FINAL PROJECT REPORT

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Deterministic Effects from Occupational Exposures to Ionizing Radiation

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A. Background of Project 2.3:

Most of our current knowledge about the various nonstochastic or deterministic effects of ionizing radiation in humans, and the radiation protection regulations to prevent or limit them, have been derived from:

extrapolations from experimental studies of various animals externally and/or internally exposed to high- and/or low-LET radiations;

studies of the Japanese populations exposed at extremely high dose rates to gamma (or gamma and neutron) radiation from atomic bombs;

data about medical side effects arising from radiation therapy for cancer, usually given in fractionated, localized doses; or

published data about the relatively rare occurrences of accidentally irradiated radiation workers, predominantly male, as well as some members of the public, who developed deterministic effects.

The exposures have been from incorporation of internal radioactive materials, or by irradiation from external beta and/or gamma as well as from alpha, beta, and gamma sources occurring singly or in combinations, usually acutely. All of these are situations that might occur in nuclear accidents or intentional incidents. However, most radiation exposure is actually acquired chronically by radiation workers and the public.

In the course of post-Chernobyl accident collaborative efforts of the U.S. and the USSR to improve radiation safety, it was recognized that over the past 50 years, defense-related activities in the Russian Federation have resulted in significant occupational radiation exposures to tens of thousands of nuclear workers. This included the Mayak Production Association (Mayak PA), a nuclear facility located in the city of Ozyorsk in the Southern Urals (1,2).

The Mayak facility, which started operations on 1 January 1948, was the first nuclear n the Soviet Union and included a reactor plant, a radio-chemical plant, and plutonium processing plant. In the first decade of its existence (1948-1958), inexperience with production techniques, combined with an emphasis on urgency of political priorities, resulted in at least 8,000 workers receiving chronic exposures cumulating to relatively high levels of external gamma radiation (1-10 Gy) and, in many cases, to acute accidental gamma exposure, as well as to internal alpha radiation from inhaled plutonium aerosols. A number of these workers developed early deterministic health impairments diagnosed by their physicians at Branch No. 1 of the Institute of Biophysics (FIB-1), now the Southern Urals Biophysics Institute (SUBI), as the Acute Radiation Syndrome (ARS), Plutonium Pneumosclerosis (PPn), or Chronic Radiation Sickness (CRS).

Systematic exposure measurements and medical examinations were carried out on more than 95% of the professional radiation workers as part of the radiation protection program that was initiated at the time of the start-up of the Mayak facility. The SUBI medical department routinely carried out pre-employment physical examinations on all newly hired workers at Mayak PA. During the first years of medical follow-up (1948-1954) each worker underwent a scheduled medical examination including routine peripheral blood counts and periodic bone marrow samples every 3 months, during 1955-1960 once every 6 months, and since 1960, once every 12 months. Those workers having radiation-related diagnoses or very high exposures had some additional clinical tests such as cytogenetic, lung function tests and other procedures (see Fig. 1).

After retirement, the former Mayak workers were followed-up by telephone or mail by the same specialized medical hospital every 24-36 months and underwent physical medical examinations if they remained resident in Ozyorsk (see Table 3). The SUBI staff has continued to collect and maintain these unique human data over the past 54 years and was willing to make them available for the collaborative study of a wide range of deterministic and other health effects, including those involving hematopoietic, nervous, cardiovascular, respiratory, visual and cytogenetic(42) systems as well as the key organs of plutonium deposition (lungs, liver, skeleton).

These detailed longitudinal data on human occupational (internal and external) exposures to ionizing radiation and their resulting clinical outcomes represent an important addition to the currently available data that can be used for research and regulatory purposes. For example, these new data hold the potential for:

a. significantly improved estimates of the human dose thresholds and dose-response relationships for the deterministic effects of acute and prolonged exposure to ionizing radiation, particularly in females who make up a significant proportion of all the diagnostic categories included in the current database (see Table 4);
b. 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;
c. the clinical description and initial dose-response 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, as well as,
d. the impact of high levels of pre-accident chronic occupational exposure on the post-accident ARS response.

The Joint Coordinating Committee for Radiation Effects Research (JCCRER) was established in 1994 by the US and the USSR originally, and subsequently the Russian Federation (RF) as a bi-national inter-governmental committee with responsibility to facilitate joint cooperative research and the exchange of information on human radiation effects resulting from the operations of the Mayak production facility. The US Department of Energy is the administrative lead agency for US participation in the JCCRER.

Investigations of deterministic radiation effects in the occupational population were assigned by the JCCRER to Project 2.3 under the initial auspices of the Department of Energy (DOE), with funding provided by the Nuclear Regulatory Committee (NRC), and subsequently with both administrative and fiscal support by the USNRC.

The resultant Mayak PA Workers' Early Clinical Effects (MWECE) Database developed by Project 2.3 is a unique longitudinal compilation of occupational and health outcome data on a cohort now including 591 Russian workers who started their employment at the first Russian nuclear facility between the years 1948 and 1958 who acquired high, mostly chronic exposures, in the course of their work there. The current database is the product primarily of 6 years of continuous collaborative work between Russian and US clinicians and scientists of the Southern Urals Biophysics Institute (SUBI) and the University of Pittsburgh.

Beyond the immediate scientific value of these data, the MWECE Database is unique and significant because its contents represent the only raw Mayak PA data permitted to leave the Russian Federation under current international working agreements. The reasons for this exception are largely historical and were a result of the earliest working agreements between SUBI and the University of Pittsburgh which were signed prior to the more recent working agreements that apply to all of the other international work being carried out by US investigators at Mayak. Current international working arrangements make it unlikely that such data will again be released directly to US scientists in the foreseeable future.

B. Project 2.3 History:

B.1. MWECE Database Development, Phase I: Feasibility Study (1996-1997):

The US team selected by the DOE and NRC to carry out the initial phase of JCCRER work on deterministic radiation effects was headed by Drs. Niel Wald and Richard Day, under the rubric of Project 2.3. Phase I of Project 2.3 was a short-term collaborative feasibility study that was designed to take 12 months and which was funded in February 1996. The most important aim of the study was to determine the feasibility of using the earliest (1948-1958) dosimetric and clinical data on the Mayak worker population to study the deterministic effects of

occupational radiation exposures. A particular objective was the preservation of the data in a computerized format to prevent its loss and facilitate its utilization.

Working together with the Clinical Department of SUBI and representatives of the Mayak Dosimetry Department, the US team collaboratively: (a) developed a viable research relationship with the members of the Russian Federation team headed by Dr. N. Okladnikova; and, (b) designed and implemented an electronic database containing selected demographic, work history, occupational exposure, and clinical information on a randomly selected sample of 221 Mayak PA workers (see Table 1) employed between 1948 and 1958 and (c) designed and carried out a quantitative quality assessment/quality control (QA/QC) study of the clinical data in this database.

B.1.1. Sampling Procedures:

The project staff used SUBI medical records as the basis for the selection of the MWECE Database cohort. From 1948 forward, all new workers at Mayak had a routine physical examination as part of the employment process. These workers were generally young and well educated and the Mayak facility was interested in insuring their continued health. Prison and military laborers were not routinely used at the Mayak PA facility due to its sensitive nature. For this reason, SUBI medical records were particularly comprehensive in their employment listing. The electronic form of these records was relatively rudimentary at the beginning of the project and this limited the sampling options that could be applied to the data. Generally, these records had date of the employment, physical exam, gender, a primary diagnosis (ARS, CRS, PPn, no radiation-related Dx), and broad work history. Reliable cumulative dose estimates were not immediately available in these records.

Given this situation, the investigators agreed upon the use of a stratified, systematic sampling method in order to select random samples of the workers for the database. The complete list of workers was initially sorted by date of start of employment (1948-1958), then by primary diagnosis and gender. A systematic selection of an agreed upon number of workers was made within each one of these sets using a circular sampling technique. This procedure insured that workers were selected in a systematic fashion across the full 10-year selection period. These results were checked to make sure that all the workers were employed for at least 12 months during the critical sampling period and resampling was carried out when necessary. This procedure resulted in a random sample of workers with a known sampling proportion (i.e., the probability of inclusion) for each one of the individual strata. The same sampling procedure was implemented in later expansions of the original database (see Table 1).

This sampling procedure produced a data set that is particularly appropriate for retrospective studies with a case-control design. Worker selection was

primarily on the basis of health outcomes (i.e., medical diagnoses). Radiation exposures, lifestyle risks, and other data were collected in order to retrospectively assess the predictors of these health outcomes. In this framework, the group of workers with no radiation-related diagnosis served the role of a "baseline" or "control" group for the planned analyses. The question of what constituted a viable "control" group was given much discussion in the development of the database. It must be recalled that the Mayak PA setting (i.e., Ozyorsk) was a closed, artificial city, where the majority of employees migrated in from other regions in the Soviet Union. These migrants were provided with superior levels of food, housing and medical care that was unrepresentative of the surrounding population as a whole.

Also discussed was the possibility of trying to draw upon a series of family members of Mayak workers who had no employment history at the plant. These individuals, however, could not be considered "unexposed controls" due to the effects of Mayak accidents during the early years and the general leakage of radiation from the early facility. Moreover, these family members did not receive the same intensity of medical care (e.g., minimum of yearly medical exams) or the lifestyle documentation found on the worker population. Given these considerations, it was decided that the Mayak workers without radiation-related diagnoses were the best baseline group for initial database comparisons.

The case-control methodology used in the development of the MWECE Database does not preclude the use of these data within the context of a prospective design. One can consider the MWECE data to be a series of specific diagnostic cohorts selected within a historical context. Each one of these cohorts is a valid random sampling of the individuals receiving these early effects diagnoses. These cohorts are amenable to analysis with routine prospective epidemiological methods such as life table analyses of cause-specific and overall mortality. For example, workers diagnosed with plutonium pneumosclerosis (PPn) died largely from fibrotic lung diseases and lung cancer. It would be possible to use prospective epidemiological methods (e.g., proportional hazards models) to examine the differential effects of internal and external exposures and lifestyle predictors on cause-specific and overall mortality within this diagnostic cohort of workers. In fact, since (a) we know the sampling proportion for each one of the database strata; and, (b) these strata represent a comprehensive picture of the whole early worker population (i.e., no worker groups were excluded), it should be possible statistically to replicate earlier studies of the median levels of internal and external exposure and the general mortality structure for the whole Mayak PA early worker (1948-1958) population (3, 4).

B.1.2. Quality Assessment/Quality Control (QA/QC):

Beyond testing our ability to carry out a viable sampling methodology, a second objective of the Phase I Feasibility Study was to develop and test quality

assessment/quality control (QA/QC) procedures to insure the integrity of the medical data in the database. US investigators proposed using the same type of QA/QC procedures routinely implemented by US National Cancer Institute (NCI) in Collaborative Clinical Trials Groups. This procedure called for the US investigators to make a random 10% selection of the workers in the database. The ID numbers for 75% of the workers selected for the QA/QC exercise were transmitted to our Russian colleagues approximately 2-weeks before a scheduled visit of the US team to . Our Russian colleagues were asked to make all of the clinical data on these subjects available at the time of the visit for review and comparison with the computerized database contents. The identification numbers for the remaining 25% of the QA/QC sample of workers were provided to the SUBI staff at the time of the arrival of the US team and they were asked to provide the clinical records for inspection within 48 hours. During the visit, members of the US team selected data items from the database (e.g., date of birth, peripheral blood count) and asked the Russian investigators to locate the same data points they had been transferred to the database.

This kind of QA/QC exercise was carried out for every scheduled expansion of the MWECE Database (see Table 1). Each one of these QA/QC exercises normally involved the inspection of the source records for 20-25 randomly selected workers and a total of 2-3,000 individual data points. An arbitrary 5% divergent and/or missing data rate was set as the lower acceptable limit for database integrity at the beginning of the project. In all cases, the frequency of divergent or missing data fell below 4%, a level that was considered adequate for database integrity.

B.1.3. Ownership of the MWECE Database:

During the course of the Feasibility Study, an agreement was signed between Mayak, FIB-1 (later SUBI), and University of Pittsburgh representatives giving permission for the US investigators to take a copy of the MWECE Database out of the Russian Federation. The agreement clearly stated, however, that the Russian Federation retained ownership of the data and that these data were to be used by US scientists only for agreed upon collaborative purposes. If the Russian/US collaborative work ceased, the data were to be revert to the Russian Federation. This basic agreement still applies to the expanded versions of the MWECE Database (see Attachment I .1 for Binational Data Access Agreement).

B.1.4. External and Internal Dosimetry Data:

The most problematic aspect of the Phase I database was the external and internal dosimetry data. In 1995, the JCCRER assigned responsibility for updated internal and external dose reconstruction in the Mayak PA work force to an independent DOE-sponsored program of research under the rubric of Project 2.4, "Development of an Improved Dosimetry System for Workers at the Mayak

Production Association." The collaborating Principal Investigators were Dr. Evgenii Vasilenko (external dosimetry) and Dr. Valentin Khokhryakov (internal dosimetry) for the Russian Federation (RF) and, initially, Dr. Lynn Anspaugh for the United States (US, 1995-1998), followed by Dr. Scott Miller (1998-present). A number of relevant papers have been published (5-10). Project 2.4 continues to have as one of its specific aims, the provision of updated dosimetry and associated uncertainty estimates for the MWECE Database.

B.2. MWECE Database Development, Phase II: Further Expansion (1999-2002):

In February 1999, a new proposal was submitted to the USNRC to support continued work on the MWECE Database. This new work was based on the evidence from the feasibility study that a viable collaborative relationship had been developed with the Russian clinicians and scientists at SUBI and Mayak and that high quality, accurate data could be extracted from the medical records. The primary objective of the Phase II work was to expand the size database through the addition of information on another 300 randomly selected Mayak Workers from the 1948-1958 cohort. The number 300 was selected because this was the maximum amount of work that could be carried out by the SUBI staff over the funding period. Primary emphasis was given to the weighted selection of workers with key diagnostic conditions. Our Russian colleagues agreed to expand the Phase I database to include: (a) all 102 remaining plutonium pneumosclerosis (PPn) cases; (2) an additional 111 cases of chronic radiation sickness (CRS); and (c) an additional 111 workers with no radiation-related diagnoses (see Table 1, below). The Project 2.4 staff was to make available updated external and internal dosimetry, as well as their uncertainty analyses on all workers in the MWECE Database.

By January 2002, the proposed Phase II addition of 300 workers, together with their medical information had been completed and checked for reliability and consistency. Updated dosimetry estimates for internal and external exposures were added to the Phase II database, but due to delays in the Project 2.4 schedule, these were not the final estimates and they were received without the expected uncertainty analysis. Further refined internal and external dosimetry estimates are still being developed through the records maintained at the Mayak PA facility. One of the primary goals of our project has been to link these refined dosimetry estimates and their uncertainty analyses to the medical data available on the 591 workers included in the Phase II MWECE database.

B.3. Current State of the MWECE Database:

B.3.1. Location and format:

The MWECE (Phase II) Database is located at SUBI in the Russian Federation and on a dedicated microcomputer at a single site in the United States – i.e., the University of Pittsburgh – under the supervision of Drs. Wald and Day. The most current version of the database exists in the form of a series of modular electronic data sets. (See Attachment I.3.). This format permits individual component parts of the database (e.g., dosimetry, socio-demographic modified or supplemented without affecting the structure or content of the other modules. This format also facilitates the transfer of the raw data into data analysis packages (e.g., STATA, SAS) that permit the construction of specialized statistical analyses and visual plots. An earlier Phase II version of the database also exists in the form of a MS Windows application which permits the selection and clinical review of individual case-by-case data for all of the workers.

B.3.2. Structure and content:

Figure 1 provides a brief summary of the current structure of the MWECE Database, showing primary data headings. Table 2 summarizes estimated cumulative gamma and plutonium doses by primary SUBI diagnosis and gender. Initial dosimetry is available on 93.7% (n=554) of the randomly selected worker cohort. Additional data from the Mayak PA files that should become available over the next two years should bring the number of randomly selected workers with complete dosimetry to approximately 100%. It should be noted that 38.9% of the workers in the MWECE Database with dosimetric information are women and that women represent, 30% of the CRS cases, 47% of the PPn cases, 17% of the ARS cases, and 49% of the workers without a radiation-related diagnosis.

The women, moreover, demonstrate median internal and external exposure levels that are similar to men. Table 3 summarizes the median length of employment and the median period of follow-up (in years) for the workers in the MWECE Database by gender and primary diagnosis. Table 4 summarizes the current vital status and follow-up status of all the workers in the database by gender. Only 11% (n=65) of the series of 591 workers are lost to follow-up, while 50% (n=297) are known to be dead and 39% (n=229) are alive and currently cooperating with the SUBI medical staff. This latter group will be periodically followed-up and examined through death by the SUBI staff.

Figures 2 and 3 extend the data on Table 4 by providing Kaplan-Meier survival curves for all cause mortality, stratified by primary diagnosis and by gender. Table 5 summarizes the major categories for the primary cause of death for the Mayak workers in the MWECE Database by gender. Finally, Figure 4 is a scatter plot showing prior cumulative gamma and accident exposures, by gender, for the 60 workers with an acute radiation syndrome diagnosis.

In summary, the current MWECE Database includes more than 17,500 person years of longitudinal follow-up data and is composed of more than 3.5 million

individual data points. Several English language publications based on the MWECE Database are available (11-15).

B.3.3. Relationship of MWECE Database to Other Russian Databases:

A number of other excellent databases exist within the Mayak PA and SUBI settings. The main database for all external exposure data is housed at Mayak PA under Dr. E. Vasilenko and a separate database for internal exposures exists at SUBI under Dr. V. Khokhryakov. The MWECE Database draws on the information in both of these sources to obtain its dosimetry data. A separate clinical database under Dr. Azizova and an epidemiological one under Dr. Koshurnikova also exist at SUBI. The MWECE Database is a subset of the data maintained by Dr. Azizova in the clinical database. When compared to the epidemiological database maintained by Dr. Koshurnikova, the MWECE has a smaller number of registered workers, but includes more detailed information on their clinical, socio-demographic and lifestyle characteristics. In addition, the MWECE is the only database: (a) that was designed "from the ground up" by Russian and US investigators working together; (b) that has been fully and repeatedly assessed using a Western QA/QC protocol; and (c) that has multiple copies, one of which is resident outside of the Russian Federation.

C. Specific Deterministic Effects Research Results:

C.1. Acute Radiation Injury:

Although all of the previous experiences with acute radiation injury, e.g., animal studies, Japanese A-Bomb victims, radiation oncology patients and industrial accident cases have provided extremely useful radiobiological data, they are limited for the purpose of one of our major objectives, ie., to identify the best clinical and laboratory correlates for clinical triage prognostication and medical management of the acute radiation syndrome in normal males and females. The value of the first source of data is limited because of the uncertainties of interspecies extrapolations. The second lacks much detailed clinical and laboratory data concerning the ARS because of the devastation of medical resources in the post-bombing period. The third suffers from the confounding manifestations of the patients primary disease, the generally protracted exposure, and the concurrent use of other forms of treatment.

A major advantage of the fourth source of data described above, despite its relative paucity, is that the worker population is generally in good health at the time of exposure and the medical management of such mishaps often includes detailed dose reconstruction in addition to close clinical observation. Thoma and Wald (26) took advantage of these features in 1959 to promulgate

recommendations for the diagnosis and management of acute radiation injury based on a study of seven accidents involving 32 patients about whom there was sufficient detailed clinical information[1]. A triage scheme for clinical diagnostic and prognostic classification according to severity of injury was proposed utilizing the time of appearance and severity of the early prodromal signs and symptoms, and of alterations in the early blood cell counts. This approach, which does not require the use of physical dosimetric information that is usually difficult to obtain promptly in an accident situation, has been generally accepted and its details disseminated in a variety of publications (27-33).

Since then, additional occupational overexposures have occurred. As of March 1996, when this project was being developed, the US Department of Energy (DOE)/Radiation Emergency Assistance Center/Training Site (REAC/TS Radiation Accident Registries include 236 U.S. accidents since 1944 involving 781 instances of "medically significant" exposure as defined by DOE and NRC (i.e., > 0.25Gy whole body, >6Gy to skin or extremity area large enough to produce symptoms, 0.75 Gy to other tissues or >half the NCRP occupational maximum internal organ burden) including 30 fatalities (34). Outside the U.S., 149 accidents led to 2,110 "significant" exposures including 82 fatalities (35).

The large majority of the significant exposures in the DOE Registry were not high enough to produce the ARS or radiation burns. This is confirmed by the relatively small number of fatalities. In addition, even in many of the severe cases in the Registry, complete detailed dosimetric, clinical and laboratory information is not available for study. The cases that are reported in the scientific literature are widely scattered as recent compilations by Oliviera (36) and by Anno et al (37) show, and do not necessarily serve for detailed analysis as Baverstock and Ash pointed out in their review (38).

In an effort to facilitate the analysis of clinically significant radiation exposure cases, Fliedner at the University of Ulm, Germany, and Baranov at the Russian Federation Academy of Sciences Institute of Biophysics, Moscow , have collaborated in developing with World Health Organization sponsorship, an international computer database for detailed radiation exposure case histories (39). In order to provide a uniform format for case reporting, a "Clinical Pre Computer Proforma" or data extraction questionnaire was published in 1994 (40).

Another objective of Project 2.3 was to add clinical information concerning the group of occupationally radiation-exposed workers who developed the acute radiation syndrome (ARS) in the Soviet Union in the period from 1948 through 1953 to that obtained from similar cases that have been collected over many decades in the Western world. It was planned to use these new data to test the triage scheme that had been developed by Thoma and Wald (26) in 1959 to provide clinicians lacking any special knowledge about radiation effects with

early diagnostic and prognostic information about the severity of such injury as a basis for medical management.

C.1.1. NIOSH-funded Study of Acute Radiation Sickness (1998-2001):

Completion of the Phase I Feasibility Study of this project left a gap in the collaborative funding for the MWECE Database development. Dr. Wald and Dr. Day (Co-PI's) addressed this problem through the submission of a competitive NIOSH proposal designed to investigate the clinical features of the acute radiation syndrome (ARS) in the Mayak PA cohort. This funding permitted the investigators to: (a) expand the Phase I database to include all 60 of the cases of ARS occurring at Mayak PA between 1948 and the present (see Table 1); and, (b) design and implement an extensive clinical database description of the signs, symptoms and clinical course of the Mayak ARS cases based on a modification of a computerized system published by Baranov and Fleidner (40).

Another major effort of the continuing NRC-supported ARS study was the completion of clinical summaries of all the key data in the remaining cases in the MWECE database. In addition, an initial analysis of the ARS subset led to a detailed presentation at the most recent Health Physics Society Annual Meeting by Dr. Tamara Azizova. (See Attachment K.3.)

Under NIOSH grant #RO1-CCR312952 we utilized the 60 ARS cases in the MWECE Database to validate a triage model using clinical data only from the first 72 hours after the accident exposure. One case had no data and was therefore omitted from the remainder of the ARS study. Of the 59 cases remaining, 22 were considered suitable based on the existence of two hematological studies within the initial 72-hour post exposure period. The 22 cases were classified into one of the 5 Thoma-Wald prognostic category groups (26) by Dr. Niel Wald based on a detailed review of the whole of the data. Categories 1&2 and 3&4 were combined due to observed difficulties differentiating between them based on hematologic parameters. Clinical vignettes for the first three days in each of the cases were then constructed and presented to four radiation-naive volunteer Emergency Department physicians in an exercise where they attempted to correctly categorize each case into one of the three injury categories. They were provided a two-page summary of relevant instruction on the assessment of ARS and a modified 3-level injury classification flow chart for quick reference during the exercise. No time limit was stipulated.

The results of this initial effort were disappointing but instructive. Overall the physicians correctly classified only 62% of the cases. However, there was a remarkable consistency among the physicians in their selection of both those cases that were correctly and those that were incorrectly assigned. This

suggested that a flaw existed in our chosen method of presentation of ARS assessment instructions to the volunteers.

Subsequent efforts have been directed toward overcoming this limitation by incorporating a more systematic approach to triage that emphasizes objective criteria in the assessment process. Preliminary findings are encouraging, suggesting that a clinically applicable triage method is achievable.

C.2. Chronic Radiation Sickness (CRS):

CRS was first described by Guskova and Baysogolov in 1971 (41) based on Russian nuclear worker experience from 1947 through 1954. It is a deterministic radiation effect occurring in the course of prolonged elevated radiation exposure. The syndrome was described by them as one that " is formed gradually, slowly, under the prolonged influence on the organism of radiation, the single and summary doses of which regularly exceed the acceptable permissible levels for occupational irradiation. The syndrome is not specific but is rather characteristic in the whole sequence of development and type of clinical manifestations, associated with general or nonuniform selective irradiation of various organs and systems".

The authors described four levels of severity of CRS, ranging from the light or first degree in which the clinical syndrome was indistinct and primarily a neuroregulatory disorder with a concurrent and unstable moderate local leukopenia, and sometimes thrombocytopenia, to the most severe level with direct signs of damage to the blood forming tissue, intestinal mucosa as well as the walls of the blood vessels and the heart.

The signs and symptoms of CRS overlap those of many other infectious and somatic diseases. The absence of exclusive CRS signs and symptoms confounds the diagnosis and leads to a dynamic diagnostic process in which the remission of the syndrome after cessation of radiation exposure is itself evidence of the syndrome.

Most of the 1,828 CRS cases in the Mayak worker population were diagnosed before 1959 when occupational exposures were high. Figures 5 and 6 show the high individual and cumulative occupational exposure of the CRS patients compared to that of their unaffected co-workers.

The objective of the analyses of Dr. Gregg Claycamp and colleagues (11,12) was to classify the exposed workers into "radiation affected" and "unaffected" groups based on a quantitative analysis of the clinical variables. Because radiation exposure was a diagnostic variable, an epidemiological case-control design was not possible. Instead, a novel combination of non-parametric statistical procedures was utilized to group the workers into "affected" and

"unaffected" clusters based solely on observed clinical measurements without information about radiation dose or work assignment. The objective "machine-determined" diagnoses subsequently served as an *a priori* classifier into "cases" or "control" in statistical analyses. Finally, the average radiation doses of each group were compared to determine the statistical difference between doses for the "affected" and "unaffected" individuals.

The results showed a better separation among clustered blood cell counts than those based on historical diagnostic classification. Using the cluster classification tree method, the differences in "affected" versus "unaffected" group means were significant ($p < 0.05$) for platelets, white blood cells, neutrophils, eosinophils, bands, and lymphocytes. Thus, the method has potential value as a diagnostic tool both in retrospective studies and in future radiation incidents.

C.3. Plutonium Pneumosclerosis:

The initial exploration of this unique Mayak worker subset was a dose-response analysis of the relationship of internal plutonium (Pu) exposures to the onset, course and outcome of pneumosclerosis of the lung. Experimental studies in animals show that inhaled Pu causes chronic inflammatory lung disease. However, there have been few human epidemiological studies due to the marginal exposures in Western workers. The MWECE Database includes demographic (age, sex), clinical diagnostic (x-ray findings, lung function tests, signs and symptoms, time to onset), lifestyle (tobacco use), work history (location), mortality (cause of death) and dosimetry (gamma and plutonium) variables on all of the 121 Mayak workers (56 females) ever diagnosed with plutonium pneumosclerosis (1). In addition, we have data on an additional 139 plutonium exposed control subjects (54 females) who were never diagnosed with this condition. Table 4 provides a summary of the dosimetry and diagnosis for these cases and controls.

These data show that the PPn cases received substantially higher internal Pu doses to the lung than the controls, while showing lesser gamma doses. This is in keeping with our primary hypothesis that exposure to Pu is the primary cause of the observed lung fibrosis in the cases. In testing this hypothesis, it will be necessary to adjust the dose response relationship for a number of other potential contributory factors such as tobacco use, sex, age, and gamma exposures.

The MWECE Database contains data on internal Pu dose and other potential contributory factors (e.g., sex and tobacco use) and the progression of signs (pulmonary function test data, x-ray results) and symptom levels (dyspnea, tachyacardia, dry cough) following the onset of the disease in the PPn patients on at least a yearly basis for the full period of their employment at Mayak and

intermittently thereafter. It should be noted that workers did not quit their employment at Mayak due to the diagnosis of PPn and the average working life for these cases extended 14 years beyond the clinical onset of the condition. Therefore, primary hypothesis could be tested that cumulative internal Pu dose is the primary factor associated with peak severity of PPn and length of life.

Currently, we know the vital status of 99% (n=120) of the PPn cases; 78% (n=94) of whom are dead (see Table 5) compared to only 47% of the 139 PPn controls that have died. The PPn cases also show a significant relative increases in the rates of malignant and non-malignant respiratory causes of death. With regard to outcome variables, the Russian clinical data is organized in stages of increasing severity (eg., 4 levels of x-ray findings and 3 levels of symptoms); lung function data for factors like vital capacity can be assessed in terms of peak severity.

Table 6 shows a statistically significant average decrease of 4.7 years of life for each quartile of internal Pu exposure; using continuous data we get an $r=-.448$ ($p<0.001$). These findings support our primary hypothesis, leaving the question of the extent to which adjustment for other factors modifies these findings. With regard to statistical power the above tables provide prima facie evidence for the adequate size of the study sample. Besides, the MWECE Database contains the total population of Russian PPn cases and, therefore, cannot be increased. Furthermore, due to the uniqueness of these worker data, they would be of interest to other epidemiological investigators, even if the final p-values were only marginally significant.

D. Dosimetric Issues:

D.1. Internal Doses:

The uncertainty for the bioassay measurement can be estimated using the standard error propagation (16) and minimum detectable activity as defined in HPS N13.30-1996 (17). or the Mayak dose reconstruction the plutonium concentrations in urine were determined using a radiometer (18). Twenty -four hour urine collections were typical. Of the total urine volume collected, typically only 200 ml were processed. The average count time increased from 20 minutes to 260 minutes and the background counts dropped in 1979 and 1990. Using HPS N13.30, the minimum detectable activity dropped from 6.38 mBq to the current level of 0.64 mBq. The minimum detectable concentration dropped from 31.9 mBq L^{-1} to 3.19 mBq L^{-1}. The error in the activity can be found using error propagation. The mathematical relationships used to determine errors excluding random errors in volume measurements are:

$$A = \left(\frac{C}{T}\right)_s - \left(\frac{C}{T}\right)_B \Big/ Eff \qquad 1.$$

$$E = \sqrt{\sigma_n^2 + \sigma_{nc}^2} + A\sqrt{\left(\frac{\sigma_{Eff}}{Eff}\right)^2} \qquad 2.$$

$$\sigma_r = \frac{\sqrt{C}}{T} \qquad 3.$$

where A = activity, C = counts, T = counting time, Eff = efficiency, s blank , σ = standard error, r = count rate.

The error is a strong function of count time. The impact, seen as the percent error, drops from 100% for the early measurements to less than 40% in the current measurements for activities less than 50 mBq.

The distribution of plutonium between organs was determined from the autopsy of 200 individuals. The fraction of plutonium found in each organ is normally distributed. The fraction of plutonium found in each organ and their respective uncertainties are reported in Krahenbuhl et al (19). This paper also includes the mass for each organ as defined in ICRP publication 23 (20).

The SUBI model uses 4 parameters that describe the transport of plutonium from the lung. The four lung parameters are part of both the excretion model and the biokinetic model (21). The parameters were determined by a least squared analysis of the distribution of plutonium between the lung and the lung lymph nodes .

The uncertainty for the each of the 10 excretion parameters is not known. Therefore, the impact of the excretion parameters (a_j and x_j) on the reported dose was determined using Monte Carlo calculations. To implement Monte Carlo calculations, each parameter was assumed to be independent and normally distributed. Different percentages of parameter variability were examined. The percentages examined were 5, 10, 15, 20 and 25%. Furthermore 10,000 histories were followed.

The two remaining variables are exposure duration and post exposure time. The SUBI model was developed using autopsy data and excretion data collected from individuals who had been exposed to plutonium over long periods of time. The model developed reflects the behavior of the plutonium at steady state. Intuitively the impact of exposure duration (t) and length of time between

end of the exposure and bioassay sample (σ should be minimal on plutonium content in the organs.

The defined uncertainty for each variable is combined using perturbation theory (22) to determine the total uncertainty in the reported dose. Lyons states that the uncertainty in a reported value determined from a complex system can be estimated by perturbing each variable separately by its specific uncertainty. The results from the perturbed solution are then subtracted from the standard solution. The differences are squared and summed resulting in an estimation of the total uncertainty in the reported value. The equations are:

$$f_o = f(\bar{x}_1,\ldots,\bar{x}_n) \qquad 8.$$

$$f_i^+ = f(\bar{x}_1,..x_i+\sigma_i..,\bar{x}_n) \text{ and } f_i^- = f(\bar{x}_1,..x_i-\sigma_i..,\bar{x}_n) \qquad 9.$$

$$\sigma_f^{2+} = \sum_{i=1}^{n}(f_o - f_i^+)^2 \text{ and } \sigma_f^{2-} = \sum_{i=1}^{n}(f_o - f_i^-)^2 \qquad 10.$$

where f is the general function, f_o is the dose determined from the general function, f_i^+ and f_i^- are the doses resulting from the perturbed functions. The perturbation techniques allows for non- symmetrical uncertainties to be used. Furthermore even with the use of symmetrical individual errors the method may produce an asymmetrical total error.

D.2. External Doses:

The error associated with external dose is a result of many different factors in the process of calculating dose. According to the traditional analytical approach to error analysis, the error must be separated into bias and random components. These components are categorized by the source of the error. The difficulty in calculating the random error of the cumulative dose as a sum of single dose measurements arrives from the following reality: every individual worked a unique number of shifts, different from other persons even those with the same title assigned to the same work location. This unique number of shifts is a result of holidays, vacations, and illness during the year. Therefore, the time period of the single dose measurement was not constant.

Bias error includes the correction coefficients for doses. For example, the corrected doses were obtained for all types of dosimeters used during the individual's monitored period. In addition, bias for each dose includes the spatial energetic influence on dose registered by the individual dosimeter for a defined work place, and the time spent at each work place.

A Bayesian statistical approach is used to estimate the unobserved quantities x_i (true dose) given the values of the observed ones z_i (recorded dose). A relationship between the true dose and the recorded dose in the form of a conditional probability distribution $P_i(x_i \mid z_i)$ is the key element of this method. The

conditional probability distribution $P_i(x_i \mid z_i)$ is called the posterior distribution. So for every dose, the estimate is expressed in the form of a probability distribution. The distribution of the single dose x_i at the recorded z_i is considered to be log normal such that $\log(x_i)$ has mean $\log(z_i)$ and parameter σ_R. Describing the scattering scale, the parameter σ_R was defined by changing of the registration, measurement and film treatment conditions. In accordance with the expert estimations of the single measurement random error it was assumed the standard deviation S of a single dose is 30 % of the measured value (i.e. in relative units S=0.3), with the parameter σ_R being written $\sigma_R=\ln(1+S^2)$.

According to this method, the conditional distribution of the true dose for a single measurement x_i is as follows:

$$P(x_i \mid z_i) = \frac{1}{\sqrt{2\pi}\cdot\sigma\cdot x_i}\exp\left[-\frac{1}{2\sigma^2}\left(\ln(x_i)-\mu_i\right)^2\right], \quad \mu_i = \ln z_i - 0.5\cdot\sigma_R^2. \quad (7.1)$$

The cumulative dose z for person exposed was calculated, using n single doses z_i measured during the monitored period: $z=\sum_{i=1}^{n} z_i$. Assuming the single measurements $\{z_i\}$ are independent, the probability distribution of the true cumulative dose $x=\sum_{i=1}^{n} x_i$ is as follows:

$$P(x \mid z)=\prod_{i=1}^{n} P(x_i \mid z_i) \quad (7.2)$$

The distribution P(x | z) was determined numerically using latin hypercubes. A sample including 2000 values of $x_m=\sum_{i=1}^{n} x_{im}$ was generated. Using these results, a posterior distribution for the cumulative dose x, with the interval and point estimates are determined.

The estimates of the total error in the annual gamma dose determined using the convolution integral were compared with the errors computed using Monte Carlo methods. The total error for a neutron dose was calculated using the convolution integral of the random and systematic errors. The uncertainty was defined by the systematic bias of the correcting coefficient and the systematic error of the coefficient used in relation to gamma dose and neutron dose).

The total error in equivalent doses of the gamma and neutron exposure was calculated using the convolution integral for the gamma dose and the neutron dose. These estimates were also benchmarked with Monte Carlo methods. Using the approach described, an influence of occupational history at the same work place on the random error of gamma dose was estimated. These calculations show that the uncertainty characterizing this process did not exceed 19%. These

slight variations were likely the result of the workers' orientation with respect to the radiation source.

The random error of the annual dose for the nuclear workers with their work place defined as the reactor central hall was determined. For these workers, the random errors varied between 5% and 15% when the standard deviation of the single dose measurement was 30% for a posterior distribution. In the case of individuals whose annual dose was based on one or two single dose measurements, the random error of the annual dose increased up to 25%.

For example, analysis of the data demonstrated a relationship between the profession and the spread in standard deviations. For a group of 202 persons exposed during the period from 1950 to 1974, the standard deviation varied between 2.5% to 22%. However, for engineers, metalworkers and laboratory assistants this interval was narrower, with the standard deviations changing from 8% to 16%, 3% to 19% and 5% to 14%, respectively.

During the period between 1948 and 1974, the random error of the annual dose varied from 4% to 25%. The systematic error (bias) of the annual dose varied from 1.8% to 27.1%, with a maximum error of 27.1% corresponding to measurements of dosimeters without a filter used in the final stages of radiochemical and plutonium production. In the other cases, the systematic error did not exceed 13%. The 99%- confidence intervals for the corrected annual dose for gamma exposure were ±60% (during 1948-1953) and ±29% (during the period beginning in 1985). For neutron exposure, the confidence interval ranged from ±115% (during 1948-1953) to ±85% (during the period beginning in 1985). The total error of the summary dose for persons who had worked at the nuclear production plant for 6 or more years, is defined only by the systematic error with the random error being negligible.

E. Epidemiologic Issues

E.1. Survival Advantage:

An important epidemiological issue arises from the preliminary data on Figure 2b that indicate a long-term, statistically significant (log rank test, $p < 0.0001$) survival advantage for women employed between 1948 and 1958 at Mayak PA. The data in Table 2 and preliminary data analyses (not shown) suggest that these findings are not simply a function of the smaller median dose received by women or the differential distribution of women in the primary diagnostic categories (23, 24). Given these findings, one suspects that lifestyle factors may contribute substantially to our ability to explain differential gender-specific survival rates among the early cohort of workers at Mayak PA, although some gender response differences to stress have been suggested (25).

In terms of general considerations regarding statistical power, it should be recalled that our series of plutonium pneumosclerosis (PPn) and acute radiation syndrome (ARS) cases are comprehensive and represent the total population of Mayak workers given these primary diagnoses. Hence, these diagnosis-specific analyses could not be improved through additional sampling. The chronic radiation sickness (CRS) and no "radiation-related disease" cases represent our two largest samples of Mayak workers; however, they also show the lowest comparative death rates (see Figure 2a), which are critical for these analyses. Given this situation, we could not provide detailed analyses of mortality patterns at a level below these larger categories.

E.2. Gender and Prior Radiation Exposure:

Effects of prior radiation exposure on the acute radiation syndrome (ARS) is another area of concern. Previous work under NIOSH grant #RO1-CCR312952 was described in Section B.2. However, the essential results of this work are vulnerable to the effects of at least two important confounding factors: (a) gender differences in the ARS cases; and, (b) chronic occupational exposures to ionizing radiation preceding the occurrence of the specific acute accident exposure. Figure 4 provides a graphical representation of the data for gender and prior cumulative exposures for the 60 ARS cases in the MWECE Database. Further analyses are needed to assess possible differences in the response of women to radiation exposure.

The impact of significant previous cumulative occupational radiation exposure on the response to an accidental high dose event is another study that this unique ARS group makes possible. Our current dosimetry suggests that the ARS cases had prior cumulative occupational exposures ranging from 0 to 716 cSv. We are concerned that these prior cumulative radiation exposures may have created a specific vulnerability to acute accidental exposures that negatively affected these patients' clinical course and outcome.

Figure 4 provides some important background to these analyses. First, it is clear that the workers with the highest accidental gamma exposures have little or no prior gamma exposures. This is due to the fact that the most serious acute exposure accidents tended to occur among the workers with the least occupational experience. Second, it is also clear that only 2 (20%) of our 10 female ARS patients had any significant ($\geq$10cSv) prior exposures, as compared to 34 (68%) of our 50 male ARS patients. It is also appears to be true that our 8 female ARS patients with little or no prior cumulative exposure received higher median accident doses (580 cSv), than the 16 male ARS patients in the same category (163 cSv). Hence, we have a very complex data set based on a reasonably small number of observations. Again, further analyses are needed for interpretation.

Similar problems arise in attempting an analysis of the effects of prior occupational exposures on the clinical course of acute accidental radiation exposures.

F. Summary of Project 2.3: Strengths and Weaknesses

F.1. Strengths:

1. These results are based on a long-term, 8 year, international collaboration by investigators who have a proven capacity to work productively together.

2. The data in the MWECE Database are unique both scientifically and historically, and are collected from a cohort of 591 Russian workers who were employed at the Mayak PA facility during the period of the highest and most prolonged internal and external exposures to ionizing radiation (see Table 2).

3. All of the medical data collected in the database has been subjected to extensive QA/QC procedures to insure its comprehensiveness and reliability compared to the source data.

4. The MWECE Database is composed of a series of true random samples from the 1948-1958 Mayak worker population which have been weighted so as to increase the sampling proportion from the most important diagnostic groups (see Table 1) – i.e., acute radiation syndrome (100% of cases), plutonium pneumosclerosis (100% of cases), chronic radiation sickness (10% of cases).

5. Women represent 38.9% of the workers in the database, including 30% of the CRS cases, 47% of the PPn cases, 17% of the ARS cases, and 49% of the workers without a radiation-related diagnosis. These women, moreover, demonstrate median internal (0.9 kBq) and external (1.8 Sv) exposure levels that are similar to men in the database and represent the largest series of occupationally exposed female workers in the literature.

6. The MWECE Database includes the most recent internal and external exposure data, together with an uncertainty analysis, available from DOE-funded Project 2.4 designed to provide state-of-the-art dosimetry for the Mayak PA worker population.

7. The MWECE Database includes a variety of lifestyle (alcohol and tobacco use) and general health indicators (BMI, blood pressure) that can be used to investigate how these factors modify the deterministic effects of internal and external radiation exposures on workers' health.

8. The MWECE Database permits the detailed comparative analysis of acute and long-term gender-specific health effects of internal and external radiation exposures.

9. Lost to follow-up rates for the MWECE database (see Table 3) are only 11% for the full 52-year follow-up period. For females, the lost to follow-up rate is only 6%.

10. The MWECE Database is the only repository of Mayak PA data that has been permitted to leave the Russian Federation.

F.2. Weaknesses:

1. The number of workers in the MWECE database is currently limited to 591 by international agreements. This number limits the statistical power of certain epidemiological analyses, the methods that can be used, and the potential specificity of the hypotheses that can be tested. In the case of the ARS and PPn groups, 100% of the Mayak cases are currently included and, therefore, further sampling would not be helpful. The CRS and baseline groups are the largest in number in the database.

2. Firm external criteria that can be used to assess independently the validity and comprehensiveness of the historical medical information contained in the SUBI and other records were not always available. For this reason, we tried to focus our attention on categories of data that were clearly of primary interest to clinicians working at SUBI during the earliest periods of operation. Our ostensible goal here was to maximize, in a prima facie manner, the expected validity and comprehensiveness of the information in the database. Consistency with source records is another issue and one for which we have been able to implement strict QA/QC procedures.

3. The Project 2.3 team did not have direct access to Mayak dosimetry and work history records for independent QA/QC purposes. However, we maintained close liaison with the DOE-sponsored project entitled JCCRER Project 2.4, Development of an Improved Dosimetry System for Workers at the Mayak Production Association. We did have to rely on that project to insure the quality of the dosimetric information in the MWECE Database.

G. Human Subjects Research:

Over the past 8 years, the collaborative research on the MWECE Database has been given exempt status by the University of Pittsburgh IRB (IRB #'970130). This action was taken under Exemption 4 which covers research involving the study of existing data, documents and records where the information is recorded by the investigator such that the subjects cannot be identified directly or through

identifiers linked to the subjects. The new data included in the MWECE Database comes primarily from SUBI clinical records and Mayak PA dosimetry files and is included in the database without personal identifiers.

The criteria for certification of exempt status were considered to be met by the University of Pittsburgh Human Experimentation Committee and the SUBI equivalent.

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Table 1: Historical Expansion of the Project 2.3 MWECE Database 1996-2001

Diagnostic Category	NRC Phase I (1996-1997)	NIOSH ARS Grant (1998-2001)	NRC Phase II (1999-2002)	% of All Workers in Category 1948-1958
Acute Radiation Syndrome (ARS)	14	60*	60*	100%
Chronic Radiation Sickness (CRS)	96	96	207	10%
Plutonium Pneumosclerosis (PPn)	13	13	115	100%
No Radiation-Related DX	98	98	209	3.5%
Total in MWECE Database	221	267	591	7.3%

- represents 100% of all ARS cases at Mayak 1948-present

Table 2: Median Internal ^{239}Pu (Bq) and External Gamma (cSv) Dose by Primary Diagnosis and Gender

Gender/DX	CRS	ARS*	PPn	No Radiation-Related Dx	Total
Male:					
number	142	50	60	94	345
Gamma	283.8	217.5	157.3	73.9	199.5
^{239}Pu	41.1	13.2	481.5	47.1	100.5
Female:					
number	63	10	53	83	209
Gamma	303.0	547.5	220.7	43.9	161.1
^{239}Pu	20.5	5.6	1239.7	8.1	50.0
Total:					
number	205	60	113	177	554
Gamma	285.9	221.1	181.3	57.9	183.3
^{239}PuTotal	31.6	13.0	594.7	19.2	89.8

*Includes accident exposure

Table 3: Vital Status and Current Contact with Workers in the MWECE

Gender/Status	Alive and In Contact with SUBI	Dead	Unknown: Lost to Follow-Up	Total
Males	113 (31.3%)	197 (54.6%)	51 (14.1%)	361 (100.0%)
Females	116 (50.4%)	100 (43.5%)	14 (6.1%)	230 (100.0%)
Total	229 (38.7%)	297 (50.3%)	65 (11.0%)	591 (100.0%)

Table 4: Internal Plutonium and External Gamma Dose to the Lung (cGy) By Diagnostic Group for Cases (n = 121) and Controls (n = 131)

Group and Diagnosis	n	Plutonium Dose to the Lungs Median (range)	n	Gamma Dose to the Lungs Median (range)
Cases:*	121	267.2 (5.6-3112.1)	121	60.4 (1.7-1325.3)
PPn Only	38	154.4 (5.6 – 1030.7)	38	36.0 (2.7 – 256.8)
PPn+CRS	82	345.3 (9.7-3112.1)	82	72.2 (1.7 – 749.0)
PPn+ARS	1	340.3 (—)	1	1325.3 (—)
Controls:*	139	8.0 (0.1-8291.8)	139	176.4 (0-530.2)
No Dx	33	8.7 (0.1 – 2860.5)	33	50.0 (0.8-299.6)
CRS Only	106	7.9 (0.2 – 8291.8)	106	208.6 (0-530.2)

*For cases, dose is cumulative from beginning of employment to onset of PPn; for controls, dose is lifetime.

Table 5: Cause of Death for PPn Cases and Controls by Median Plutonium Dose to Lung*

Underlying Cause of Death	PPn Dx n = 94 n (%)	(77.6 %) median lung dose (cGy)	Controls n = 65 n (%)	(46.8%) median lung dose (cGy)
Malignant Respiratory	35 (37.2)	441.0	5 (7.6)	49.90
Non-malignant Respiratory	9 (9.6)	767.0	2 (3.1)	3.14
Other Malignancy	28 (29.8)	613.0	10 (15.4)	7.63
Circulatory	14 (14.9)	130.3	38 (58.5)	13.40
Other COD	8 (8.5)	235.0	10 (15.4)	18.00

*X^2 (4df) = 37.5 $p<0.001$

Table 6: Mean Length of Life of Pn Patients by Lung Dose (cGy)

Pu Lung Dose Quartile	Mean Yrs of Life (se)
1	68.4 (1.9)
2	61.8 (2.2)
3	58.3 (1.5)
4	54.3 (1.5)

ANOVA $p<0.001$

FIGURES:

Figure 1
MWECE Database Structure 1/1/2002

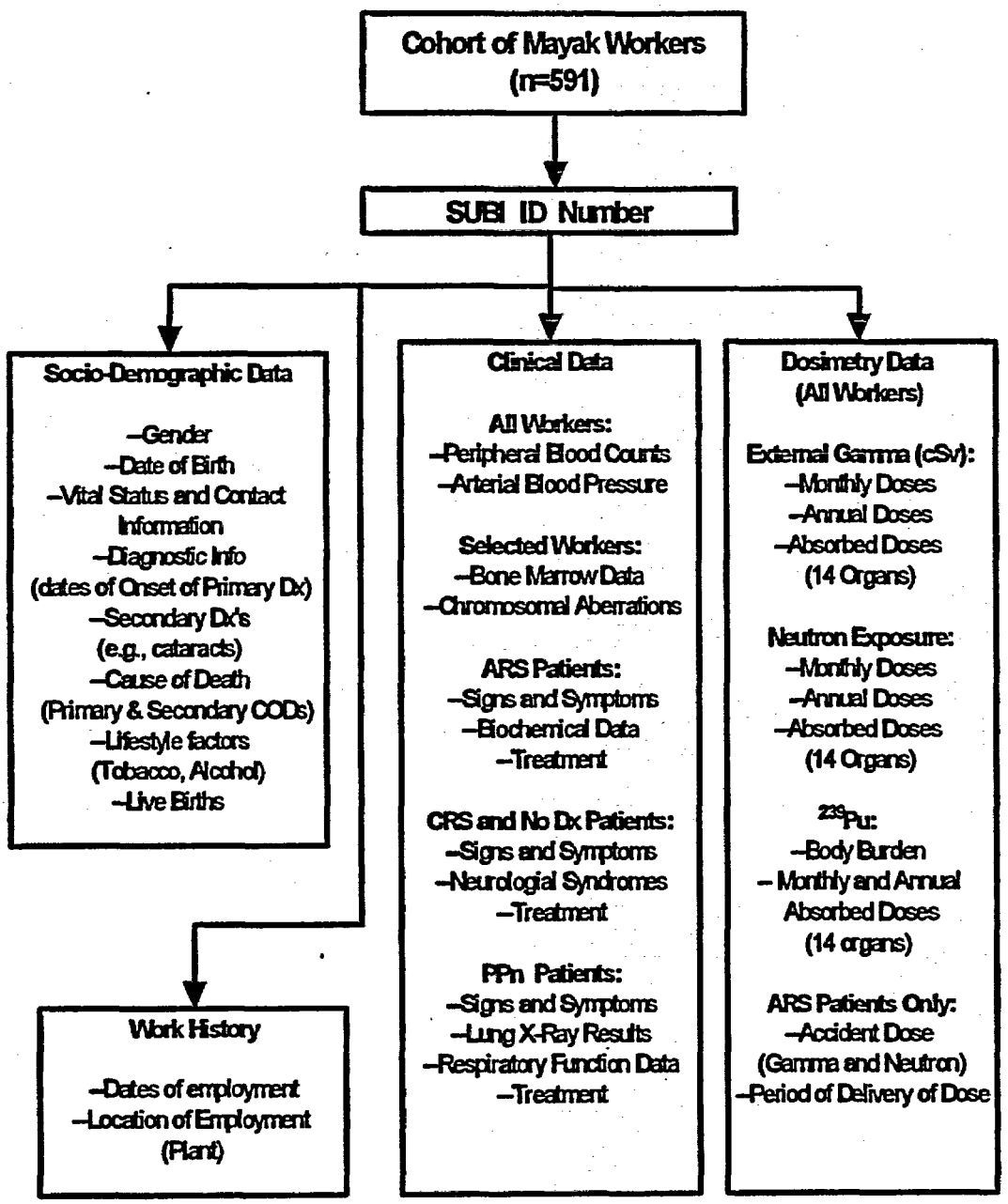


Figure 2: Kaplan-Meier Plots of Survival Probabilities by Primary Diagnosis and Years Since Beginning Work at Mayak PA

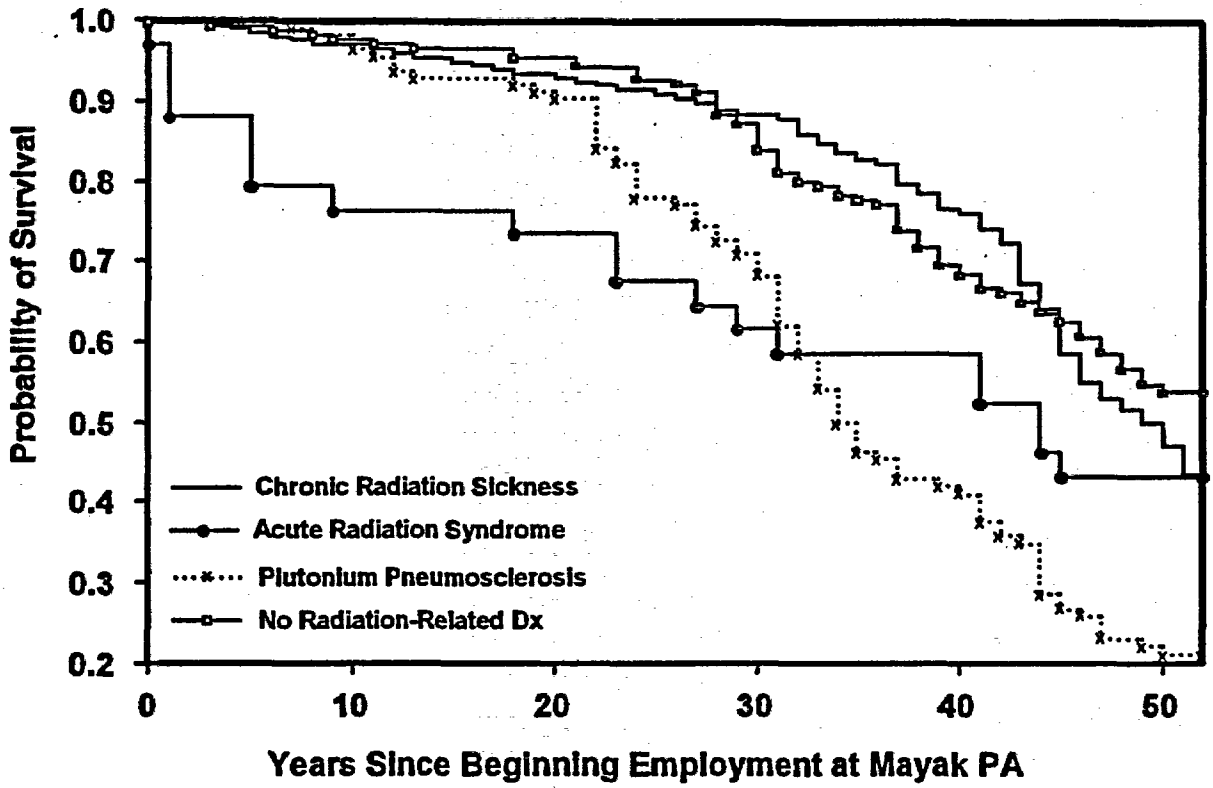


Figure 3: Kaplan-Meier Plots of Survival Probabilities by Gender and Years Since Beginning Work at Mayak PA

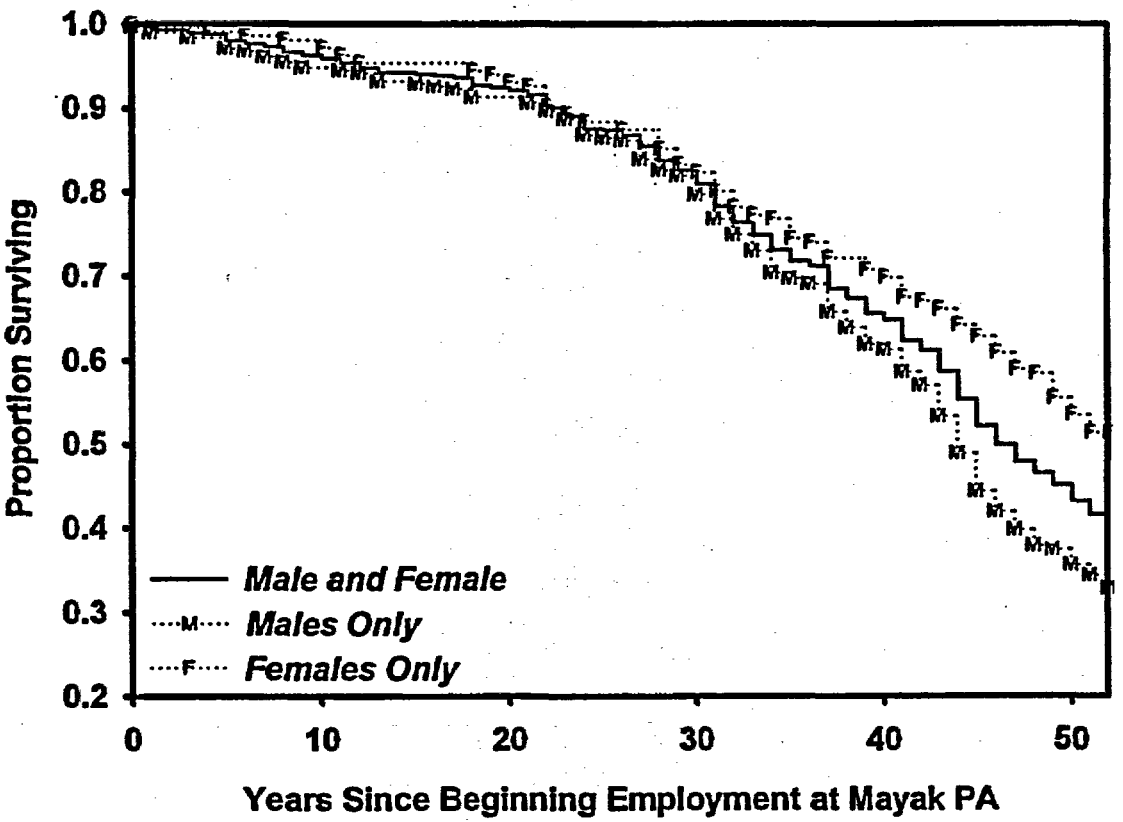


Figure 4: Scatter Plot for Acute Radiation Syndrome Cases Prior Cumulative Gamma Dose by Accident Dose, By Gender

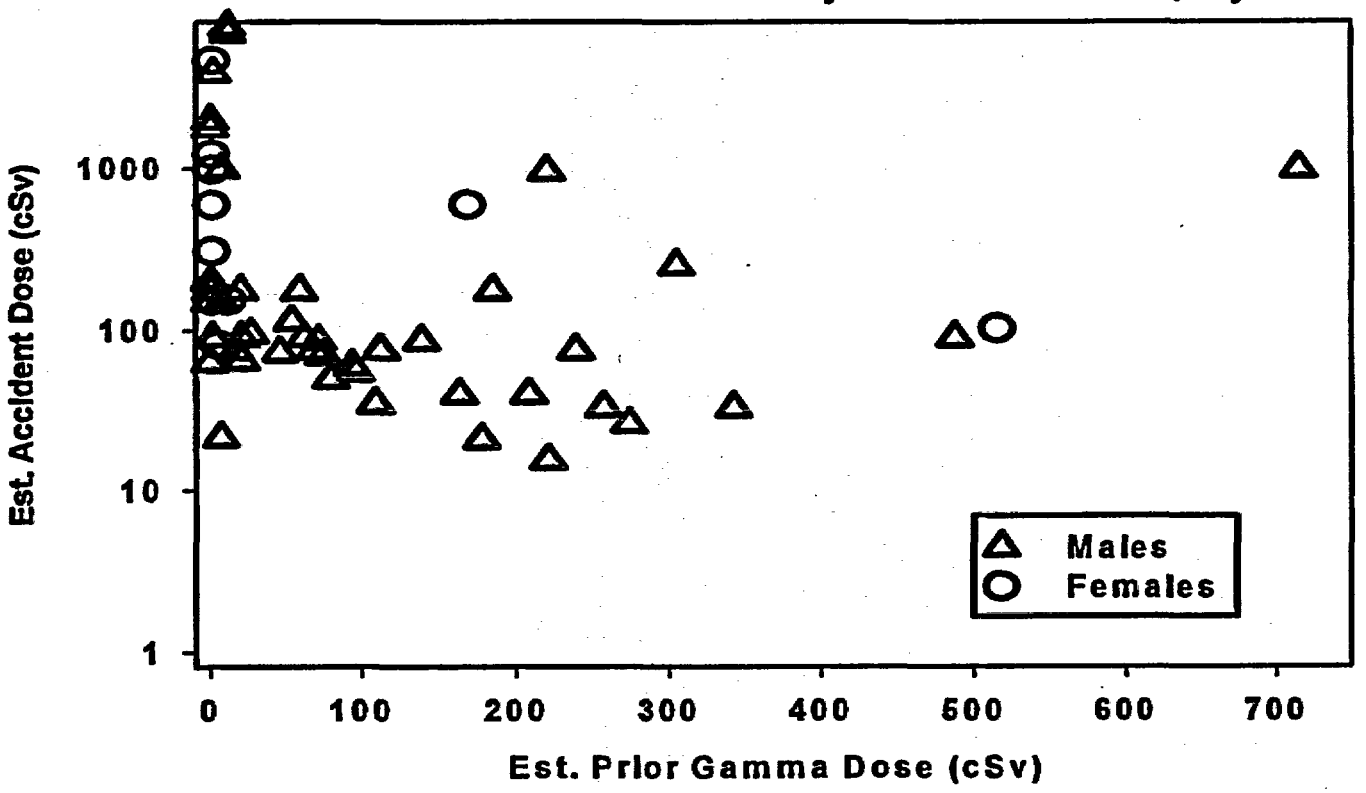


Figure 5. Distribution density by absorbed dose for CRS and uninjured workers

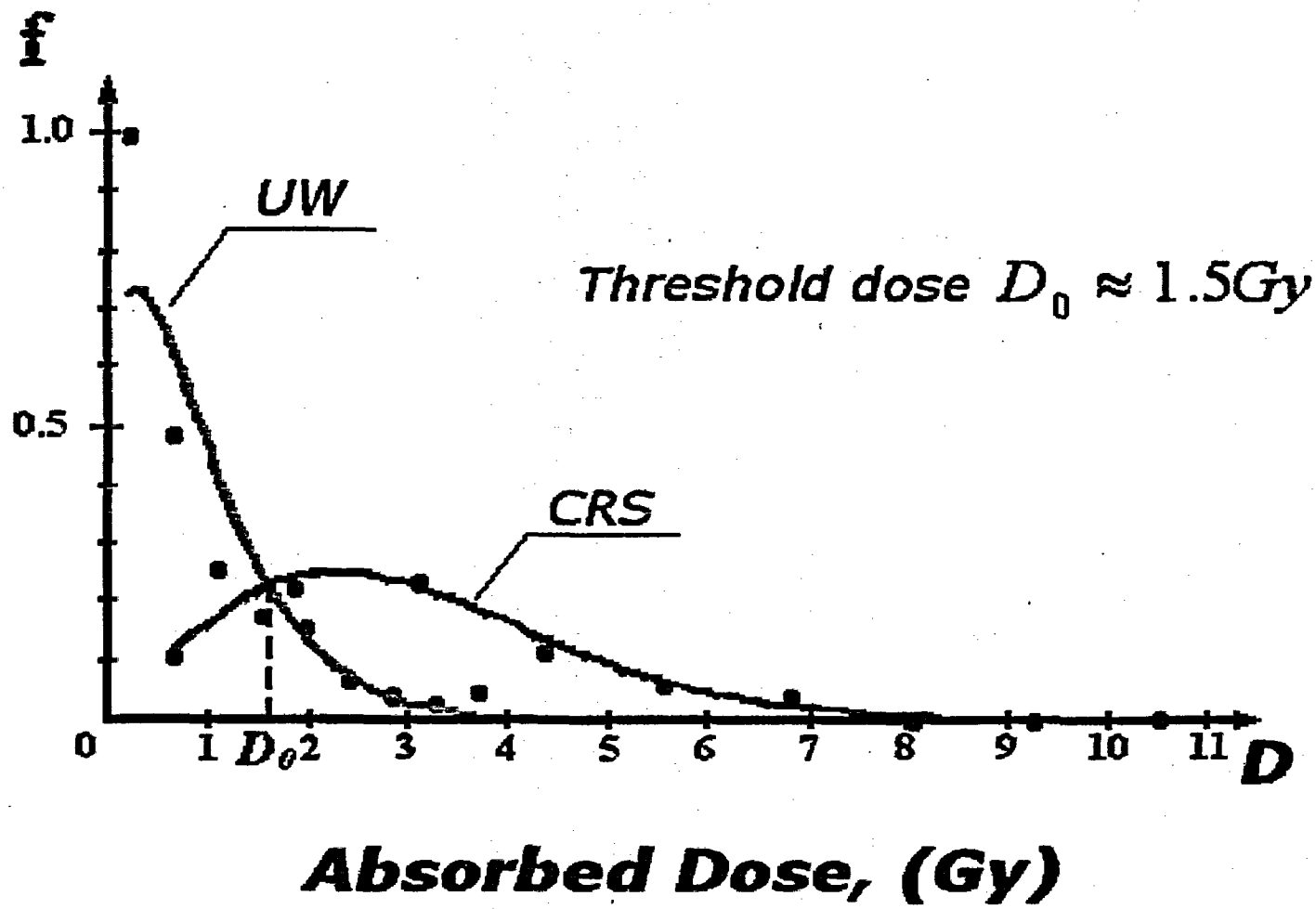
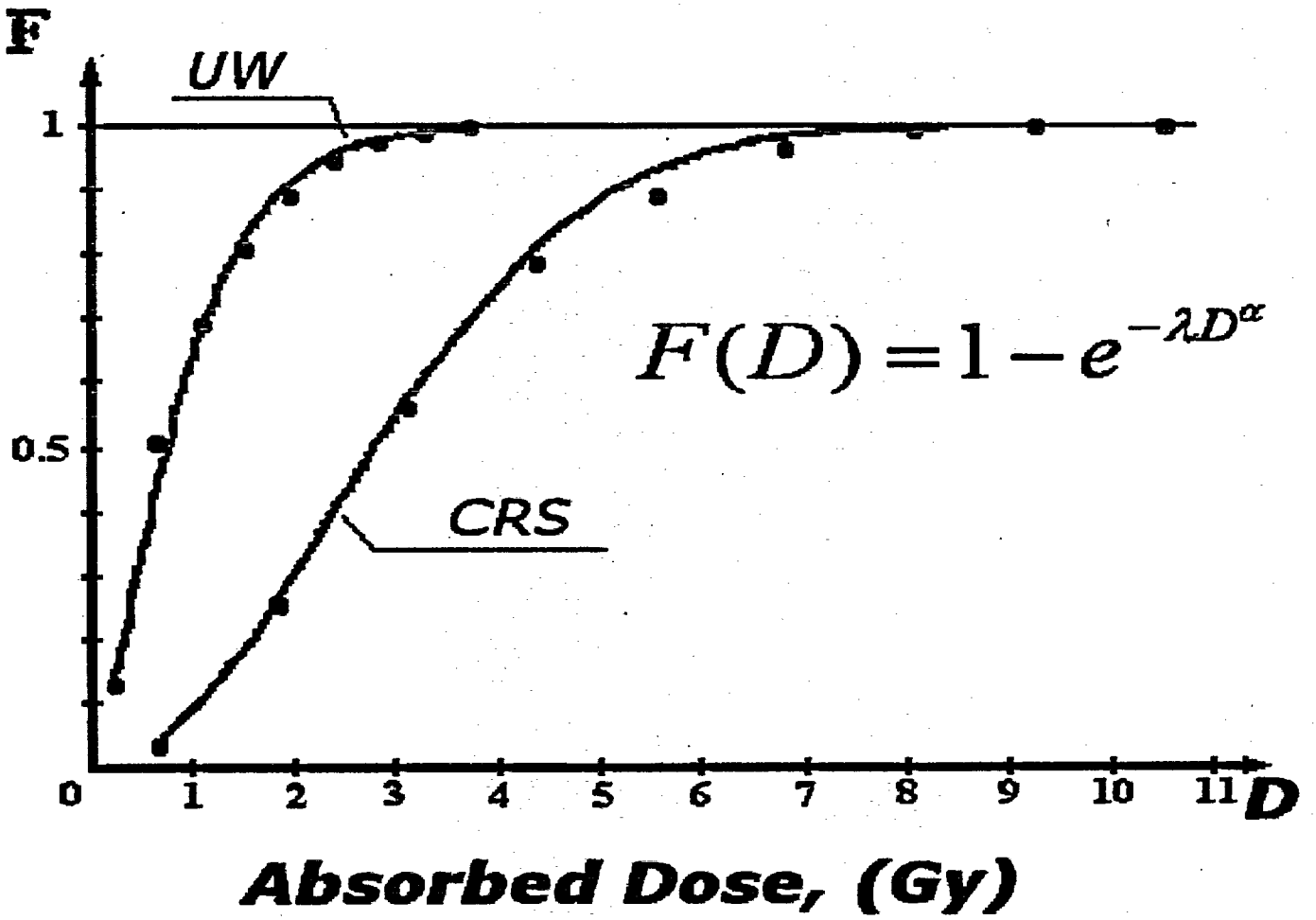


Figure 6. Cumulative Integral distribution by absorbed dose for CRS and uninjured workers



K.1. Binational Agreements Controlling MCEWE Database Use

Data Access Agreement for Work to be performed by Organizations of the MINZDRAV (Russian Ministry of Health; Federal Department for Medical, Biological and Extreme Problems) and MINTOM (Russian Ministry of Atomic Energy) under the agreement between the Government of the Russian Federation and the government of the United States of America on Cooperation in Research on Radiation Effects for the purpose of Minimizing the consequences of Radioactive Contamination on Health and the Environment (JCCRER Agreement).

This agreement incorporates the provision developed at the meeting of the Executive Committee of the Joint Coordinating Committee on Radiation Effects Research (JCCRER), Moscow, January 21-22, 1998 as follows:

INTRODUCTION

The purpose of this data access agreement is to ensure that Russian and American scientists working on projects under the Agreement between the Government of the Russian Federation and the Government of the United States of America on Cooperation in Research on Radiation Effects for the Purpose of Minimizing the consequences of Radioactive Contamination on Health and the Environment (JCCRER Agreement) have equal access to all primary and original Russian and American data necessary to conduct the work described under Directions 1 and 2 of the JCCRER Agreement. Such access will ensure the highest quality of scientific research conducted in an atmosphere of mutual trust and cooperation.

General Provisions

1. **For the purpose of this agreement of data access, data is defined as all information, in whatever format or media, that is identified by the Principal Investigators and Directors of Participating Institutes as necessary to carry out the project.**

2. **Privacy statutes in Russia and the United States generally restrict access to data which includes personal identifiers. Individual data, however, is the basis of much of the research work of the JCCRER. Therefore, where necessary adherence to these statutes will be ensured by substituting unique numerical identifiers which project individual privacy while allowing analysis of individual and aggregate data.**

3. **Data covered by this access agreement include original or raw data, compiled data created before these projects were begun, and second generation or summarized data and information compiled according to project requirements.**
   The specific project agreement provisions will specify the actual data which fall under each of these categories. Appropriate access to all these data must be ensured; however, original or raw data, and compiled data created before these projects were begun remain the property of that organization and that country where the data were obtained and are currently maintained.

4. **Secondary data created as part of JCCRER projects, which are a joint scientific product, will be jointly owned by the Russian and the American institutions participating in the project. Each project will determine what is a scientific product of the collaboration and therefore subject to joint ownership.**

5. Project participants have the right to appropriate access to original, compiled and secondary data on the territory of the organization which owns and maintains the data.

6. The specific project agreement provisions will identify the kind and extent of unpublished primary, compiled and secondary data that may be transferred out of the country of ownership to achieve specific project goals such as technical analyses, modeling, etc. at the home institution of researchers. When such data transfers occur, they must also be approved in writing by the Director of the institute or organization to which the data belong. Transferred data cannot be used for purposes other that those specified by the agreement, even after the project is completed or the researcher is no longer associated with the JCCRER. In cases where such data are transferred to people who are not participants in the project for the purposes of furthering the project, the same conditions and limitations of use of data apply. Such transfers will be carefully scrutinized.

7. No transfers, publications, presentations, press releases or any other form of communication to the outside world regarding details of the unpublished data or the unpublished results of studies conducted under the authority of the JCCRER will be made without the written consent, and participation of the institutions maintaining the data sets and the scientists involved in the research. Any agreement to make data publicly available must be approved by the Directors of the organization performing the research. Scientists and specialists participating as current members of the JCCRER Joint Committee, Executive Committee and Scientific Review Groups have a right to review data and unpublished results of studies as appropriate to their responsibilities but are similarly bound by the restrictions on communication as described in this paragraph.

8. Dissemination of scientific results, in the form of presentation at scientific meetings and publication in refereed journals, is regarded as an essential product of the JCCRER work. To ensure that such communications take place while complying with the requirements of the participating institutions and funding agencies, procedures will be developed for the expeditious review and approval of such communication requests from the principal investigators.

9. Data published in the open, peer-reviewed literature shall be referenced and used according to generally understood and accepted conventions or scientific conduct; it is expected that proper reference and credit to the origin of the published material will be made.

10. After the publication of reports, third parties may request access to unpublished study data that does not contain individual identifiers in order to conduct independent analyses. Third parties are defined as experts in the fields of radiation health effects and dosimetry who are not part of any JCCRER project. Procedures will be developed for requesting and approving such third party access to primary data.

SPECIFIC PROVISIONS

Introduction: Project 2.3, "Deterministic effects of occupational exposure" involves clinical and dosimetric data on a randomly selected sample of at least 600 Mayak PA workers employed for at least one month between the years of 1948 and 1958. Project 2.3 has the following purposes:

a. Improved estimates of the human dose thresholds and dose-response relationships for the deterministic effects of acute and prolonged exposure to ionizing radiation;
b. 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;
c. The clinical description and initial dose-response modeling of possible radiation-related deterministic effects in human begins (e.g., Plutonium Pneumosclerosis, chronic radiation sickness that has not been encountered by western scientists and physicians.

I. In the present Agreement the expression "data" concerns the information in any format and in any medium and includes the following:
   1.) Primary Data:
      a) Original written clinical records maintained at and owned by FIB-1.
      b) Original written dosimetry records maintained at and owned by Mayak, PA.
      c) Original written demographic data maintained and owned by the Ozyorsk City Administration.
   2.) Compiled Data, collected prior to the beginning the present project; Clinical, dosimetric and demographic databases in any format or medium, created by the scientists and administrators up to the beginning of the Project 2.3, containing the information, received from the original written documents, described in Items I.1. These databases and the information supported in them are the exclusive property of FIB-1, PA Mayak and Ozyorsk City Administrations accordingly.
   3.) The secondary data includes the clinical, dosimetric and demographic data sets developed from the primary data and the analyses performed on them. The secondary data, created within the framework of the project 2.3, are the joint scientific product and represent the joint property of organizations participating in Project 2.3 from Russia and America: FIB-1, PA Mayak, the University of Pittsburgh. In case of the statement of the altered or new models they will be available to, in equal degree, Russian and American partners

II. Russian and American participants of Project 2.3 have the right of access to primary clinical, dosimetric and demographic data necessary for the fulfillment of the research problems on the territory of organizations owning these data.

III. To achieve the purposes of the project, the perfection of the existing models of the deterministic effects, the American scientists engaged in the project can be given unpublished primary, compiled and secondary data with the right of export from RF, the country of the owner. The transfer of such data requires the written approval of the director FIB-I and the director or their designees of Mayak. The transferred data cannot be used for other purposes except those which are determined by Project 2.3 and the Data Access Agreement of Project 2.3. This applies even after the Project is completed or the participants no longer work under the aegis of the JCCRER.

IV. Any transfers, publications, presentations, press conference or any other forms of promulgation of details of unpublished secondary data or unpublished results of research on Project 2.3, performed under the aegis of the JCCRER cannot be used without the written consent of participating organizations and researchers on this work. Such consent will not be unreasonably withheld, (for example, more than 180 days), by the parties to this agreement. Any arrangement about the promulgation of data should be authorized by the directors of organizations carrying out research (FIB-1 and PA Mayak, and the University of Pittsburgh working on Project 2.3). Scientists and specialists

participating as current members of the JCCRER, Joint committee, Executive Committee and Scientific Review Groups have a right to review data and unpublished results of studies as appropriate to their responsibilities but are similarly bound by the restrictions on communications as described in this paragraph.

V. The rights on the intellectual property will be protected in the conformity with the laws of the RF and the USA, and also on the Data Access Agreement between the governments of RF and the USA concerning cooperation in research on radiation effects with the purpose of minimization of health effect consequences of the radiation contamination of the environment.

K.2. Project 2.3 MWECE Code Book, Version 2.0, in 3 Parts.

K.3. Presentation of Dr. Tamara Azizova on: Acute Radiation Syndrome Among Nuclear Workers of Mayak Production Association*

Acute Radiation Syndrome Among Nuclear Workers of Mayak Production Association*

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Abstract

Radiation accidents (e.g. at Chernobyl, in Guyana, and in Tokai-mura) have led to exposure of humans (nuclear workers and the public) to large radiation doses. Now it is recognized that there are nuclear terrorism threats to humans from individuals and organizations committed to carrying out such acts. In order to make better predictions of radiation risks and to minimize the consequences to society of nuclear accidents and nuclear terrorist incidents, it is important to make full use of currently available data on radiation effects in humans. Research results to be reported in this presentation relate to data about the acute radiation syndrome (ARS) among Mayak Production Association (MPA) workers exposed to external gamma rays and neutrons. The MPA was the first Russian nuclear enterprise (established for producing plutonium). The MPA workers were exposed to a wide range of radiation doses and there has been a long-term follow-up (50 years) of the workers including detailed clinical and dosimetry information. During 1948-1958, there were 19 accidents at MPA resulting in 59 cases of the ARS registered for 49 males and 10 females as follows: 8 individuals with degree IV of the ARS (most severe); 6 individuals with degree III (severe); 9 individuals with degree II (moderate); 36 individuals with degree I (mild). This presentation will include a clinical description of all ARS cases (diagnostics and treatment, classification by degree of severity, ARS consequences, and results of long-term follow-up for survivors).

*Research funded primarily by U.S. Nuclear Regulatory Commission Contract 04-98040 with additional funding from U.S. National Institute of Occupational Safety and Health Grant 01- RO1-CCR312952.

Radiation accidents (e.g. at Chernobyl, in Guyana, and in Tokai-mura) have led to exposure of humans (nuclear workers and the public) to large radiation doses. Now it is recognized that there are nuclear terrorism threats to humans from individuals and organizations committed to carrying out such acts. In order to make better predictions of radiation risks and to minimize the consequences to societies of nuclear accidents and nuclear terrorist incidents, it is important to make full use of currently available data on radiation effects in humans. The purpose of this presentation is to share with you results of clinical follow-up for 59 workers of "Mayak" nuclear enterprise with acute radiation syndrome (ARS).

"Mayak" Production Association was the first Russian nuclear facility located in Southern Urals. It was commissioned in June 1948. "Mayak" facility consists of the weapons-grade plutonium

production plants: industrial reactors, radiochemical plant and plutonium production plant. During the first years of "Mayak" operation, most of workers were significantly exposed to chronic radiation from γ-rays and internal radiation from incorporated ^{239}Pu due to the lack of experience in maintenance of nuclear technologies and the short time allowed by the Soviet Government to initiate nuclear weapon production. At that time, i.e. more than 40 years ago, several radiation accidents occurred. Involved individuals experienced a single exposure to intense radiation that resulted in the development of ARS (Table 1).

All 59 patients with ARS were cared for in a specialized hospital, where medical diagnostic aid is still provided for "Mayak" nuclear workers. The clinical pattern of acute radiation syndrome is presented by different degrees of severity. Distribution of the patients by degrees of ARS severity is shown in Table 2.

In retrospective analyses of clinical data, a group with a "latent" clinical pattern was distinguished from the group of patients with a mild degree of ARS severity. Involvement of the former individuals in a known radiation accident was the indicator for their detailed medical examinations, which led to accumulation of a complex of inconsistent slight deviations from "normal, probably secondary to the nonspecific stress of their accident involvement. We have identified this group symbolically as having a "latent" type of ARS.

Thus, the analysis of clinical cases was carried out for 5 groups of individuals exposed to acute radiation. Table 3 presents doses of the accidental acute exposure. It is necessary to point out that the ARS that developed was for most workers superimposed on the background of past chronic occupational radiation exposure (Table 4).

There are several stages in the clinical pattern of ARS: a prodromal phase (primary response), a latent phase, a critical phase and a recovery phase. Clinical indicators of acute exposure during the first hours, i.e. in the prodromal phase, include nausea, vomiting, headache, and fatigue.

The pattern of blood counts for our patients during first 38 days after exposure is illustrated in the figures 1 – 10. Here one can see: leukocytosis in the first 24 hours after exposure (by neutrophils); 2) lymphopenia by the 2 - 3rd day; 3) leukopenia on the 4 - 9th day; 4) thrombocytopenia over the 1-3rd week. Lymphopenia on the 2-3rd day and time of granulocytopenia occurrence are prognostic characteristics that correlate with exposure dose and injury severity.

In this series, 7 individuals died (Table 5). Surviving patients (except for 6 individuals) were consistently observed in our hospital. Almost all patients showed a recovery of peripheral blood counts. During the recovery period their peripheral blood counts were within normal limits.

Results of limited bone marrow studies indicated only a moderate decrease of granulocytopoietic cells in bone marrow in 2 cases with ARS of the mild and moderate degrees of severity.

In addition, qualitative post-radiation findings at the subcellular level included normal bone marrow cellularity, normal ratio of the main hematopoietic stems and recovery of morphological composition in peripheral blood counts in the late stage of ARS. Chromosome analyses of lymphocytes in peripheral blood indicated an excess level of cells with chromosome aberrations and structural failures per 100 analyzed cells (Table6). The prognostic significance of the genome damage revealed for our patients is unclear as yet.

Radiation cataract was diagnosed for 5 patients exposed to doses from 4.0 to 9.8 Sv. The time of its forming was 2.5 – 9 years. Clinical analyses did not reveal any other peculiarities in the occurence and progression of somatic diseases in these patients.

At present, we know about survival in 53 of the 59ARS patients, of which 19 (35.8%) have died (Table 7). I would like to emphasize that in 1950s – 1960s physicians did not have the current up-to-date medicines to treat ARS. However, the knowledge of radiation injury mechanisms and experience in general therapy and hematology provided a successful recovery for patients with ARS not only of a moderate degree but also a severe ARS (exposure doses, 7.13-9.98 Sv).

In closing, it is evident that Russian scientists and physicians already had experience in the diagnostics, treatment and successful rehabilitation of ARS patients in the 1960s. Unfortunately, for a long time this experience remained classified and could not be published in the open scientific literature. During the recent years after declassification of our material, we have collected all primary and dosimetry data on a group of individuals with ARS and established a computer database (MCEWE) with financial support from the USNRC and NIOSH, in collaboration with colleagues from the University of Pittsburgh and Lovelace Respiratory Research Institute. A detailed publication analyzing these data is in preparation.

Our tasks for the future include the utilization of this database:

- To test current ARS prognostic models;
- To assess the influence of previous high chronic exposure on the ARS process; and
- To explore the effects of gender on the clinical response to acute radiation overexposure.

Tables:

Table 1. Distribution of accidents by years

Year of accident	Number of accidents	ARS cases
1950	3	3
1951	3	8
1952	3	4
1953	5	23
1954	1	1
1955	2	5
1957	1	11
1958	1	4
Total	19	59

Table 2. Distribution of ARS patients by a degree of severity

ARS severity degree	Males	Females	Total
IV. Most severe	6	2	8
III. Severe	4	1	5
II. Moderate	7	2	9
I. Mild	21	2	23
O. "Latent" form	11	3	14
Total	49	10	59

Table 3. Mean dose from external exposure during the accident (Sv)

Severity degrees	Males	Females
IV. Most severe	57,5 ± 19,4	29,08 ± 14,81
III. Severe	6,15 ± 1,32	12,01
II. Moderate	2,33 ± 0,79	5,80 ± 1,25
I. Mild	1,45 ± 0,20	2,00 ± 0,78
O. "Latent" form	0,85 ± 0,09	0,96 ± 0,09

Table 4. Mean dose from chronic exposure to γ-rays received prior to the accident

ARS severity degrees	Past-exposure	
	Males	Females
IV. Most severe	0,04 ± 0,01	0,0 ± 0,00
III. Severe	2,34 ± 3,12	0,0 ± 0,00
II. Moderate	1,30 ± 0, 97	0,83 ± 0,16
I. Mild	0,79 ± 0,28	2,57 ± 0,74
O. "Latent" form	0,70 ± 0,14	0,05 ± 0,01

Table 5. ARS Deaths

ID number	Date of accident	Dose, Sv	Day of death
4611	1951	2,50	34
687	1953	18,00	11
7483	1953	20,00	12
9685	1957	46,03	12
2119	1958	69,50	6
25864	1958	30,20	9
53992	1958	76,30	7

Table 6. Chromosome aberrations in the late period of Acute Radiation Syndrome

ARS severity degree	Number of individuals	Number of analyzed metaphases	% Cells with chromosome aberrations	Number of chromosome aberrations per 100 cells
IV. Severe	2	1300	20.3	44.0
III. Moderate	2	800	4,7	7,2
II. Mild	9	2200	2,1	2,59

Table 7. Causes of death

Cause of death	Number of Individuals	%
Acute Radiation Syndrome	7	36,8
Circulatory diseases	5	26,3
Neoplasms	4	21,0
Digestive diseases	1	5,3
Injuries and poisoning	1	5,3
Unknown	1	5,3
Total	19	100

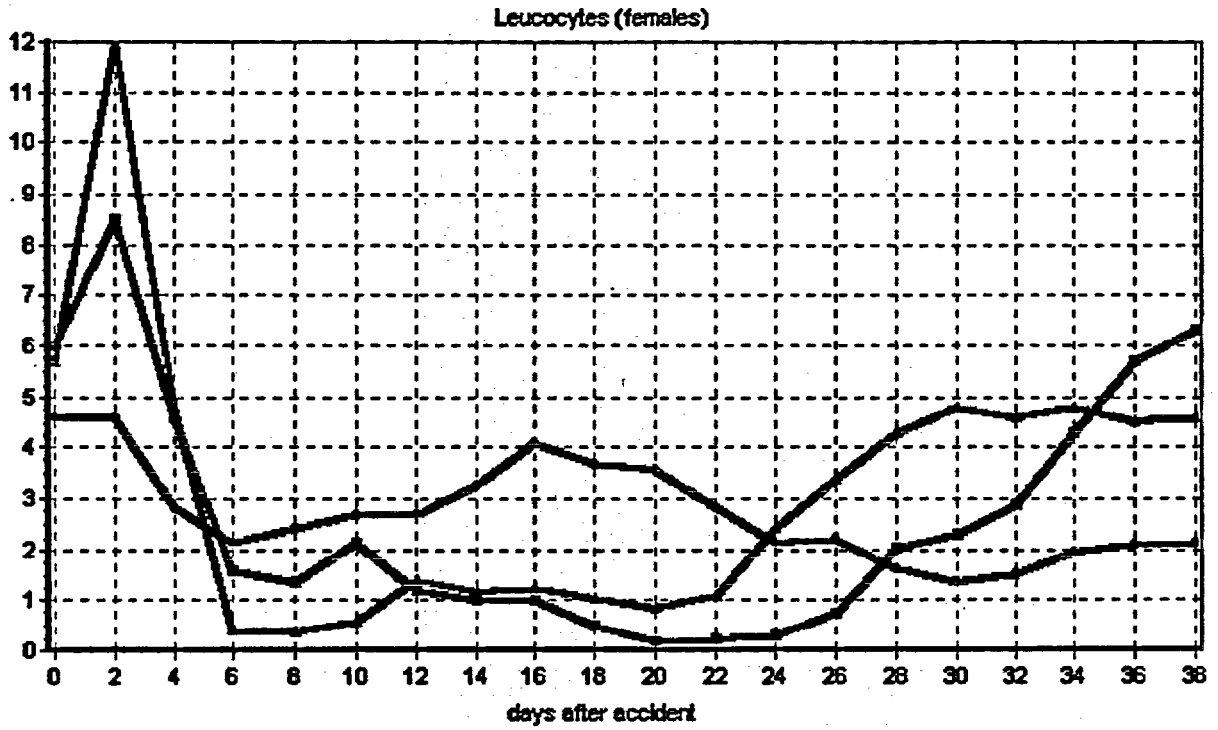

Fig. 1 Pattern of leucocyte counts in female patients with ARS of different severity (IV – green line, III – blue line, II – red line)

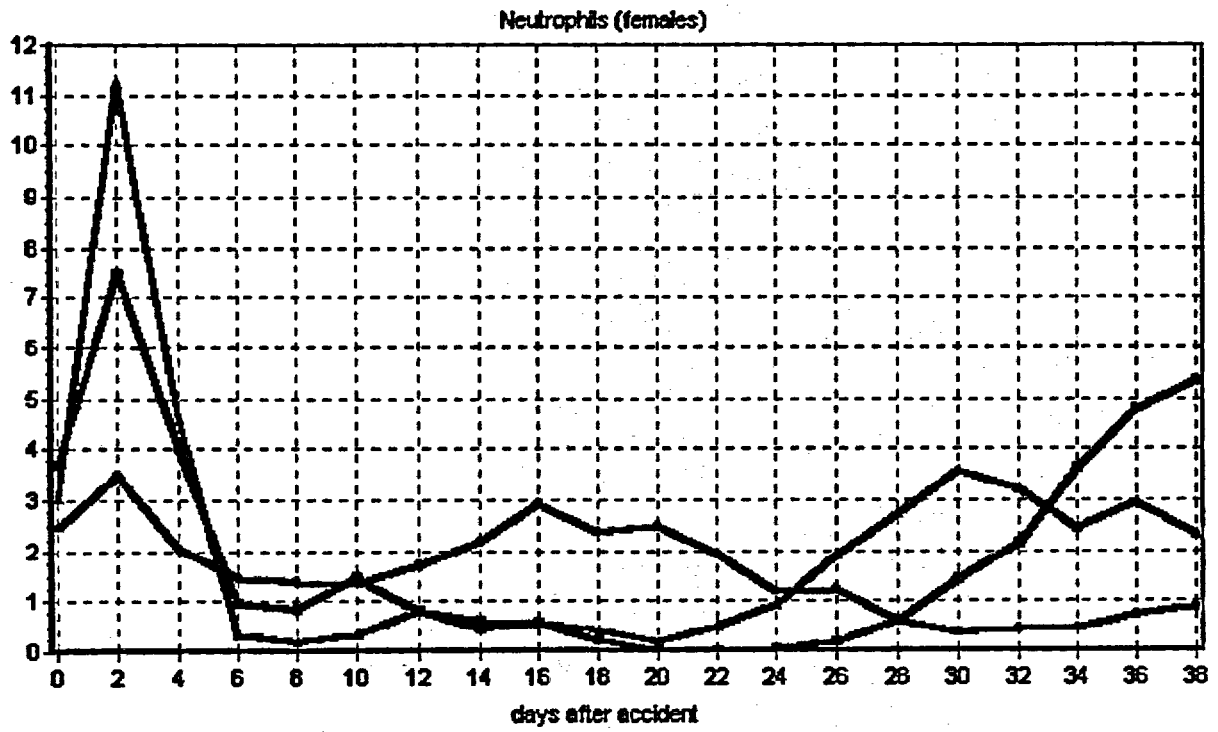

Fig.2. Pattern of neutrophils in female patients with ARS of different severity (IV – green line, III – blue line, II – red line)

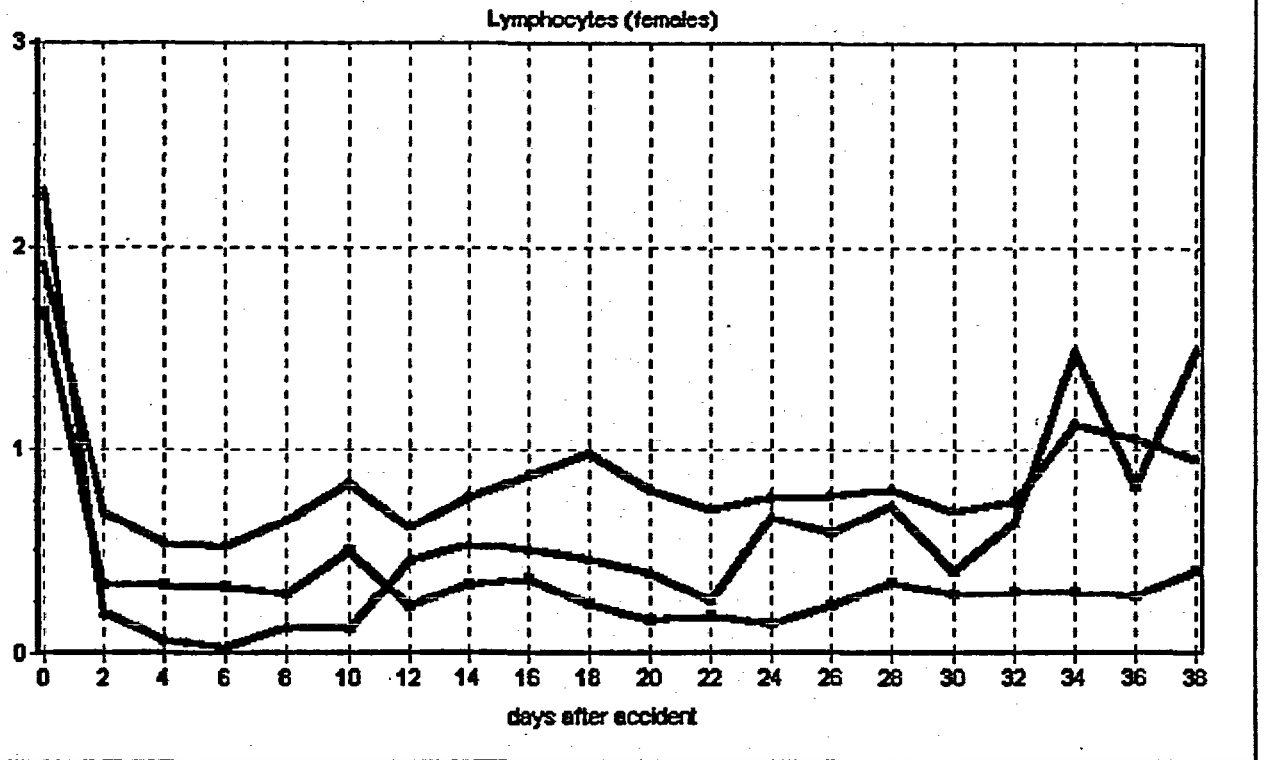

Fig.3. Pattern of lymphocyte counts for female patients with ARS of different severity (IV – green line, III – blue line, II – red line)

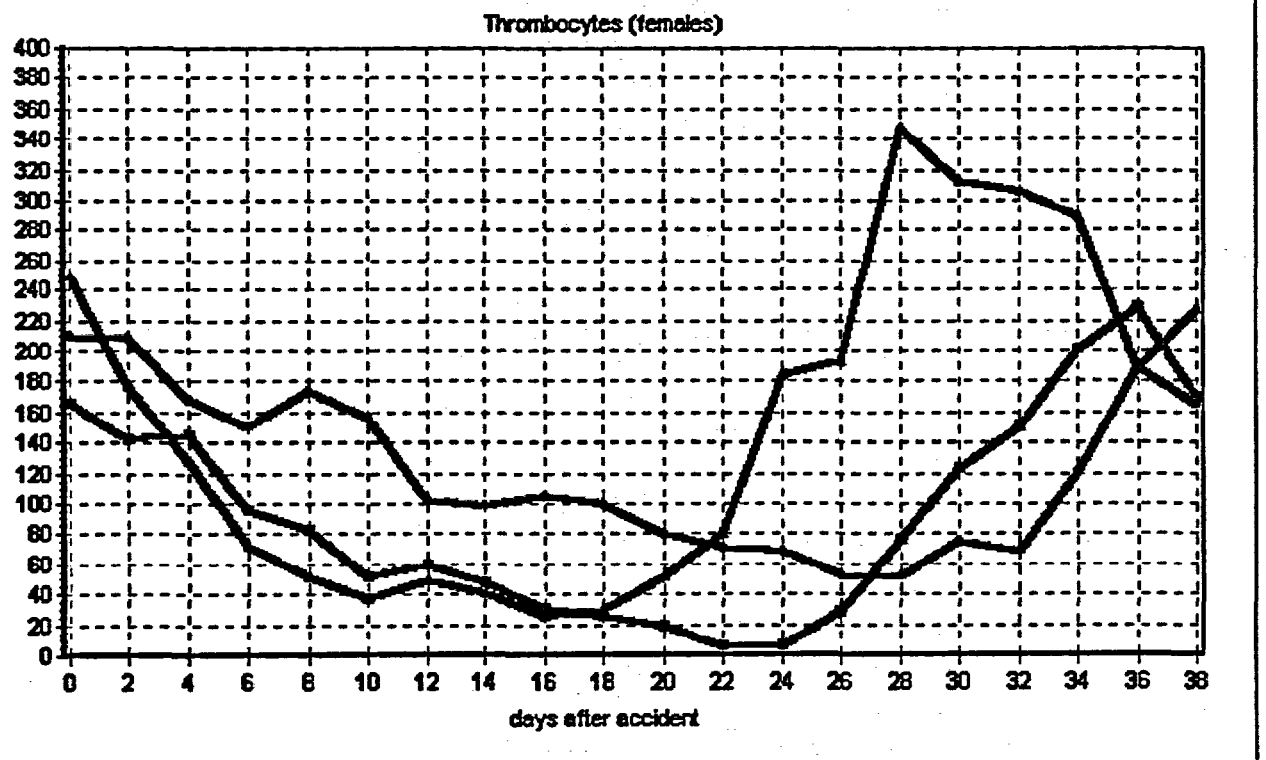

Fig. 4. Pattern of thrombocyte counts for female patients with ARS of different severity (IV – green line, III – blue line, II – red line)

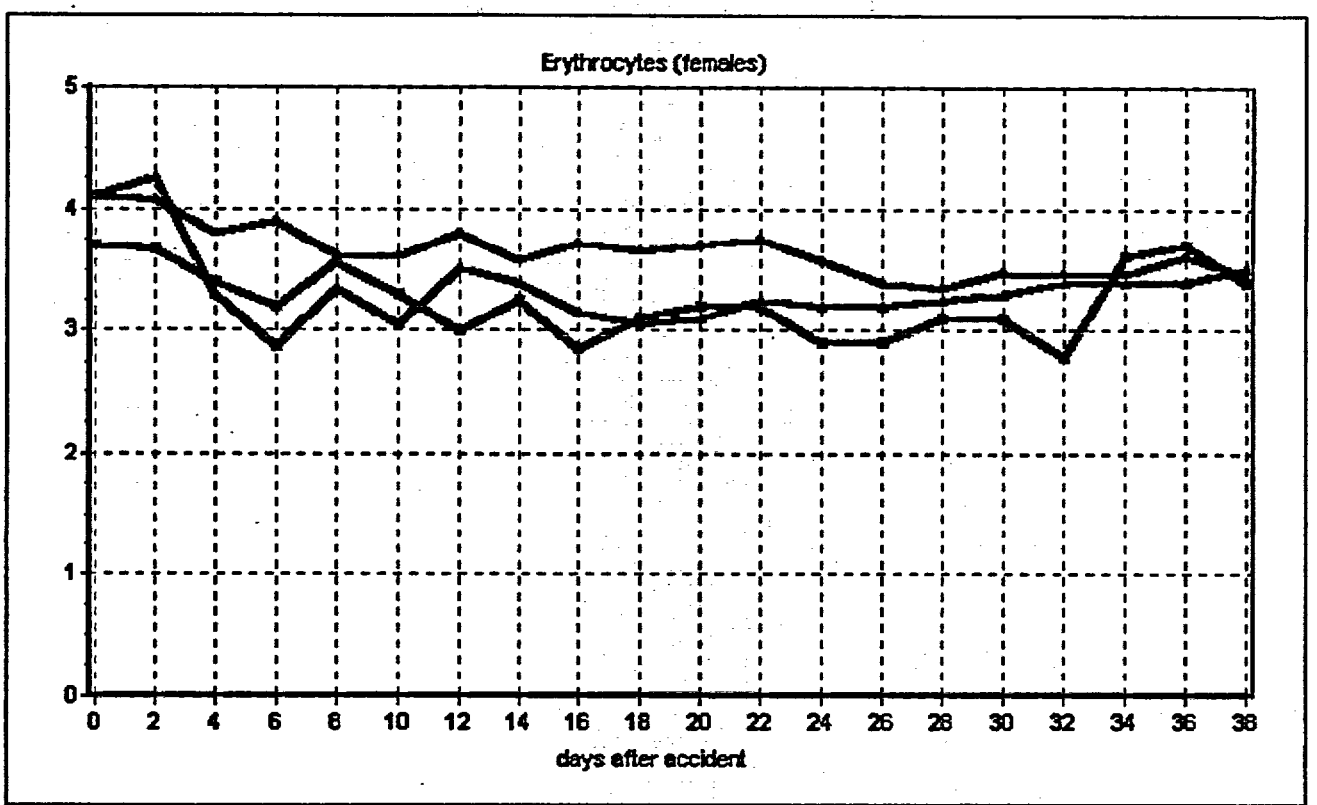

Fig.5. Pattern of erythrocyte counts for female patients with ARS of different severity (IV – green line, III – blue line, II – red line)

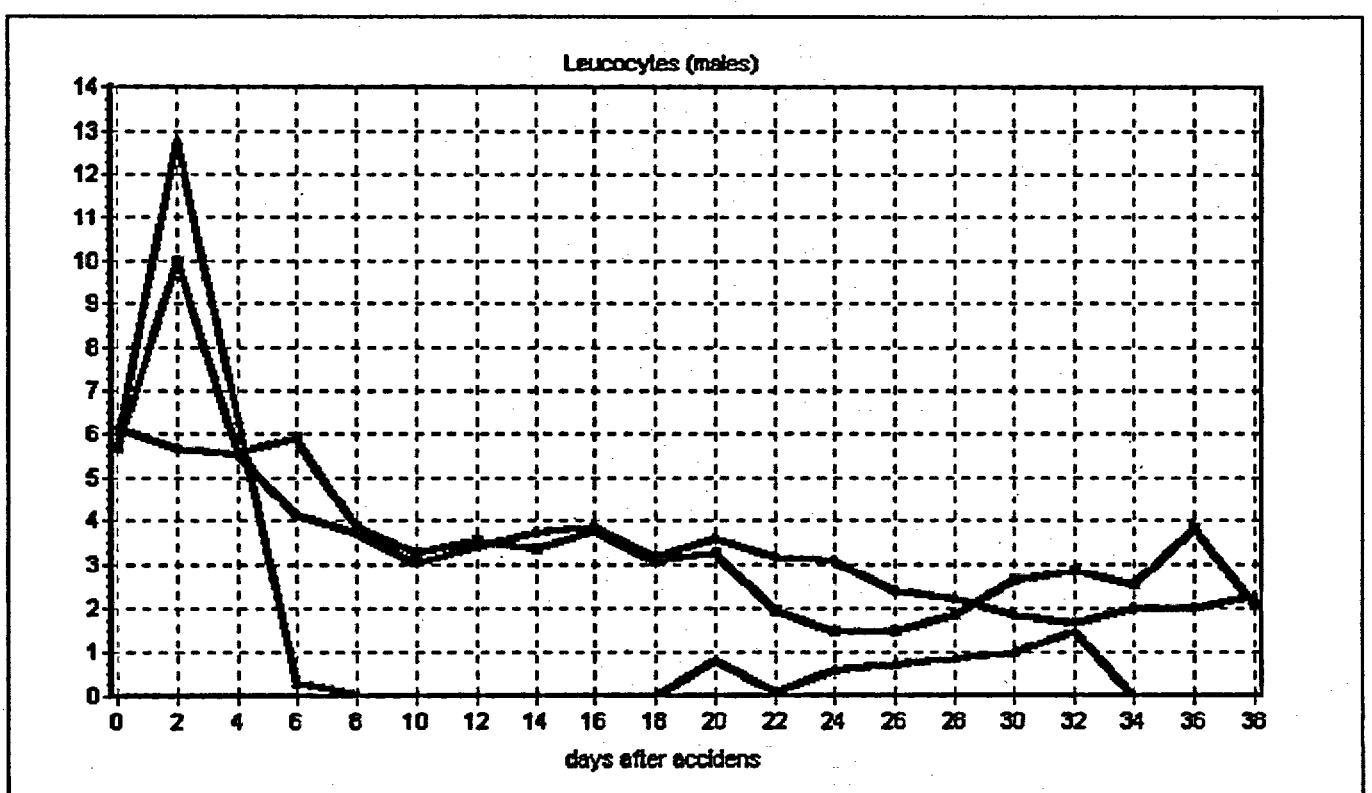

Fig. 6. Pattern of leucocyte counts for male patients with ARS of different severity (IV – green line, III – blue line, II – red line)

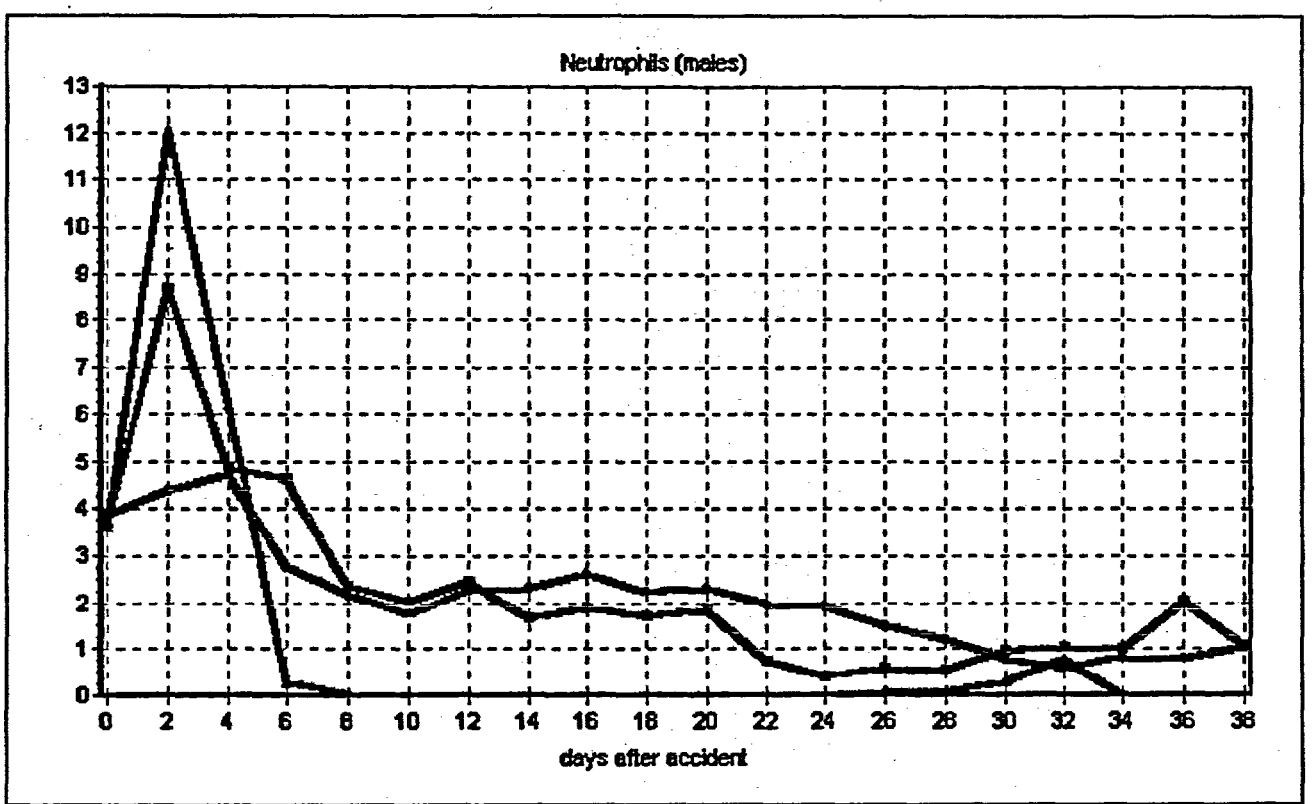

Fig. 7. Pattern of neutrophil counts for male patients with ARS of different severity (IV – green line, III – blue line, II – red line)

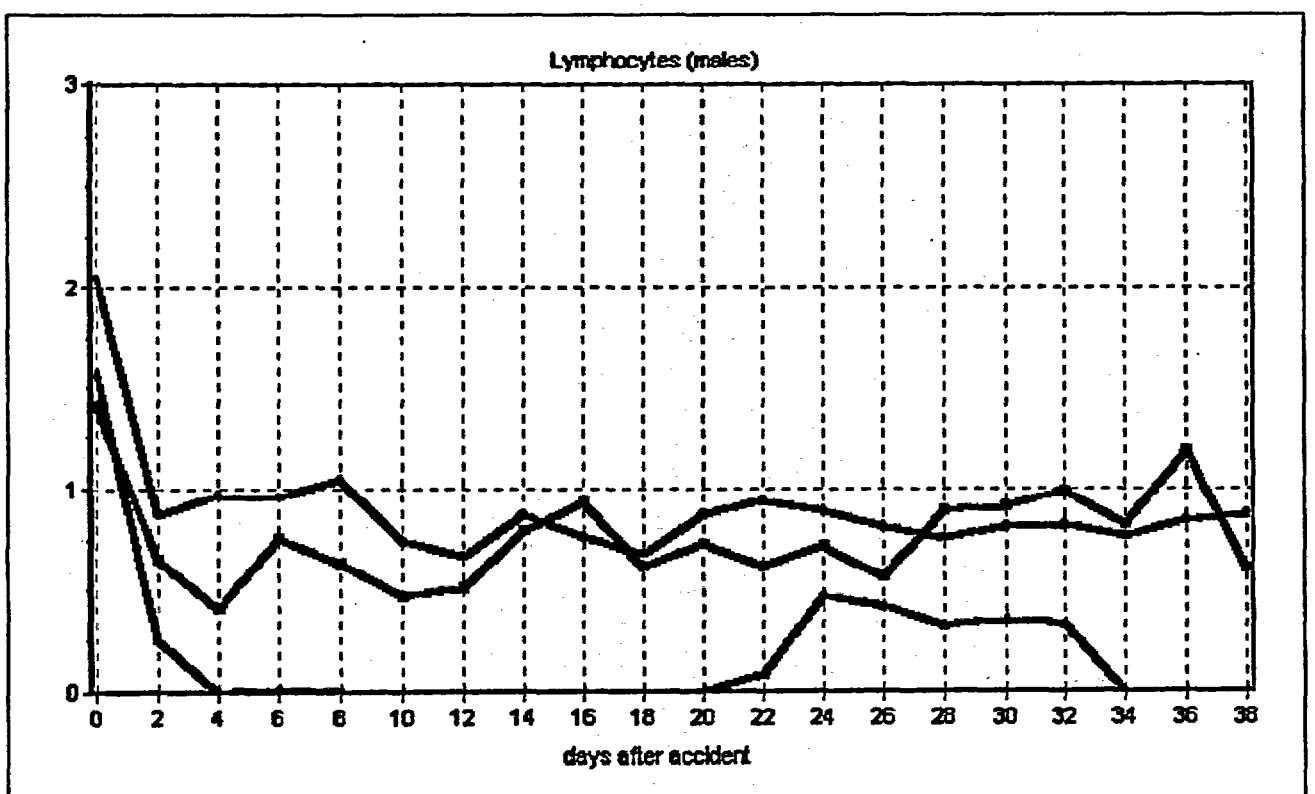

Fig.8. Pattern of lymphocyte counts for male patients with ARS of different severity (IV – green line, III – blue line, II – red line)

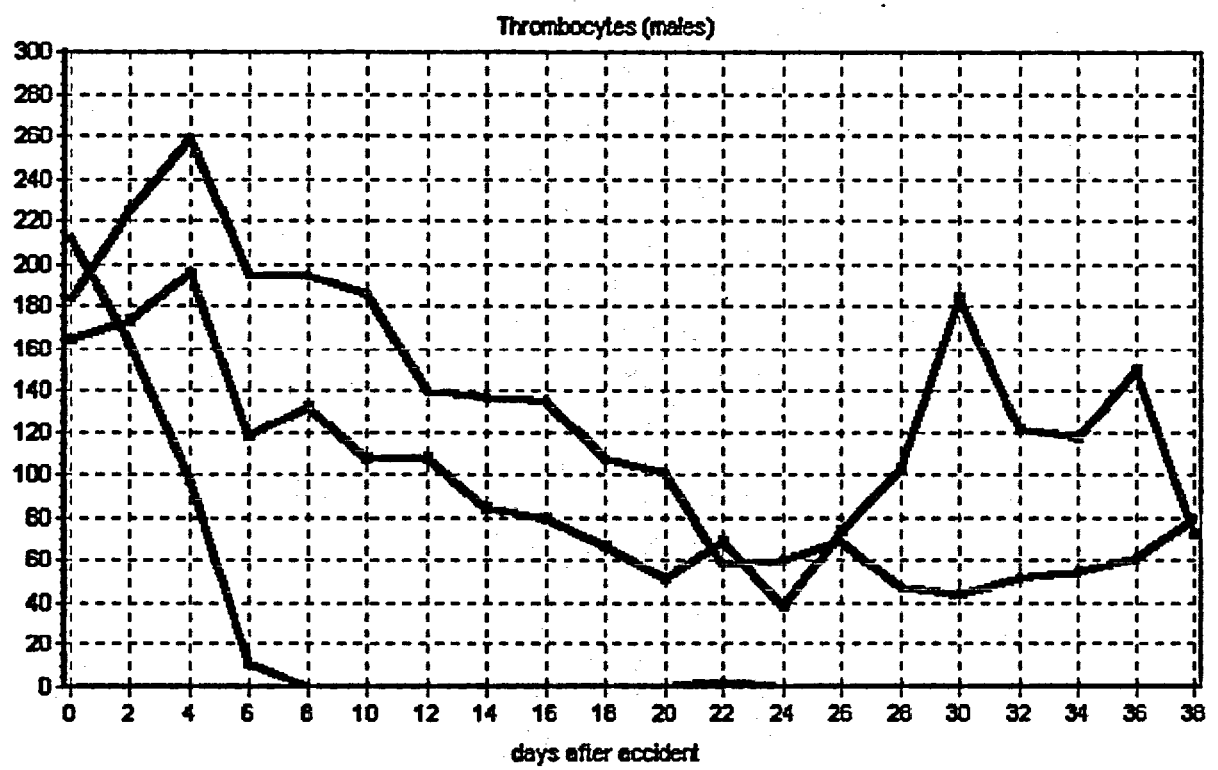

Fig. 9. Pattern of thrombocyte counts for male patients with ARS of different severity (IV – green line, III – blue line, II – red line)

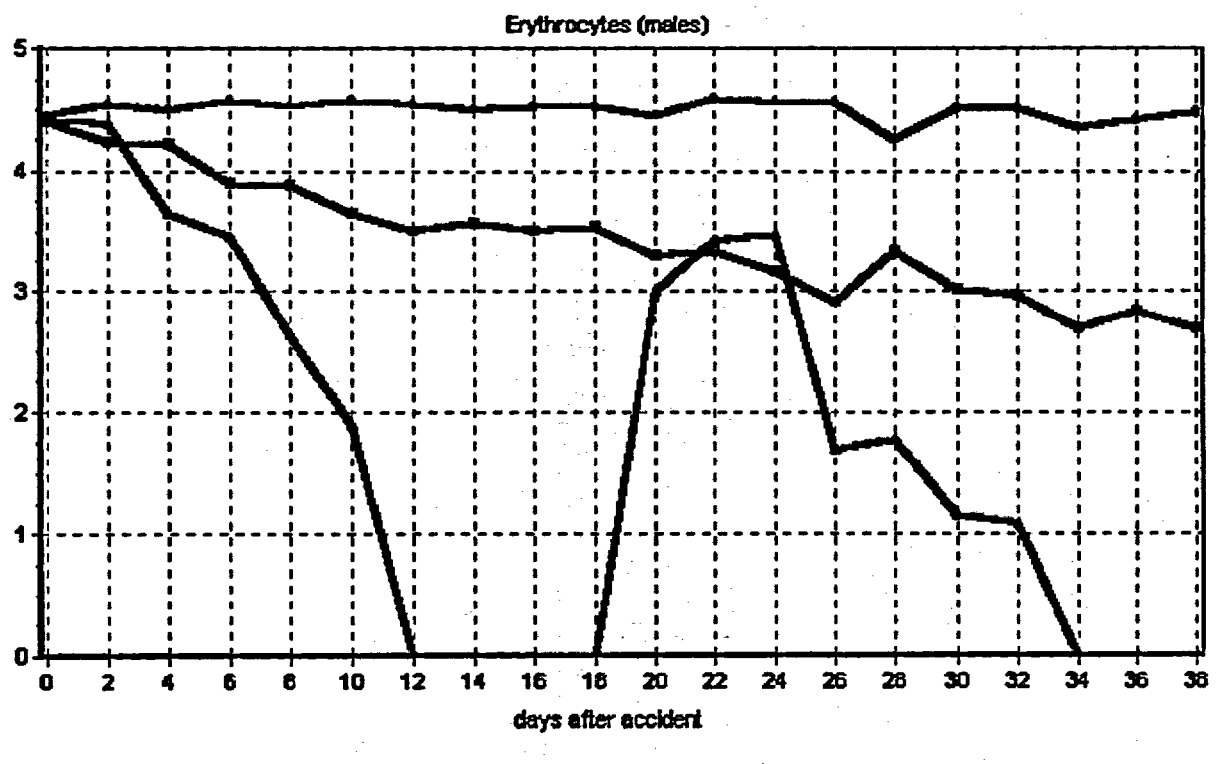

Fig. 10. Pattern of erythrocyte counts for male patients with ARS of different severity (IV – green line, III – blue line, II – red line)

K.4. Project 2.3 Publications.

K.4.1. Okladnikova ND, Claycamp HG, Azizova TV, Belyaeva BD, Pesternikova VS, Scott BR, Sumina MV, Teplyakov II, Boecker BB, Vasilenko EK, Khokhryakov VF, Fevralyov AN, Schekhter-Levin S, Wald N. Deterministic Effects of Occupational Radiation Exposures in Some Workers of the First Atomic Plant. Medical Radiology and Radiation Safety, 2001, Vol. 46, No. 6, pp. 84-93.

K.4.2. Claycamp HG, Sussman NB, Okladnikova ND, Azizova TV, Pesternikova VS, Sumina MV, Teplyakov II. Classification of chronic radiation sickness cases using neural networks and classification trees. Health Phys. 2001 Nov; 81(5):522-9.

K.4.3. Claycamp HG, Okladnikova ND, Azizova TV, Belyaeva ZD, Boecker BB, Pesternikova VS, Scott BR, Shekhter-Levin S, Sumina MV, Sussman NB, Teplyakov II, Wald N. Deterministic effects from occupational radiation exposures in a cohort of Mayak PA workers: data base description. Health Phys. 2000 July; 79(1):48-54.

K.4.4. Scott BR, Lyzlov AF, Osovets SV. Evaluating the risk of death via the hematopoietic syndrome mode for prolonged exposure of nuclear workers to radiation delivered at very low rates. Health Phys. 1998 May; 74(5):545-53.

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DETERMINISTIC EFFECTS OF OCCUPATIONAL RADIATION EXPOSURES FOR WORKERS OF THE FIRST RUSSIAN NUCLEAR PLANT (MEDICAL-DOSIMETRIC DATABASE)

Key words: *personnel, external γ-rays, ^{239}Pu, chronic radiation sickness (CRS), acute radiation syndrome (ARS), plutonium pneumosclerosis (PPn), symptoms, hematological data, functional studies*

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ABSTRACT

Purpose: Evaluation of deterministic effects of occupational exposures based on results of the long-term medical observation (JCCRER Project 2.3).

Material and methods: The complete health information on 591 workers of the first Russian nuclear enterprise, MAYAK Production Association (MPA), employed during 1948-1958 and exposed to occupational radiation in doses exceeding permissible ones for the personnel was obtained from the primary medical records. This information contains data of the long-term medical follow-up (1948-1999) including annual examinations in the medical hospital and regular examinations in the specialized hospital. Individual dosimetry data on external and internal (due to incorporated ^{239}Pu) exposures were obtained from the MPA Radiation Safety Department and SUBI Biophysical Laboratory.

Results: The medical-dosimetric database was established for a selected workers cohort including 4 groups: (1) workers with chronic radiation sickness (CRS) diagnosed in the 1950s due to high doses from external γ-rays (202 individuals); (2) workers with acute radiation syndrome (ARS) due to external exposure (medical information is available for 59 individuals); (3) workers with occupational plutonium pneumosclerosis (PPn) (120 individuals); and (4) workers without any radiation disease (control group, 209 individuals). The database includes detailed records of multiple studies on the morphological composition of peripheral blood, bone marrow, clinical symptoms, neurological syndromes, results of functional studies of the lung for PPn patients, treatment specification, individual monthly and annual doses from external γ-rays and neutron exposures, and internal exposures due to incorporated ^{239}Pu, absorbed doses per 14 organs due to external and internal exposures. The vital status was evaluated for each case at the last observation period, and the death cause was specified in case of death.

Conclusion: The unique medical-dosimetric database was established, which will enable to verify and improve the current models of deterministic effects, develop new models and apply the obtained prognostic estimates to accidental exposure incidents.

Introduction

During 100 years of utilizing the external and internal radiation sources, a large practical experience was accumulated in radiation medicine. Acute general and local radiation injuries, consequences of incorporation of different radionuclides, changes after chronic and fractionated human exposures were described. At the same time it is rather difficult to estimate risk of stochastic and deterministic effects in many cases due to the lack of registered individuals doses, application of calculated doses obtained by imperfect computation techniques, differences in exposure rates, combination of several radiation factors, non-availability of initial data on health of exposed individuals, and difficulty in evaluating the radiation factor contribution to changes in human health resulting from exposure to ionizing radiation sources. In domestic and foreign literature there are research summaries of radiation effects with analyses of exposure incidents and accidents, clinical description of consequences of occupational and therapeutic exposures, presentation of registries of the exposed individuals [2, 8, 9, 24, 30-33].

This paper is focused on evaluation of deterministic effects of occupational exposures for workers of the first Russian nuclear enterprise, MPA, employed during first years of the enterprise commissioning and development. To accomplish this goal, the first work phase was completed, i.e. establishment of the computer database of medical and dosimetry data for the large cohort of MPA workers, who were exposed during first years of the enterprise development to radiation in doses resulting in occupational diseases: acute radiation syndrome (ARS); chronic radiation sickness (CRS) due to external γ-ray exposure; and occupational plutonium pneumosclerosis (PPn) for those who worked with ^{239}Pu aerosols.

Material and Methods

Radiation environment at the nuclear enterprise during first years of its commissioning and development was detailed in publications [14, 25]. The overall advantages of studying deterministic effects for the cohort of MPA workers are as follows:

- preservation of the health information on each worker prior to his/her employment for work with ionizing radiation sources (results of examination by a physician, neurologist; full-scale blood count, and additional laboratory and functional studies) in medical records;
- availability of the archived results of regular medical examinations (on quarterly-basis during first years, on annual-basis during the following years) with required peripheral blood study and examination by a physician, neurologist and other specialists;
- complete succession in the system of medical follow-up for the long-term observation period;
- availability of registered individual doses from external exposures (monthly, annual, total) for each worker since the started work with ionizing radiation sources;
- developed system of ^{239}Pu body burden determination and estimation of internal doses due to incorporated radionuclide.

The clinical examination of workers was performed not only in health centers and medical hospital but also in a specialized hospital. The state-of-the-art complex of laboratory and functional research techniques was used in each observation period. Research results were duplicated in work journals of the appropriate consulting rooms and laboratories. This enables to reconstruct the health pattern for each worker and evaluate the condition of most radiosensitive systems and organs for the long-term observation period: for residents of the city situated in the MPA vicinity up to date; for migrants up to the date of their departure from the city; for the deceased up to the date of their death. The archived and current medical records (medical cards, out-patient cards, case histories) are kept in Central Medical Sanitary Department No. 71 and Southern Ural Biophysics Institute (SUBI). External doses are registered in the personal data file of each worker kept in the MPA Radiation Safety Department. The system of ^{239}Pu body burden evaluation and calculation of absorbed doses per organs was developed in the SUBI Biophysical Laboratory, and it is effectively used during several decades [23]. To solve the stated task, a cohort of MPA workers employed during 1948-1958 was selected. The cohort was divided into 4 groups:

- random sampling of workers with chronic radiation sickness (CRS) (202 individuals);
- random sampling of workers without occupational radiation diseases, i.e. the control group (209 individuals);
- workers with acute radiation syndrome (ARS) mainly due to external γ-ray exposure (59 individuals);
- individuals-^{239}Pu carriers with occupational plutonium pneumosclerosis (PPn) (120 individuals).

For one ARS case it was impossible to restore medical data.

The effort of establishing the medical-dosimetric database was initiated in the frame of pilot Russian-American project [21] and continued in the frame of long-term project under subcontract with University of Pittsburgh "Deterministic Effects of Occupational Exposures in the MPA Workers Cohort" with NRC financial support.

Results and Discussion

The database includes medical and dosimetry information on 591 MPA workers exposed to different doses of external and internal radiation. The general database scheme is presented in Fig. 1 with a focus on the nosological nature of the entered information. There are more nosological forms of occupational diseases described in the database than individuals in the corresponding groups, since one person might have more than one occupational radiation diseases. As a result the database including 591 individuals contains information on 382 workers with occupational radiation diseases (209 individuals had no radiation pathology) and medical data on 469 cases (diagnoses):

- CRS – 290 cases;
- ARS – 59 cases;
- PPn for individuals-Pu carriers – 120 cases.

Doses of external γ-ray exposure and radionuclide body burdens for workers in groups with one diagnosis or a combination of diagnoses, and without any occupational disease are given in Table 1. The primary medical and dosimetry characteristics of each studied nosological form of occupational radiation disease are given below. This primary information addresses the Project tasks on CRS, PPn risk

evaluation and testing of the ARS severity predicting model by symptoms and syndromes of the initial ARS response.

Chronic Radiation Sickness (CRS) due to external γ-ray exposure

Long before the term "CRS" was introduced into practice, the radiation cytopenia was known as a consequence of external and internal radiation exposure in experiment and clinical observations (by research laboratory staff, X-ray radiologists, patients exposed during radiation therapy). In the late 1930s and early 1940s, a conception about the symptom complex after chronic radiation exposure with prevailing hematological alterations (reduction of leukocytes, thrombocytes, and much rarely reduction of erythrocytes due to high doses) was established in the literature. A detailed description of the symptom complex characteristic of CRS as a single nosological form in case of chronic occupational exposure at high doses was presented in two monographs by SUBI scientists and physicians [1,7]. Studies summarized in these monographs were initiated due to a rather complicated radiation environment at the MPA reactor, radiochemical and plutonium production plants during their startup and development. For a long time these research summaries were not available for scientists and physicians in our country and in the world, and only in 1971 the experience of the lead scientists in this field, A.K. Guskova and G.D. Baysogolov, was summarized in monograph "Radiation Disease in Human" [8]. The studies were continued, and results of the long-term follow-up of the health of CRS patients were published with retrospective evaluation of the hematopoietic system (peripheral blood, bone marrow), changes in the nervous and other systems and organs in the period of maximum radiation exposures and in the late times (up to 40 years) [15, 16, 28, 29].

The medical database for workers with CRS and for workers without any occupational radiation disease (control group) contains the following characteristics marked with their registration date:

- symptoms (fatigue, dizziness, head-ache, disturbance of sleep, etc.);
- data of blood counts (monthly, quarterly, annual – up to 50-70 studies per 1 patient): erythrocytes, hemoglobin, reticulocytes, thrombocytes, leukocytes, differential count;
- bone marrow: total number of bone marrow cells, megakaryocytes, granulopoietic and erythropoietic elements, leuko-erythroblastic ratio, maturing index of neutrophils and erythroblasts;
- neurological syndrome as a result of the symptom complex evaluation (vascular dystonia, hyposthenia, micro-organic changes in central nervous system);
- cerebral atherosclerosis with the indicated degree of expressiveness (initial, moderate and marked signs of discirculatory encephalopathy);
- cytogenetic data on some patients (number of the analyzed metaphases, dycentrics, rings, acentric chromosome fragments and other unstable aberrations, stable aberrations, multiaberrant cells);
- treatment description (blood transfusion, vitamins, glucose, steroids, etc.).

The peripheral blood and bone marrow data included into the database and compared to monthly and annual doses of external γ-ray exposure allow to evaluate the nature and depth of changes in the blood-forming system in the period of maximum radiation exposure (forming of the CRS symptom complex), degree of recovery, consequences and outcomes at different times after exposure cessation. Fig. 2 demonstrates the pattern of leukocytes, neutrophils and lymphocytes in peripheral blood compared to the initial data on worker I. born in 1927, who had clinical

manifestations of CRS in 1953 (total dose of chronic γ-ray exposure, 2.54 Sv; annual dose, 0.9 Sv). During the period of CRS forming, leukocytes and neutrophils were reduced by 40-50% of the initial values (i.e. prior to started work with ionizing radiation sources). In the late-time observation these values were within the physiological standards. Registration of neurological symptoms, syndromes, and the date of cerebral atherosclerosis diagnosing provide for an indirect evaluation of the initiation and expressiveness of involution processes. The vital status was determined for each case, and the death cause was indicated in case of death.

Acute Radiation Syndrome (ARS)

ARS developed after a single total external exposure in dose of 1 Gy and over is well-known from domestic and foreign publications. Systematization of clinical data is based on the information obtained from cases of exposure incidents, accidents, acute exposures due to A-bomb explosions in Hiroshima and Nagasaki, Chernobyl accident, cases of careless utilization of ionizing radiation sources [2, 6, 8-10, 19, 20, 26, 27, 30, 31, etc.]. At the same time, there is a risk of massive radiation exposures due to the large-scale utilization of ionizing radiation sources in different sectors of national economy and availability of nuclear weapons. In such a situation the reliability of prediction of the nature and severity of radiation exposures by symptoms of primary response is very important. In our country and abroad there are ARS classifications, instructions and methodical guidelines addressed to physicians for the right choice of diagnostic medical treatment and prediction of exposure severity [3, 11, 12, etc.]. At the same time, the analysis of any additional information allows to test reliability of the current estimations by the exposure severity prediction models and make necessary corrections. The adequate prediction of exposure severity can be achieved by evaluating the symptom complex of primary response [3, 18, 21, etc.].

In our database, the ARS clinical pattern is presented from the first day up to 90 days after acute exposure by 78 coded clinical-functional signs and results of laboratory studies. The coded signs (symptoms) reflect health of patients, changes in the hematopoietic, nervous, cardiovascular, genitourinary systems, gastrointestinal tract, eyes, skin and mucous membranes. Clinical symptoms are presented by the following characteristics: anorexia, nausea, vomiting, diarrhea, stomach-ache, abdomen swelling, head-ache, conjunctivitis signs, erythema, jaundice, high temperature, infection signs, hyperemia, hemorrhages, epilation, sweating, oliguria, weakness (fatigue), prostration, weight loss, hyperesthesia, paresthesia, ataxia, disorientation, shock, coma, etc. Laboratory data include peripheral blood data (erythrocytes, hemoglobins, reticulocytes, leukocytes, differential count, erythrocyte sedimentation rate), bone marrow data from sternal aspirates, biochemical studies of blood serum (blood sugar, total protein, albumins, globulins, bilirubin, chlorides, cholesterol, urea nitrogen, alkaline phosphatase, transaminase). It should be noted that all ARS cases occurred in the 1950s, which determined the corresponding number of biochemical data. This refers also to medical treatment procedures. The remedy file includes sedatives, analgesics, antiemetics, antispasmodics, parenteral liquids, electrolytes, transfusion of blood, plasma and thrombocytic mass, antibiotics, vasoconstrictors, vitamins, steroids, hemostimulants.

Retrospective estimation of the primary response symptoms, latent period, symptoms during the period of clinical manifestation (disease progress) allowed to distinguish an erased form of ARS, and the mild, moderate, severe and most severe degrees. Doses of acute exposure during an exposure incident and external doses of chronic radiation prior to acute exposure are given in Table 2. Thus, prognostic

estimates of exposure severity can be compared with ARS severity estimates by symptomatology of the full-scale ARS clinical pattern. Solution of this task is one of the essential stages of physicians training in diagnostic and treatment tactics in case of radiation exposure incidents or accidents.

Plutonium Pneumosclerosis (PPn)

The lung is an organ of main deposition due to inhaled ^{239}Pu. Experimental studies proved risk of sclerotic alterations developed in the lung at radionuclide deposition in large amounts [4]. First clinical observations of sclerotic changes date back to the late 1950s and early 1960s [5, 13]. The clinical examination revealed sclerotic changes in the lung of female plutonium workers, who had no effective individual protection devices (respirators) during first years of work, though there were no indications in their histories or clinical-rontgenological evidences of acute bronchopulmonary inflammations at the previous examinations. Pneumosclerotic changes varied from mild diffusive ones on both sides to rough fibrosis more pronounced in the upper pulmonary sections, with marked deformation of the vascular pattern, and response of the interlobar and costal pleura. The retrospective analysis indicated that in all cases, when PPn was diagnosed, the leading role in its forming belonged to the radiation factor. Absorbed doses due to ^{239}Pu deposited in the lung exceeded permissible doses for the personnel [16, 17]. In some cases the etiological role of other occupational hazards in the past (dust, dust-radiation, chemical factors) and lung diseases prior to started work with ionizing radiation sources (tuberculosis, pleurisy, pleuropneumonia, etc.) was not excluded [17].

The established medical-dosimetric database includes individual clinical characteristics for 120 plutonium workers employed before 1954, who had the verified diagnosis of occupational PPn. Complains of patients (cough, dyspnea), cardiovascular data (pulse, arterial pressure), results of rontgenological and functional studies were registered during 45 years. Surveillance X-rays of the lung were performed annually along with magnified X-rays of the upper right lung sections to refine the revealed changes. The bronchopulmonary system is also presented in the database by data characterizing the vital capacity (VC, %), forced expiration volume (FEV, %), diffusing capacity (D_{ca}, %), lung tissue distensibility ($C_{ml/sm}$ H_2O). There could be 18 - 20 functional examinations per worker during the long-term follow-up period. Fig. 3 illustrates an example of VC and FEV for the long-term follow-up of a male plutonium worker (Fig. 3a) born in 1927 (Pu body burden, 96.53 kBq; total dose from external γ-rays, 4.67 Gy), and a female worker (Fig. 3b) born in 1921 (^{239}Pu body burden, 92.28 kBq; total dose from external γ-rays, 1.16 Gy). The trend of curves indicates a stable decrease of VC (less than 80%) during the whole observation period, i.e. restrictive changes, and the bronchial lumen value remaining within the physiological standard. The database includes information on the following prophylactic treatments: antibiotics, steroids, resort treatment.

Exposure doses

In establishing the computer database, a special focus was the detailed development of its structural part, which should include the maximum complete information on the worker's occupational history, amount and nature of external and internal doses. The occupational history file contains the date of employment; description of plant, shop, site; occupation; dates of workplace changing; and the date of retirement.

Individual doses of external and internal exposures were estimated by the MPA specialists and SUBI Biophysical Laboratory staff in collaboration with American colleagues in the frame of DOE Project 2.4 "Development of the Improved Dosimetry System for MPA Workers".

The dose files include the following information:

- monthly (during first years) and annual doses from external γ-rays;
- monthly and annual neutron doses;
- absorbed external doses in 14 organs: the lung, liver, skeleton, bone surfaces, bone marrow, gonads, stomach, small intestine, spleen, thyroid, urine bladder, gullet, thorax, skin;
- ^{239}Pu body burden determined by the radiochemical method based on spontaneous excretion with urine and by autopsy data;
- monthly and annual absorbed doses due to ^{239}Pu in the above listed organs.

In addition to the quantitative estimation of radiation factor, a special work was performed to refine non-radiation risk factors. The smoking information as a risk factor was obtained not only from medical records but also from patients' interviewing, which provided a reasonable reliability of these data. The alcohol information was also entered into the database.

Thus, the basic work phase of Project "Deterministic Effects of Occupational Exposures" implemented in the frame of the RF/US Government Agreement on cooperation for studying radiation effects in humans, was completed. In accordance with the Project aims and tasks, the computer database was established including all medical data of the long-term health follow-up for workers with clinical manifestations of occupational radiation diseases and comparison groups. Practically all clinically described cases are included into the ARS and PPn groups. The CRS group is a random sampling of CRS forms varying by pronounced syndromes over the wide dose range (from few cGy up to 10.13 Gy). Completeness and extensiveness of medical data and availability of individual exposure doses are essential characteristics of the database. At the next work phase it's planned to extend the analysis of qualitative alterations in most radiosensitive systems using mathematical approaches, and possibly reveal new quantitative patterns that could be defined as criteria of the syndrome, diagnosis, and prediction. First studies in this direction were already performed in the frame of the pilot project [22]. We hope that clinical-dosimetric information on ARS will extend the existing databases for purposes of practical public health. PPn is undoubtedly a vanishing nosological form [17]. However, ^{239}Pu is still world-wide used as a power source, so scientists and physicians should be aware of this occupational disease and able to estimate its risk. In this aspect, it is very important to test the risk models obtained earlier based on experimental data.

CONCLUSIONS

The unique medical-dosimetric database was established in the frame of international project for the large cohort of workers exposed to occupational radiation in doses resulting in deterministic effects, i.e. ARS, CRS, and PPn.

The database is a basis for testing the existing and new risk models, and predicting the early and late effects of exposures.

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Fig. 1. Description of the medical dosimetric database for the MPA workers cohort.

Fig. 2. Some peripheral blood data for a CRS patient for 20 years of follow-up.

Fig. 3a. VC (%) and FEV (%) values for a male PPn patient.

Fig. 3b. VC (%) and FEV (%) values for a female PPn patient.

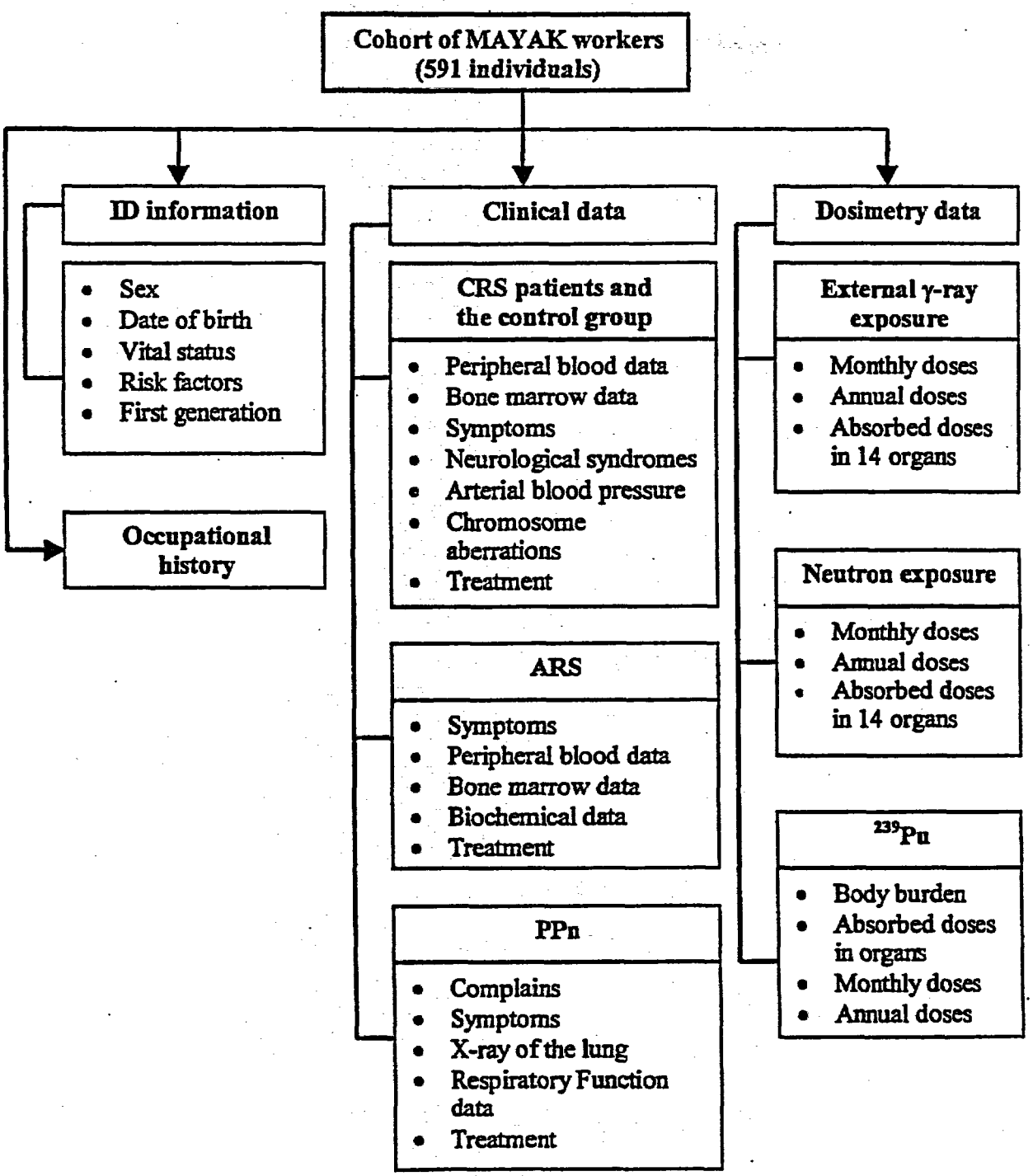
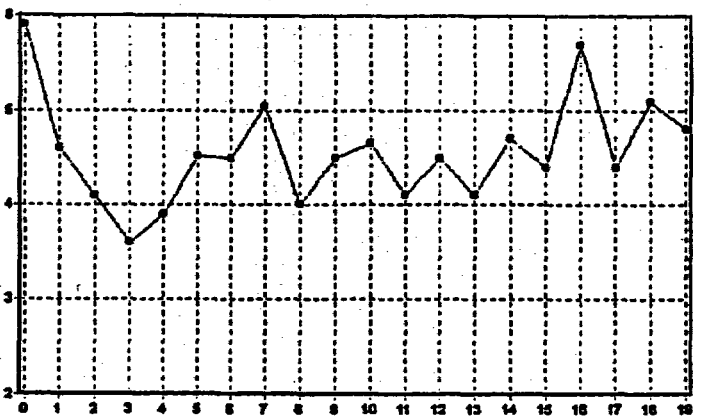
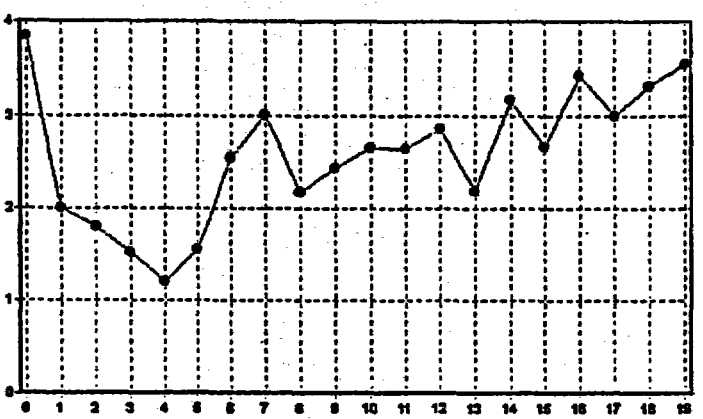

Cohort of MAYAK workers (591 individuals)
ID information
Sex
Date of birth
Vital status
Risk factors
First generation
Occupational history
Clinical data
CRS patients and the control group
Peripheral blood data
Bone marrow data
Symptoms
Neurological syndromes
Arterial blood pressure
Chromosome aberrations
Treatment
ARS
Symptoms
Peripheral blood data
Bone marrow data
Biochemical data
Treatment
PPn
Complains
Symptoms
X-ray of the lung
Respiratory Function data
Treatment
Dosimetry data
External γ-ray exposure
Monthly doses
Annual doses
Absorbed doses in 14 organs
Neutron exposure
Monthly doses
Annual doses
Absorbed doses in 14 organs
239Pu
Body burden
Absorbed doses in organs
Monthly doses
Annual doses

Fig. 1



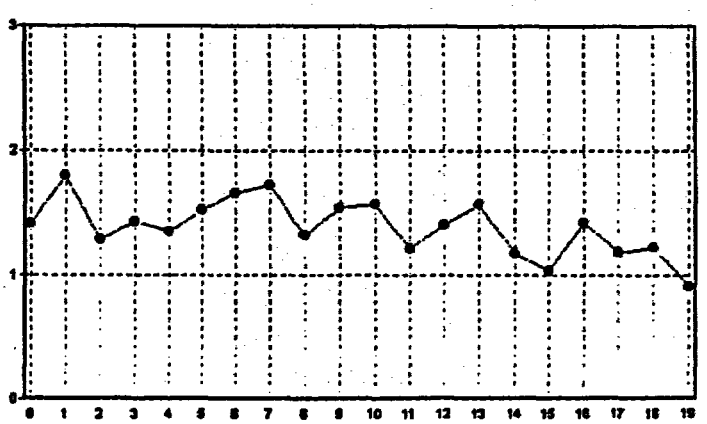
Follow-up years

Leukocytes (10^9/L)



Follow-up years

Neutrophils (10^9/L)



Follow -up years

Lymphocytes (10^9/L)

Fig. 2

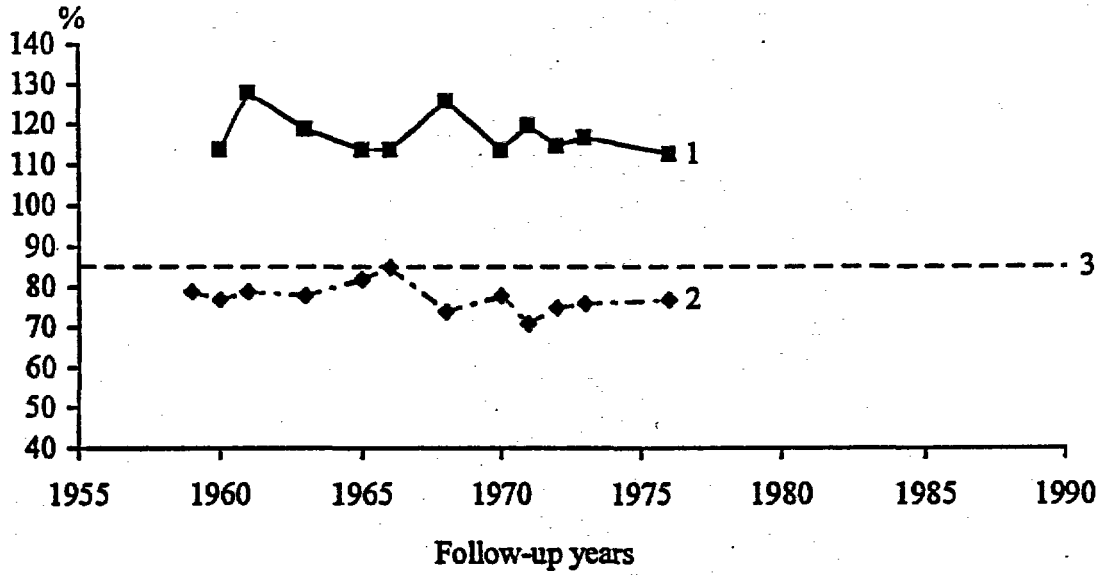


Fig. 3a

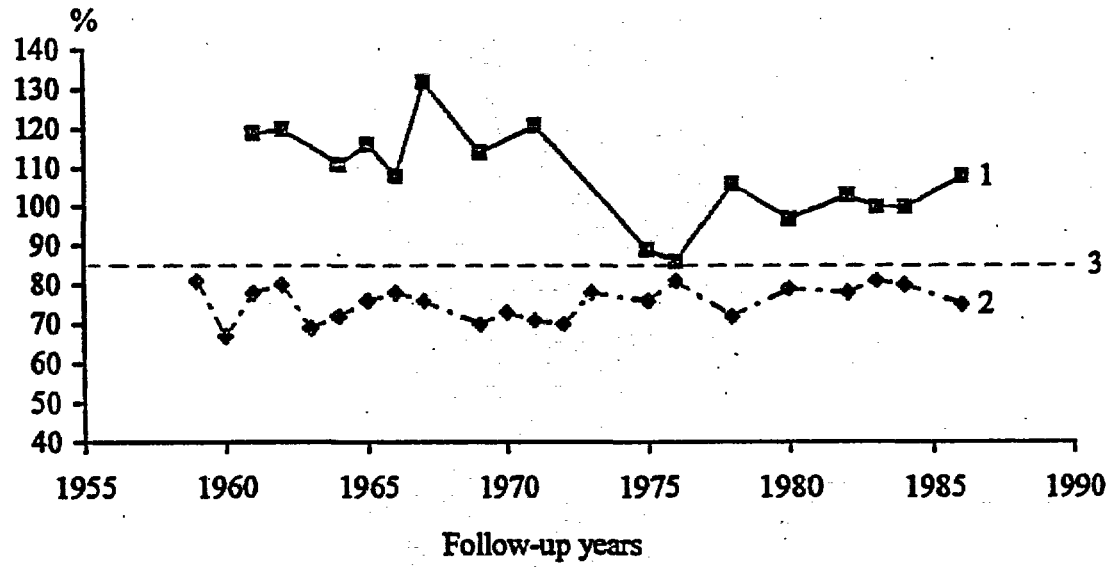


Fig. 3b

1 – VC
2- FEV
3 – Lower limit of physiological standard for VC and FEV

Table 1
External doses from γ-rays and ^{239}Pu body burdens (M±m)

Groups	External dose from γ-rays (Sv)	Pu body burden (kBq)
Chronic radiation sickness (CRS)	3.12±0.13	8.86±5.51
Acute radiation syndrome (ARS)	10.08±3.56	0.40±0.97
Plutonium pneumosclerosis (PPn)	0.94±0.15	22.10±4.11
CRS in combination with PPn	2.50±0.17	48.92±6.13
CRS in combination with ARS	3.07±0.48	1.82±0.53
PPn in combination with ARS	11.81±0.00	28.76±0.00
Without occupational radiation disease	0.85±0.65	4.65±3.58

Table 2
Exposure doses for workers with ARS of different severity (M±m)

ARS severity	Number of individuals	Dose of acute exposure (Sv)			Total dose of chronic exposure prior to accident (Sv)
		Maximum	Minimum	Mean for the group	
Most severe	7	55.86±16.2	44.37±18.7	43.75±12.81	0.03±0.01
Severe	4	9.98±1.38	7.13±1.29	9.36±1.55	2.39±2.07
Moderate	14	2.55±0.82	0.80±0.14	2.21±0.83	1.76±0.48
Mild	15	1.47±0.11	0.66±0.12	0.93±0.13	1.57±0.36
"Erased"	19	1.11±0.09	0.47±0.06	0.85±0.07	1.17±0.29

Paper

CLASSIFICATION OF CHRONIC RADIATION SICKNESS CASES USING NEURAL NETWORKS AND CLASSIFICATION TREES

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Abstract—Chronic radiation sickness is a deterministic radiation health effect observed among the Mayak Production Association workers in Russia. In this study, unsupervised neural networks were used to cluster hematological measurements in a subset ($n = 88$) of the Mayak Production Association population while excluding from the analysis the radiation dose and the historical clinical diagnosis. Clusters of observations that had lower average leukocyte and thrombocyte counts were labeled "affected" and those having higher average blood cell counts were labeled "unaffected." The class (cluster) membership for each individual was used subsequently as a dependent variable in a classification tree model in order to identify significant features of the underlying classification model. After re-classification of cases using this method, the results showed a better data separation between the blood cell counts for affected vs. unaffected groups compared to those based on historical classification, and a greater difference between group means for differential blood counts was observed than for the historical diagnosis. The re-classification of diagnostic groups changed the group mean radiation doses. The geometric means (and 95% CL) of cumulative radiation dose equivalent from external exposures, based on the historical diagnosis, are 0.31 (0.0035, 3.4) vs. 1.7 (0.0007, 18) Sv. After clustering and classification tree analyses, the group geometric means were 0.78 (0.0014, 8.6) vs. 1.5 (0.0007, 17) and 0.82 (0.0013, 9.0) vs. 1.4 (0.0008, 16) Sv, using (respectively) whole blood cell counts or differential counts as the independent variables. The approach presented here is useful as a diagnostic aid for both retrospective analyses and in the event of future radiation accidents.

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Key words: health effects; radiation effects; exposure, occupational; modeling, dose assessment

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INTRODUCTION

A SIGNIFICANT gap in information remains for health risks from radiation doses in the high-occupational (e.g., >50 mSv y^{-1}) to the sub-clinical dose range. The sparse data available in this dose range includes, for example, studies on populations who received radiation treatment for benign diseases such as tinea capitis, ankylosing spondylitis, or mastitis (NRC 1980; UNSCEAR 1988, 1993, 1994). These studies have been used to provide information for health risks between the high-dose and dose-rate analyses in the A-bomb population studies and the low-dose and low dose-rate studies in occupationally exposed populations (Strom 1998). Recently, there has been much interest in health effect studies on nuclear workers from the Mayak Production Association (PA) in the Ural Mountains of Southern Russia. (Okladnikova et al. 1994; Seligman 2000; Lubchanskiy and Romanov 2000). Retrospective studies on the Mayak PA workers, for whom occupational doses averaged about an order of magnitude greater than similar western occupational groups, offer much information for health effects in the high-occupational dose range. The present study is part of ongoing research on deterministic health effects from chronic occupational doses typically exceeding 0.05 Gy y^{-1}.

Chronic radiation sickness

Chronic radiation sickness (CRS) was first identified and described by Guskova and colleagues (Guskova and Baysogolov 1971) from observations in the Russian nuclear worker population from 1947 through 1954 (Guskova and Baysogolov 1971). The clinical course of CRS was further described by Okladnikova et al. (1991, 1994). CRS is a deterministic radiation health effect occurring during prolonged high doses of radiation. In the translation of Guskova and Baysogolov (1971), the clinical syndrome of CRS was described as one that "is formed gradually, slowly, under the prolonged influence [on] the organism of radiation, the single and summary doses of which regularly exceed the acceptable maximum permissible levels for occupational irradiation. The syndrome is not specific, but is rather characteristic in the whole sequence of development and type of clinical manifestations, associated with general or nonuniform (selective) irradiation of various organs and systems" (Guskova and Baysogolov 1971, p. 499).

Guskova and Baysogolov (1971) described four degrees of severity of the CRS, beginning with the "light" or first degree, in which the clinical syndrome was indistinct and described as primarily neuroregulatory disorders with a concurrent and unstable moderate leukopenia and, sometimes, thrombocytopenia. There are two intermediate degrees before the "severe" and "terminal" degrees in which the there are direct signs of damage to the most radiosensitive tissues in the body, including pronounced leuko- and thrombo-cytopenia in the peripheral blood, in addition to the development of anemia. The "severe" level includes changes in the intestinal mucosa along with microstructural dystrophic changes in relatively resistant organs, such as the walls of the vessels and the heart. If the radiation exposures are not eliminated, the disease can progress to "terminal" fourth degree.

There is significant overlap among the signs and symptoms of CRS (Table 1) and those observed for a variety of infectious and somatic diseases. None of the symptoms or signs can be regarded as exclusive of CRS, thereby confounding diagnosis and leading to a dynamic diagnostic process in which the remission of the disease after discontinuing radiation exposures is itself evidence of the disease (Kossenko et al. 1994, 1998).

Most of the 1,828 CRS cases in the Mayak PA population were diagnosed in workers at a time when some individuals received annual radiation doses of 2.0–4.5 Gy (Okladnikova et al. 1991, 1994). Approximately 97% of the cases occurred before 1958 with the remainder following in the early 1960's (Shilnikova et al. 1996). An additional group of CRS cases was identified retrospectively in 222 persons who had cumulative externally-derived doses <1 Gy (Shilnikova et al. 1996); however, it is suspected that the majority of these workers were involved in emergency procedures for which the records of radiation exposures either were not kept or were otherwise misplaced.

The difficulty in assigning a diagnosis of "CRS" was exemplified in the Techa River studies, in which 944 CRS cases were identified upon the initial screening of the exposed population. After consideration of overlapping infectious or chronic diseases, however, only 66 cases were classified as likely to represent CRS (Kossenko 1994, 1998).

Table 1. Clinical signs and symptoms of chronic radiation sickness (CRS) among Mayak PA workers.

CRS symptoms	
Headache	Excessive sweating
Dizziness	Irritability (rare)
Fatigue	Insomnia (rare)
Weakness	
CRS signs	
Leukopenia	Decreased secretory function of the stomach
Thrombocytopenia	Asthenia
Decreased arterial pressure	Rhomberg test positive
Nonuniform reflexes	

The objective of the analysis in the present study is to classify radiation exposed workers into "radiation affected" and "non-affected" groups based on quantitative analyses of clinical features (variables). An epidemiological case-control design is obviated in the present situation because radiation exposure is a diagnostic variable. Thus, calculation of the odds ratios (Selvin 1996) for radiation exposure or the assessment of doses-related relative risks cannot be made directly since the "case" or "control" assignments were based partly on radiation exposure. These conditions are common in databases derived from occupational settings because the patient's medical history often includes likely or known exposures from hazardous agents in order to rule out alternative diagnoses (Marsh 1998). In fact, standard textbooks of occupational medicine typically recommend assessments of radiation or chemical exposures as part of the complete occupational medical history (La Dou 1997; Marsh 1998).

The present study applies a novel combination of non-parametric statistical procedures in order to avoid the circular reasoning that arises in the quantitative classification of CRS cases when either radiation exposures or work assignments are known prior to diagnostic classification. Using the new approach, the observations (individuals) are grouped into "affected" and "unaffected" clusters based solely on observed clinical measurements without information about radiation dose. The objective, "machine-learned" diagnoses subsequently serve as *a priori* classification of "case" or "control" in statistical analyses. Finally, the average radiation doses of the groups are compared to determine the statistical difference between doses for the "affected" and "unaffected" individuals.

A second objective of the present study is to provide a diagnostic aid for CRS based on blood cell counts. Diagnostic instruments based on artificial intelligence and conventional statistical tools are finding increasing use in clinics throughout the world (e.g., Eskelinen et al. 1995; Taichenachev et al. 1998; El-Solh et al. 1999; Furness et al. 1999; Rowland et al. 1998; Anthony et al. 2000). In each example, the computational tool is not intended to supplant the physician's final diagnosis; rather, computational tools provide a rapid, quantitative compilation of signs and symptoms into a single diagnostic call that can complement other data that the attending physician analyzes prior to a diagnosis. In the present situation, a new diagnostic tool might be useful in helping to resolve disputed cases of CRS, such as problematic observations in the Techa River studies (Kossenko et al. 1994, 1998), in addition to providing a diagnostic tool for use in future radiation incidents.

MATERIALS AND METHODS

The data were from a clinically-derived subset from the clinical data base Russian nuclear workers described recently (Claycamp et al. 2000). The clinical records were entered into the data base (maintained in Ozyorsk,

Russia) under "IRB Exempt" human use protocols, which included removal of personal identifiers from the data records used for analyses. Additionally, the data were shared with the U.S. investigators under a data access agreement among MINATOM, the First Institute of Biophysics in Russia, and the U.S. Nuclear Regulatory Commission. The present report involves data from the first portion of the database ($n = 225$) completed recently (Claycamp et al. 2000).

During preliminary investigations, it was observed (predictably) that sex was a strong confounder for blood count measures. Therefore, males only were used in the present study. Additionally, blood count records were restricted to 1954, since it has been shown that the nadir in the average blood counts among the radiation exposed individuals in the Mayak cohort occurred during this period of high annual radiation exposures (Okladnikova et al. 1994; Shilnikova et al. 1996; Claycamp et al. 2000). The resulting subset had 61 individuals diagnosed as CRS and 27 individuals labeled as "unaffected workers" (Claycamp et al. 2000).

Cluster analysis

Numerous approaches for clustering either observations or features (variables) have been reported in both the statistical and the artificial intelligence literatures (Weiss and Kulikowski 1991; Bishop 1995; Gordon 1999). In the present study, a simple unsupervised approach to clustering is used in which the Euclidean distance between observations is used to assign an observation to a given cluster. "Unsupervised" refers to the fact that an *a priori* assignment of an observation to a class or cluster is not used during the model building. This contrasts with other classification approaches, such as linear discriminant analysis, in which an *a priori* assignment to one of the classes is required to begin the calculations.

A simple competitive neural network algorithm was implemented using the NeuroSolutions Version 3.0[§] workbench and used to assign the subjects to one of two or more clusters (Appendix). The competitive clustering algorithm was chosen for its simplicity and because more advanced algorithms for unsupervised learning, such as the Kohonen network, create outputs that can be difficult to interpret in the present experimental setting. The networks were designed for 100 iterations; however, real time observations of the clustering in the network procedure revealed stable clusters typically within approximately 25 iterations (epochs). Although convergence of the cluster models was apparent, nevertheless, 100 iterations were performed for all analyses to ensure that the models had fully converged. In addition to saturating convergence, the network weight changes applied at each iteration were given a "conscience" in order to avoid large corrections in the coefficients after each iteration that can lead to a single cluster (Appendix).

[§] Neurodimension, Inc., 1800 N. Main Street, Suite D4, Gainesville, FL 32609.

Two groupings of the variables were used in the cluster analysis. The first included gross cell counts only, consisting of leukocytes, thrombocytes, and erythrocytes. The second approach involved blood counts in which the total leukocyte count was replaced by the differential white cell counts, including lymphocytes, monocytes, eosinophils, basophils, bands, and polymorphonuclear cells. Since the assignment of a class label (0 or 1) to a given class depends on the original set of random weights (i.e., the sign of the weights) in the neural network, the final assignment of "affected" or "unaffected" to the groups was accomplished by examining the group means. Consistent with the medical reports on CRS the class having a lower mean leucocytes and thrombocyte counts was assumed to represent the "affected" individuals and the remaining class, "unaffected" individuals.

Classification trees

Once cluster memberships were assigned by the neural network procedure, the data and class assignment were submitted to a classification tree procedure to determine the underlying structure of the classification model (Breiman et al. 1984; Steinberg and Colla 1997). Classification trees were generated using CART software.[‖] The CART procedure creates a hierarchical decision tree that classifies the data based on decision levels determined from each significant variable and class association. The CART procedure was used to predict class membership and to validate the predictions using a 10-fold cross-validation calculation (Steinberg and Colla 1997).

The CART methodology for classification trees is technically known as binary recursive partitioning. The process is binary because parent nodes are always split into exactly two child nodes and recursive because the process can be repeated by treating each child as a parent. The key elements of a CART analysis are a set of rules for 1) splitting each node in a tree; 2) deciding when a tree is complete; and 3) assigning each terminal node to a class outcome. To split into two child nodes, CART asks a "yes" or "no" question. An observation goes to the left or to the right depending on the answer. CART looks at all possible splits for all variables included in the analysis at each decision point. Any analysis will have a finite number of candidate splits, and CART will conduct a brute force search through them all. Each splitting rule at a decision point is ranked on the basis of quality of split. Once a best split is found, the process is repeated for each child node, continuing recursively until splitting is impossible or stopped. All cases falling within a terminal node are given the class assignment of the majority. A maximal tree is grown and a set of subtrees are derived from it. The best tree is identified by testing for error rates or "costs." After cross-validation to assess the predictive accuracy, the CART tree can then be used to predict the class. CART is a nonparametric procedure

[‖] Salford Systems, Inc., 8880 Rio San Diego Drive, Suite 1045, San Diego, CA 92108.

and does not require priori specification of a parametric model.

Once that class membership was determined, the cumulative external radiation dose equivalent (Sv) and the historical clinical diagnosis ("CRS" or "Uninjured Worker") were linked with the case identification number. Descriptive statistics were calculated for each group assignment using Minitab (Version 12)[1] or SAS[2] statistical software. Sensitivity (the proportion of accurately predicted "affected" individuals) and specificity (the proportion of accurately predicted "unaffected" individuals) were calculated on both the learning data and the cross-validation sets. Smoking status was also examined, since smoking has a significant effect on leukocyte counts (Sunyer et al. 1996; Schwartz and Weiss 1991).

RESULTS

Figs. 1–3 show the effect of clustering on separation of blood count groups using either the clinical diagnosis or the clustering algorithm. The quantitative clustering approach both reduced the observed class variance for the significant variables and improved the separation of the groups on the basis of thrombocyte and leukocyte counts; however, no significant differences were observed in the case of the erythrocyte counts (Fig. 3). For models in which the differential leukocyte counts were used in the clustering algorithm, the separations of the classes were less distinct (not shown).

In this subset of 88 males, only thrombocyte counts were statistically different ($p < 0.05$) in diagnostic groups based on the historical diagnosis and the "whole blood count" design (Table 2). In the cluster-classification tree (CCT) procedure, the differences between group means (affected vs. unaffected) for both the thrombocyte and leukocyte counts were statistically significant (Table 2). In either case, the difference between mean erythrocyte counts did not differ significantly.

The observations for the differential count model show that only the thrombocyte count means were statistically different at the 95% confidence level (Table 3). In contrast to the historical model, significant differences ($p < 0.05$) between the group means were observed for thrombocytes, leukocytes, eosinophils, neutrophils, lymphocytes, monocytes, and bands (Table 3). The data in Tables 2 and 3 demonstrate numerically the variance reduction for the significant variables (leukocytes and thrombocytes) shown in Figs. 1–3.

Table 4 and Fig. 4 show the geometric mean radiation dose equivalents for the affected and unaffected groups based on either the historical diagnosis or the CCT approach. The geometric means and confidence intervals are given reflecting the fact that the population radiation dose equivalents were highly skewed. These results show that the standard error of the mean estimate was reduced in the CCT approach compared to that

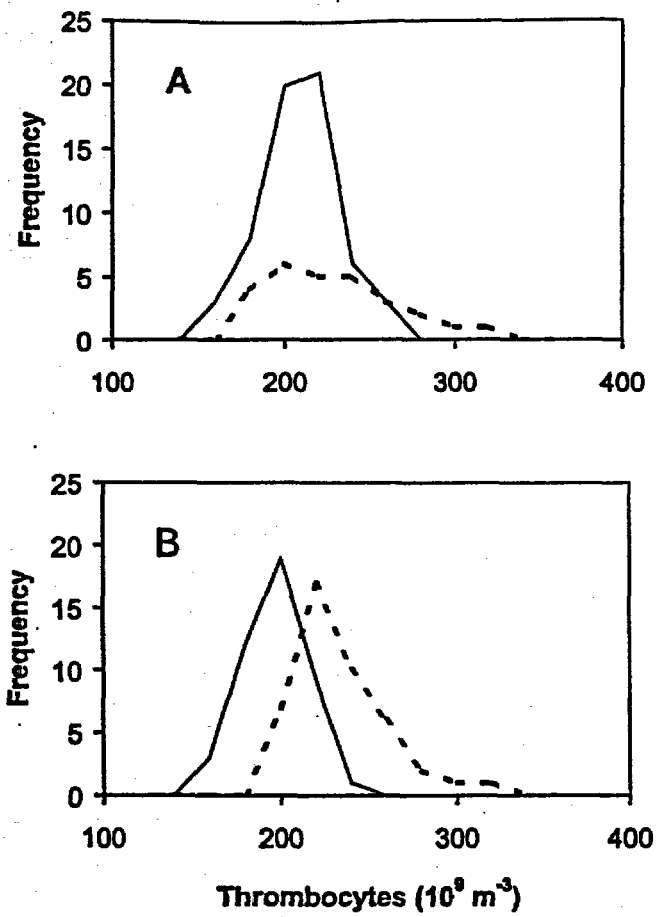

Fig. 1. Thrombocyte frequencies before and after classification using neural networks. The data in panel A are for the 88 males in 1954 who were clinically diagnosed as CRS (solid line) or "uninjured workers" (dashed line). The frequency polygons in panel B show the results of cluster classification: The two populations have greater separation and similar variances. These results are from the "whole cell counts" model.

observed in the original historical clinical diagnosis; however, the difference between the group means also decreased after the CCT analysis.

The cross-validation accuracy of the two CCT submodels is shown in Table 5. These models show that only 8 individuals are "misclassified" according to the CCT models. When the better of the two submodels—the "whole cell counts" classification model—was applied to the data using the historical diagnosis in place of the neural network classification, the sensitivity decreased to 56% and the specificity decreased to 63%. The results show that, according to the CCT approach, 27 affected individuals were misclassified as "unaffected" and 10 individual workers were misclassified as CRS or "affected" in the historical diagnosis. Other diagnostic factors might have generated this discrepancy (see "Discussion").

The frequencies of smoking in the classified groups, under either model design, were not significantly different. The X^2 analysis, using 2 × 2 contingency tables

[1] Minitab, Inc., 3081 Enterprise Drive, State College, PA 16801-3008.

[2] SAS Institute Inc., SAS Campus Drive, Cary, NC 27513-2414.

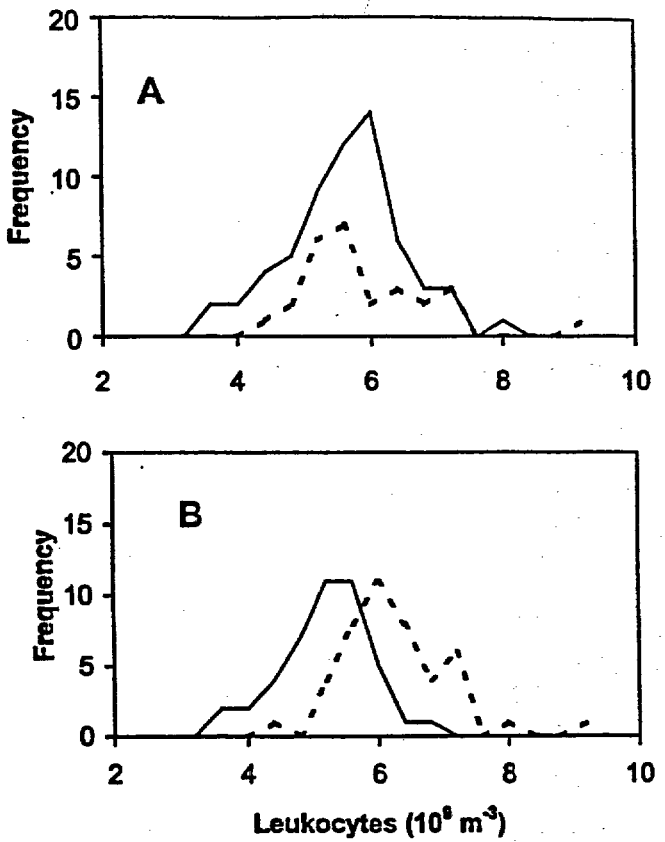

Fig. 2. Leukocyte frequencies before and after classification using neural networks. The frequency polygons in panel A are for the 88 males in 1954 who were clinically diagnosed as CRS (solid line) or "uninjured workers" (dashed line). The polygons in panel B show the results of cluster classification: The two populations have greater separation and similar variances. These results are from the "whole cell counts" model.

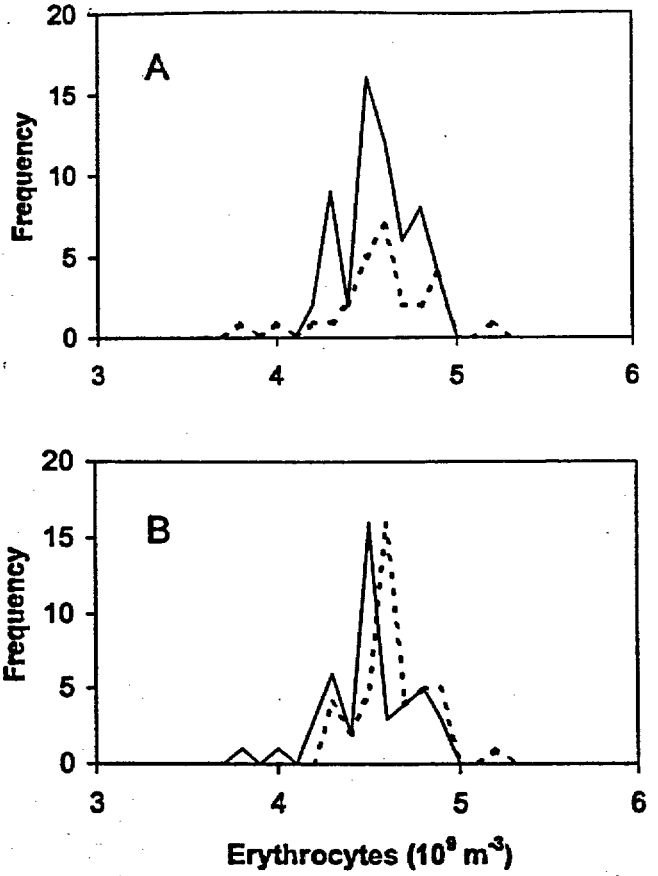

Fig. 3. Erythrocyte frequencies before and after classification using neural networks. The frequency polygons in panel A are for the 88 males in 1954 who were clinically diagnosed as CRS (solid line) or "uninjured workers" (dashed line). The polygons in panel B show the results of clustering into "affected" and "unaffected" groups. As anticipated, erythrocytes were not a significant factor in the separation of affected and unaffected classes.

("disease status × smoking"), resulted in values of $X^2 = 0.036$ ($p = 0.849$) and $X^2 = 1.725$ ($p = 0.189$) for the whole cell count and differential count models, respectively.

DISCUSSION

Occupational health studies often rely on clinically derived data for which the classification of cases was based in part on the *a priori* information about exposures to a hazardous agent. Such studies have been referred to as "uncontrolled case studies" (Marsh 1998) and are common in the occupational medicine literature (e.g., Creech 1974; Enterline 1976). Indeed, knowledge about occupational exposures is typically sought during the diagnosis and enters into the final decision to classify the patient as a "case" of disease (La Dou 1997). The present database is comprised of cases for which occupational radiation exposures were assumed since all of the subjects in the clinical population were workers from facilities in which radiation exposures were the norm.

The present study used data analysis tools from the artificial intelligence and statistical fields in order to generate new, objective diagnostic groups in the absence of information about radiation dose or the existing diagnosis. The results showed a remarkably clear separation of the classes according to the depression of blood counts and association of blood count depression with cumulative radiation dose equivalents. The CART method, used here principally to learn the features of the model underlying the classification, revealed a model that is conceptually similar to the clinical diagnostic model (Fig. 5). Interestingly, the CART model showed that the groups were separable on the key blood cell counts alone, and that additional information about specific cell types did not improve the model. This finding is not unusual, since the fluctuations of the differential cell counts can reflect many other processes in the body, i.e., infections or underlying chronic diseases. For example, the occurrence of many other factors that can contribute to aberrant blood counts certainly confounded the analyses of blood counts in the Techa River studies (Kossenko et al. 1998).

Table 2. Whole blood cell counts before and after neural network classification.

Blood cell type	Clinic diagnosed: Mean counts ± SD (10^9 m^{-3})	p^a	NN classified: Mean counts ± SD (10^9 m^{-3})	p^a
Thrombocytes	220 ± 36.4[b]	0.0022	223 ± 27.1[c]	0.0001
	200 ± 22.4		188 ± 17.9	
Leukocytes	5.80 ± 0.937	0.1003	6.10 ± 0.812	0.0001
	5.45 ± 0.900		5.02 ± 0.710	
Erythrocytes	4.56 ± 0.293	0.4640	4.87 ± 0.221	0.0513
	4.72 ± 1.11		4.48 ± 1.29	

[a] Significance level for a Student's *t*-test for the difference between the means. All had 86 degrees of freedom.
[b] Under a given blood cell type, the first line shows "uninjured workers" and the second line, "Chronic Radiation Sickness."
[c] Under a given blood cell type, the first line shows "unaffected" and the second line, "affected" individuals.

Table 3. Differential blood cell counts before and after neural network classification.

Blood cell type	Clinic diagnosed: Mean counts ± SD (10^9 m^{-3})	$(p < x)^a$	NN classified: Mean counts ± SD (10^9 m^{-3})	$(p < x)^a$
Thrombocytes	220 ± 36.4[b]	0.0022	214 ± 29.0[c]	0.0086
	200 ± 22.4		198 ± 26.7	
Leukocytes[d]	5.80 ± 0.937	0.1003	6.11 ± 0.806	0.0001
	5.45 ± 0.900		4.98 ± 0.667	
Erythrocytes	4.56 ± 0.293	0.4640	4.82 ± 1.29	0.1248
	4.72 ± 1.11		4.51 ± 0.239	
Basophils	0.0153 ± 0.0175	0.7348	0.0190 ± 0.0181	0.0724
	0.0165 ± 0.0142		0.0132 ± 0.0107	
Eosinophils	0.130 ± 0.0747	0.9682	0.164 ± 0.0764	0.0001
	0.131 ± 0.120		0.0972 ± 0.0539	
Polymorphonuclear leukocytes	3.22 ± 0.706	0.0979	3.29 ± 0.706	0.0002
	2.96 ± 0.657		2.77 ± 0.542	
Lymphocytes	1.74 ± 0.334	0.2713	1.86 ± 0.336	0.0001
	1.65 ± 0.359		1.48 ± 0.243	
Monocytes	0.343 ± 0.0863	0.0617	0.427 ± 0.0725	0.0001
	0.384 ± 0.0967		0.314 ± 0.0807	
Bands	0.306 ± 0.155	0.7846	0.341 ± 0.164	0.0041
	0.297 ± 0.136		0.256 ± 0.0958	

[a] Significance level for a Student's *t*-test for the difference between the means. All had 86 degrees of freedom.
[b] Under a given blood cell type, the first line shows "uninjured workers" and the second line, "Chronic Radiation Sickness."
[c] Under a given blood cell type, the first line shows "unaffected" and the second line, "affected" individuals.
[d] Not used in the cluster model due to redundancy with differential counts.

Table 4. External radiation dose equivalent (whole-body) for three sub-models.

Model	External dose-equivalent and 90% confidence limits (Sv)[a] "Unaffected" workers	"Affected" workers	Probability[b]
Clinical classification	0.31 (0.0035, 3.4)	1.7 (0.0007, 18)	0.000001
	21	60	
Whole counts	0.78 (0.0014, 8.6)	1.5 (0.0007, 17)	0.0298
	43	39	
Differential counts	0.82 (0.0013, 9.0)	1.4 (0.0008, 16)	0.0728
	42	40	

[a] The first line shows the geometric mean (bold) and 90% confidence limits. The second line is the group *N*. Doses of "zero" were eliminated from the calculation (see text).
[b] Student's *t*-test for the difference between the log means.

The notion that our quantitative approach yielded a biologically valid model was supported by the fact that, similar to the historical diagnosis, the "affected" group was statistically associated with a greater cumulative external dose equivalent. This study independently confirms the observations (Guskova and Baysogolov 1971; Okladnikova et al. 1994) that statistically significant changes in blood cell counts occur with prolonged high exposures to external radiation. However, the present study is not intended to refute the clinical significance of the historical classification or diagnosis. For example, the average leukocyte and thrombocyte counts for the affected groups, either by clinical diagnosis or by the cluster approach, are still considered to be in the hematologically "normal" range. The small changes observed in this population are similar in magnitude to the persistent increases in leukocyte counts in smokers (Schwartz and Weiss 1991; Sunyer et al. 1996), even the small

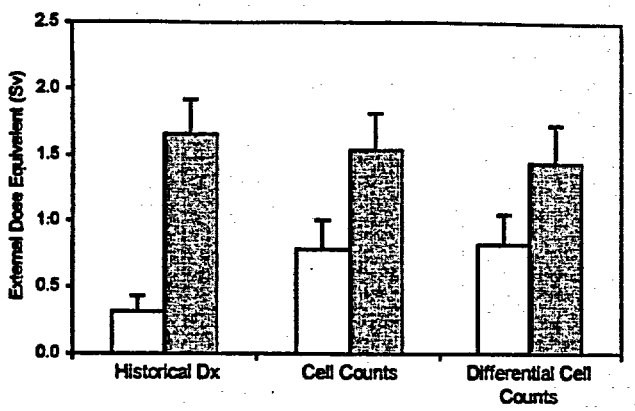

Fig. 4. Geometric mean radiation dose equivalent from external sources under three different sub-models. Error bars are for the standard error of the mean estimate (under a log transformation). The geometric means are reported in Table 4.

Table 5. Cross validation classification accuracy of the sub-models.

Model	Sensitivity (%)	Specificity (%)
Whole cell counts	93.2	88.6
Differential cell counts	80.0	62.8

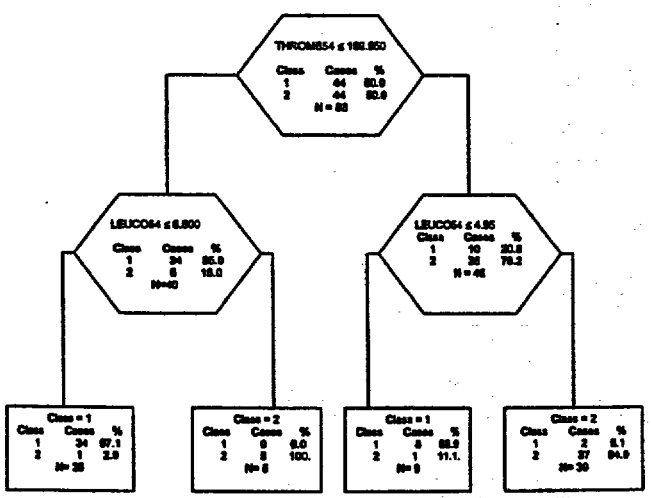

Fig. 5. Classification tree from the Cluster-CART model for Whole Blood Cell counts. The nodes show the splitting criteria for the model. Branches to the left are "true" and to the right are "false." THROMB54 is the thrombocyte count and LEUCO54 is the leukocyte count. The rectangles are terminal nodes showing the final classification. Here, Class 1 = affected individuals and Class 2 = unaffected individuals.

changes observed in smoking are associated with clinically significant outcomes (Friedman et al. 1974). Certainly, other factors are at play in the etiology of chronic malaise in CRS; and, it is likely that the diagnostic teams of the 1950's considered these qualitative factors in their decision making. These factors are the subject of ongoing study on CRS and other deterministic health effects from exposures to ionizing radiation.

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APPENDIX

Each example (or subject) in the data base is presented to the network as an input vector, $x = (x_1, x_2, \ldots x_n)^T$ where each x_i represents an independent variable (input) in the model. The modeler sets the expected number of clusters (or classes) in the output, represented as the output vector, $y = (y_1, y_2, \ldots y_K)$. The input data are "normalized," which in the neural network literature usually refers to scaling the variables from 0 to 1. The input vector is connected to a matrix of weights (w_{ij}) where i is the index of the output vector y^T and j is the index of the input vector, x^T. In matrix notation, the competitive network can be written as

$$X^T W = Y^T. \tag{A1}$$

The initial weights are typically drawn from a uniform distribution ($U[0,1]$). Once initial conditions are established, the competitive learning algorithm is implemented in the following steps:

1. Present an example to the input of the network;
2. Calculate the outputs (y_i) where y_i is given by a distance or similarity function, such as the Euclidean distance,

$$y_i = \sum_j (y_i - w_{ij})^2;$$

3. Assign the winning output index (i^*) from $= max_i(y_i)$;
4. Update the weights connected to only the winning index (i^*), using the correction where η is the learning rate parameter supplied by the user;

$$\Delta w_{i^*j}(t) = \eta(x_j - w_{ij});$$

5. Continue with steps 1–4 for the remaining examples in the data set; and
6. Repeat steps 1–5 for the number of epochs set by the user. The full competitive learning model suffers from the fact that many data sets lead to a condition in which a single winning index is quickly favored and then dominates the learning process. In a classification problem, this situation leads to a possible single class label on the outputs. In order to avoid this artifact, "conscience" is used to apportion the weight update calculations. This is accomplished changing eqn (A1) to:

$$i^* = \max_i(y_i + b_i) \tag{A2}$$

where

$$b_i = \Gamma(KF_i - 1).$$

The expectation value for winning outputs is $1/K$, where K is the number of outputs. The factor F_i is $0 \leq F_i \leq 1/K$ where $F_i = \beta(1 - F_i)$ when i is a winning index and $F_i = -\beta F_i$ for the losing output indices. The constants β and Γ are set by the user to control the rate of learning.

■ ■

individual measurements to validate models used to calculate external and internal dose in the TRDS-2000 and to establish an updated TRDS-2004 dosimetry system.

TPM-B.2

DETERMINATION OF RADIATION DOSES RECEIVED BY WORKERS AT THE MAYAK PRODUCTION ASSOCIATION. E. Vasilenko,[1] V. Khokhryakov,[2] S. Miller,[3] and J. Rabovsky[4] ([1]Mayak Production Association, Ozyorsk, Russia 456780; [2]Southern Ural Biophysics Institute, Ozyorsk, Russia 456780; [3]University of Utah, Salt Lake City, UT 84112; [4]Department of Energy Gemantown, MD 20874-1290)

Under the sponsorship of the Joint Coordinating Committee on Radiation Research (JCCRER) the United States and Russian Governments have been conducting research into the health effects arising from radiation exposure of workers at the Mayak Production Association (PA). As part of this project a set of databases has been assembled containing dosimetric information on external exposure to approximately 19,000 individuals and on internal exposure to approximately 6,000 individuals. A related database on occupational history has been developed to compliment the dosimetry database. The doses cover the period from 1948 until 1996. The external sources of exposure were gamma and neutron radiation, and internal source of exposure was from uptake of plutonium and other transuranic elements. External worker doses range from nearly 100 cGy per year during the early years of operation to well within established international standards since the 1960's. These doses were received both from protracted and acute modes of exposure. Current research efforts are focused on following general approaches for refining the dosimetric data: improved correction factors for the individual dosimeter results; improved methods for calculating neutron doses; enhancement of the biokinetic model for plutonium; improved models for calculating organ doses from internal and external sources of radiation; and improved estimation of uncertainties.

TPM-B.3

ACUTE RADIATION SYNDROME AMONG NUCLEAR WORKERS OF MAYAK PRODUCTION ASSOCIATION. T.V. Azizova,[1] M.V. Sumina,[1] V.S. Pesternikova,[1] S.V. Osovets,[2] and N. Wald[3] ([1]Southern Ural Biophysics Institute, Russia; [2]University of Pittsburgh; [3]LRRI, USA and MPI, Russia)

Radiation accidents (e.g., at Chernobyl, in Guyana, and in Tokai-mura) have led to exposure of humans (nuclear workers and the public) to large radiation doses. Now it is recognized that there are nuclear terrorism threats to humans from individuals and organizations committed to carrying out such acts. In order to make better predictions of radiation risks and to minimize the consequences to societies of nuclear accidents and nuclear terrorist incidents, it is important to make full use of currently available data on radiation effects in humans. Research results to be reported in this presentation relate to data for the acute radiation syndrome (ARS) among Mayak Production Association (MPA) workers exposed to external gamma rays and neutrons. The MPA was the first Russian nuclear enterprise (established for producing plutonium). The MPA workers were exposed to a wide range of radiation doses and there is long-term follow-up (50 years) of the workers including detailed clinical and dosimetry information. During 1948-1958, there were 19 accidents at MPA resulting in 59 cases of the ARS registered for 49 males and 10 females as follows: 8 individuals with degree IV of the ARS (most severe); 6 individuals with degree III (severe); 9 individuals with degree II (moderate); 36 individuals with degree I (mild). This presentation will include a clinical description of all ARS cases (diagnostics and treatment, classification by degree of severity, ARS consequences, and results of long-term follow-up for survivors).

TPM-B.4

INFLUENCES OF RADIATION AND NON-RADIATION FACTORS IN THE OCCURRENCE OF LIVER AND BILIARY TRACT MALIGNANCIES AMONG PLUTONIUM PRODUCTION WORKERS. Z. Tokarskaya,[1] G. Zhumtova,[1] B. Scott,[2] V. Khokhryakov,[1] and E. Vasilenko[3] ([1]Southern Ural Biophysics Institute, P.O. Box 456780, Ozyorsk, Russia; [2]Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive, Albuquerque, NM 87108; [3]Mayak Production Association, P.O. Box 456780, Ozyorsk, Russia)

This case-control study, based on Mayak Production Association (Mayak PA) nuclear workers, has focused on the influence of external g radiation, ihhaled ^{239}Pu, and non-radiation factors (e.g., virus hepatitis, chronic digestive diseases, alcohol consumption) on the occurrence of liver and biliary tract cancers. The study is in progress and preliminary results are summarized here. Internally incorporated ^{239}Pu exceeding 14.8 kBq was found to influence the development of both hemangiosarcoma and hepatocellular carcinoma. The odds ratio (OR) for hemangiosarcoma at ^{239}Pu body burdens of 14.8–74.0 kBq is 11.1. For ^{239}Pu body burdens of 74.0–172.1 kBq, OR=55.5; attributable risk (AR) due to ^{239}Pu is 74%. The OR for hepatocellular carcinoma at ^{239}Pu body burdens of 14.8–96.3 kBq is 6.4 (AR=11%). A contribution of