

## MEMORANDUM

**DATE:** January 10, 2000

**TO:** Tom Bell, Mohandas Bhat, Frank Hawkins, Ruth Neta, Joe Weiss, and Libby White

**FROM:** Barrett Fountos *BFF*

**SUBJECT:** Summary of the January 10, 2000 Meeting of the Chernobyl Oversight Panel

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The Chernobyl Oversight Panel (COP) of the National Cancer Institute's (NCI) Division of Cancer Epidemiology and Genetics (DCEG) met at NCI to review the status of the Chernobyl thyroid and leukemia studies. Shelia Zahm, Deputy Director, chaired the meeting. Attendees included Dr. Gil Beebe, Dr. Andre Bouville, Ms. Betsy Duane, Dr. Patricia Hartge, Dr. Robert Hoover, Dr. Jay Lubin, Dr. Nick Luckyanov, Dr. Ihor Masnyk, Ms. Sharon Miller, Dr. Jacob Robbins, Dr. Elaine Ron, Ms. Kathi Stine, and Mr. Barrett Fountos.

Dr. Richard Klausner approved the revised Phase II leukemia study in principle. A copy of the approval memorandum is attached. NCI staff members are working on a revised protocol. Dr. Ron announced that funds are available for Phase II. It was agreed that Dr. Beebe would develop epidemiology rules for discontinuing Phase II in 3 months (April 1) and that the dosimetry would be evaluated every 6 months. Much work is needed to be done on the dosimetry. Dr. Bouville estimated that it may take 6 to 9 months to determine whether the data are sufficient to proceed with Phase II. During this time, he plans to: obtain more information as to what dosimetric data are available in the Ukrainian State Chernobyl Registry; improve newly evolving analytical methods, such as soft expert assessment of doses (SEAD); and ensure that EPR technology is as good a dosimetric tool as NCI thinks that it is.

Dr. Ron has obtained funds for another dosimetrist. Dr. Steve Simon, scheduled to begin on February 1, will be responsible for dosimetry related to the NCI-sponsored Iodine<sup>131</sup> study. This will enable Dr. Bouville to work full-time on the Chernobyl dosimetry.

Dr. Zahm reported that the ACERER subcommittee reviewing the NCI Chernobyl studies was more than satisfied about the progress of the studies since the change to DCEG. The subcommittee plans to visit key Ukrainian and Belarussian scientists in March.

The American component of the Binational Advisory Groups of the thyroid studies wrote to Dr. Klausner that its members are pleased with the progress of the thyroid studies. A copy of the letter is attached.

The COP will meet on February 7 at 10:30 a.m. at NCI.

**Division of Cancer Epidemiology and Genetics  
Chornobyl Oversight Panel  
Monday, January 10, 2000  
10:30 a.m.- 12:30 p.m., EPS 7101**

**AGENDA**

**I. Leukemia Study**

Approval for Phase II from Dr. Klausner  
Strategy for developing "stopping rules" within three months  
On-going six-month evaluations  
Working Group: role, composition, changes in status?

**II. 2000 Calendar of Events**

Meetings: US members of advisory groups, binational meetings of advisory groups, annual trinationaional meeting, others  
Reports  
Study milestones

**III. Status of ACERER Review**

**IV. Thyroid Study**

Report to Dr. Klausner from U.S. members of the Binational Advisory Group  
Revised action items  
Plan to develop protocol for rescreening

**Future COP Meetings, 10:30-12:30, EPS/7107:**

Feb. 7	July 17
Mar. 13	Sept. 5
April 10	Oct. 2
May 1	Nov. 6
June 5	Dec. 11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

912-0321

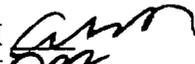
National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** December 20, 1999

**FROM:** Chair, DCEG Chernobyl Oversight Panel

**SUBJECT:** Recommendation Concerning Continued Research on Leukemia Among Chernobyl Liquidators

**TO:** Director, NCI 

**THROUGH:** Deputy Director, NCI   
Director, DCEG, NCI 

The NCI Chernobyl Research Program includes a project to evaluate the feasibility of studying leukemia among Chernobyl liquidators from Ukraine. A report on the feasibility study (Phase I) was submitted this Fall and evaluated by a binational Working Group and the DCEG Chernobyl Oversight Panel. This memo summarizes the results of Phase I, the evaluations, and the DCEG Chernobyl Oversight Panel's recommendation concerning continued research (Phase II).

The liquidators were emergency workers who helped extinguish the Chernobyl nuclear reactor fire and decontaminate the surrounding area after the accident. The liquidators included atomic energy workers, active duty military, partisans (military reservists), and civilians. Liquidators came from many countries of the former Soviet Union. The NCI project is limited to Ukrainian liquidators. Workers from some of the other countries have been or are being studied by other organizations.

The main scientific objective of a study of liquidators would be to elucidate the dose-response and time-response characteristics of the target diseases and to estimate the dose-rate risk reduction factor in comparison to the experience of the A-Bomb survivors. When Phase I was launched in 1996, the anticipated study design for Phase II was a case-cohort design of leukemia, lymphoma, and related disorders, with case accrual over 25 years from 1986.

Phase I assessed the quality of the data in the State Registry of Ukraine, a database containing identifying information, medical examination results, and official radiation doses for approximately half of the liquidators. Phase I also evaluated the ability to obtain medical records maintained at the oblast level via computerized record linkage, the confirmation of leukemia diagnoses made by the oblast hematologic departments, the availability of diagnostic materials, the completeness of follow-up within the Registry, and the feasibility of obtaining questionnaire data and biospecimens from liquidators.

The report on Phase I states that the Registry provides a suitable source for establishing a roster

of liquidators, important variables are generally complete (except for dose), the quality of diagnoses and availability of diagnostic material are good, the follow-up and biospecimen response rates are excellent, and the questionnaire response rates acceptable. On the other hand, the dosimetry data are extremely incomplete and various methods of estimating dose appear to have limited reliability in comparison with the Electron Paramagnetic Resonance method, the 'gold standard' dosimetric method based on subjects' teeth. Teeth are available for only a small proportion of the cohort, so other methods must be used to estimate doses for most subjects. The validity of these methods is an extremely important limitation which, if not remediable, would render the investigation of little scientific value.

In addition, Phase I found that the Registry does not identify all cases of the target diseases and that case ascertainment should be done at the oblast hospital level. Also, the Registry appears to be missing certain military and Ministry of Interior workers, so that many high-dose individuals are not included. Most of the remaining workers have doses well below the level at which a leukemia effect was seen among A-bomb survivors. Subjects have been and continue to be added to the Registry regularly, and care must be taken to avoid bias if their recent inclusion was because of health reasons.

The results of the leukemia feasibility study were reviewed by the U.S. members of the binational Working Group at meetings in August and October and by the U.S. and Ukrainian members at their joint meeting here in November. Major changes to the 1996 plans for Phase II were suggested:

- 1) The epidemiologic design would be changed from a case-cohort approach to a case-control approach.
- 2) The target diseases would be leukemia, myelodysplasia, and multiple myeloma. Lymphoma would be omitted because there is little evidence that radiation causes leukemia at the doses experienced by liquidators.
- 3) Research on molecular biology and on the pathogenesis of leukemia and lymphoma among high-dose subjects, with its requirement for banking tissue, would not be attempted at this time, because of the paucity of high-dose cases.
- 4) The study would be essentially retrospective in scope, covering cases occurring in 1987-2001, and would be conducted in 2000-2003.
- 5) The role of cytogenetics in dosimetry and diagnosis would be reduced in favor of physical dosimetry and dose reconstruction.
- 6) Attempts would be made to gain access to information on military and Ministry of Interior workers.

Members of the DCEG Chernobyl Oversight Panel reviewed the Phase I report, attended the Working Group meetings, and evaluated the Working Group recommendations. At its December meeting, the Panel voted to support initiation of the revised proposal for a nested case-control study while more work on dosimetry is conducted. Because the Panel thought that most radiation-related leukemia cases among the cohort would have occurred by 2001, the Panel

Leukemia Among Chernobyl Liquidators

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strongly endorsed the change from prospective accrual of cases over 25 years to a retrospective case ascertainment through 2001 only. COP endorses taking steps to initiate a revised Phase II; however, clearly defined stopping rules should be developed, particularly in relation to the quality of the dosimetry data. The DCEG Chernobyl Research Unit should immediately renew international agreements and other actions needed to continue research on liquidators. The Unit should submit draft stopping rules to the Panel for review within the next three months. The progress and further feasibility work should be evaluated every six months. If the specified conditions for a successful study are not met, the study would be stopped.

Please indicate below your concurrence with the recommendation of the DCEG Chernobyl Oversight Panel to proceed to study leukemia among Ukrainian liquidators via a nested case-control study based on cases accruing from 1987 through 2001. Please return to me at EPS 8074 or FAX: (301) 402-3256. Thank you.

  
Shelia Hoar Zahm, Sc.D.

Approval:   
Richard D. Klausner, M.D.

Date: 1/3/00

Disapproval: \_\_\_\_\_  
Richard D. Klausner, M.D.

Date: \_\_\_\_\_

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# Pacific Northwest National Laboratory

Operated by Battelle for the  
U.S. Department of Energy

November 4, 1999

Dr. Richard D. Klausner, M.D.  
Director  
National Cancer Institute  
Bethesda, MD 20892

Dear Dr. Klausner:

## Observations of the Bi-National Advisory Group for Chernobyl Thyroid Studies

The US/Belarus and US/Ukraine Bi-National Advisory Groups met in Minsk, Belarus and Kiev, Ukraine on 11-12 and 14-15 October 1999. Our Belarusian and Ukrainian colleagues on the Bi-National Groups were pleasant and there was no friction. After making statements they seemed happy to let the American delegates draft the report to the project directors. We have provided you with copies of our individual reports of these meetings. There are some additional observations that we would like to direct to NCI management about these projects.

The study of thyroid cancer in the population of Belarus and Ukraine as a result of the Chernobyl accident bears many resemblances to the studies of the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki. Despite total control by an occupation force and American investigators in place, the initial years of the study were chaotic. In contrast, Belarus and Ukraine are independent countries and hostile to one another. Furthermore, American workers are not located there on a full-time basis. Numerous international organizations are competing to study the problem, and local physicians who desperately require funds will accommodate anyone. Taken in this context, the NCI sponsored study in Belarus and Ukraine is making good progress.

The epidemiology component of the study has very strong leadership on the American side, as both Drs. Gilbert Beebe (NCI) and Geoffrey Howe (on contract from Columbia University) are outstanding epidemiologists with a strong commitment to the study. Their efforts are having a great effect in shaping both the Belarussian and Ukrainian studies into scientifically valid studies. The recent addition of Dr. Terry Thomas to NCI's Chernobyl Research Unit is also a distinct asset, as she is a very competent epidemiologist and manager who has considerable experience with studies in Eastern Europe.

The project directors in both Belarus and Ukraine appear to be primarily interested in the funding and would like to use the project to augment their meager resources, which understandable.

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Dr. Richard D. Klausner, M.D.  
October 27, 1999  
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However, they appear to be cooperating with Dr. Howe and the US group. The various scientific workers in Belarus appear to be less sophisticated but more eager to learn. The Ukrainian scientists appear to be more sophisticated but more rigid in their willingness to listen.

We have a general concern about the ability of both projects to enroll and retain sufficient participants to meet the numbers necessary for unequivocal epidemiological results. Based on the power studies conducted by Dr. Howe, about 12,000 people are needed in both studies. We have recommended that the studies attempt to have this many enrolled by the end of next year, although this target date is probably overly optimistic. Achieving that number is an ambitious undertaking. If the studies miss this number by a wide margin, there would be reason to reconsider their feasibility or scale back the resources being invested.

Data management is weak in both studies. There will be pressure from each country for new equipment, but at this point, the more important priority is planning and software development to support the needs of the projects.

Pressure exists in both countries to expand the studies beyond the current epidemiological focus. This comes from the projects' staffs, interested for humanitarian reasons in focusing help on the "most likely" victims. The critical factor in the examinations is to avoid selection bias. Because surgery is, by and large, determined by the results of FNA thyroid biopsy, the criteria for biopsy are important. Allowing the studies to be swayed in this way would undoubtedly add an uncontrolled bias to the data. Beyond this, there is also pressure from our counterparts on each country's Advisory Group to add additional parochial research (from which their individual institutions could benefit). Until the project is on a more solid footing, these expansions should be avoided.

In the Ukraine, it appears that Dr. Derevyanko is doing a competent job in directing the epidemiological effort. Preliminary indications are that, under her guidance, the epidemiologic aspects of the study are making good progress. Given that she is young and not highly experienced in analytic epidemiology studies and perhaps has a limited background in epidemiologic methods and approaches, it is suggested that she again be brought to the USA for a month or two of more advanced training (e.g., epidemiologic summer school courses, etc).

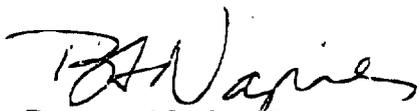
It is probably also worth commenting on the NIH coordinator of the project, Dr. Ihor J. Masnyk. He appears to be very effective in dealing with the groups in both Belarus and Ukraine. Clearly his language skills are a great advantage. He seems to use an approach that might be described as "tough love" in that he is supportive but demanding, which appears to be working.

Finally, the studies protocols call for annual reviews of the projects by the Bi-National Advisory Groups. This is a long interval for us to go without information while we try to remain current, at least at this stage of project development. At the same time, we do not wish to travel too frequently or get in the way of progress. We understand that the project directors prepare quarterly reports; it would be useful if we could receive these. We would also appreciate receiving the results of any other NCI reviews of the project.

Dr. Richard D. Klausner, M.D.  
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We would like to reiterate that these large and complex projects are uniquely important to understanding human risk from exposure to radionuclides. We wish to emphasize that we have presented our impressions after spending only 3 days in each country and could easily be mistaken. However, we thought it important to provide you with our initial impression. We appreciate the opportunity to work with NCI in making the studies successful.

Sincerely,



Bruce A. Napier, CHP, US Chair, for  
Gerard N. Burrow, M.D.  
Roy Shore, Ph.D, DrPH.

cc: Dr. Joseph Fraumeni  
Dr. Elaine Ron



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Pacific Northwest National Laboratory  
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Richland, WA 99352

Dear Mr. Napier:

Thank you for your November 1999 report as U.S. Chair of the Bi-National Advisory Group for the NCI Chernobyl Thyroid Studies. Your report is very helpful to us as we evaluate the current status and future plans for our Chernobyl research effort. The NCI Chernobyl Research Unit is working with Columbia University and our collaborators in Ukraine and Belarus to improve subject recruitment and retention, data management, and epidemiologic training of the staff, as you recommended. Your advice to maintain the current epidemiologic focus of the screening program is also useful as we draft the protocol for future rounds of screening.

As you requested, we will take steps to keep you informed about the project throughout the year. I have asked Dr. Ihor Masnyk to send you the quarterly reports submitted by the project directors from Belarus and Ukraine and any other important documents produced between now and the next meeting of the Bi-National Advisory Group.

We are grateful to you and the other members of the Advisory Group for your willingness to share your expertise and to travel overseas to help us maximize the scientific opportunities presented by this accident.

Sincerely,

Richard D. Klausner, M.D.  
Director

cc: Gerard N. Burrow, M.D.  
Roy Shore, Ph.D., Dr.P.H.  
Alan S. Rabson, M.D.  
Joseph F. Fraumeni, Jr., M.D.