The Future of Risk Assessment: a Round Table

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Introductory Remarks (Schimmerling):

In the movie "Marathon Man" Dustin Hoffman is pursued by a mad dentist who keeps asking him, "Is it safe?" It takes a number of painful moments before the issue is resolved (not in the affirmative) and the meaning of "it" becomes clear. At a less dramatic level, the concern and its urgency are daily felt by the public: is it safe? This, at the barest and most primitive level, is the critical question addressed by risk *assessment*. However, safety is always relative and never permanent. Risk *prediction* (or risk *estimation*) addresses the question: will it be safe? If either of these answers turns out to be negative, risk *management* has to address the issue of how to make "it" safe. Finally, *archival* risk assessment is required, for legal as well as moral reasons, to assure that, indeed, it was safe (or to establish who was to blame if it was not!).

What is "safe"? And how can we tell? The participants in this round table were asked to consider these two interrelated questions in addressing the future of risk assessment.

In order to answer the first question, it was suggested that the following should be addressed:

- How does one establish confidence levels and how does one use them to determine a "safe" risk level?
- Who decides what is safe?
- What are ethical criteria for deciding?
- What are risk endpoints to use?
- What are critical data needs to improve the current approach to risk assessment and to develop models?

There are two complementary paradigms to examine ethical approaches to risk assessment and risk management.[1] One of these is based on utilitarian ethical principles seeking to balance the societal versus the individual responsibility for risk while the other is an informed consent paradigm, whereby each individual accepts risks based on his or her individual cost/benefit estimates. The former derives from a consideration of societal needs for individuals (e.g., soldiers, firemen, police officers, miners, research subjects) to assume risks for a perceived greater good. The current NASA radiation limits[2] are based on a comparison of space radiation risks with risks

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common to industries with a median level of risk. The assumption made is that, in these industries, the levels of risk accepted represent a social consensus.

The informed consent paradigm is an extension of the principle that establishes government by consent of the governed. However, there are limits to consent: no one may sell himself into slavery and society also establishes limits on other risks to which individuals might otherwise wish to consent. On the other hand, contractual rights and obligations of any employment imply acceptance of a compact, whereby the employer is engaged to minimize the risks associated with the workplace (most often enforced by law), and the worker accepts to incur the risks associated with the work performed.

The determination of what is acceptable is an ongoing ethical task that needs to be reexamined continually. Its foremost purpose is the protection of individual human beings but, in defining the limits of exposure to risk, the process also provides for work requirements that meet societal needs.

How can we tell? The answer to this question requires the development of risk endpoint predictors. Among predictors of radiation risk are dose, flux, dose equivalent and biomarkers. The use of risk predictors involves consideration of a different set of questions:

- What are the criteria for their validity?
  - They are different for individual vs. population risk predictors
- How should we use them:
  - To limit career exposure?
  - To limit mission operations?
  - To initiate aggressive medical surveillance? (e.g., should everyone with a certain number of chromosome aberrations of a certain type have medical diagnostic procedures every 6 weeks, or have a restricted diet, or take a Vitamin E pill every day?)
- Which biomarkers are ready to be used? For those that are not ready to be used (all?) when will they be ready?
- What is the statistical power for predicting risk of various predictors?

The following requirements for such risk predictors, in particular for biological indicators of radiation risk, need to be considered:

- **sensitivity** to the levels of radiation exposure of concern
  - <u>unequivocal</u>: not sensitive to confounding factors (high signal-to-noise ratio)
- **accuracy** of predictions
  - predict risk and health care decisions at a <u>well-defined</u> <u>level</u> <u>of confidence</u>
- **specificity** of prediction
  - plausible <u>causal</u> relationship based on testable mechanisms of radiation action, rather than just a contingent <u>correlation</u> with radiation exposure

- **precision:** the results are not significantly distorted by individual or circumstantial variations in radiation response
- lead to **diagnostic procedures** that are:
  - practical under actual circumstances of exposure rather than only under highly restricted laboratory conditions
  - cost-effective , to screen large populations where required

Notes for the Round-Table Discussion (Fry)

Most, if not all, human endeavors and even daily activity involve risk. The dividing line with regard to attitude to risk is a combination of whether the risk is taken voluntarily and a personal unscientific and pragmatic assessment of the risk/ benefit.

Risk has been examined more extensively in the case of radiation than any other agent. In medicine the ethical use of radiation is a fairly easy decision because the benefit can almost always be shown, even if precise values cannot be placed on the risk and the benefit.

Occupations involving radiation have been long regulated, in part because it is possible to measure the amount of exposure involved. What has not been so easy is to assess the risk and having done so come to a mainly arbitrary decision of what risk workers (and the general population) should be asked to accept. In the case of radiation risk and space activities the risks involved in hurtling into space seem much more significant. But it is the question of what risk there is of late effects, in particular, cancer later in life after the career in space is over that is important. The first attempt to deal with this problem was based on a doubling of the risk of leukemia in a certain age range. In 1989 NCRP[2] suggested that a 3% excess in lifetime cancer mortality might be “acceptable.” This was based on the comparative risks entailed in different occupations. The 3% was representative of occupations that were neither the safest nor the most risky. Risk in agriculture, manufacturing and other occupations is based on fatal accidents which result in a greater loss of lifespan than is the case for cancer, a disease, in general, late in life. NCRP introduced for the first time different dose limits taking into account age and gender. The reasoning was to have the same risk independent of age at first exposure or gender, which was thought to be more equitable and non-discriminatory.

The new recommendations[3] are more restrictive and reflect the increase in data for the atomic bomb survivors. The limits are still based on 3% excess lifetime cancer mortality but now to make the risks comparable to those incurred by the occupationally exposed on Earth. The ICRP and NCRP limits for terrestrial workers have the potential for about a 3% excess of stochastic effects. While there may be a greater probability of the maximum dose limits being reached in space NASA has in the past designed its missions taking into account ALARA (as low as reasonably achievable).

Hopefully, nobody will be talking to the public about a space mission that “it is safe” but using the information given above to make the case that the approach to radiation

protection is both reasoned and reasonable. It is easier to identify areas of uncertainties than to establish confidence levels but quantification of the uncertainty of risk estimates of stochastic effects is still a difficult task and full of uncertainty!

Astronauts and cosmonauts are eager to be chosen for missions but full information about the risks of effects that may occur both during and after the career must be available and kept up to date as information improves. NASA has to have OSHA's agreement on radiation protection practices and that puts bounds on what missions NASA can undertake. NCRP's recommendations are based on protection against risk but cognizant of the problems of accomplishing missions if limits are over restrictive.

Currently the radiation protection standards for stochastic effects used internationally are based on mortality and while a move to the use of incidence may take place in the future it seems sensible to base the risks to those exposed in space on the same criteria as those used for occupationally exposed workers.

The major areas of uncertainty in the current estimates of risk for low-LET radiation lie in the adjustment of the effect of protracting exposure and lowering the dose rate on both stochastic and deterministic effect, and in the case of stochastic effects, how to transfer the risk estimates based on the atomic bomb survivors to other populations.

The choice of the risk projection model has a significant impact because about 50% of the atomic bomb survivors are still living and what happens to those that were at a young age when exposed will influence subsequent risk estimates. The fact that no data exist for the risk of the effects of exposure of humans to protons, neutrons or heavy ions means we must rely on experimental data, mainly experimental animal data, and have an acceptable method of extrapolating the results across species. The lack of new data for the stochastic effects of the types of radiation experienced in space is regrettable and has stifled any improvement in the relevant risk estimates.

While obviously there would be advantages in going to the use of fluence it appears that we should stick with equivalent doses for the meantime and that these should be based on quality factors and not WR s.

In the case of deterministic effects there is a need for estimates of threshold doses of neutrons in the relevant energy range and of heavy ions for effects in the tissues such as skin, the bone marrow, the lens of the eye and the gonads. It is the threshold doses of late deterministic effects for protracted low-dose-rate-exposures that are particularly important.

Limiting career exposures and preventing high doses of high dose-rate exposures seem to be to the most effective way of protecting space workers. Family medical histories presumably will become increasingly important but is there any evidence that approaches other than good medical practice in both the selection and surveillance will improve the chances of space workers of avoiding the risks of radiation? Reduction of exposure must remain central to protection.

Gene Induction after Radiation Exposure (SA Amundson and AJ Fornace, Jr.)

The focus of our efforts has been to determine the transcriptional (mRNA) responses of human cells to ionizing radiation. Our results indicate that responses in both a human myeloid tumor cell line (ML-1)[4] and in peripheral blood lymphocytes (PBL)[5] irradiated ex vivo are proportional to dose. Thus, our studies so far indicate a linear rather than a threshold type dose response at doses as low as 2 cGy. In the case of high LET radiation, we have observed a shift in the dose response that is roughly proportional to the RBE and again a linear dose response was observed.

Gene expression profiling, while not yet at a stage where it can be used to predict risk, is very promising for future risk prediction. The key will be defining sets of genes that are informative for different outcomes of interest One approach could exploit differences in gene expression patterns between different individuals, and using an informatic analysis determine which expression patterns correlate with unusual sensitivity to environmental exposures such as ionizing radiation, or an increased tendency to manifest a certain disease state, such as cancer. Additional and perhaps more specific information may be obtained by defining changes in expression profiles that occur after exposure to a specific agent. A generalized post-exposure profile may aid in identifying exposed individuals within a population, and it may even be possible to find identifying fingerprints for different agents, and for the time and approximate dose of exposure. As such work continues, it may be possible to identify individual variation in post-exposure profiles that may correlate with the outcome of exposure. One example of this might be identifying patients likely to fail radiotherapy from their gene expression profile following the first fraction. This would allow alternate therapies to be begun at an earlier stage of treatment. In the case of occupational or environmental exposures, such profiles may identify those individuals most in need of preventive treatment to avoid long term effects

Patterns indicating previous exposure are probably closer than those defining individual susceptibility. Issues such as dose, time of exposure and radiation quality may be discernable from gene expression signatures, although it is likely such diagnosis will be more difficult if all are unknown. Current technology is at the point of collecting expression profiles. A significant amount of data will be needed to search for meaningful correlations with various risks, and any suspected correlation between profile and outcome must be established and tested for this tool to become of practical use.

Notes for the Round Table Discussion (Goodhead)

I should like to make a few comments about what is a “safe” dose, what are small risks and how we explain these to the people concerned. In summary, I believe we must be fully open about what we do know, what we don’t know and the very large uncertainties in any numerical estimates.

From the current state of scientific knowledge, we cannot say with confidence that there is any level of radiation, however small, that is totally safe. There is quite strong evidence that a single particle (even a single electron) can produce a chromosome aberration or other mutation. This may well contribute to cancer. Unless we become nearly certain that this cannot contribute to cancer under any circumstances, then we cannot say that each electron does not carry some risk, even though very small. So, although there are very large uncertainties about low level effects, even possible thresholds in some or all situations, we cannot deny from present knowledge that there may be a risk. We may individually reach different judgements on the likelihood of these options, but we cannot say that low level radiation is definitely safe.

For high-LET radiations the problem is somewhat less complicated. The evidence is much stronger that a single high-LET particle does carry a risk, and so the evidence for a threshold for carcinogenesis in general (or other effects) is corresponding weaker.

In summary, we cannot with honesty claim a safe level of radiation. Therefore we are forced to make quantitative estimates of risk, even at very low levels, to explain to the public; and at higher levels, to set limits and to take avoidance measures according to what is deemed to be an acceptable level of risk – acceptable by society and the individuals concerned.

Then I see the major problem that the risk estimates we come up with have very large uncertainties, not only within the estimation approach taken but even more so between possible approaches (paradigm shifts).

Uncertainties are large for low levels of low-LET radiation, such as when the risk estimates are based on very large extrapolations from the A-bomb survivors, to low doses, dose-rates, across populations, to individual sensitivities, etc. But for low-LET radiations we do at least have some firm, although very wide, limits available on the possible range of the risk. At the one extreme there is the lower limit of zero risk (to correspond to a true threshold for all cancers and for all low-level scenarios of relevance). At the other extreme an absolute upper limit is set by the number of so-called “natural” cancers if these were attributed entirely to natural background radiation. Geographical variations would almost certainly suggest that radiation risks are well below this.

For high-LET radiation in general, the problem is very much worse because we have so little relevant epidemiology; and we are looking to quantify the risk for radiation exposures for which large population experiences are not available.

As I discussed previously[6] I believe that the quality factors or tissue weighting factors inevitably have very large uncertainties (order of magnitude, or maybe even more) when applied to particular radiations. RBEs for human tumors collectively or for individual type are essentially not available. Large variations in RBE between tumor types are to be expected. I should expect that uniform whole body irradiation of humans with HZE or high energy neutrons would lead to a substantially different frequency spectrum of

tumor types than that of low-LET exposure (such as from the A-bomb). Thus any suggested quality factor must be highly uncertain for overall risk, and much more so for specific tumor sites.

Extreme limits of possible risk are much more difficult to set for high-LET radiation because there is little natural environmental exposure (apart from radon and progeny to the lung). The radon epidemiology of miners suggests that the dosimetric/quality factor approach is in error by at least a factor 3 for the case of radon α-particles and the lung – and that is after strong attempts to manipulate the lung dosimetry model to reach agreement. The miners show a smaller risk than expected (by the factor of about 3).

But for other high LET exposures, there is very little information to put limits on the risk. Few people have been exposed to the very different tracks from HZE ions or high-energy neutrons, so this really is a step into the unknown. Some limits may be set by epidemiology of aircrew and space crew but such studies have low power. As an illustration, the study of some 2700 Canadian pilots by Band *et al* [7] should not nearly approach the power needed to detect a risk based on ICRP risk factors. The actual observation of significant excesses of prostate tumors and AML (based on quite small numbers) would indicate large underestimates in the ICRP-based estimates if the excesses were indeed due to the cosmic radiation. But, alternatively, the observed excesses may be due to chance or other factors not related to radiation. So very large uncertainties remain.

In conclusion, it seems that we must continue to make the best estimates of risk that are possible with current knowledge, but that we must openly acknowledge that the uncertainties may be very large.

Some Comments on the Future of Radiation Risk Assessment (Groer)

The following, mostly technical, comments are divided into two parts. Part I considers the situation when human data on cancer incidence and/or mortality after exposure to ionizing radiation are available. The shorter Part II deals with the situation when such data are not available. Both parts describe to some extent the *status quo* of radiation risk assessment and give my opinion on what could/should or cannot be done in the future.

Part I:

If human data are available the tasks of risk assessment are estimation of survival model parameters and prediction of future probabilities of cancer occurrence with uncertain parameters. I feel strongly that Bayesian methods should be used for parameter estimation and prediction. These methods use exclusively probability to characterize uncertainty. Graphs of probability densities can be used to show the remaining uncertainty in figures. Probability based confidence intervals have the natural interpretation of containing the true value of an uncertain quantity with a certain probability. The usual frequentist confidence intervals have a more complicated interpretation, which cannot be rigorously translated into a probability statement. This causes problems when derived probabilities (e.g. Probabilities of Causation), are wanted by decision makers. Formalized decision making under uncertainty requires assignment of probabilities to uncertain outcomes. Bayesian methods deliver these probabilities conditioned on available information. Point estimates are available gratis as the means and/or modes of probability densities.

A greater variety of survival models should be considered and compared by calculating the probability of fixed data conditional on the different models. For example models with and without effect thresholds should be compared.

A particular endpoint (e.g. leukemia) occurs “entangled”—to borrow an adjective from physics—with other endpoints (e.g. lung cancer) in data sets on exposed individuals. Since the common exposure influences both endpoints they are at a minimum dependent through the effect of the common exposure. The majority of present analyses assume independence of times to the occurrence of different endpoints. Influence of dependence on parameter estimation and model comparison should be studied with biologically supported forms of dependence.

Often marginal distributions for single parameters are derived from joint distributions by multidimensional numerical integration. This poses challenging numerical problems.

Multi-stage (sub) cellular mathematical models for cancer rates may provide supportive information on aspects of phenomenological models for the analysis of epidemiological data (e.g. existence of a threshold). I am however skeptical that it will be possible to formulate a multi-stage model for cancer and estimate all parameters from the observed cancer appearance and censoring times. (The “pure” endpoint is modeled the “entangled” endpoint provides the observations.).

Presently “transportation” of risk estimates between human populations presents challenges without practical solutions in sight.

Part II:

When human data are not available for the radiation type of interest extrapolation from animal data and/or other systems exposed to the radiation of interest is the next best thing. Extrapolation with quantitative characterization of the uncertainty is best done with hierarchical models. One model is encapsulated in another larger model and so on…Probability calculus provides the linkage between known and unknown probabilities and permits calculation of desired quantities and their uncertainties. (Trigonometric exercises where a missing angle etc. is determined from certain given pieces provide a good analogy for extrapolation.)

Anchoring of the extrapolation with a pivotal data set on humans exposed to a different type of radiation seems absolutely necessary for credible extrapolation results. The data on A-bomb survivors will be the pivotal data set for all extrapolations involving external radiation exposures.

An open challenge is extrapolation of the appearance time distribution for a radiation type of interest from the pivotal data set with the help of auxiliary information from other systems exposed to the radiation of interest. Until now only risk parameters have been estimated by extrapolation.

Bioethics Perspective (Cucinotta)

NASA applies an informed consent paradigm to radiation exposures below the accepted limits, as part of the implementation of ALARA (as low as reasonably achievable) risk management. This requires training astronauts to follow proper procedures when dealing with radiation and to acquire a balanced perspective of the risks involved. There exists a need for expanding this aspect of astronaut training, as well as raising the consciousness of all personnel involved of the importance of implementing ALARA.

Adequate support of research on which to base risk assessment is essential. As shown elsewhere,[8] a rational approach to risk management will result in operational limits based on confidence levels for risk. At present, acceptable confidence levels cannot be established for very long duration missions. Even for low Earth orbit, establishing acceptable confidence levels at current levels of uncertainty leads to expenses far in excess of the cost of research to reduce uncertainty. Thus, research is the most cost-effective way to manage risk.

Ethical and practical considerations require continuous examination of the guidelines for radiation exposure limits. This is an ongoing task, currently performed by the NCRP in the United States, and the ICRP in Europe. Reconciliation of the sometimes incompatible approaches used by different national and international organizations will

be an important aspect of ensuring radiation risk management for the International Space Station and space exploration beyond Earth orbit.

Selected Questions and Comments from the Audience (responses are from several panel members if none are identified)

- What is the importance of genetic predisposition?
  Not very great, although there are individuals with a family history of radiosensitivity (e.g., *Ataxia telangiectasia*), and loss of heterozygocity may be a factor to consider.
- Can one find cancer resistant individuals?
  (Fornace/Groer) Cancer is a disease of aging and occurs late in life. It is possible to define a practical threshold, such that the delay in expected occurrence is greater than the expected life span.
- What other risks are there besides cancer?
  (Cucinotta) NASA is working on identifying such risks; they are part of the "critical path" used for risk management
- How does one compensate for current lack of knowledge?
  (Groer) It is better to use existing studies and their uncertainties as the basis of subjective probability distributions; this is the reverse of the NCRP approach, where probabilities are assigned to the risk and not to the inputs.
- Are there any tests for individual risk using measured fluctuations in individual responses?
  Individual risks can be assessed by analogy with other fields, e.g., car insurance, where different groups are assigned different risk levels, even if there are large fluctuations in the individual risk
- Can one do "stress profiles" as a function of time as a risk predictor?
  (Fornace) It is too early to tell at this point, but such longitudinal studies may become feasible in the future – aging generally shows up late in life!
  (comment from M. Story) It is important to note that radiosensitivity changes with age.

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[1] For an exhaustive discussion of risk in the context of space flight, cf. National Council on Radiation Protection and Measurements, 1997. Acceptability of Risk from Radiation – Application to Human Space Flight. Symposium Proceedings No. 3.
[2] National Council on Radiation Protection and Measurements, 1989. Guidance on Radiation Received in Space Activities, NCRP Report No. 98
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[8] Cucinotta, FA.. Radiation Risks and Uncertainties for Astronauts. These Proceedings