

April 18th, 1996

**Report Of The Scientific Review Group
Joint Coordinating Committee For Radiation Effects
Research**

January 30th, 1996

Washington, D.C.

Introduction

The U.S. Scientific Review Group (SRG) for the Joint Coordinating Committee for Radiation Effects Research (JCCRER) held its first meeting on January 30th, 1996 in Washington, D. C. Participants in the meeting included Drs. Jonathan Samet (Chairman), Marvin Goldmann, Geoffrey Howe, John Poston, David Rush, and Rodney Withers. Attending by telephone conference were Drs. John Till and Alice Whittemore. Staff from the Department of Energy included Drs. Mohandas Bhat, Elaine Gallin, Maria Pavlova and Ruth Neta, and Sue Anderson. Dr. Paul Seligman was able to attend portions of the meeting.

The meeting began with an introduction by Dr. Seligman that addressed the charge to the Committee. There was an exchange between the SRG and Dr. Seligman and others from the Department of Energy concerning the scope of the charge and the functioning of the group. There was general acceptance of the written charge presented to the SRG and also of the SRG's charge as stated in the Record of the First Meeting of the JCCRER. It was noted, however, that only a single review group had been constituted. The early history of the research program was reviewed as further background for the Committee.

The group then proceeded to review the individual proposals, completing this review during the afternoon. During an executive session the SRG addressed its charge as well as general issues related to its work. The following report provides the results of these discussions, including reviews of the individual projects and the SRG's general recommendations.

General Considerations

The SRG considered the context that has given rise to the research program conducted under the auspices of the JCCRER and also the scientific potential of this research. The SRG was unanimous in its view that the community and worker populations in the Urals afforded the opportunity to address the risks of ionizing radiation at doses and dose rates of great interest from the public health and regulatory perspectives. Successful research could help in completing our understanding of the links between sources of radiation, exposure, and dose and address gaps in our knowledge of the health risks of internal emitters, particularly plutonium. To fully realize this potential, the SRG reaffirms that a major research program will be needed with sustained funding for many years, as the exposed children and adults are

followed for a scientifically meaningful length of time. The group thus urges the members of the JCCRER to begin to seek sustained funding at needed levels, so that a research program can evolve smoothly from the present pilot studies, in the event that a high likelihood of success for the long term is demonstrated.

With input from members who had traveled to the region, the SRG devoted substantial time to discussing the context of the research. The projects are being undertaken on the publicly sensitive issue of the health effects of radiation exposure among communities and workers where much of the information on exposure and risks was previously guarded. Openness in conducting the research at all levels was viewed as important for the credibility of the scientific findings. To this end, the SRG advocates public involvement throughout all phases of the research. The Record of the First Meeting of the JCCRER is clear in calling for the development and implementation of a public involvement plan. Activities related to public involvement should proceed synchronously with the development of the research projects themselves.

Data access will also be important to the credibility of the findings. The SRG assumes that there will be free exchange of data between the U.S. and Russian research partners. Once the key findings have been reported, the SRG also recommends that data be made available to other investigators to replicate findings, if warranted or requested. The U.S. Department of Energy has made data publicly available through CEDR and this model might be used. We urge the JCCRER to begin to address the specifics of the plans for future data sharing.

All research is to be approved by appropriate human subjects review boards. In this regard, again for assuring the credibility of the data, the SRG requests that human subjects submissions be provided for the review of this group. This is an area of sensitivity in which the involvement of the SRG can only add to the credibility of the research.

The SRG carefully considered the project proposals and progress reports. Problems in documentation and level of detail in some of this material were evident. The SRG asks for rigorous documentation of all proposals and progress reports. We ask that all documents be carefully labeled as to their origin and purpose. Reflecting the collaborative nature of the research, these materials should be prepared jointly by the Russian and U.S. investigators and signed by both parties.

All research projects need a written protocol, which should be submitted to the SRG for

comment. The suggested elements for the protocol are provided in the attached table, as specified in the Proposed Guidelines established at the first JCCRER meeting. We emphasize the need for a well-defined and comprehensive quality control and quality assurance program, again with the goal of assuring the credibility of the research. The Research Plan should also address communications between investigators and the approach to project management. A detailed timetable is encouraged.

The SRG requests brief progress reports every four months. These reports should describe progress along time lines set out in proposals. Any deviations from these time lines need to be explained, along with any attendant changes in plan. These progress reports do not need to be lengthy and the SRG does not want them to become burdensome.

The SRG was impressed by the scope and quality of much of the work that has been implemented. The members of the review group anticipate that the review process will be collegial and we look forward to working with and learning from our scientific colleagues.

Principles For Communication

In follow-up to its meeting, the SRG developed a set of operating principles which were accepted by all members. These principles include the following:

There will be a report published following every meeting of the Scientific Review Group.

The report will be sent to the JCCRER, project scientists and the general public.

The reports may have two sections: a section of general committee recommendations, appropriately worded for general dissemination; and a section related to individual projects, not intended for general dissemination.

All discussions of individual projects are to be kept confidential.

Committee members will not communicate individually about committee meetings until the committee's report has been released. They are then free to communicate about non-confidential aspects of the meetings and of the reports.

Comments On Progress Reports

Project 1.1: *Dose Reconstruction For The Urals Population*

Description

This feasibility project assesses the potential for individual dose reconstruction for the Urals population. It has a number of specific aims including:

the creation of a data base of available information that would be used for dose calculations.

- the development of a conceptual model for sources and pathways of exposure of the Urals population.

the calibration of the URCRM whole body counter.

- improvement of individual exposure data bases.

- an assessment of the feasibility of mathematical modeling for dose reconstruction.

pilot studies on the feasibility of ESR, TLD and biodosimetry methods for dose reconstruction.

Only limited information had been provided to the group prior to the meeting. A 17 page progress report, received at the time of the meeting, was subsequently considered by the reviewers.

Comments

The group noted that the pilot work could potentially lead to a large-scale dose reconstruction effort. The effort would be warranted if the population has the potential to contribute information in a dose and dose-rate range of current interest. Additionally, the doses would need to be estimated with sufficient certainty to improve our understanding of the risks of radiation exposure. In general, the group thought that the scope of the project seemed too large. The group offered the suggestion that data may be more available and informative for some of the groups within the population and that emphasis should be placed on those subgroups. For example, exposure through the contamination of the river may have been responsible for most of the dose for some individuals and dose might be estimable with reasonable validity for these individuals.

There is no question that the significant contamination events that have occurred in the Urals region lend a valuable opportunity to reconstruct historical doses. Such a dose reconstruction study has many possible contributions to science if carried out properly.

Among the most important results that could be of significant value are a better understanding of transport and fate of radionuclides in the environment. Materials released at these sites include a broad spectrum of fission products, activation products, and transuranic elements. The land mass and surface water areas contaminated are expansive, and much of the area appears to be undisturbed. Many of the methods developed to reconstruct doses in the U.S. could be applied to this study. Environmental monitoring data collected over the years could be extremely important in validating estimates of dose. In addition, measurements using state-of-the-art dosimetry techniques could also be helpful in validating dose estimates. Assuming doses could be estimated with reliability and with moderate uncertainties attached, the results could be combined with data on the incidence of disease to provide important insight into estimates of risk resulting from exposure to elevated levels of radionuclides in an inhabited environment.

Dose reconstruction research in this area would be very worthwhile, not only because of what could be learned to improve the state-of-the-art of methods for environmental dosimetry, but also the potential value in understanding more about risk.

Although the proposed research is worthwhile, the difficulties associated with carrying it out have been seriously underestimated. Further, the scope of the study as it is proposed in the materials received to date, is far too broad for an initial collaborative effort. A study of both the air and river pathway, when considering contamination levels that are as significant as those that occurred, is an effort of enormous scale if carried out properly. The Department of Energy must recognize that entering into an agreement to carry out a project of this scale is a very long-term and expensive effort. In order for it to be successful, the lessons we have learned from studying our own facilities in the U.S. must be synthesized and implemented. More importantly, it must be borne in mind that although we must apply many principles learned from U.S. studies, dose reconstruction, if carried out properly, involves an extensive component based on site-specific data and modeling. The research is tedious and must include considerable time spent gathering data in the area being studied.

This research is far too broad in scope, as an initial effort in dose reconstruction, considering the difficulties that are inherent in a bi-national project. It seems much more

prudent before going into a study of this magnitude, that priorities should be established in order to narrow the focus considerably. If dose reconstruction cannot be carried out on a small population of persons with the highest exposure, for limited pathways, radionuclides, and organs, it certainly cannot be carried out on the scale proposed here.

A number of specific concerns with regard to the investigators' strategies were raised at the meeting and in the follow-up review of the submitted material. The biomarker work was viewed as potentially informative, but the strategy needed to be more fully developed. There needed to be better integration of the biomarker data with other estimates of dose. The plan was viewed as overly emphasizing modeling. The need for studies of T-cells was questioned and the importance of rigorous laboratory procedures for the FISH was discussed.

Given the scope of the research proposed, it was suggested that a careful management plan be developed, including milestones and a timeline. A matrix that showed the integration of the various lines of information would be helpful.

Project 1.2: Risk Estimation For Deterministic And Stochastic Exposure Effects And The Results Of Actual Observations Of Population Health In The Region Of The Mayak Industrial Association

Description

This project concerns the long-term effects on health of low-level exposures to radiation among a cohort of 29,000 residents of an area around a nuclear weapons plant in the Southern Urals. The weapons plant, hereafter called the MIA, discharged radioactive waste into the Techa River from 1948 to 1958, and experienced an accident in 1957 (the so-called East Urals Radiation Trace (EURT) that emitted additional levels of radioactivity into the nearby area. The residents were exposed to external gamma rays and internal exposure to radioactive particles through ingestion of contaminated food and water.

The project consists of three parts: 1.2a) management of existing data concerning birth, death and migration in the cohort. The plan is to conduct an inventory of existing data from medical records, personal interviews, and death certificates. There is need to assess its adequacy. Much of the data are on unduplicated index cards and are at risk of damage or loss. These data need to be computerized; 1.2b) assessment of cancer mortality in the cohort, and 1.2c) pilot work to set up a long-term international collaborative study of the cohort to better understand the effects of low-level radiation.

The present document contains two reports. The first, entitled "Milestone 3", concerns the identification of a suitable unexposed comparison group for the exposed Techa River cohort. Previous assessment of cancer mortality in the cohort have used the population of the surrounding area as an unexposed comparison group. This is problematic because the exposed cohort has a large representation by Tartars and Bashkirs, while the comparison group consists largely of Russians. Cancer rates differ considerably between the Tartar/Bashkir and Russian populations.

This report assesses the strengths and limitations of five possible comparison groups. The following is a summary of the groups and their suitability:

Cohort members with low exposures: Strengths: similar follow-up using similar methods. Weaknesses: Confounding by ethnicity; many are Russians with different cancer rates than the Tartar/Bashkir members of the cohort.

Late arrivals to the Techa River area when radiation levels have decreased.

Strengths: similar follow-up using similar methods. Weaknesses: a) small numbers (18-26% of exposed cohort); b) lack of controls for temporal events shortly after exposures; c) potential confounding due to differences in social factors between exposed and unexposed groups.

1. People living in nearby clean villages. Strengths: large amounts of medical data are available on this group. Weaknesses: a) members of this group were examined only once and have no follow-up data; b) some of the clear villages actually did receive radiation exposures; c) difficulty of follow-up; there has been substantial outmigration from the unexposed villages.

Regional mortality rates. Strengths: the populations used for the regional rates are similar to the exposed population with respect to potential confounding variables. Weaknesses: this would require regular monitoring of the population.

National Statistics Data: Strengths: these rates are stable and are available over extended time periods, making it feasible to adjust for time trends. Weaknesses: a) these data are not available by ethnicity. Moreover, the national rates for site-specific cancers vary greatly across geographic regions.

Because no one group is likely to be entirely satisfactory, the report recommends the use of multiple comparisons groups.

The second report, titled "Milestone 1", concerns methods for determining vital status of the Techa River cohort through 1992. This report gives the following summary of the current status of follow-up efforts for the cohort. Of 26.5 thousand people included in the registry, 3,426 (13%) were lost to follow-up between 1950 and 1982, largely because of outmigration. An additional 3,300 (12%) were lost to follow-up between 1983-1990. Of those not lost to follow-up, 8,015 (30%) of the original cohort died between 1950 and 1983. Death certificates have been obtained for 5,394 (67%) of the deceased subjects. An additional 3,565 cohort members have died between 1983 and 1990. Death certificates have not yet been obtained for these individuals.

The report describes several methods for determining vital status, and discusses the findings of tests of these various methods.

Comments

This project has the potential to provide new information on the long-term adverse effects of chronic low doses of ionizing radiation on human cancer risk. The potential may be compromised by loss to follow-up of the cohort under study, by problems of exposure assessment, and by insufficient sample size for adequate power. The current document does not provide enough information on these potential problems for this reviewer to have a good feel for the prognosis of the work. To adequately assess the future utility of further efforts in this area, the following information would be helpful:

The report refers to a Techa River cohort of some 29,000 people who were residing near the plant during the peak exposure period. It also refers to a EURT cohort of some 30,000 people. Does this cohort consist of the same people as the Techa River cohort. If not, how are they related to each other?

What is the status of the existing dosimetry information?

How was the Techa River cohort defined? What are the eligibility criteria for membership in the cohort? Among those eligible, what fraction were enrolled?

What is the prognosis for locating and determining the vital status of the 25% of cohort members who have been lost to follow-up? What is the prognosis for determining cause of death for those known to have died?

Based on results from the Life-Span Study of Japanese exposed to the atomic bomb and other cohorts, what magnitude of increased risk is expected for the various radiogenic site-specific cancers of interest? For each of these cancers, what level of statistical power can be expected based on the anticipated person-years of follow-up available?

Comment About Project 1.2 Added After Review Discussion

If a feasibility study is recommended, it should have two goals: 1) to determine if it is possible to conduct a minimally acceptable study; 2) if it is possible, to estimate the cost in U.S. dollars. The cost estimates should cover the resources that would be needed to complete the follow-up and cause of death ascertainment to a minimally acceptable level, to reconstruct exposures, and to conduct a minimally acceptable study, assuming that such an undertaking might be possible.

Project 2.1: *Metabolism And Dosimetry Of Plutonium Industrial Compounds*

Description

This project involves comparison of two human tissue research programs, the Dosimetry Registry of the Mayak Industrial Association and the United States Transuranium and Uranium Registries. Both registries have been in operation for approximately the same length of time and each has extensive information available from occupationally exposed workers from plutonium production facilities. The methods of the two registries have been documented and compared. The report on the first year of the project notes that the two registries are generally comparable, except for certain identified differences and combined uses of the resources seem appropriate. Two milestones remain to be accomplished including the development of the unified approach to address long-term objectives and the exploration of methods to combine the two databases.

Comments

The Committee looked favorably on this project and its progress to date. The combined resources should provide valuable data. The emphasis on quality control was welcomed and the opportunity to validate and improve the ICRP actinide metabolic-dosimetry model was judged to be unique and deserving of support.

The approach to handling lung tissue could be strengthened; the lung has received little emphasis in the work to date. As lung cancer is a health outcome of concern, this aspect of the work should be expanded. For example, autoradiography of terminal samples, where lung burden is anticipated to be high, would provide unique information on the spatial and temporal fate of "hot particles". The use of the FISH assay for those with internal burdens should also be fostered.

Study 2.2: *Risk Estimation For Stochastic (Carcinogenic) Effects Of Occupational Exposure*

Description

This study has two components, namely, a cancer mortality follow-up of workers employed at Mayak, and a follow-up of 40,000 children born near the plant. Since no details are provided regarding the latter component of the study, it is not further considered in the present report.

Comments

With respect to the workers study, it is clear that this has substantial potential for contributing knowledge of cancer mortality risks following exposure to external low LET radiation and internal plutonium deposition. The strengths of the study include the reasonably large size of the cohort (18,875 individuals), the protracted nature of the exposures, the large cumulative doses experienced by some members of the cohort and the rare opportunity to examine occupational radiation effects amongst women who constitute about 25% of the cohort. However, it should be noted that the study will not directly address issues of risks at low doses, since risk estimates will primarily be driven by high-dose individuals and that there may be insufficient individuals with low doses to lead to adequately precise low-dose risk estimates by direct observation of the cohort.

At the moment the biggest difficulty in considering the study is the lack of a detailed scientific protocol; presumably such a protocol would a) address in detail questions of what has been done in the past and b) specifically consider detailed plans for future research over the next several years. There are several potential concerns with the study as described below which probably could be addressed by such a scientific protocol. The concerns are:

Is the cohort complete, i. e., is it known for sure that it includes all workers who ever worked at Mayak. If not, what individuals were excluded?

Is there any possibility that records for individual study subjects are fragmented, e. g., when an individual worked in more than one place in the facility can one be sure that all relevant records for that individual were subsequently centralized?

What is the quality of the external dosimetry data? It is a matter of some concern that approximately 20% of the cohort do not have film badge data, nor is there any explanation given for this discrepancy. Is it possible that some individuals

were badged at some times but not others as occurred for example in the Chernobyl situation? Is it just a coincidence that the average annual dose rate was 50 mSV per year either from 1957 or 1963 (the current text is contradictory on the year in question) which corresponds with current occupational standards? How complete is the plutonium dosimetry data both in terms of whole body counts or urine samples?

Vital status is known for about 90% of the cohort. It is not clear how well this has been confirmed. For example, if an address is obtained for an ex-worker, how is it confirmed that he is alive or indeed that the person identified really is the person who worked at Mayak?

Similarly, there is a question about the completeness of mortality follow-up. How sure are the investigators that individuals identified as having died really are the same individuals who worked at Mayak?

To what extent have the causes of death recorded on death certificates been confirmed by independent assessment?

No plans have been provided for the proposed statistical analysis.

No time line is given for the study, nor is there any indication as to which individuals would be responsible for which phase, or where the various components of the study are to be conducted.

As stated, most of the concerns could be addressed presumably by an adequate scientific protocol. In particular, an effective use of resources would be to confirm the validity of data based on random stratified samples. For example, the dosimetry records for a sample of 200 individuals could be inspected and the availability of film badge data compared with their occupational history to ensure that badge data were available for the entire time the individual was employed. Similarly, sampling could be used to estimate the accuracy of cause of death as recorded on death certificates.

Finally, one potential limitation of the study is that 65% of the cohort had the potential for plutonium exposure. This could limit the interpretability of risk estimates for external radiation for the lung and possibly other sites since there presumably would be much greater uncertainty for doses arising from plutonium than doses from external radiation.

Project 2.3: *Deterministic Effects Of Occupational Exposure To Radiation*

Description

This is a joint feasibility study (about six or seven scientists each from U.S. and R.F.) to assess information relevant to studying deterministic effects from low dose exposures of the Mayak worker cohort (for 1948-1953). They will examine records of a total sample of 226 workers selecting for having:

no occupational ill health

- chronic radiation disease
- acute radiation syndrome
- plutonium pneumosclerosis

Specific aims will be to assess quality of records, to characterize chronic radiation disease (or diseases), to determine dose and time-dependent health effects and to develop the software necessary to analyze data, in particular of hematologic effects. The project is scheduled to take one year and to reach agreement between U.S. and R.F. investigators, the two groups will meet on at least two, and probably more occasions.

Comments

The project represents a logical, modest exploratory effort to evaluate the relative and dose responses of deterministic effects of low dose-rate occupational exposure, using a unique cohort of workers exposed to a fairly wide range of doses. The project will relate to other projects, especially the dose reconstruction efforts.

Additional Comments

Since slowly proliferating tissues may be especially susceptible to chronic injury, it may be interesting to sample sera from a selection of patients to analyze for various hormone levels--as part of an exploratory survey for endpoints of chronic radiation injury which may be included in the definitive study.

The researchers might assess the feasibility of including in a definitive study the archiving of serum and cells. These would be available for investigation using evolving technologies. The question of control of the distribution of such archived specimens would be addressed.

Table

Elements Of The Written Protocol

Abstract

1. Specific Aims
2. Background And Significance
3. Preliminary Studies
4. Research Design And Methods
5. Quality Assurance/Quality Control
6. Collaborators/Collaborating Institutions
7. Human Subjects Considerations
8. Itemized Budget