of effect"**. We mislead ourselves, and those who depend on our judgments, to imply otherwise.

Consider for example the situation of a typical ARW who works 20 years at a NGS and receives an average exposure of 2-1/2 mSv per year. This 50 mSv total dose would place this person at an estimated occupationally-related fatal cancer risk increment of 0.2%--this on a natural probabilistic risk of 25% in the normal course of events. We don't have a hope of detecting such a risk increment, a relative risk of 1.008 (assuming that risk exists at all), given the size of the study population and all the 'natural' reasons for why cancer rates vary. In this sense we should take little comfort from the numerous occupational studies showing SMR's < 1 (given the myriad reasons for a "healthy worker effect") for cancer mortality, or even from those which additionally fail to elicit a dose-related trend within the cohort. The recent 3-country IARC study of the health of nuclear industry workers (7) is illustrative of the "dilemma" we find ourselves in when we rely on this approach.

THE IARC STUDY OF NUCLEAR INDUSTRY WORKERS

One high-visibility attempt to address the question of risk of induced cancer in persons occupationally exposed to ionizing radiation was the International Agency for Research on Cancer (*IARC)* study of cancer mortality rates among nuclear industry workers in the UK, USA and Canada (7). This involved data on 95,673 workers (85% men) employed for six months or more and who had been monitored for external exposure to ionizing radiation. The excess relative risk for leukemia (excluding chronic lymphocytic leukemia, deemed not to be radiogenic) was 2.18 per Sv, with 90% confidence intervals (CI) of 0.1 and 5.7. This was the only—and just barely so--statistically significant result. When they analyzed the data for males in the A-bomb survivor cohort in a strictly comparable way, the resultant value of ERR/Sv was 3.67 (90% CI: 2.0, 6.5). The IARC risk coefficient was 0.6 of this value, implying an effective DDREF value of 1.7 for this class of cancer. The apparent congruity of these results led to assertions that "These estimates are the most comprehensive and direct estimates of cancer risk associated with low dose protracted exposures obtained to date", and "Overall, the results of this study do not suggest that the current radiation risk estimates for cancer at low levels of exposure are appreciably in error".

Yet the leukemia conclusion rests on a total of 119 fatal cases, and the finding of statistical significance rests on 6 cases compared to 2.3 expected in the highest dose category (> 400 mSv). I for one would like to see a firmer ground for such far-reaching statements as quoted in the preceding paragraph. Perhaps where we have erred is too far on the side of caution, and it is semantics which is confusing the debate.

For "all cancers excluding leukemia", the ERR was -0.07 per Sv (90% CI: -0.4, 0.3). Unfortunately, although this result provides no evidence indicating that there is <u>any</u> increase in risk with increasing dose in these workers, it also lacks sufficient statistical power to "prove" that the result is statistically different from the risk estimate derived using the A-bomb survivor data; worse, it does not even exclude the possibility that the risk might not be higher than in the LSS.

This type of "no-win" situation holds for other cases where it has been posited that there is no risk: people living in high natural background areas, workers in a plethora of situations of technologically-enhanced exposure, *et cetera.* Stripped of rhetoric, none of these models is ever likely to provide a sound case that there is demonstrably no risk—only that there is no excess risk demonstrable. A similar conclusion holds for a thesis that low-dose exposure may have some benefit.

In debating this issue, it is not what we believe to be the case that is important but what we can prove to be the case. We have to acknowledge that our regulators are obliged to insist upon adequate proof. I submit that as responsible scientists, we are remiss if we are willing to settle for providing less than a rigorous standard of proof in this matter—that indeed we are doing ourselves a disservice and a discredit if we compromise on less than we would demand of others. We would be admitting we were not worthy of self-regulation and the public's trust.

I suggest that the issue may be addressable if only we "stop looking under the streetlight".

THE ROAD AHEAD

I submit that we have been looking in the wrong places to demonstrate whether or not low dose, low dose-rate radiation is less dangerous than the present formal risk coefficients imply. Statistics will defeat us every time. We can never prove that <u>low dose</u> radiation is less dangerous than the formal ICRP coefficients imply, and we can never prove that it has benefit. We ought to give up trying. Radiation is a relatively weak carcinogen, and the reality is that radiation protection practices and philosophy has gotten *per caput* doses down too low for scientific resolution firmly one way versus the other.

It undoubtedly seemed "right" initially to query ARW health and cancer mortality directly, but it is past time we recognize that all this does is prove that the risks are not a lot larger than we assume. It will never prove the risks are smaller, or that an exposure may be beneficial. We have to address higher radiation doses if we are going to

develop scientifically credible data as to whether low levels of radiation are less dangerous than regulations presently assume. At higher doses we gain statistical power.

To do this, we have to look at what the most crucial difference is between the LSS cohort and the occupational-type of exposure situation whose risk we want to evaluate credibly. This difference is not dose but it is dose-rate. What this all boils down to is that the single most important and relevant question for radiation protection is the following: **What DDREF is appropriate for the manner in which ARW's receive their exposure?** While 50 mSv in a prompt exposure (see RERF results in first part of this manuscript) may be more risky than we suppose, presumably there is some lower dose where the risk per Sv does drop. This decline may be a continuous one, and not a step function. Similarly, at 50 mSv (or even much higher total dose) there is presumably some effect of dose fractionation where, again, the risk per Sv decreases.

The difficulty is in assessing the envelope of parameters wherein we humans marshall sufficient biological resources to substantially minimize risk, and the issue to evaluate is how substantial this minimization may be. We have remained fixated on dose, save for crumbs represented by the DDREF, while burgeoning radiobiological insight into the roles of DNA repair, genetics of cancer, multistage carcinogenesis, *et cetera*, was alerting us to the importance of the way in which the dose was received.

I want to show you how this insight can be used. If we can prove that higher doses and/or higher dose rates than attains occupationally are less dangerous that the ICRP risk coefficients, it sets for the first time a scientifically defensible upper bound on radiogenic risk for the way exposures are received in the workplace situation. The risk study on tuberculosis patients who received multiple fluoroscopic examinations illustrates what I consider to be "the road ahead".

LUNG CANCER RISK IN TB PATIENTS GIVEN FLUOROSCOPIC EXAMINATIONS

The study I refer to is an epidemiological study of lung cancer mortality in 64, 172 Canadian tuberculosis patients who had been given multiple fluoroscopic examinations as a guide to treatment and disease control; some patients received these exposures in relation to pneumothorax treatment. Salient features of this study cohort in comparison to the Japanese A-bomb survivors are summarized in Table 2. The average tissue dose (to the lung) in the Canadian study is four times larger than the Japanese study, and the cohorts are of comparable size. The Canadian study has considerable statistical power: for example, although possessing comparable total person-years at risk, the Canadian fluoroscopy study has from four- to ten-times more person-years at risk than the A-bomb survivors study in the dose categories above 1 Gy.

For radiation risk assessment, the crucial thing is how the exposures were received in the case of the Canadian TB patients. The dose rate involved, 0.6 mGy per second (36 mGy per minute) was appreciable; for example, the current legal quarterly limit for ARW's would be reached in 50 seconds [the new annual dose limit recommended in ICRP Publication 60, already effectively pracice in Canada, would be reached in just over half a minute], and the present legal annual dose limit in a minute and a quarter. This dose rate is much higher than holds for ARW exposures; on the other hand, this dose rate is much lower than was the case for the Japanese A-bomb survivor population.

The average dose to the lung, per [individual] fluoroscopic session, was 11 mGy. Again, this is much higher than for individual ARW exposure episodes but much lower than for A-bomb survivors' exposures (these average 240 mGy and may be considered a single, acute episode).

However, the single most important aspect of the TB patients' exposures is that they were highly fractionated: their mean total lung tissue dose was 1.02 Gy, which indicates that *their dose* (larger than that of the A-bomb survivors) *was delivered in an average of 92 separate fluoroscopic sessions*. The TB patients' doses were accumulated over 31 months on average (in excess of 6 years for only 10% of patients), which is a relatively short period compared to ARW exposures.

In summary, the various aspects of ARW exposure patterns -- in terms of the radiologically important parameters of dose, dose rate, and degree of fractionation (the latter two being protective in terms of risk) -- are as far in one direction from the fluoroscopy patients' experience as that of the Japanese cohort is in the other direction. What all of this means is that any diminution in risk which might be shown in this epidemiological study can be assumed to hold "in spades" for occupational exposures.

Table 2

Précis of cohort characteristics for the Canadian fluoroscopy study versus Japanese A-bomb survivors

STUDY CHARACTERISTIC	CANADIAN FLUOROSCOPY STUDY	ATOMIC BOMB SURVIVORS STUDY
Number of subjects in the study, total	64,172	75,725
(Men)	(32,255)	(30,296)
(Women)	(31,917)	(45,429)
Exposed subjects with lung tissue dose >10 mSv; number	25,007	41,453
Unexposed (control) subjects; number	39,165	34,272
Total lung tissue dose; range in Sv	0-24.2	0-3.99
Mean total lung tissue dose, Sv (exposed subjects only)	1.02	0.24
Average number of fractions in which total dose was received	92	1
Dose per fraction; average	0.011 Sv	0.24 Sv (one fraction, therefore same as mean dose)
Length of time over which total dose was received	2.6 years, on average. (For 10%, >6 years)	<1 second (Virtually instantaneous)
Mean time since exposure	37 years	34 years
Mean age at exposure	28 years	29 years
Person-years at risk, total	1,608,491	1,693,026

Selected important parameters of the results for the Canadian fluoroscopy cohort are presented in summary form in Table 3. As before, the corresponding values for the Japanese A-bomb cohort are included for comparison. The results given are for all subjects combined (i.e., both sexes). Values are available for men and women separately within both studies, but these need not be given here: I will simply note that the overall conclusions given also hold for each gender separately.

This study shows no positive association between risk of lung cancer and dose. It also does much more. The point estimate is zero excess relative risk, and the critical finding concerns the narrow 95% confidence intervals (-0.06,0.07). For comparison, the corresponding values for the atomic bomb survivors are 0.60 (0.27, 0.99). In fact, the study had sufficient statistical power to set an upper limit of risk for highly-fractionated exposure which is more than 5-fold *below* the point estimate from the A-bomb survivors.

The individual doses in the study, the dose rate at which these exposures were received, and the total dose received, are in each aspect above the situation which holds for ARW exposures. The overall importance of these results is that they indicate that radiation protection practices and dose limits are highly conservative for lung cancer risk; the real risk to occupational workers is highly likely to be notably lower than we have supposed.

A number of points deserve emphasis concerning the results summarized above:

(i) No risk, for any dose category of exposed Canadian fluoroscopy patients, is significantly elevated compared to the unexposed, internal control, group.

In contrast, the risks for all exposed groups in the Japanese cohort, even the lowest dose group, is significantly increased.

(ii) There is no evidence of any positive association of lung cancer mortality with dose in the Canadian study population, even when the higher doses (above 1 Gy) are considered.

In the Japanese cohort, risk increases monotonically with dose.

(iii) The confidence values around the point estimates of ERR are narrow, and suffice to exclude values of excess relative risk of 0.11 per sievert or greater. This limit of exclusion is less than 20% of the point estimate from the Japanese cohort.

(iv) The study is statistically powerful. Even in the higher dose categories, sufficient lung cancer deaths occurred in the Canadian cohort to able to exclude ERR of 0.6 or above. That is, even for the higher dose categories, a risk as high as that in the A-bomb survivors is ruled out.

(v) The results from the study of Canadian TB patients subjected to fluoroscopic examinations are statistically incompatible with the results from the A-bomb survivors. By far the most likely explanation is that even at the moderate doses and dose rates characteristic of fluoroscopic examinations, a very substantial fractionation/dose rate effect exists for low-LET radiation in respect to causing lung cancer.

(vi) Consideration of the doses and dose rates which apply to ARW exposures supports the conclusion that a similar or greater degree of protection is likely to hold for them.

Table 3
Results for lung cancer mortality in the Canadian fluoroscopy study compared to A-bomb survivors
Excess Relative Risk per Sv

PARAMETER	CANADIAN FLUOROSCOPY STUDY	JAPANESE A-BOMB SURVIVORS
Lung cancer deaths, total (occurring 10 or more years after first exposure)	1,178 (for 1950-1987)	619 (for 1950-1985)
Expected number of lung cancer deaths	1,181	386 (calculated)
Excess relative risk (ERR) of lung cancer mortality, with 95% confidence intervals in brackets, by category of radiation dose to the lung:		
<0.01 Sv	0.0 (control)	0.00 (reference control)
0.01-0.49	-0.13 (-0.26, 0.03)	0.26 (0.06, 0.50)
0.50-0.99	-0.18 (-0.34, 0.02)	0.45 (0.03, 1.06)
1.00-1.99	-0.06 (-0.23, 0.15)	0.93 (0.30, 1.85)
2.00-2.99	0.09 (-0.2., 0.50)	
>3.00	0.04 (-0.28, 0.53)	1.65 (0.51, 3.66)
OVERALL ERR per sievert	0.00 (-0.06, 0.07)	0.60 (0.40, 1.76)

The author went to a great deal of effort to show that there were no hidden biases in this study which might have masked a true underlying association. Some of these points will be discussed briefly:

(i) There seems to be no bias from misclassification of death from lung cancer as being from TB. One wouldn't expect this to be manifest anyway, as the degree of misclassification would have to be dose-related for it to be a factor. Also, different "stages" (maximum severity of development) of lung cancer were assessed separately to support a conclusion that lung cancer deaths were not missed to any significant extent.

(ii) Smoking seems not to be a bias. To mask a "true" positive association with dose would require that smokers with low doses be sampled preferentially to those with high doses, and no study has seen this. Here, in fact, dose and smoking were, if anything, very weakly *positively* correlated, which would tend to suggest more of a positive association than actually existed.

(iii) The patients with TB could possibly be different in susceptibility from the Japanese. One mechanism might be fewer cells at risk in part of the fluoroscopy cohort due to surgical removal of parts of their lungs. However, when such individuals were removed from the analysis, there was still no positive association with dose.

The most likely explanation for the marked difference between the results in these two cohorts with respect to lung cancer mortality has to do with the way the radiation is delivered: highly fractionated exposures in the fluoroscopy study, with typically days to weeks intervening between exposures (which averaged 11 mGy), and with dose rates

in the order of 0.6 mGy per second (36 mGy per minute), which are several orders of magnitude lower than for the survivors of the atomic explosions at Hiroshima and Nagasaki.

What we need is this kind of information for other sites of cancer. These results pertain to lung cancer only. The *tissue weighting factor* (w_r) for the lung is 0.12. While as strong a fractionation/dose rate effect such as seen here for lung cancer is almost certainly *not* going to be observed for all sites of radiogenic cancer, it may hold for enough of them that we can say with confidence to the regulator and the public that by controlling exposure in the way we currently do, the risk is really lower than present assumptions suppose.

It is incumbent on us to ensure that data becomes available. There are other study populations which can be used, including second primary malignancy rates (especially of leukemia) in patients who received radiotherapy. Once we get away from the flawed mind-set that we can resolve this question by looking at the mortality experience of people who have received low incremental doses, the relevant data will be developed.

THE RERF UPDATE IS THEREFORE GOOD NEWS

This is why I'm so positive about the recent RERF update of cancer mortality in the LSS, described in the first portion of this paper. The statistical power of these studies is growing, and one only has to look back 10 or 15 years to note how strikingly the uncertainty in these assessments has been reduced.

This is a very positive benefit for us in a number of ways, but the one I'm going to emphasize may be one you haven't appreciated yet. The new LSS results are going to make it possible, as never before, to look at the new "higher dose" scenarios I have descibed (and yes, even the occupational, ARW, situation) and to demonstrate whether or not these are demonstrably distinct from the risk paradigm entrenched in collective consciousness as "the results from the A-bomb survivors". The manner in which occupational exposures are received are different from the way the LSS cohort received their exposure in all the ways that count.

It is time to cut that link to the A-bomb survivors.

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TRITIUM β-RADIATION INDUCTION OF CHROMOSOMAL DAMAGE: A CALIBRATION CURVE FOR LOW DOSE, LOW DOSE RATE EXPOSURES OF HUMAN CELLS TO TRITIATED WATER

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ABSTRACT

Radiation exposures from tritium contribute to the occupational radiation exposures associated with CANDU reactors. Tritiated water is of particular interest since it is readily taken up by human cells and its elimination from the body, and, consequently, the radiation exposure of the cells, is spread over a period of days. Occupational exposures to tritiated water result in what are effectively chronic β-radiation exposures. The doses and dose rates ordinarily used in the definition of cellular responses to radiation *in vitro*, for use in biological dosimetry (the assessment of radiation exposures based on the observed levels of changes in the cells of exposed individuals), are usually much higher than for most occupational exposures and involve radiations other than tritium β-rays. As a result, their use in assessing the effects from tritiated water exposures may not be appropriate. We describe here an *in vitro* calibration curve for chronic tritium β-radiation induction of reciprocal chromosomal translocations in human peripheral blood lymphocytes (PBLs) for use in biodosimetry.

INTRODUCTION

Tritium exposures contribute to the occupational radiation exposures that are associated with CANDU reactors and much of the concern that is expressed by the public in discussions of the safety of nuclear power stations in Canada. Consequently, a clear understanding of the effects of tritium β-rays on human cellular material at the dose and dose rate levels that might be experienced by atomic radiation workers in such facilities is important. This is particularly so, given the wide range of estimates of the relative effectiveness of tritium β-rays that have been reported in the scientific literature [1].

The most significant exposures in the occupational context are to tritiated water (HTO). Since HTO is taken up readily by cells, and is eliminated over an extended period, the

exposures are chronic in nature: doses are accumulated at relatively low dose rate over several days. Reference curves derived from cells exposed *in vitro* are the norm in the evaluation of radiation exposures using biological dosimetry, that is, assessing the exposure based on the level of an induced effect in the cells of the exposed individuals. For most cellular effects used in such work, the dose response relationship is best described by a linear-quadratic relationship ($y = \alpha D + \beta D^2$, where y is the yield of events, and D is dose). The exposures used in defining these calibration curves are usually acute (delivered over a short period of time at high dose rate). One of the limitations of such curves is that they do not lend themselves particularly well to the definition of the linear portion of the induction curve at low doses or at low dose rates. Consequently, they are inappropriate for evaluating HTO exposures.

The work described in this report was undertaken to define a calibration curve specifically for HTO exposures in a dose range and at a dose rate that would allow us to stay within the linear portion of the dose response curve. This, in turn, allows for better definition of the α–coefficient of the induction curve.

The end-point used in this study is reciprocal chromosomal translocation. These cellular anomalies are rearrangements of cellular DNA, brought about by the incorrect rejoining of broken chromosomes, themselves a consequence of radiation damage. Reciprocal translocations are characterized by cellular stability (they do not necessarily result in cell death), making them the end-point of choice for evaluation of acute exposures long after their occurrence, or for multiple exposures over an extended period. This does not, however, preclude their use in the evaluation of acute exposures.

While the doses and dose rates used here are still well above occupational levels, they were chosen to be low enough to keep the induced levels of effect within the linear portion of the induction curve, a necessity in defining the induction rate at low doses.

METHODS

Blood from a healthy male donor was collected by venipuncture in heparinized vacutainer tubes and maintained at room temperature until treatment. To mimic the conditions to which cells *in vivo* would be exposed, aliquots of blood were diluted 1:1 with culture medium (RPMI 1640, containing 20% (v/v) fetal bovine serum, 2mM glutamine , 100 I.U./mL penicillin, 100 µg/mL streptomycin), prewarmed to 37°C. The culture medium was spiked with tritiated water at activity concentrations calculated to deliver 0.3, 0.6 or 0.9 Gy over a 48 hour incubation period. A modification of the methods of Scarpa et al. [2] and Prosser et al. [3], assuming lymphocytes to be 82% water and correcting for the non-aqueous components of the medium, was used in dose calculation. The suspensions were incubated at 37°C in sealed tubes with continuous, gentle agitation.

The isolation of the lymphocytes from the whole blood mixture using standard density-based separation methods [4] was begun at a fixed time before the end of the exposure.

The tritiated water exposure was ended effectively when the separated cells were removed from the gradient and diluted in a large volume (45 mL) of non-tritiated medium. The cells were washed three times, sufficient to reduce the residual tritium in the supernatant fluid to background levels.

The washed cells were resuspended in fresh medium containing phytohemagglutinin (PHA) to stimulate cell growth, and incubated at 37°C in a humidified atmosphere containing 5% CO_2 in air. The procedures for preparing metaphase spreads from the cultured cells were as described in Lin et al. [5]. Reciprocal chromosomal translocations involving chromosomes 1, 2 and 4 were scored using fluorescence *in situ* hybridization, a technique that allows ready microscopic identification of rearranged chromosomes [6,7]. The chromosome-specific fluorescent tags used were from Vysis Inc. (Downers Grove, IL 90515).

For this work the scoring criteria were those employed by Lucas et al. [7]. Only the results for complete reciprocal translocations are reported here. Because only events involving chromosome 1, 2 or 4 were measured, a correction factor to scale to full genome equivalents is applied [6]. Curve fitting of the data was carried out using SigmaPlot (Jandel Scientific Software, San Rafael, CA 94901).

RESULTS AND DISCUSSION

The numbers of metaphases scored and reciprocal translocation events observed following chronic exposures to tritiated water are shown in Table 1. A total of 21 117 metaphases were scored in tritiated water exposed cells. The number shown for the control (zero dose) is a composite number for several donors, and includes 4 318 from the specific donor whose cells were used in the HTO work.

The frequencies of reciprocal events, corrected to full genome levels, are plotted in Figure 1. The best fit of the data to a simple linear regression model ($y = C + \alpha D$) is indicated by the plotted line. The α-coefficient is estimated at 0.026 +/- 0.002 translocations per cell per Gy. The estimate for the y-intercept, **C**, is 0.003 +/- 0.001 translocations per cell.

Estimates for the α-coefficient, as defined by the initial slope of the induction curve, for radiations of other qualities have been made. The values obtained, 0.023 ± 0.005, 0.031 ± 0.001, and 0.035 ± 0.005 translocation per cell per Gy for ^{60}Co γ-rays [7], ^{137}Cs γ-rays [8], 250-kVp X-rays (Lucas, unpublished data), respectively, were obtained from lymphocytes exposed under somewhat different conditions, and, consequently, are not strictly comparable. The data for ^{137}Cs γ-rays [8] are plotted in Figure 1. Definition of an estimate for the relative biological effectiveness (RBE) for tritium β-rays for this sensitive, and very relevant end-point with respect to radiation exposures, must await an analysis of data from cells exposed to a reference radiation under the conditions described in this work. These were designed to approximate the conditions that the lymphocytes of an exposed individual would experience *in vivo*. The cells were supplied with nutrients

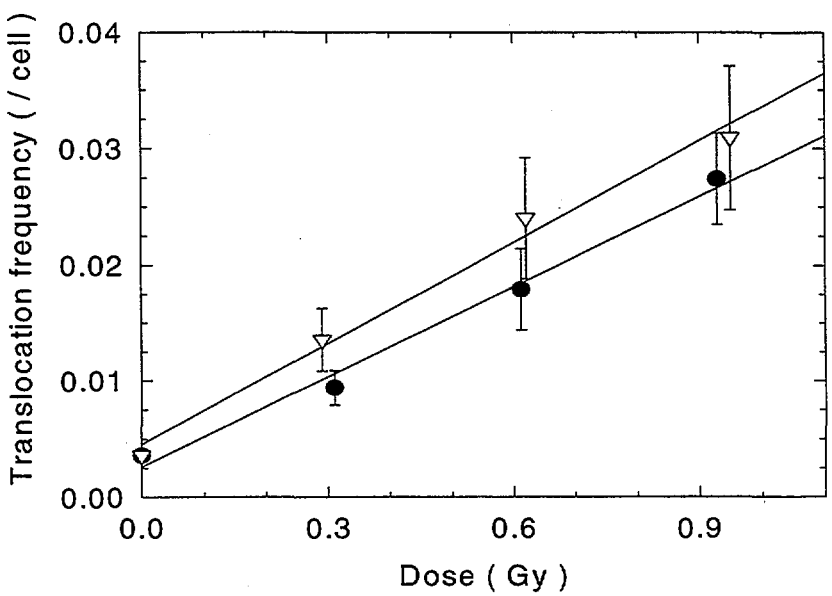
in a medium designed to maintain cellular metabolic capacity during the prolonged exposure. The medium was buffered to keep the pH in the physiological range and the blood/medium

Table 1
Reciprocal translocation induction in human lymphocytes by exposure to HTO at 37°C.

Dose (Gy)	Metaphases scored	Full genome equivalents*	Number of translocations observed	Translocation frequency per cell (1 std.dev.)
0.00	25 435	8 902	37	0.0042 (0.0007)
0.30	12 502	4 376	41	0.0094 (0.0015)
0.61	4 156	1 455	26	0.0179 (0.0035)
0.93	5 319	1 862	51	0.0274 (0.0039)

* Because chromosomes 1, 2 and 4 together represent only a fraction (0.35) of the total chromosome length in the cell, this correction factor is applied to allow the frequency to be expressed in terms of whole cells.

Figure 1
Induction of reciprocal translocations in human lymphocytes by tritium β-rays (•) and ^{137}Cs γ-rays (∇) under different exposure conditions (see text).



suspensions were held at normal body temperature, 37°C. This was not the case in the earlier work.

The dosimetry of tritium β-ray exposures to HTO is based on three critical assumptions; the HTO diffuses freely and rapidly into the cells, the water content of the cells is known and the distribution within cellular compartments is uniform. There is no disagreement in the literature that, for the lengths of exposures that are ordinarily used, the diffusion of HTO into cells is sufficiently rapid to be assumed to be instantaneous. In the absence of specific information on the distribution of intracellular HTO, its uniformity remains an unsubstantiated assumption. The water content of cells is another matter. Values for mammalian cells in general range from 45% (9) to 84% (10). The value used in this work, 82% (2), is the only specific estimate for human lymphocytes known to us. Clearly, any uncertainty in this value will reflect on the results obtained. Methods for measuring the water content of cells under the conditions used for our *in vitro* exposures are being assessed. When completed these measurements will allow us to define with confidence the α-coefficient for low dose HTO exposures. This together with the definition of the *in vitro* induction curve for the reference radiation under the same normal physiological conditions will allow us to provide a sound estimate of the RBE of tritium β-rays for this very relevant and sensitive biological end-point.

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