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## DISCLAIMER

# JCCRER PROJECT 2.3

# DETERMINISTIC EFFECTS OF OCCUPATIONAL EXPOSURE TO RADIATION

## PHASE I: FEASIBILITY STUDY

# FINAL REPORT

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## 1. BACKGROUND AND RATIONALE

Most of our current knowledge about the non-stochastic (deterministic) radiobiological effects of ionizing radiation has been derived from:

- studies of populations exposed briefly at high rates to gamma rays (or gamma rays and neutrons) from atomic bombs;
- data about medical complications arising from fractionated, localized photon exposure during radiation therapy for cancer; or,
- studies of external and/or internal exposure of laboratory animals to high- and/or low-LET radiations.

There are only limited data on deterministic effects in humans caused by the inhalation of radioactive materials or by irradiation from combined external gamma and internal alpha, beta, and gamma sources, particularly from exposures occurring over an extended period of time -- situations that might occur in nuclear accidents or other incidents.

Over the past 50 years, defense-related activities in the Russian Federation have resulted in significant occupational radiation exposures to thousands of nuclear workers. Information has recently become available about the MAYAK production facility in the South Urals, where at least 8-10,000 workers were exposed to relatively high levels of external gamma radiation (1-10 Gy) and, in many cases, to internal alpha radiation from inhaled plutonium as well. A number of these workers developed health impairments diagnosed by their physicians at Branch No. 1 of the Institute of Biophysics (FIB-1) as the Acute Radiation Syndrome (ARS), Plutonium Pneumosclerosis (PPn), and Chronic Radiation Sickness (CRS).

Systematic exposure measurements and medical examinations were carried out on practically all of these workers as part of the radiation protection program that was initiated with the start-up of the MAYAK facility in January 1948. MAYAK and FIB-1 continued to collect these unique human data over the past 49 years and are willing to make them available for the collaborative study of a wide range of deterministic effects, including those involving the hematopoietic, nervous, cardiovascular, visual and cytogenetic systems as well as the key organs of plutonium deposition (liver, lungs and skeleton).

These detailed longitudinal data on human occupational exposures and their resulting clinical outcomes hold the potential for:

- significantly improved estimates of the human dose thresholds and dose-response relationships for the deterministic effects of acute and prolonged exposure to ionizing radiation;

- the development of more precise prognostic models to predict the long and short-term consequences of prolonged and intermittent radiation exposures ranging from the sub-lethal to the sub-clinical; as well as,

- the clinical description and initial mathematical modeling of possible radiation-related deterministic effects in human beings (e.g., Plutonium Pneumosclerosis, Chronic Radiation Sickness) that have not been encountered by Western scientists and physicians.

Phase I of Project 2.3, a short-term collaborative Feasibility Study, was funded for 12 months starting on 1 February 1996. The overall aim of the study was to determine the practical feasibility of using the dosimetric and clinical data on the MAYAK worker population to study the deterministic effects of radiation exposure. Phase I efforts were limited to the period of greatest worker exposure (1948-1954) and focused on collaboratively:

- assessing the comprehensiveness, availability, quality, and suitability of the Russian clinical and dosimetric data for the study of deterministic effects;

- creating an electronic data base containing complete clinical and dosimetric data on a small, representative sample of MAYAK workers;

- developing computer software for the testing of a currently used health risk model of hematopoietic effects; and,

- familiarizing the US team with the Russian diagnostic criteria and techniques used in the identification of Chronic Radiation Sickness.

## 2. COLLABORATING INVESTIGATORS

### A. RUSSIAN FEDERATION

**Nadejda D. Okladnikova**, M.D., Ph.D., D.Sc., Co-Principal Investigator, Chief of Clinical Division, Branch No.1 of the Institute of Biophysics, Ozyorsk.

**Andrey F. Lyzlov, Ph.D.,** Co-Principal Investigator, Chief Engineer, Radiation Safety Division, MAYAK PA, Ozyorsk.

**Valentina Pesternikova**, M.D., Ph.D., Collaborating Investigator, Branch No.1 of the Institute of Biophysics

**Margarita Sumina**, M.D., Ph.D., Collaborating Investigator, Branch No.1 of the Institute of Biophysics

**Tamara Azizova**, M.D., Collaborating Investigator, Branch No. 1 of the Institute of Biophysics

**Andrei Fevralev**, M.S., Collaborating Investigator, MAYAK PA

**Zinaida Belyaeva**, M.S., Collaborating Investigator, Branch No.1 of the Institute of Biophysics

**Ludmila Burak**, M.S., Collaborating Investigator, Branch No.1 of the Institute of Biophysics

### B. UNITED STATES

**Niel Wald**, M.D., Co-Principal Investigator, Professor, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA

**Bruce B. Boecker**, Ph.D., Co-Principal Investigator, Assistant Director, Inhalation Toxicology Research Institute, Albuquerque, New Mexico

**Richard Day**, Ph.D., Collaborating Investigator, Graduate School of Public Health, University of Pittsburgh

**Bobby Scott**, Ph.D., Collaborating Investigator, Inhalation Toxicology Research Institute

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**Igor Linkov**, Ph.D., Collaborating Investigator, Graduate School of Public Health, University of Pittsburgh

## 3. PROJECT PLANNING AND IMPLEMENTATION

Project planning and implementation was carried out through a series of exchanges of visits and by means of electronic communications.

### A. WORKING VISITS

**Washington, D.C., February 8, 1996** - The US team met with Dr. Okladnikova and other representatives of FIB-1, as well as representatives of the sponsoring agencies (Dr. Yaniv and Dr. Neta). The purpose of this visit was to discuss and agree upon the primary objectives of the Phase I Feasibility Study.

**Ozyorsk, 7 -19 March 1996** - The US team met with the Russian team at FIB-1. The subjects for the data base were selected and the content of the data base agreed upon.

**Pittsburgh, 15-22 September 1996** - Mr. Andrei Fevralev, the FIB-1 computer programmer, visited the University of Pittsburgh. The purpose of this visit was to complete the design and programming of the computer data base prior to data entry in Ozyorsk.

**Ozyorsk, 9-19 December 1996** - Drs. Wald, Day and Shekhter-Levin visited FIB-1 in order to carry out a quality control assessment of the data in the Feasibility Study data base.

**Pittsburgh, 12-19 February 1996** - US team met with Drs. Okladnikova, Pesternikova, Sumina and Azizova to complete the final tasks of the Feasibility Study and to draft this final report.

### B. ELECTRONIC COMMUNICATION WITH FIB-1 AND MAYAK

Over the course of the Feasibility Study, e-mail increasingly became the chief means of day-to-day communication between the US and Russian teams. Routine mails were very slow, while telephones and, *particularly, telefax communications* to FIB-1 were found to be difficult and unreliable for research purposes. These were avoided whenever possible and, if necessary, faxes via MAYAK were substituted with better success. E-mail communications with Eastern sites in the Russian Federation have certain limitations with regard to the size of the files that can be transferred. As a consequence, it was necessary to develop routine procedures and to identify common freeware computer programs (e.g., UUENCODE/UUDECODE) that permitted large word processor files to be transferred via e-mail. Problems still remained, however, in cases where original documents or specialized non-word processing files had to be transferred. In such cases, documents had to be hand carried by the

next JCCRER visitor traveling to Ozyorsk. This often resulted in substantial delays in routine work, compounded by insufficient internal dissemination of JCCRER travelers' plans.

## 4. PROGRESS REPORT

Progress achieved on the Feasibility Study will be reviewed in terms of the Specific Tasks enumerated in the original Research Protocol ( see Attachment 1, 2/1/96, Sec. 6, pp. 6-7).

### TASK A

*Develop agreement on operational meaning of the scientific and medical terminology to be employed, including quantitative classifications of clinical signs, symptoms and nosologic forms.*

### Progress on TASK A

Work on this task was initiated during the March 1996 work period of the US team at Branch No.1 of the Institute of Biophysics. Extensive discussions were held over a period of several days in which each clinical and dosimetric component of the proposed data base was reviewed in a detailed fashion and initial classification schemes were agreed upon. Few inherent difficulties were experienced in the dosimetric and certain clinical areas such as hematology, cytogenetics and bone marrow data. For the most part, these discussions focused on the level of detail that would be included in the Feasibility Study data base. The single most important exception occurred in the area of workers diagnosed as having Chronic Radiation Sickness (CRS) by the FIB-1 physicians. The final classification of CRS reflected the US team's understanding that the three component syndromes identified by the Russian clinicians --

- Vascular Dystonia
- Asthenia
- Diffuse Encephalomyelosis

-- represented differential levels of severity of a set of common non-specific symptoms (e.g., fatigue, headache, dizziness, disturbance of sleep). However, it became clear *with time* that the Russian colleagues were uncomfortable with this formulation and felt that it was a foreign misunderstanding of their true diagnostic approach. Similar difficulties were encountered in reaching agreement upon a quantitative classification of the Russian diagnosis of Cerebral Atherosclerosis. It was concluded that further discussion was required to resolve the remaining questions impeding completion of this task.

**TASK B**

*Prepare a mutually agreed upon coding plan for the extraction and summarization of relevant clinical, hematopoietic, cytogenetic, and dosimetric data from existing primary records for the group of MAYAK workers employed between 1/1948 and 12/1954.*

**Progress on TASK B**

It was agreed at the conclusion of the March 1996 visit to Ozyorsk that the US team would have responsibility for setting down the initial operational definitions and quantitative classifications in the form of a pre-computer Data Extraction Questionnaire (DEQ) and Code Book. These documents were to serve as the framework for data extraction from FIB-1 and MAYAK records, and for the design of the Feasibility Study's computerized data base. Initial versions of the DEQ and the Code Book were completed by the US team by early May 1996. The DEQ and the Code Book, with a combined length of 75 pages, were transferred to Ozyorsk via e-mail in the form of coded word processor files. These documents were reviewed by the Russian team in Ozyorsk and served as the foundation for the initiation of data extraction and the design of an electronic data base. The actual extraction of data from the FIB-1 clinical and MAYAK dosimetric records began in June 1996 using the coding plan in the DEQ and Code Book.

**TASK C**

*Assess need for and agree upon necessary computer hardware and software to be used by RF in Phase I feasibility work and retained for further work. Specific attention is to be given to the need for compatibility between RF and US hardware and software to assure collaborative use of the feasibility data base.*

**Progress on TASK C**

Discussions about computer hardware and software compatibility were carried out during the March 1996 work period of the US team in Ozyorsk and completed during the September 1996 visit of Mr. Andrei Fevralev to Pittsburgh. The following primary agreements were concluded:

- hardware would be standardized on DOS-based IBM PC compatible machines using Window 95 or Windows 3.11 as the basic operating systems;

- word processing would be standardized on Microsoft Word for Windows, Versions 6 or 7, and e-mail transfers of files would use UUENCODE freeware ;

- the Feasibility Study data base would be written in Borland's Delphi language using the basic Paradox data base engine.

The FIB-1 investigators purchased PC compatible, Windows-based Pentium systems locally to carry out the project work.

**TASK D**

*Implement the coding plan for a randomly selected stratified feasibility sample of MAYAK workers and create a computerized data base to contain the coded information.*

**Progress on TASK D**

A sample of 226 workers employed at MAYAK for at least one year was randomly selected from existing FIB-1 data bases during the March 1996 work period of the US team in Ozyorsk. The 226 workers selected were stratified in the following manner:

| | males | females |
|---|---|---|
| • No Known Occupational Injuries (controls) | 50 | 50 |
| • Chronic Radiation Sickness | 67 | 33 |
| • Acute Radiation Sickness | 13 | 1 |
| • Plutonium Pneumosclerosis | 7 | 5 |
| | 137 | 89 |

To maintain confidentiality, the US team was not permitted to have the names of workers selected for the data base. Hence, a FIB-1 identification number, the sex and the year the individual started work at MAYAK were also recorded at the time of sample selection in order to have a means to cross-check whether the clinical and dosimetric information for the proper individual was included in the data base. This information was transferred to Pittsburgh where the cases were assigned sequential Feasibility Study identification numbers to go along with their FIB-1 identification numbers.

The actual programming of the computerized data base was carried out in Ozyorsk by Mr. Andrei Fevralev. The structure of the computerized data base followed the final structure of the Data Extraction Questionnaire (DEQ) and Code Book. The initial version of the data base was programmed over the three month period between June and August 1996. The initial version of the data base was reviewed and finalized during Mr. Fevralev's work period in

Pittsburgh in September 1996. The data on the 226 individuals selected for the Feasibility Study were entered into the data base during the three month period from October through December 1996.

The coding plan for the Feasibility Study data base was reviewed one further time during the work period of the US team in Ozyorsk in December 1996. It became clear during the scheduled Quality Assessment/Quality Control (QA/QC) visit that certain "interpretive and definitional problems" remained in the data base. These problems were identified and solutions agreed upon.

At the conclusion of the QA/QC visit, the US and Russian teams signed a protocol agreement (see Attachment 4, Exchange of Data and Programs in Pilot Project 2.3) setting forth the conditions under which a copy of the Feasibility Study data base could be taken back to the University of Pittsburgh and be used for research purposes. Following the signing of this protocol, a copy of the December 1996 version of the Feasibility Study data base was transported to the University of Pittsburgh on floppy disks and installed on a computer in the Department of Biostatistics.

In January 1997, Mr. Fevralev revised the data base to include the final modifications agreed upon at the QA/QC visit in December 1996. This revised version of the data base was transported to Pittsburgh by Dr. Okladnikova and her colleagues during their February 1997 work period and installed in the Department of Biostatistics. It represents the final version of the Feasibility Study data base (see Attachment 2 for details).

**TASK E**

*Compare randomly selected elements of the coded information in the computerized data base to the contents of the primary records in order to assess the reliability and completeness of the coding and extraction procedures*

**Progress on TASK E**

This task was carried out during the December 1996 project work period of the US team to Ozyorsk. The QA/QC protocol called for the review of a randomly selected stratified 10% sample of the 226 cases in the study population. All of the clinical and exposure data on these subjects had to be made available for review and comparison with the computerized data base contents. The identification numbers for 78% of the sample of subjects (n=18) were sent to the FIB-1 center one week prior to the arrival of the US team. The identification numbers for the remaining 22% of the QA/QC sample (n=5) of subjects were provided to the FIB-1 staff on the arrival of the US team. Prior to the visit, it had been agreed that the data base contents would be

considered acceptable if less than 7% of the data items were divergent from the source and less than 3% are missing. In other words, a minimum overall accuracy of at least 90% was required in order to consider the quality of the data in the data base to be acceptable.

During the QA/QC visit, all sections of the data base were assessed for data accuracy using the randomly selected stratified sample of 23 workers. A general sequence of assessment of the sections of the data base emerged after review of the first 5 workers' records:

- demographics and medical history
- occupational exposures
- clinical symptomatology and treatment
- laboratory tests (hematology, cytogenetics, bone marrow)

In carrying out the reviews of specific sections the US team had varied access to official records. The primary demographic and work history information was contained on a summary sheet provided by the Ozyorsk city government, occupational exposure data was contained on a summary form provided to FIB-1 by Dr. Andrei Lyzlov, whereas diagnostic, clinical and laboratory test data were available directly from the original records kept at FIB-1.

The assessment procedure was bi-directional in the sense that items were randomly selected from both the data base and the primary data records then checked against the other source -- i.e., (i) data base vs. primary records and (ii) primary records vs. data base. Randomly selected items were checked in this bi-directional fashion for all 23 workers in the QA/QC sample. The precise number of items checked for each subject was a function of the length of the record and the amount of time available to the investigators. Similarly, the number of items checked in each data base section was a function of the number of patients with relevant information and the overall number of entries. Sections that were relevant only to one or two subjects (e.g., cytogenetics) were checked comprehensively.

In carrying out this QA/QC procedure two types of problems were identified within the data base:

- Transcription errors - These are the accuracy errors that the QA/QC procedure was designed to identify. They represent entries in the source documents that differ from or are missing in the data base. In most patients, these errors occurred in a singular, apparently random, fashion. In at least two subjects, however, "chunks" of data were missing from the data base. The larger-scale transcription errors appear to have occurred in the final patients entered into the data

base just before the QA/QC visit when the FIB-1 staff was working under a substantial time pressure that prevented performance of the routine checks used for other patient records. To the extent possible, individual transcription errors were corrected at the time of identification.

- Interpretive and definitional problems - These problems resulted from practical decisions that were made in the interpretation and implementation of the data base code book by the FIB-1 staff. The QA/QC assessment provided an opportunity to identify and find solutions for these interpretive and definitional problems.

For 18 (78.3%) of the QA/QC subjects, transcription errors were below a 5% level. For 2 (8.7%) subjects, transcription errors fell between 5-10% and for 3 (13.0%) subjects the error percent was above 10%. The cause of the increased error percent for the latter three subjects was a lack of integration of the occupational exposure dosimetry with other components of the record - e.g., work history. This was due to the fact that data was being submitted by two sources and routine consistency checks were occasionally forgotten in the pressure to complete the data base for the QA/QC visit. An exact 99% confidence interval for the overall mean error percent (4.2%) was calculated. The result indicates that we can be 99% confident that the true mean percent of transcription errors in the existing data base falls between 3.18-5.44%. This is well within the QA tolerance limits set in the original protocol.

**TASK F**

*Develop a mutually agreed upon plan for analyzing the computerized feasibility sample of MAYAK workers and carry out the analyses required to assess the validity of the information in the data base and its suitability for use in a larger study.*

**Progress on TASK F**

The complete plan for the collaborative analysis for the Feasibility Study data base is attached as Attachment 2 , a separate deliverable at the end of this report. The plan of analysis was reviewed and agreed upon during the February 1997 project work period in Pittsburgh and was the final component of the Feasibility Study to be addressed. Briefly summarized, the proposed analysis will have four major components:

- Data cleaning and preparation for statistical analysis is the first required task. The clinical and dosimetric information will have to be extracted from the data base, transformed (where necessary) from a textual to a numerical form, reviewed and checked for data entry errors. Once this

has been completed control files can be prepared for statistical processing.

- An initial descriptive analysis, using tables and graphs, should be carried out covering all of the major variables in the data base such as exposure, work history, sociodemographic, vital status, laboratory, and clinical diagnostic variables. Tables should be created that cross-classify important variables such as sex with clinical diagnosis, sex with mean cumulative exposure, and mean cumulative exposure with clinical diagnosis.

- Comparative analyses of cumulative radiation exposures for the MAYAK workers experiencing occupational injuries (ARS, CRS, PPn) versus uninjured controls should be carried out, while controlling for potential confounding factors (e.g., age, sex, time period, plant). This analysis should use logistic regression and other multivariate categorical statistical techniques.

- Testing specific clinical and biological hypotheses developed in collaboration with the Russian team for different subgroups of workers. An example of a relevant hypothesis to be tested would be the Russian observation that certain changes occur in specific hematological variables (e.g., leukocytes and thrombocytes) prior to the development or intensification of CRS symptoms. A second hypothesis to be tested is the Russian conclusion that secondary factors such as sex, age, reproductive history (in women), alcohol use, tobacco smoking and other co-morbidities do not explain the observed development or intensification of CRS symptoms.

## TASK G

*Develop a computer program that will allow testing of the health effects model for hematopoietic death. The program should allow for the use of a time dependent organ dose rate.*

## Progress on TASK G

Work conducted under TASK G involved developing a computer program that will allow testing of the risk model for radiation-induced hematopoietic death (i.e., death resulting from severe damage to bone marrow) presented in a series of US Nuclear Regulatory Commission reports entitled NUREG/CR-4214, "Health Effects Models for Nuclear Power Plant Accident Consequence Analysis" published between 1989 and 1993. References cited here are provided in Attachment 3. The cited hematopoietic death risk model was

developed for simultaneous or sequential (uninterrupted) exposure to alpha, beta, and gamma radiation following nuclear accidents. Work on this task had already been initiated before the US team visited FIB-1 in March 1996. It was thought that MAYAK workers at Site A were exposed only to gamma rays. Thus, the MAYAK data for Site A could be used to test the hematopoietic-death risk model presented in the cited NUREG/CR-4214 reports when applied to a nuclear accident scenario involving external and internal gamma exposures. Therefore, the initial research plan for Phase I was to set up a computer program that would allow use of the mortality and gamma-ray dosimetry data for workers at Site A to test (in Phase II) the cited hematopoietic-death risk model.

During the March 1996 visit of the US team to FIB-1, it was pointed out by the Russian scientists that some workers at Site A were exposed to neutrons in small doses. Also, occupational exposures mainly occurred during 6-hour daily work shifts, which differs from the exposure patterns considered in NUREG/CR-4214 reports. In addition, individual work-shift dose estimates for workers at Site A were available in roentgens (rather than organ absorbed doses, differentiated by radiation type). Thus, in order to used the MAYAK data for Site A for model testing, some unplanned modeling research had to be conducted in Phase I. Also, it was realized that more details about the form in which dosimetric data will be presented to Project 2.3 (now to be provided by Project 2.4, entitled "Reconstruction of Individual Exposure Doses of Mayak Facility Workers") were needed before a computer program for model testing could be set up. These dosimetry details are still needed. A desired form for presenting the data to Project 2.3 has been given to participants in Project 2.4.

The summary information presented here is largely a result of a cooperative US/Russian Federation effort conducted mainly by Dr. B. R. Scott, Dr. A. F. Lyzlov and Dr. S. V. Osovets (Engineering and Physics Institute, Ozyorsk).

The hematopoietic-death risk model presented in the cited NUREG/CR-4214 reports which was set up for combined simultaneous or sequential exposure to alpha, beta, and gamma radiation was adapted in Phase I for repeated simultaneous exposures, at very low dose rates, to gamma rays and neutrons over prolonged periods, such as occurred to some MAYAK workers at Site A. This work is summarized in Attachment 3. The adapted form of the hematopoietic-death risk model will facilitate setting up a computer program that will allow use of the MAYAK mortality data for Site A for model testing. It has also led to other computer programs.

Computer programs were set up in Phase I by both the US and Russian Federation participants, related to research needs based on the adapted hematopoietic-death model. For example, the US team set up a computer

program that allows assignment of a long series of random workshift gamma-ray doses judged to be of similar size to the doses to some workers at Site A to evaluate the cumulative normalized dose (a key variable in models presented in NUREG/CR-4214 reports) as a function of time and absorbed dose-rate patterns. This allowed some analyses to be conducted in Phase I to compare cumulative normalized dose (e.g., dose in units of $LD_{50}$) and cumulative absorbed dose (or adjusted dose) to bone marrow, for prolonged repeated exposures, at very low work-shift dose rates. Adjusted dose is the RBE-weighted dose used in NUREG/CR-4214 reports related to combined exposure to alpha, beta, and gamma radiation. Normalized dose is represented by X. A value of X=1/2 represents 1/2 of an LD50 exposure irrespective of dose rate pattern when lethality is considered. Both the US and Russian teams set up computer programs to calculate the number of work shift exposures it would take to exceed the population threshold dose for hematopoietic death, based on results summarized in Attachment 3. The Monte Carlo method was used for uncertainty evaluation. Good agreement was found between the two teams for a specific set of low dose-rate exposure scenarios, judged to be relevant to MAYAK worker exposures at Site A.

**TASK H**

*Study materials concerning diagnostic criteria and techniques for defining the neurovascular syndrome of CRS and identify appropriate US scientists to participate in the development of a comparative investigation in this area.*

**Progress on TASK H**

Initial discussions were held about Cerebral Atherosclerosis (CA) during the March 1996 working visit to Ozyorsk. These discussions resulted in the basic coding categories used in the Feasibility Study data base. These include a five point rating scale of CA severity and a binary scoring of the five major treatment techniques. CA and CRS are extremely complex clinical and biological issues and the short time we had together did not permit a thorough investigation of these concepts. The data in the data base may shed some further light on CA (e.g., mean cumulative exposure level, association with alcohol abuse). It was concluded that further discussion, possibly including an international workshop, might be considered to clarify the diagnostic concepts. It was considered premature during the feasibility study to introduce additional US scientists to design an investigation of this problem.

## 5. FINDINGS AND CONCLUSIONS

The findings and conclusions about the feasibility of the work undertaken will be summarized in terms of the Specific Aims enumerated in the original Research Protocol (2/1/96, Sec. 4, pg. 5, provided as Attachment 1).

### AIM 1

*To review the existing MAYAK PA data bases for quality, completeness, and suitability of dosimetric, clinical, hematological and cytogenetic data.*

### Findings and Conclusions for AIM 1

The conclusions to be drawn regarding the quality, completeness, and suitability of the FIB-1 clinical and MAYAK dosimetric data are based on the limited experience gained in the construction of the Feasibility Study data base and through the quality control assessment of 23 randomly selected cases. A far stronger set of conclusions could have been drawn here *if the initial statistical analysis of the full 226 workers in the data base could have been carried out as the final component of the Feasibility Study* but the reduction of the originally proposed 18 month feasibility study to 12 months precluded any analyses.

Based on the available experience it is possible to make the following points. The construction of the data base demonstrated significant coordination between the FIB-1 and MAYAK facilities. Once the 226 workers were randomly selected for the data base, the two institutions were capable of producing clinical and dosimetric information for these individuals dating back to the earliest periods of operation. However, it should be noted that the US team was limited in the extent to which they were able to review the original records for these individuals. In the case of FIB-1, the US team was allowed to examine the *actual clinical records* for selected workers and to compare randomly selected pieces of information from the records to the material contained in the Feasibility Study data base. The US team was able to determine that no large gaps appeared in these clinical data, nor did they appear to be limited by administrative problems.

The situation was quite different with regard to the dosimetric information from MAYAK. The US team never had the opportunity to select and review a random sample of the original dosimetric records that are maintained at the MAYAK facility. The quality control assessment of dosimetric entries in the data base was carried out on paper summaries provided by Dr. Lyzlov. With regard to the dosimetric data on the 23 workers selected for the QA/QC review, extensive material was available, but unexplained gaps of varying length also appeared in the records. Plutonium body burden measurements were

particularly sparse for the workers employed from 1948-1954 and were usually limited to a single measurement when available at all. Although dosimetric information was provided for the Feasibility Study data base, it was impossible for the US team to make any independent assessment of its overall quality by using the same QA/QC methodology as was applied to the FIB-1 clinical

**AIM 2**

*To determine the feasibility of defining a study cohort drawn from the 1948 to 1954 worker population based on availability of both individual dose history and clinical effects data.*

**Findings and Conclusions for AIM 2**

It was found to be feasible to draw a representative cohort of MAYAK workers from the 1948-1954 period and to incorporate the detailed clinical data on these workers beginning with the earliest period of operations. It therefore appears feasible to expand this clinical data base to carry out a long-term study of deterministic radiation effects. However, the U.S. team feels that a comprehensive unified dosimetric data base (or Master File) that would permit Quality Assessment and Quality Control procedures and would guarantee the completeness of the long-term study sampling frame is essential to the design and performance of Phase II of project 2.3.

**AIM 3**

*To develop computer software that will allow testing of a health effects model for hematopoietic death. The program will use time-dependent organ dose rates.*

**Findings and Conclusions for AIM 3**

Major findings and conclusions are summarized below:

- Neutron doses should be initially evaluated in Project 2.4 for a small number of persons that were at high risk for neutron exposures at Site A so that the importance of neutron doses for deterministic effects can be assessed by members of Project 2.3.

- Organ absorbed doses should be time-dependent and radiation-specific.

- Neutron and alpha absorbed doses can be accounted for through use of adjusted dose.

- Effect-specific and dose-rate dependent RBEs (and their uncertainty) will be needed for calculating adjusted doses (and their uncertainty).

- Alpha radiation RBEs may be needed only for low dose rates. Adjusted (or absorbed) doses or normalized doses should not be averaged over different individuals with dissimilar doses.

- Project 2.4 should provide dosimetric information to members of Project 2.3 that will allow deciding whether radiation exposures occurring while away from the MAYAK facility can be ignored in Project 2.3 (e.g. exposures that occurred in the town of Ozyorsk).

- If workshift, adjusted dose rates were fairly constant over periods such as a month at Site A, then adjusted doses over that period and adjusted dose rates averaged over work shifts during that period can be used in a dose-response study of hematological effect of irradiation of MAYAK workers at Site A.

- Equivalent doses (e.g. in Sv) should not be used in characterizing dose-response relationships of MAYAK workers for deterministic effects.

**AIM 4**

*To study materials provided by the RF scientists concerning the diagnostic criteria and techniques defining the neurovascular syndrome of CRS after external exposure with the goal of developing a cooperative investigation in this area.*

**Findings and Conclusions for AIM 4**

A substantial amount of time during the Feasibility Study was given over to direct discussions of the clinical features and to the examination of clinical records from MAYAK workers diagnosed as having Chronic Radiation Sickness (CRS). Although these discussions resulted in simplified rating scales for levels of clinical severity and methods for recording primary treatment modalities in the Feasibility Study data base, they failed to produce a sense of underlying intellectual satisfaction in the members of either the US or Russian teams. These discussions exposed important cultural differences in the clinical experience and training of the members of the two research teams and in the scientific approaches routinely used to establish the validity of medical diagnostic concepts. The problems were made all the more difficult by the fact that the exposure conditions under study are *currently* historical (or retrospective) in nature and their postulated effect, CRS, can only be approached through clinical records -- i.e., it was impossible to examine a

young, newly diagnosed CRS patient or to propose a prospective scientific study. It was considered premature to design an investigation of CRS prior to the proposed analysis of the Feasibility Database.

Despite these cultural and methodological problems, the Russian and US members of Project 2.3 continue to feel strongly that CRS is a potentially important clinical entity that should not be ignored by Western scientists and clinicians. Despite the admitted limitations of retrospective clinical studies, it is important for Western clinicians and scientists to have a systematic description and assessment of this Russian diagnostic concept in case future nuclear accidents and/or conflict situations create the conditions where new cases of CRS might emerge, requiring diagnostic understanding and medical management.

## GENERAL CONCLUSIONS FROM THE FEASIBILITY STUDY

The Conclusions and Findings summarized under each Specific Aim were intended to provide a critical perspective on the data collected in the Feasibility Study. These remarks need to be considered within the context of the work successfully carried out in the Feasibility Study. Specifically, an ongoing collaborative relationship was developed between the US and Russian teams. A mutually agreed upon plan of work was established and e-mail procedures were developed permitting day-to-day communication between the members of the two teams. Operational definitions of complicated clinical and dosimetric concepts were agreed upon and methods were devised to extract and summarize a large and diverse body of research data. Scientifically acceptable random sampling methods were implemented in the Feasibility Study and strict quality assessment procedures were applied to at least the clinical side of the data. Finally, it was possible to reach mutually acceptable collaborative agreements (see Attachment 4) on the analysis and proper use of these data such that the Russian team allowed a copy of the Feasibility Study data base to be transferred to the participating scientific institutions in the United States. Given the inherent problems of conducting international research of this complexity, each one of these administrative and scientific achievements represents a major success for the Feasibility Study.

In terms of assessing the overall quality of these data, the Feasibility Study has collected a large body of clinical and dosimetric information on deterministic effects of ionizing radiation that is *potentially* of great significance for the field of radiation protection. At the same time, we have found that certain steps should be taken to *improve the methodological quality of the underlying collaborative research environment* (e.g., a unified MAYAK worker Master File, improved QA/QC for MAYAK dosimetry, improved coordination across all the Direction 2 research components regardless of differences in their administrative and funding agencies) before these or any future data can be considered "definitive" enough to be used for a basis for clinical and regulatory decision-making. The members of both the US and the Russian teams remain very optimistic about the possibility of undertaking these methodologically critical improvements in the research environment in future studies.

## 6. RECOMMENDATIONS FOR FUTURE WORK

In view of the demonstrated ability of the US and Russian research teams to successfully carry out the collaborative tasks described in the Feasibility Study Research Protocol (Attachment 1,Sec. 6, pgs. 6-8), it is the conclusion of the US and Russian research teams that substantial evidence exists for the feasibility and value of successfully implementing Phase II of JCCRER Project 2.3. It is further recommended that the Phase II long-term component of Project 2.3 include at least five specific components, all of which assume for their success the implementation of the *methodological improvements to the underlying collaborative research environment* discussed above:

1. An in-depth analysis of the data contained in the Feasibility Study data base. This specific aim would involve the implementation of the Plan of Analysis attached to this document and discussed in the Progress Report (Sec. 4, Task F). There are no special problems involved in the implementation of this protocol and it should be a straight-forward piece of work. The primary deliverables would be an overall report and manuscripts for publication in the scientific literature.

2. Expansion of the existing clinical and dosimetric data base to support Components 4 (Risk Modeling) and 5 (CRS case-control study) described below. The Feasibility Study demonstrated that future studies of deterministic effects cannot be carried out on the *entire* MAYAK worker cohort because it would take the FIB-1 clinical staff several years to abstract all of the relevant clinical information into the current data base. This means that future work will have to be carried out on an *expanded sample* of MAYAK workers. The exact size and content of this sample will have to be worked out on the basis of experimental design requirements and in collaboration with the Russian team. The Russian team felt that over a 24 month time period, ending soon after the Project 2.4 intermediate dosimetry estimates should become available, they could add another 375 cases to the Project 2.3 data base. This requirement for an expanded sample for future research further highlights the need to set up a *Master File of workers employed at the MAYAK plant* (see above discussion of Feasibility Study Specific AIM 2) that has been validated for all of the FIB-1 data bases. Without such a Master File, there is no way to guarantee that future research samples do not contain biases that would compromise the scientific validity of the results.

3. Maintenance of close liaison with dosimetry work of Project 2.4. It is currently proposed that the dosimetric reconstruction required for Phase II of Project 2.3 be carried out by a separate group of investigators. It is clear that the Project 2.3 Principal Investigators must have significant input into the design of this project, that close liaison must be maintained

with Project 2.4 throughout the course of that work, and that the US investigators must play a significant role in certain vitally important aspects such as quality control assessments. Without such direct involvement, there is no guarantee that the data emerging from Project 2.4 will be of adequate quality to support the other Specific Aims in Project 2.3. This content of this recommendation should be taken to reflect the clear need for *substantial future improvements in cross-project coordination* in Direction 2 during the long-term phase of research on the M AYAK worker cohorts.

4. Testing and improving currently available risk assessment models for deterministic health effects utilizing the expanded data base. This component would include the following subcomponents:

   - RBEs (and their uncertainty) for specific deterministic effects will be obtained from published literature on deterministic effects in animal studies, clinical studies (e.g., with therapeutic radionuclides), and cell survival studies for use in analyzing and characterizing deterministic effects observed among MAYAK workers.
   - Organ absorbed dose uncertainty is important for both model testing and model development and organ dose uncertainty characterization will have to be received from Project 2.4.
   - MAYAK data will be used to test models presented in NUREG/CR-4214 reports where possible; both model-parameter uncertainty and organ dose uncertainty will be accounted for when MAYAK data are used to test model predictions.
   - New models will be developed for serious deterministic effects observed in MAYAK workers that were not modeled in the NUREG/CR-4214 reports.
   - If models presented in NUREG/CR-4214 reports are invalidated by MAYAK worker data (assuming dose estimates are reasonably reliable), then the models should and will be revised or new models recommended.

5. Implementation of a case-control study of Chronic Radiation Sickness (CRS) on the expanded MAYAK worker sample. A case-control study of CRS would permit an improved assessment of exposure factors (e.g., radiation dose and hematological changes) that are associated with the development of CRS. Again, exact sample sizes and the selection of the control group would have to be decided on the basis of scientific design and following consultations between both research teams. The expanded data would serve as the basis for a clearer clinical assessment of the role of radiation exposure in the etiology of CRS.

# ATTACHMENT 1

# PROJECT 2.3

## DETERMINISTIC EFFECTS OF OCCUPATIONAL EXPOSURE TO RADIATION

**PHASE 1:** **Feasibility Study**

**PRINCIPAL INVESTIGATORS**


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*19 February 1996*
*DOE5.DOC/NW & RDD*
*ITRI & RF Rev./US EC Revised*
*update milestones bosed on 2/1/96 start*

## 1. SUMMARY

This Phase I short-term feasibility study between the Russian Federation (RF) and the United States (US) is divided into two major areas, clinical aspects; and dosimetry and risk assessment modeling. It will last 12 to 18 months and relates to the evaluation of deterministic (nonstochastic) clinical radiation effects in a unique population, the Russian Federation MAYAK PA workers chronically and/or acutely exposed to internal and/or external radiation.

The feasibility study focuses on the clinical, hematological and cytogenetic effects resulting from doses that can lead to deterministic effects. The MAYAK PA data will be critically reviewed and assessed for availability, suitability and adequacy. A parallel investigation will be conducted into external and internal dosimetry. Computer software will be developed during Phase I to test a prognostic model for hematopoietic effects (NUREG/CR-4214). Pending the successful completion of the feasibility phase, a full proposal for continued collaborative research encompassing the whole MAYAK PA worker population will be submitted to the Executive Committee.

## 2. BACKGROUND

During the past 50 years, defense-related activities in the Russian Federation and in the United States has resulted in occupational radiation exposures of defense nuclear workers as well as population exposures. For many years, most of the data related to such exposures were classified. Recently, information became available about activities

of the first Russian nuclear facility, MAYAK PA, in the South Urals (Ilyin, 1995). Several thousands of workers were exposed to relatively high levels of external gamma radiation and, in many cases, to internal alpha radiation from inhaled plutonium as well. The cumulated doses over 1 to 7 years (1948-1953) were as high as 1-10 Gy. A number of these workers developed health impairments that are considered to be forms of radiation sickness. More than 1,800 cases of occupational diseases were diagnosed in 1960 and chronic radiation sickness was a major contributor to the total. This syndrome was described by A.K. Guskova and G.D. Baisogolov (1971). Also included among early deterministic effects were cases of the acute radiation syndromes, local radiation injuries, and cataracts as well as pulmonary pneumosclerosis following large plutonium inhalations (Okladnikova et al., 1992, 1994a,b,c and 1995).

Systematic medical observations were carried out as part of the radiation protection program that began with the start-up of MAYAK PA. For 45 years these unique data were collected, now allowing the study of a wide range of deterministic effects, including those involving the hemopoietic, immune, nervous, cardiovascular, visual and cytogenetic systems as well as the key organs of plutonium deposition, i.e., liver, lungs and skeleton.

These clinical and dosimetric data provide the basis for ascertaining the dose thresholds and dose-response relationships for the deterministic effects of prolonged radiation exposure, and permit comparisons to the same aspects of acute effects observed in other members of the same cohort. These data will facilitate the

development and testing of prognostic models for predicting the consequences of prolonged and intermittent radiation exposures ranging from sublethal to subclinical. This would obviate the need to rely entirely on extrapolations from the clinical outcomes of single high dose rate exposures such as the experiences of Atomic Bomb survivors or occupationally exposed ARS patients.

## 3. RATIONALE FOR THE PROJECT

Most of our current knowledge about nonstochasic (deterministic) radiobiological effects of ionizing radiation has been derived (1) from studies of populations exposed briefly at high rates to gamma rays (or gamma rays and neutrons) from atomic bombs; (2) from data about medical complications arising from fractionated, localized photon exposure during radiation therapy for cancer; or (3) studies of external or internal exposure of laboratory animals to high- and/or low-LET radiations. There are few published data about deterministic effects in humans caused by inhalation of radioactive materials, or by irradiation from combined external gamma and internal alpha, beta, and gamma sources occurring acutely and/or chronically--situations that might occur in nuclear accidents. The MAYAK PA data provide an opportunity to test existing models for deterministic effects of chronic exposure to ionizing radiation (external or external plus internal) and to develop new models for key effects of prolonged radiation exposure, such as chronic radiation sickness (CRS) and plutonium pneumosclerosis.

## 4. SPECIFIC AIMS FOR PHASE I

The major aim of the proposed pilot project is to determine the feasibility of a collaborative health study of the entire MAYAK PA worker population for deterministic effects of their occupational radiation exposure. Because Phase I efforts are limited in time, they will have to focus primarily on MAYAK PA workers employed at any time in the period from 1948 to 1953.

Specific aims for the Phase I feasibility study are:

A. To review the existing MAYAK PA data bases for quality, completeness, and suitability of dosimetric, clinical, hematological and cytogenetic data.

B. To determine the feasibility of defining a study cohort drawn from the 1948 to 1953 worker population based on availability of both individual dose history and clinical effects data.

C. To develop computer software that will allow testing of a health effects model for hematopoietic effects. The program will use time-dependent organ dose rates.

D. To study materials provided by the RF scientists concerning the diagnostic criteria and techniques defining the neurovascular form of CRS after external exposure with the goal of developing a cooperative investigation in this area.

## 5. RESEARCH DESIGN AND PROCEDURES

A. Perform an on-site visit by US team to Chelyabinsk-65 (Ozyorsk) to attain familiarity with available data and materials and to participate in developing the feasibility study.

B. Jointly make a detailed review of fundamental components of the clinical data of the selected group of MAYAK PA workers (1948-1953 employees).

C. Reach agreement on procedures to select the primary clinical data for insertion into a jointly accessible computerized data base for the study of human deterministic radiation effects.

D. Perform an on-site visit by RF team to Pittsburgh to participate in the development of a summary report.

## 6. SPECIFIC TASKS TO BE CARRIED OUT

A. Develop agreement on operational meaning of the scientific and medical terminology to be employed, including quantitative classifications of clinical signs, symptoms and nosologic forms. (US to initiate dialogue.)

B. Prepare a mutually agreed upon coding plan for the extraction and summarization of relevant clinical, hematopoietic, cytogenetic, and dosimetric data from existing primary records for the group of MAYAK PA workers employed between 1948 and 1953. (US to propose initial coding plan for discussion.)

C. Assess need for and agree upon necessary computer hardware and software to be used by RF in Phase I feasibility work and retained for further work. Specific attention is to be given to the need for compatibility between RF and US hardware and software to assure collaborative use of the feasibility data base. (RF and US to assess needs collaboratively.)

D. Implement the coding plan for a randomly selected stratified feasibility sample of MAYAK PA workers (see attached plan) and create a computerized data base to contain the coded information. (US to propose the sampling plan including randomization procedure, and, following mutual agreement, work to be carried out by RF in collaboration with US.)

E. Compare randomly selected elements of the coded information in the computerized data base to the contents of the primary records in order to assess the reliability and completeness of the coding and extraction procedures. (US to carry out in collaboration with RF.)

F. Develop a mutually agreed upon plan for analyzing the computerized feasibility sample of MAYAK workers and carry out the analyses required to assess the validity of the information in the data base and its suitability for use in a larger study. (US to initiate dialogue, RF to perform.)

G. Develop a computer program that will allow testing of the health effects model for hematopoietic death. The program should allow for the use of a time dependent organ dose rate. (US to perform.)

H. Study materials concerning diagnostic criteria and techniques for defining the neurovascular form of CRS and identify appropriate US scientists to participate in the development of a comparative investigation in this area. (RF to initiate implementation.)

## MINIMUM SAMPLING PLAN FOR THE NON-STOCHASTIC EFFECTS (2.3) PHASE I FEASIBILITY STUDY

| WORKER CATEGORY | ESTIMATED TOTAL SIZE | PROPOSED SAMPLE SIZE |
|---|---|---|
| A. NO KNOWN OCCUPATIONAL CONDITIONS* | 6366 | 100 |
| Male | 4170 (65.5%) | 50 |
| Females | 2196 (34.5%) | 50 |
| B. CHRONIC RADIATION DISEASE** | 1528 | 100 |
| Local Injuries | 188 | 19 |
| Other | 1340 | 81 |
| C. ACUTE RADIATION SYNDROME** | 41 | 14 |
| High Severity | 13 | 5 |
| Lower Severity | 24 | 5 |
| Deaths | 4 | 4 |
| D. PU PNEUMOSCLEROSIS** | 120 | 12 |
| Pure | 66 | 7 |
| Combined | 54 | 5 |
| TOTALS | 8055 | 226 |

* category and size estimates from Ilyin, 1995
** category and size estimates from Okladnikova, 1994a

## 7. TENTATIVE TIME TABLE

| TASK | MONTH | MILESTONE |
|---|---|---|
| Preparatory Work for Phase I including: | 1 | 1 |
| --agreement on terminology | | |
| --development of coding plan for primary data | | |
| --agreement on plan of feasibility data analysis | | |
| Discuss, Jointly Decide Upon (per Pg.6, Sec.6.C.), Deliver, | | |
| Set-up and Test Computer Equipment | 1 | |
| Data Base Programming | 2-3 | |
| Extraction of Primary Data | 3-6 | 2 |
| QA/QC Visit | 4 | |
| Feasibility Data Analysis | 6-9 | 4 |
| Develop Model Testing | 1-9 | 3 |
| Review Neurovascular CRS Information | 1-10 | |
| Prepare Summary and Long-Term Plan | 11-12 | 4 |

**Milestones:**

1. Agreement on content of feasibility data base and completion of data base programming. (By 31 March 1996.)

2. Extraction of clinical and dosimetric data for a randomly selected stratified sample of the MAYAK PA workers employed from 1948-1953 and completion of quality assessment procedures on the data base. (By 31 July 1996.)
3. Completion of the program for testing a computerized risk assessment model for hematopoietic death. Completion of study of neurovascular diagnostic criteria and techniques and recommendations concerning an investigation in this area. (By 31 October 1996.)

4. Analysis of data base materials to assess the validity of the data and their suitability for use in modeling deterministic health effects. Completion of final Phase I report on reliability, validity and suitability of MAYAK PA data, including recommendations concerning expanded studies (By 31 January 1996.)

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## ATTACHMENT 2

### Plan of Analysis for the Project 2.3 Data Base

### 1. Data Base Construction

At the present time, the data collected on the MAYAK worker cohort resides in a separate Windows data base written in the Borland Delphi language and using the Paradox data base engine. This data base has the appearance of and functions like a separate pass-word protected, Windows-based (3.11 or 95) software application. The final version of the Feasibility Study Data Base (FSDB) was delivered to the University of Pittsburgh, Graduate School of Public Health during the February 1997 visit of the Russian research team to Pittsburgh. This version of the FSDB includes all revisions agreed upon during the December 1996 visit of the US research team to Ozyorsk.

### 2. Data Base Contents

The Project 2.3 FSDB contains a stratified random sample of 225 MAYAK workers who were employed for at least one-year during the period of 1 January 1948 to 31 December 1954. This was the time period of the highest mean occupational exposure levels in Facilities A and B (the reactor and the radiochemical plants). Table 1 (pg. 2) provides a summary of the occupational injury categories from which the 225 individuals were chosen and Figure 1 (pg. 3) shows the flow of data in the FSDB. These data may be separated from the data base structure in the form of ASCII files using the pass-worded Export facility included in the FSDB.

### 3. Objectives of the FSDB Analysis

There are four primary objectives involved in the initial analysis of the FSDB contents:

- Determination of the frequency of missing and unknown data for key variables (e.g., occupational radiation exposures, plutonium body burden) in the data base.

- Identification of incomplete or missing categories of data required for the analysis of the contents of FSDB.

- Determination of whether the patterns of data (e.g., dose-response information on the symptoms of Acute Radiation Sickness, ARS) in the FSDB are compatible with what is already known from Western studies.

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- Identification of incomplete or missing categories of data required for the analysis of the contents of FSDB.

- Determination of whether the patterns of data (e.g., dose-response information on the symptoms of Acute Radiation Sickness, ARS) in the FSDB are compatible with what is already known from Western studies.

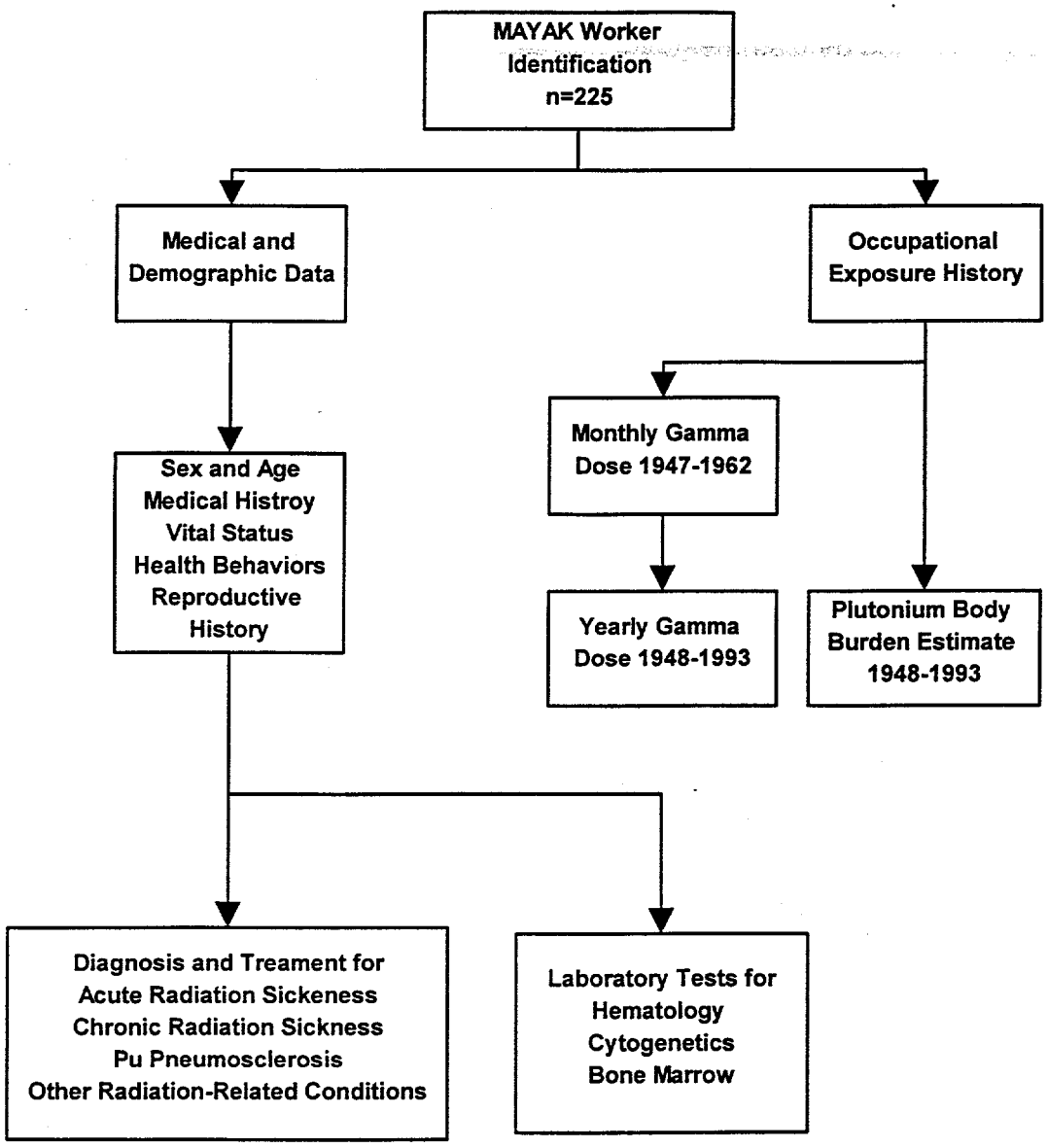
- Analysis of the FSDB contents for new knowledge useful to the field of radiation protection (e.g., the natural history and progression of symptoms in cases of Chronic Radiation Sickness, CRS, and Plutonium Pneumosclerosis, PPn).

**Table 1**
**Summary of the Project 2.3 Feasibility Study Data Base (FSDB)**

| WORKER CATEGORY | ESTIMATED TOTAL SIZE | FSDB SAMPLE SIZE |
|---|---|---|
| A. NO KNOWN OCCUPATIONAL CONDITIONS* | 6366 | 100 |
| Males..... | 4170..... | 50 |
| Females..... | 2196 ..... | 50 |
| B. CHRONIC RADIATION DISEASE** | 1528 | 99 |
| C. ACUTE RADIATION SYNDROME** | 41 | 13 |
| D. PU PNEUMOSCLEROSIS** | 120 | 13 |
| TOTALS | 8055 | 225 |

* category and size estimates from Ilyin, 1995
** category and size estimates from Okladnikova, 1994a

**Figure 1**
**Flow Chart of Project 2.3 Feasibility Study Data Base**




The first three objectives state above are intended to:

- systematically assess the *comprehensiveness and validity* of the FSDB;
- determine whether it is feasible to use this data base structure in the performance Phase II component of Project 2.3; and,

- identify specific additions or modifications required to improve the suitability of the FSDB for continuation of the long-term Phase II component of Project 2.3.

The fourth objective focuses on hypothesis testing and hypothesis generation using the information included in the FSBD. This objective necessarily assumes that a generally positive conclusion has already been reached concerning the validity of the information included in the FSDB.

The actual work on the data base during the analysis phase will be discussed under five headings:

- Data Cleaning and Preparation
- Descriptive Analyses
- Comparative Analyses
- Comparison to Existing Literature
- Investigating Clinical and Biological Hypotheses

## 4. Data Cleaning and Preparation

Data cleaning and preparation for statistical analysis is the first required task. The clinical and dosimetric information will have to be extracted from the data base using the Export facility, transformed (where necessary) from a textual to a numerical form, reviewed and checked for data entry errors. Individual ASCII will finally be assembled into larger files that link different components of the FSDB. Once this has been completed control files can be prepared for statistical processing using SAS and other statistical programs.

## 5. Descriptive Analyses

Descriptive analyses will be carried out in order to inspect the distribution of data for key variables in the FSDB. These analyses can be classified in terms of major components in the FSDB.

a. Demographics and Medical History

- distribution of age at hire
- sex distribution
- starting dates by year (1948-1954)
- use of tobacco and alcohol
- reproductive history (live births by time period:1948-54; 1955-present)
- radiation-related diagnoses stratified by:
  - ⇒ age at diagnosis,
  - ⇒ sex,

⇒ years since hire
⇒ facility of occurrence

b. Vital Status

- percent of cohort with known vital status
- percent alive/dead by sex
- distribution of age at death by sex
- primary causes of death by sex
- percent dead with autopsy data

c. Work History

- mean and median person years of exposure in each facility (A,B,C) stratified by:
  ⇒ sex
  ⇒ year (1948-present)
  ⇒ occupational injury group (ARS, CRS, PPn, control)
- percent of workers employed in multiple settings and person years of mixed exposures stratified by:
  ⇒ sex
  ⇒ five-year period (1948-present)
  ⇒ occupational injury group (ARS, CRS, PPn, control)

d. Occupational Exposure History

- percentage of workers with missing or unknown monthly and yearly data on gamma dose stratified by:
  ⇒ sex
  ⇒ year period (1948-present)
  ⇒ facility (A,B,C)
  ⇒ occupational injury group (ARS, CRS, PPn, control)
- mean and median cumulative worker exposure to gamma radiation stratified by:
  ⇒ sex
  ⇒ year period (1948-present)
  ⇒ facility (A,B,C)
  ⇒ occupational injury group (ARS, CRS, PPn, control)
- mean and median dose rate for worker exposure to gamma radiation stratified by:
  ⇒ sex
  ⇒ year period (1948-present)
  ⇒ facility (A,B,C)
  ⇒ occupational injury group (ARS, CRS, PPn, control)
- mean and median cumulative plutonium body burden stratified by:

⇒ sex
⇒ facility (A,B,C)
⇒ occupational injury group (ARS, CRS, PPn, control)

## 6. Comparative Analyses

The primary goal of the comparative analyses is to investigate the natural histories of various conditions in FSDB and to test whether a clear dose-response relationship can be observed between radiation exposure and symptomatology. Different categories of occupational injury will be considered and compared to data from the uninjured control group.

### a. Acute Radiation Sickness (ARS)

- What were the range and the mean of gamma and neutron doses received by workers in the incidents resulting in the diagnosis of ARS? What were the range and mean cumulative doses of gamma radiation received prior to the incidents resulting in the diagnosis of ARS?

- What were the locations (facility) of the incidents resulting in the diagnosis of ARS?

- Calculate the Profile Values for each occurrence based on the methodology in Thoma and Wald (1959). Investigate whether there is a clear dose-response relationship between the acute exposure and the observe Profile Value in each case. Does inclusion of cumulative exposure prior to the acute exposure improve the observed dose-response relationship?

- Compare the symptoms and overall outcome in each Profile Value against what would be predicted using the Thoma-Wald model.

- Carry out the same analysis as above using the Pyatkin and Baranov (1980), Baranov (1980), Baranov et al. (1990) and the Fliedner et al. (1988a, b), Densow, Fliedner, and Arndt, (1994) predictive models for ARS.

### b. Plutonium Pneumosclerosis (PPn)

- What percentage of PPn cases have estimates of cumulative plutonium body burden?

- What is the distribution of the severity of PPn as measured by various indices (X-ray evidence, symptoms, air flow measures) in the Mayak worker population? How do the various measures of severity relate to one another?

- What is the mean and median cumulative gamma dose and dose rate for workers up until the time of diagnosis of PPn.

- Is there a clear dose-response relationship between estimated plutonium body, with and without considering cumulative gamma dose, and the observed severity of PPn.

### c. Chronic Radiation Sickness (CRS)

- Compare scoring of syndromes in CRS patients across time. Is there a natural progression of the disease towards a more sever form or does it ebb and flow in terms of overall severity.

- How do changes in overall levels of CRS severity relate to various exposure measures?:
  ⇒ cumulative exposure to gamma radiation
  ⇒ overall dose rate of exposure to gamma radiation
  ⇒ cumulative exposure to gamma radiation since prior diagnosis of CRS
  ⇒ dose rate of gamma radiation since prior diagnosis of CRS

- How do mean and median cumulative exposures to gamma radiation and dose rates compare to what is observed among uninjured controls?

- How are specific symptoms of CRS related to the overall diagnosis? How many uninjured controls show CRS symptoms? Does the time of onset of CRS symptoms relate to dose? Does the time of onset of CRS symptoms in CRS cases differ from that in controls?

- Do episodes of leukopenia and thrombocytopenia (as defined by FIB-1 hematologists) precede the initial diagnosis of CRS and increases in the severity of the diagnosis? Do similar episodes precede increases in the severity of CRS symptoms? Do control subjects show a similar incidence of leukopenia and thrombocytopenia in their blood tests?

- What percentage of CRS patients develop Cerebral Atherosclerosis (CA)? At what age and following what cumulative exposure? Is there a dose-response relationship between cumulative exposure to gamma radiation and severity?

## 7. Comparison to Existing Literature

The goal in this component of the analysis is to compare the data in the FSDB to known materials in the existing literature in order to provide additional external validation for the data in the FSDB.

- ARS data in the FSDB with regard to the dose-response for symptoms and death should be compared to the observations include in the Thoma-Wald (1958) and Fliedner et al. (1988a, b), Densow, Fliedner, and Arndt, (1994) papers and the material recently published by the IAEA on recent accidents worldwide.

- The basic dose-response data for PPn should be compared to the animal studies of Bair et al. (1974a,b) and to the information in the Transuranic Registry (Kathren 1989).

- The FSDB subjects can be compared with regard to dose on other deterministic effects for which reasonable criterion data exists (e.g., cataracts).

- Finally, the material in FSDB needs to be compared to the data already published in Western journals by Russian investigators (e.g., Okladnikova et al. 1994) in order to check the representativeness of the achieved sample.

## 8. Investigating Clinical and Biological Hypotheses

The Thoma-Wald model is as sensitive and accurate as the Pyatkin and Baranov (1980), Baranov et al. (1990), Fliedner et al. (1988a, b), Densow, Fliedner, and Arndt, (1994) models in predicting the outcome of ARS, while using less complicated data inputs.

Certain changes occur in specific hematological variables (e.g., leukocytes and thrombocytes) prior to the development or intensification of CRS symptoms.

Secondary factors such as sex, age, reproductive history (in women), alcohol use, tobacco smoking and other co-morbidities do not explain the observed development or intensification of CRS symptoms.

Clear dose-response distinctions cannot be observed between CRS patients and controls, suggesting the possibility that a certain genetic radiosensitivity can be important in determining the development of deterministic effects.

Workers with the highest dose level of inhaled plutonium are the most likely to die from PPn. Those with lower dose levels survive PPn and tend to die of stochastic effects.

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# ATTACHMENT 3

ATTACHMENT 3

# ADAPTING THE WEIBULL NORMALIZED DOSE MODEL FOR DEATH VIA THE HEMATOPOIETIC SYNDROME MODE TO BE APPLICABLE TO MAYAK WORKERS CHRONICALLY EXPOSED AT SITE A TO GAMMA RAYS AND NEUTRONS

## 1. Background

Research reported on here relates to development of a computer program that will allow testing of the risk model for radiation-induced hematopoietic death (i.e., death resulting from severe damage to bone marrow) presented in U. S. Nuclear Regulatory Commission NUREG/CR-4214 reports (NRC, 1989, 1990, 1993a, 1993b). Before the US side first visited FIB-1 in March of 1996, it was thought that Mayak workers at Site A were exposed to only gamma rays and thus the Mayak data for Site A could be used to test the model presented in the cited NUREG/CR-4214 reports for evaluating the risk of hematopoietic death. Therefore, the initial intent was to set up a computer model that would allow use of the mortality and gamma ray dosimetry data for workers at Site A to test the model for hematopoietic death presented in the cited NUREG/CR-4214 reports. During the March 1996 visit of the U. S. side to FIB-1 in Ozyorsk, Russia, it was pointed out by the Russian side that some workers were exposed to neutrons, including criticality-accident exposures. Also, occupational exposures mainly occurred during 6-h daily work shifts, which differs from the exposure patterns considered in NUREG/CR-4214 reports. In addition, dose estimates for workers at Site A were expressed as exposures in roentgens (rather than organ absorbed doses, differentiated by radiation type). Thus, in order to used the data for model testing, some unplanned modeling research had to be conducted in Phase I. Also, it was realized that more details on the form in which dosimetric data will be presented to Project 2.3 (now to be provided by Project 2.4) was needed before a computer program for model testing was set up.

Computer programs were indeed set up in Phase I by both the US and Russian sides but relate to research efforts discussed below. For example, the US side set up a computer program that allows assignment of a long series of random work-shift gamma ray doses (of similar sizes as the doses to some workers at Site A) to evaluate the cumulative normalized dose (a key variable in models presented in NUREG/CR-4214 reports) as a function of time and absorbed dose rate pattern. This allowed exploratory analyses to be carried out in Phase I, related to comparing cumulative normalized dose and cumulative absorbed dose to bone marrow for prolonged repeated exposures at very low work-shift dose rates.

Research findings presented here mainly relate to results obtained in Phase I, associated with evaluating the risk of death via the hematopoietic syndrome mode, for Mayak workers exposed at Site A to gamma rays and neutrons. Evaluations were based on the Weibull, normalized-dose model presented in a form applicable to combined exposure to high- plus low-LET radiations in a NUREG/CR-4214 report (NRC, 1993a). Here, the model is called the W model. The two variables used in the W model are adjusted dose (i.e., RBE weighted dose) and adjusted dose rate. Parameters for the W model presented in NUREG/CR-4214 (NRC, 1993a), as well as the way normalized dose is arrived at from adjusted dose apply to continuous exposure to radiations. However, the RBE for deterministic effects of high-LET irradiation of

bone marrow presented in NUREG/CR-4214 (NRC, 1993a) does not apply to neutrons delivered at very low rates. Furthermore, the manner of calculating normalized dose from adjusted dose and adjusted dose rate presented in NUREG/CR-4214 (NRC, 1993a), does not directly apply to repeated combined exposure to gamma rays and neutrons at very low rates or during a criticality accident, as occurred for some workers at Site A.

The research summarized here is threefold: (1) to adapt the W model for death via the hematopoietic syndrome mode (set up for combined simultaneous or sequential exposure to alpha, beta, and gamma radiations) to be applicable to repeated simultaneous exposures, at very low dose rates, to gamma rays and neutrons over prolonged periods as occurred for some Mayak workers at Site A; (2) to investigate the state of knowledge about neutron relative biological effectiveness (RBE) for deterministic effects when the dose is delivered at very low rates, over years, and (3) to use results of the Phase I research to recommend specific dosimetric information and research undertakings that would facilitate the conduct of the follow-on Phase II research in Project 2.3.

The summary information presented here, some of which is presented in more detail in a draft manuscript (Scott et al., 1997), is the result of a cooperative US/Russian Federation effort conducted mainly by Dr. B. R. Scott (Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM), Dr. A. F. Lyzlov (Mayak PA, Ozyorsk) and Dr. S. V. Osovets (Engineering and Physics Institute, Ozyorsk). While Dr. Osovets was not an official member of our team, in working with Dr. Lyzlov and Dr. Scott, he has made important contributions to the research summarized here. In addition to summarizing research results, we also judged it important to discuss problems presented by threshold-type dose-response relationships in designing a Phase II study of deterministic effects among Mayak workers. Because our Phase I research focused on hematological effects, we discuss these problems here only so far as they relate to hematopoietic effects. However, similar problems arise for all deterministic effects for which the dose-response curve has a threshold and a curvilinear shape.

## 2. Problems Presented by Threshold-Type Sigmoidal Dose-Response Relationships in Designing a Phase II Study of Hematological Effects Among Workers at Site A

Unlike for stochastic effects, where one generally assumes a linear (and sometimes linear-quadratic) nonthreshold dose-response relationship, for deterministic effects such as hematopoietic death, one is dealing with a sigmoidal dose-response curve with a population threshold. Both the population threshold and characteristics of the dose-response curve for the risk of death would be expected to depend on dose rate and the gamma-to-neutron dose ratio. This complicates conducting Phase II studies of deterministic effects among workers at Site A (as well as for other sites), because for an efficient study design, one should have answers to the following questions:

A. Over what time periods should doses and dose rates be evaluated (e.g., daily, weekly, monthly, yearly, etc.) to adequately account for dose-rate effects?
B. Can doses and dose rates be averaged over different individuals?
C. Can population doses be used (e.g., person-Gy)?

Phase I research results presented elsewhere (Scott et al., 1997) and summarized here answer these

questions for workers at Site A.

## 3. The W Model: Continuous Exposure to Gamma Rays and Neutrons

### *A. Gamma Rays Only*

With the W model for non-competing risks, the risk R for a given deterministic effect is related to a cumulative hazard function (indicated here as $\Lambda$) through the equation

$$R = 1 - e^{-\Lambda}, \tag{1}$$

where $\Lambda$ is related to the normalized dose X through the equation

$$\Lambda = (\ln 2)X^{V}. \tag{2}$$

In NUREG/CR-4214 reports, H is used for the cumulative hazard function but confuses some readers because H is also used for equivalent dose. The shape parameter V has lower, central, and upper estimates of (4, 6, 8) for the hematopoietic mode of death (NRC, 1993a). The normalized dose is dimensionless and represents the dose expressed in units of $LD_{50}$ or $ED_{50}$ so that for lethality, X = 0.5 corresponds to one-half of an $LD_{50}$. For continuous exposure to gamma rays, X is evaluated as an integral over the exposure period given by

$$X = \int r(t)\, \theta(r)^{-1} dt. \tag{3}$$

The variable r(t) is used here to represent the time-dependent dose rate to the target tissue or organ; $\theta(r)$ is the absorbed dose that should affect 50% of those exposed ($LD_{50}$ or $ED_{50}$) evaluated at dose rate r(t); and dt is an infinitesimal increment in exposure time. The variable $\theta(r)$ is given by

$$\theta(r) = [\theta_1\, r(t)^{-1}] + \theta_\infty. \tag{4}$$

For healthy humans who do not have wounds or beta burns of the skin and who receive little protection from radiation-induced injury from medical support provided, the parameter $\theta_1$ (expressed here in $Gy^2/h$) has lower-bound, central, and upper-bound estimates of (0.06, 0.072, 0.084); the parameter $\theta_\infty$ (expressed here in Gy) has lower-bound, central, and upper-bound estimates of (2.5, 3, 3.5) (NRC, 1989, 1993a). The parameter, $\theta_1$, when divided by dose rate r(t), determines the increase in the $LD_{50}$ or $ED_{50}$ above its asymptotic value, $\theta_\infty$ (i.e., the $LD_{50}$ or $ED_{50}$ seen at very high dose rates), when the dose is delivered at a fixed rate equal to r(t). The fixed dose rate at which the $LD_{50}$ or $ED_{50}$ takes on a value twice as large as its asymptotic value $\theta_\infty$ is given by

$$\text{Doubling dose rate} = r_{[2]} = \theta_1 / \theta_\infty. \tag{5}$$

### B. *Gamma Rays Plus Neutrons*

For combined exposure to gamma rays and neutrons, neutron dose can be included by multiplying the absorbed neutron dose to bone marrow by an appropriate RBE and adding the results to the absorbed gamma-ray dose before calculating the normalized dose. Dose and dose rates obtained by multiplying absorbed doses and dose rates by an RBE have been called adjusted doses and adjusted dose rates (NRC, 1993a) as they are not based on International Commission on Radiological Protection (ICRP) radiation weighting factors (NRC, 1993a). Use of ICRP radiation weighting factors leads to equivalent doses (e.g., in Sv) and equivalent dose rates (e.g., Sv/h), which are based on an RBE for stochastic rather than deterministic effects. For combined exposure to gamma rays and neutrons, when r(t) represents the adjusted dose rate, then $\theta(r)$ would represent the $LD_{50}$ or $ED_{50}$ evaluated in terms of adjusted dose.

For combined exposure to gamma rays and neutrons at very low dose rates over several years, a major uncertainty is what value to use for the neutron RBE for the hematopoietic-syndrome mode of death (similar uncertainty also applies to the RBE for alpha radiation). Available information indicates that the RBE should increase as dose rate decreases and should reach a maximum value $RBE_m$ at very low dose rates. Low dose rates would apply to many Mayak worker exposures. Based on cell survival studies with neutrons with energies ranging from 1 to 50 MeV, $RBE_m$ may be in the range of 3-12 (Scott et al., 1997). Using the middle of this range as a crude central estimate of the neutron RBE for deterministic effects of very low dose rates yields a value of 7.5 or approximately 8. However, because Mayak workers at site A were exposed to relatively high dose rates during the early years of the Mayak facility, with dose rate progressively decreasing over years, and because the RBE for deterministic effects increases as dose rate decreases, it is recommended that research be conducted early on in Phase II and focus on obtaining better information on how neutron (and alpha) RBE for deterministic effects differs for high and for low dose rates. More specifically, the high- and low-dose-rate RBEs for neutrons should apply to deterministic effects observed in Mayak workers at Site A, while low-dose rate RBEs obtained for alpha radiation may apply to deterministic effects observed in workers at Sites B and C. Because RBE can differ for different deterministic effects, this is not a trivial issue. A comprehensive evaluation of RBEs for deterministic effects has not been carried out since 1990 (ICRP, 1990). Since that time, much new relevant data has been published in Europe, Russia, Canada, Japan, USA , and other places including data related to therapeutic applications of radionuclides.

## 4. The W Model: Multiple work-Shift Exposures to Gamma Rays and Neutrons

### A. *Single-Shift Exposure at Site A*

For work-shift exposure at Site A, the normalized dose can be evaluated in increments for each shift. We have considered the case of very low adjusted dose rates (Scott et al., 1997). For calculating the adjusted dose rate r(t) to bone marrow, the low-dose-rate, neutron RBE is recommended except for criticality accidents. The increment in the normalized dose for the $i^{th}$ work-shift exposure (criticality accident excluded) is given for a specific worker by

$$X_i = \tau r_i^2 / \theta_1 = r_i D_i / \theta_1 = D_i^2/(\tau\theta_1) \qquad (6)$$

(assuming that r(t) remains fairly constant for a single shift exposure [Scott et al., 1997]), where $D_i$ is the adjusted dose to bone marrow for the $i^{th}$ shift exposure. Thus, the increment in the normalized dose for a single work-shift exposure would be expected to be proportional to the (adjusted dose rate)*(adjusted dose) product (and to the square of the adjusted dose, for fixed $\tau$). A more general equation that applies to many different dose rate patterns is discussed elsewhere (Scott et al., 1997).

### *B. Work-Shift Exposures Over 1 Wk at Site A*

We have also considered the case where the shift dose rate remains fairly constant over work shifts evaluated over 1 wk and little recovery of hematopoietic damage occurs between shifts (Scott et al., 1997). In this case, $D_i$ in Equation 6 can be used to represent the adjusted dose to bone marrow evaluated for a 1 wk exposure, with $r_i$ representing the shift-adjusted dose rate averaged over the 1 wk exposure. Thus, $X_i$ would represent the increment in the normalized dose during the $i^{th}$ week of exposure.

### *C. Work-Shift Exposures Over 1 Mo at Site A*

We have also considered the case where the shift dose rate remains fairly constant over work shifts evaluated over 1 mo and little recovery of hematopoietic damage occurs between shifts, which is likely to be the case at least for the first few years of operation of the Mayak PA, based on hematological data (Okladnilova et al., 1994). In this case, $D_i$ in Equation 6 can be used to represent the adjusted dose to bone marrow evaluated for a 1-mo exposure, with $r_i$ representing the shift-adjusted dose rate averaged over the shifts worked during a given month of exposure. Then $X_i$ would represent the increment in the normalized dose during the $i^{th}$ month exposed (Scott et al., 1997).

Continuing along this line of reasoning, $X_i$ could be evaluated for longer time periods; however, the assumption of a fairly constant adjusted dose rate over work shifts becomes less plausible as the time period over which the adjusted dose rate is evaluated increases.

Thus, the answer for the question related to which time period should doses and dose rates be evaluated (daily, weekly, monthly, yearly, etc.) depends on how the shift dose rates change over time. Based on available information related to shift doses at Site A for randomly selected individuals, it is recommend that adjusted doses be evaluated for 1-mo intervals and that adjusted dose rates be averaged over the shifts that occur during each month at Site A (Scott et al., 1997). These doses and dose rates refer to an individual rather than to a group average. For a given individual, the total normalized dose is obtained by summing the dose increments $X_i$.

## 5. Influence of Medical Support on Normalized Dose

Medical support received by Mayak workers for radiation-induced injury to the hematopoietic system can also influence the normalized dose. Protection provided by medical support can be accounted for by reducing X by a constant factor called the protection factor (PF) which takes on a value of 1 when no protection occurs, and a value greater than 1 depending on the level of protection provided (Scott et al., 1997). For minimal treatment (basic first aid), no significant protection from radiation damage would be expected (NRC, 1989).

## 6. Number of Shifts to Exceed the Threshold Dose for Death via the Hematopoietic Mode

If N is the number of consecutive work-shift exposures, at a fairly constant adjusted dose rate r per shift, required to exceed the population threshold normalized dose $X_o$ (criticality accidents excluded here; minimal medical support assumed), then the solution for N has been found to be (Scott et al., 1997)

$$N > X_o\theta_1/(r^2\tau), \qquad (7)$$

where r is the average (over work shifts) adjusted dose rate to the bone marrow, and $\tau$ is the assumed constant number of hours worked during a shift. Because of uncertainty in r, the above equation is reliable only for r greater than a lower-bound dose rate $r_{[1]}$ which depends on the uncertainty and is discussed in detail elsewhere based on an analysis carried out by Drs. Osovets and Lyzlov and validated by Dr. Scott (Scott et al., 1997). For $r < r_{[1]}$, the standard deviation for N exceeds the mean.

Equation 7 was evaluated by both the US and Russian Federation sides, for r ranging from 0.001 to 0.01 Gy/h. An uncertainty of 0.001 Gy/h was recommended by the Russian side based on their previous dosimetric evaluations (Lyzlov et al., 1995). Monte Carlo calculations were conducted to facilitate uncertainty evaluation. Triangular distributions were used for model parameters, and were based on lower-bound, central, and upper-bound estimates presented in NUREG/CR-4214 (NRC, 1993a). The US side used 10,000 trials and Crystal Ball (1993a) software. The Russian side used 2000 trials because of limitations of the Mathcad (1994) software they used. Mean values for N obtained by the US and Russian sides were found to be in good agreement, although as expected, there was some divergence between standard deviations for N because of the different number of trials used by the US and Russian Federation sides. The adjusted dose rate $r_{[1]}$ to bone marrow below which mean values for N were found to be unreliable [i.e. standard deviation > mean] was approximately 0.002 Gy/h (Scott et al., 1997).

## 7. A Proposed New Type of Dose for Use In Studies of Deterministic Effects

One question addressed in this Phase I research was whether or not doses can be averaged over different individuals (the traditional approach in dose-response studies). The answer to this question is that it depends on the unit of dose used. If adjusted dose (or absorbed dose) is used, the answer is no because the dose-response curve is nonlinear (see Equations 1 and 2). Even at doses near the threshold $X_o$, risk is a nonlinear function of X (and therefore a nonlinear function of adjusted dose), so that adjusted dose (or absorbed dose) or normalized dose should not be averaged over different individuals with dissimilar doses.

However a new dose has been proposed for use in such studies, as it was constructed so that the dose-response curve is expected to be a linear function of that dose (Scott et al., 1997). The new dose is expressed in units of Oklad (in honor of Dr. Nadezhda D. Okladnikova who heads the clinic that has provided long-term medical support to Mayak workers injured by chronic exposure to ionizing radiation) and can be averaged over a given population at risk when each or most members of the population have a risk that is small in comparison to 1. The dose in Oklad was developed so that it takes on a value of zero for adjusted or absorbed doses below the population threshold for the deterministic effect considered. If for a given effect (e.g., hematopoietic death), the average dose to bone marrow, in Oklad, has a value w for n

persons being irradiated, then the expected number of deaths is given by the product (n)(w)[ln(2)], where the product (n)(w) is the collective dose in POklad (i.e., person-Oklad). Thus, the risk increases as a linear function of the collective dose in POklad. For the majority of the Mayak workers and for the lethality endpoint, their individual dose in Oklad is expected to be zero. Thus in designing dose-response studies, this should be taken into consideration.

With the lethality model used in NUREG/CR-4214 (NRC, 1993a), lethality hazard functions (also called lethality hazards) for competing risks are added to obtain the total lethality hazard. The total lethality hazard for the three competing risks (lethal injury to bone marrow, lethal injury to the intestines, lethal injury to the lung) considered in NUREG/CR-4214 (1993a) add to determine the total lethality hazard. This is equivalent to adding individual organ doses to the bone marrow, intestines, and lung when expressed in organ-specific Oklad, provided individual risks remain small in comparison to 1 for most persons exposed. Thus, for competing causes of death, and for the model presented in the NUREG/CR-4214 report (NRC, 1993a) for lethality from competing deterministic effects, organ-specific doses in lethality Oklad would be additive for different individuals for large populations with only a small number of deaths from radiation-induced deterministic effects (e.g., Mayak worker population). Thus, expressing individual doses in units of lethality Oklad and collective doses in lethality POklad provides a convenient way of testing the competing-effects, lethality risk model presented in NUREG/CR-4214 reports (NRC, 1989, 1990, 1993a, 1993b). However, to obtain such doses, radiation-specific organ absorbed doses (time-dependent) are needed for Sites A, B, and C. Time-dependent doses are needed in order to assess organ absorbed dose rate changes over time.

## 8. Major Implications of Our Phase I Research Related to Phase II Research

- Neutron doses should be initially evaluated in Project 2.4 for a small number of persons that were at high risk for neutron exposures at Site A so that the importance of neutron doses for deterministic effects can be assessed by members of Project 2.3.
- Organ absorbed doses should be time-dependent and radiation-specific.
- Neutron and alpha absorbed doses can be accounted for through use of adjusted dose, normalized dose, or dose in units of Oklad, for a given deterministic effect.
- Effect-specific and dose-rate dependent RBEs (and their uncertainty) will be needed for calculating adjusted doses (and their uncertainty).
- Alpha radiation RBEs may be needed only for low dose rates.
- Adjusted (or absorbed) doses or normalized doses should not be averaged over different individuals with dissimilar doses.
- Project 2.4 should provide dosimetric information to members of Project 2.3 that will allow deciding whether radiation exposures occurring while away from the Mayak facility can be ignored in Project 2.3 (e.g. exposures that occurred in the town of Ozyorsk).
- If work-shift, adjusted dose rates were fairly constant over periods such as a month at Site A, then adjusted doses over that period and adjusted dose rates averaged over work shifts during that period can be used in a dose-response study of hematological effects of irradiation of Mayak workers at Site A.
- Equivalent doses (e.g. in Sv) should not be used in characterizing dose-response relationships for

deterministic effects.

## Specific Recommendations for Phase II Research

- It is recommended that RBEs (and their uncertainty) for specific deterministic effects be obtained from published literature on deterministic effects in animal studies, clinical studies (e.g., with therapeutic radionuclides), and cell survival studies for use in analyzing and characterizing deterministic effects observed among Mayak workers.
- Organ absorbed dose uncertainty is important for both model testing and model development and therefore it is recommended that organ dose uncertainty characterization should be a key task for Project 2.4.
- It is recommended that Mayak data be used to test models presented in NUREG/CR-4214 reports where possible.
- It is recommended that both model-parameter uncertainty and organ dose uncertainty be accounted for when Mayak data are used to test model predictions.
- It is recommended that new models be developed for serious deterministic effects observed in Mayak workers not modeled in NUREG/CR-4214 reports.
- If models presented in NURER/CR-4214 reports are invalidated by Mayak worker data (assuming the dose estimates are reasonably reliable), then the models should be revised or new models should be recommended.

## 9. Literature


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# ATTACHMENT 4

**Memorandum**

**Exchanges of Data and Programs in Pilot Project 2.3**

Ozersk
15 December 1996

In accordance with memorandum of the Joint Coordinating Committee on Radiation Effects Research (JCCRER) and memorandum of the Executive Committee on 26-28 October 1996 concerning Pilot Project 2.3:

1. Russian side provides to US side for completion of Pilot Project 2.3
   - medical and dosimetry data on the sample of 226 people;
   - program for support of these data.

   1.1 Data on 226 people will be used exclusively for completion of the scientific research in Pilot Project 2.3.

   1.2 Primary data which are provided cannot be given to any other organization(s) or third party(s), published or made public in any way.

   1.3 The results of scientific research based on these data cannot be published without the mutual agreement of both groups (RF and US) of participating investigators.

2. US side provides to the Russian side for completion of Project 2.3
   - use or the license on the package for statistical analysis SAS 6.11.

   2.1 The package SAS 6.11 will be used exclusively for the analysis of the data concerning Project 2.3 without the right to transfer this package to any other organization(s) or third party(s), or to copy or make it public in any way.

**for the Russian side**
Director of FIB-1
SSC RF - Institute of Biophysics

E.R. Lyubchansky

**for the US side**
Professor and Director, Radiation Medicine
University of Pittsburgh

Niel Wald

Chief Engineer, PO "MAYAK"

A.P. Suslov

Scientific Leader

N.D. Okladnikova

# Протокол

## *Обмена данных и программ по пилотному проекту 2.3*

г. Озёрск 15 декабря 1996 г.

В соответствие с Меморандумом объединённого координационного комитета по изучению радиационных воздействий (ОКК ИРВ) от 26-28 октября 1996 г. и от Меморандумом исполнительного комитета ОКК ИРВ от 28 октября 1996 г. в рамках пилотного проекта 2.3

1. Российская сторона представляет Американской стороне

- медицинские и дозиметрические данные на выборку в 226 человек;
- программу для поддержки этих данных.

1.1 Эти данные на 226 человек должны использоваться только участниками пилотного проекта 2.3 для окончания научных исследований.

1.2 Представленные данные нельзя передавать другим юридическим и физическим лицам, публиковать или обнародовать тем или иным образом.

1.3 Результаты научных исследований, полученные при использовании этих данных не могут быть опубликованы в одностороннем порядке.

2. Американская сторона представляет Российской стороне

- использование лицензии на одну копию пакета статистической обработки SAS 6.11.

2.1 Пакет SAS 6.11 должен использоваться для обработки данных в рамках проекта 2.3 без права передачи другим юридическим и физическим лицам, без права копирования или обнародования тем или иным способом.

***от Российской стороны***

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