OAK RIDGE NATIONAL LABORATORY
OPERATED BY MARTIN MARIETTA ENERGY SYSTEMS, INC.
POST OFFICE BOX X, OAK RIDGE, TENNESSEE 37831

ORNL/FTR--2530

DE89 017346

ORNL

FOREIGN TRIP REPORT

ORNL/FTR-2530

DATE: April 12, 1987

SUBJECT: Report of Foreign Travel of Paul B. Selby
Research Staff Member, Biology Division

TO: Herman Postma

FROM: Paul B. Selby

PURPOSE To serve as a Scientific Advisor in the U.S. Delegation to the Thirty-sixth session of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) held in Vienna, Austria, March 23-27, 1987.

SITES VISITED 3/23-27/1987 UNSCEAR Meeting, Vienna, Austria

ABSTRACT The traveler attended the Thirty-sixth session of UNSCEAR where he took an active part in the deliberations of the Genetic Sub-subgroup. Good progress was made in discussing the two documents that are in preparation that deal with genetics. Approximately one-third of the traveler's time was spent observing sessions of the main UNSCEAR committee itself, and the remainder was spent in the Genetic Sub-subgroup. Important contacts were made with several prominent geneticists. It was apparent how important it is to ORNL, to DOE, to the United States Government, and to UNSCEAR itself to have at least one representative from the United States on the Genetic Sub-subgroup who has firsthand familiarity with the mouse data that are used to such an important extent in genetic risk estimation. Many of these data were collected in the Biology Division of ORNL.

DISCLAIMER

The UNSCEAR meeting began and ended with plenary sessions. These sessions were chaired by Professor Bo Lindell (Sweden). The People's Republic of China was welcomed to membership in UNSCEAR, and its delegate, Dr. Wei Luexin, also served on the Genetic Sub-subgroup. The next meeting of UNSCEAR will be from June 6-17, 1988. Such a long meeting will be necessary to complete work on the documents that are scheduled to be published next year. It is expected that the Genetic sub-subgroup will only have to meet from June 13-17.

Besides the representative from the People's Republic of China, other new members of the Genetic Sub-subgroup were Dr. N. K. Notani from India and Dr. P. H. M. Lohman from The Netherlands (representing Belgium). Dr. Lohman now has the position at the Sylvius Laboratories in The Netherlands that had been held by Dr. Frits Sobels (a long-time participant in UNSCEAR). Through a special arrangement between their countries, several Dutch scientists serve as scientific advisors to the delegation from Belgium.

Dr. A. G. Searle was unanimously elected to act as Chairman of the Genetic sub-subgroup. The work of the Genetic Sub-subgroup involved review of the following two documents scheduled for publication in 1988: A/AC.82/R.462 "Genetic Hazards" and A/AC.82/R.454 "Report to the General Assembly."

The document entitled "Genetic Hazards" spans the entire history of organized efforts to estimate genetic risk. It discusses the origins of the currently used methods and various methods that have been abandoned. Because this document is historical in nature and because it was written by someone very familiar with the field, it is not surprising that this document prompted relatively little discussion or argument. Some mistakes were corrected and omissions noted, however.

It appears unlikely that there will be any changes in the genetic risk estimates in 1988 from those made by UNSCEAR in 1986. After the 1988 report, it seems likely that the UNSCEAR will return to its usual cycle of producing a reevaluation of the genetic risk estimates once about every four years, with the next detailed report being published in 1992 or thereabouts.

The "Report to the General Assembly" required much more work on the part of the Genetic Sub-subgroup because it contained many serious omissions and errors as the result of its being drafted by someone with much less familiarity with genetics.

At the committee's request, I compiled a table for inclusion in this report that shows the UNSCEAR estimates of risk made in 1977, 1982, and 1986 using the direct method of estimation. The text that is to accompany it reads as follows: "The estimates by the direct method include risk from induction of dominant mutations, as well as from deletions, balanced reciprocal translocations with dominant effects, and unbalanced products of reciprocal translocations. The latter estimate is based

mainly on data collected in primates including humans. The estimates also relate to irregularly inherited disorders in people because the data upon which they are based include mutations with low penetrance for serious effects. It should be realized that these estimates may be too low because of the omission of mutations that are so severe that they cause death prior to the time of detection in mouse experiments. The extent of the omission is thought to be 5-10 cases per million live born, but this estimate has not yet been included in the table pending further thought and forthcoming data. The estimates for women are currently based primarily on their risk as compared to that of men, as judged from specific-locus mutation induction experiments in mice."

As will be mentioned later, there is presently much uncertainty about how genetic risk should be estimated for the irregularly inherited disorders by the other method that is used, which is the indirect (doubling-dose) method. This uncertainty is a serious problem because such disorders make up the great majority of human genetic disorders. For a long time, I have stressed the importance of developing methods for measuring dominant induced damage that can detect mutations of low penetrance so that the data found also relate to serious irregularly inherited disorders. It is good to have this important aspect of the direct method pointed out in the above paragraph of the "Report to the General Assembly."

The original "Report to the General Assembly" contained serious errors and misinterpretations related to the risk estimates made by the doubling-dose method. Much time was spent in correcting this material and in discussing how it should be presented to the General Assembly. This material is complicated to present because of the great uncertainties that occur when trying to apply the doubling-dose approach to less severe types of disorders. One of the figures used in the calculation of risk by the doubling-dose approach is the estimate of the current incidence of genetic disorders. Because of a detailed analysis of the incidence of human genetic diseases in Hungary by K. Sankaranarayanan (who writes the genetics reports for the committee) and A. Czeizel, it now appears that the current incidence of severe hereditary disorders in the population is approximately 676,000 per million live-born individuals. This estimate is approximately six times higher than the current incidence figures that were used in 1982 when the doubling-dose method was last applied by a committee for estimating risk for all hereditary disorders. If all other parts of the calculation were now made in the same way as in 1982, there would be a large increase in the estimates of risk made by the doubling-dose method.

A second complicating factor in applying the doubling-dose method is that most of the reason for the large increase in the estimate of the current incidence results from the inclusion of somewhat less severe multifactorial disorders. There is much uncertainty about how to estimate risk for such disorders. It is felt that the incidence of many of these in the population may have little relationship to the mutation frequency. For such disorders, one of the numbers that must be multiplied by, when calculating the risk, is the mutational component. The mutational

component was assumed to be 5% when, in 1982, UNSCEAR last made risk estimates for such disorders by the doubling-dose method. Now it seems possible that the mutational component might be substantially higher, and there are grave doubts about our ability to make reasonable estimates of it. Should the mutational component be much higher than 5%, there would be a considerable increase in estimates of risk by the doubling-dose method even if the current incidences were as low as they were thought to be in 1982. Stated briefly, the situation regarding doubling-dose estimates is that the committee now feels that such estimates can be made reasonably well only for the disorders that have a combined current incidence of approximately 13,000 per million live-born individuals. No attempt is being made to apply this method to disorders that have a combined current incidence of approximately 663,000 per million live-born individuals.

A major reason for the huge increase in the more recent estimates of the current incidence of genetic disorders is that there has been a considerable widening of the range of disorders considered to have an important genetic component. The following question is thus of much importance: "Is it justified to try to estimate genetic risk for such disorders, or should risk estimates be restricted to more severe conditions that are better understood?"

The current incidence of approximately 676,000 per million includes some overlap. That is, some individuals have two or more disorders, with the result that the current incidence does not mean that 67.6% of all individuals are affected, as many would interpret it to mean. This complication also causes difficulties in the application of the doubling-dose method. Unfortunately, it would be very difficult to determine the incidence of affected individuals from the data base that yields the high incidence of disorders. While many less severe disorders are included in the incidence of 676,000, some very severe anomalies were, surprisingly, not included because the scientists doing the analysis plan to deal with them in more detail later. Thus, the estimates of the current incidences, which are critical for calculations by the doubling-dose method, are probably still subject to considerable changes. Many members of the committee strongly question whether there is any justification for trying to estimate risk for the less severe and very common genetic disorders.

I am one of the members of the committee who feels uneasy using the doubling-dose method of risk estimation. I much prefer the direct method, which is based on damage actually detected in offspring of irradiated experimental animals. I think that methods must be improved for measuring actual induced damage in offspring of exposed mammals before significant improvements can be made in genetic risk estimation.

There was open discussion of the problems involved in the doubling-dose method of risk estimation at this meeting, and it seems likely that there will be increased emphasis on the direct methods of risk estimation in years to come. Most of my research effort is aimed at providing the types of information necessary for improved risk estimates by the direct

method, and thus DOE and ORNL can expect that research that they support will continue to form much of the basis for improved estimates of genetic risk for many years to come.

Dr. Searle distributed a report by himself entitled "Evidence for induction of early-acting dominants by irradiation of male and female germ cells in mice." He has demonstrated the induction of many mutations that result in stunted growth. For example, for males exposed to 5 Gy + 5 Gy, with 24 hours between treatments, the frequency of "small" mice in the first-generation progeny, following spermatogonial irradiation, was 1.5% in comparison to the 1.2% frequency in the concurrent control. Twelve of the small males in the experimental group were shown to transmit their effects. These showed dominant inheritance, sometimes with reduced penetrance. Because a fair number of these "small" animals died before testing for transmission was possible, Searle concluded, based on the transmission demonstrated for many that survived, that "many were probably dominant sub-lethals and steriles which mainly act between weaning age and maturity. Thus they are not included in risk estimates based on heritable dominants."

I pointed out that in my skeletal studies, which provide a major part of the experimental basis for direct risk estimates, I had also found many mice that had skeletal mutations and small size. In fact, 3 of 5 small mice that were also sterile in my original study had been counted as mutations based on "presumed mutation criteria." Because those mice were included in the data used in estimating risk, the category about which Searle was justifiably concerned was, judging from his frequency of induction, probably reasonably well accounted for in the current risk estimates. He is correct that more attention must be paid to this category. Indeed, his presentation was very timely for us because we have recently demonstrated a high frequency of induction of mutations causing stunted growth following exposure of male mice to ethylnitrosourea. Our methods were more sophisticated in that we, unlike Searle, had randomized parents, weighed all offspring as adults, and accounted for differences in weight that result from the number of offspring in the litter. The committee had a good discussion of this new endpoint, which may be of considerable importance in improving estimates of organismic damage from radiation or other mutagens.

For several years now, UNSCEAR has been trying to decide what to do regarding the claims by R. L. Dobson that genetic risk in the female might be considerably higher than had been thought. So far, its position has been that risk in the female is at most 44% of that in the male and perhaps it is negligible. The crux of Dobson's argument was his claim that those oocytes that received more than about 10 R in Russell's 50-R study would have been killed. W. L. Russell has argued that it would be impossible for any oocytes to get as little as 10 R of exposure in a mouse irradiated with 50 R of the type of X irradiation that he used. A paper by Dobson is expected to appear on this issue soon in Radiation Research, and, according to what Sankaranarayanan has learned, it now appears that in Dobson's view the risk in the female is probably no

higher than that estimated for mature and maturing oocytes. Since the upper limit of the committee's current estimate is the same as that for mature and maturing oocytes, it now appears that this controversy really has no effect on risk estimates. Thus far I am unconvinced by Dobson's arguments, but I am anxious to see his paper.

For some time now the UNSCEAR has assumed that the doubling dose, taken to be 1 Gy, is equal in the two sexes. I questioned whether this was consistent with our conclusion that the induced frequencies are much lower in the female than in the male for low-level irradiation. After some discussion, it was concluded that an equal doubling dose is probably reasonable because all indications are that the spontaneous frequency is also lower in the female. The UNSCEAR would like to make a combined single-number risk estimate for somatic and genetic effects (for the first two generations) in the "Report to the General Assembly." The Genetic sub-subgroup spent much time discussing this and argued that it should not be done. Furthermore, because of complications that I pointed out in applying the doubling dose to both sexes, the Genetic sub-subgroup concluded that it was unclear how to separate the risk for the two sexes. There should be some interesting discussion on this point next year.

I had a long discussion with Professor Luening of Sweden regarding some of his work on cytoplasmic inheritance in Drosophila melanogaster and about various topics of common interest in mouse genetics research. We discussed various ways of dealing with preexisting mutations in the stocks. He suggested that the skeletal methods might be very useful for studying cytoplasmic inheritance in the mouse. His studies in the fly suggest that if a nucleus is put into a foreign cytoplasm and then back into its original cytoplasm again, it retains a "memory" of the cytoplasm that it was in. He suggested that it would be very useful in the mouse, where nuclei can be transplanted, to put the nucleus of one inbred strain into the cytoplasm of another and then check to see whether there might be some effects on the skeleton. I agree with Professor Luening that such experiments could be of considerable interest; however, I have so many experiments waiting to be done that I see no chance of doing anything like this myself anytime in the near future.

The UNSCEAR meeting this year was especially worthwhile because there was unusually open discussion of many of the uncertainties that must be dealt with in genetic risk estimation. I learned many things and made major contributions to the discussion. It is certainly vital to the interests of the U.S. Government and to DOE programs and interests to have quantitative estimates of the genetic risks of radiation be as accurate as possible. Because so much of the information useful in making genetic risk estimates is the result of research at the Biology Division, it is in ORNL's best interest to make sure that the UNSCEAR is aware of the ORNL data and their implications. In view of this, it seems wise to continue having the Mammalian Genetics Section represented at future UNSCEAR meetings.

The UNSCEAR meeting also provided a good background for a meeting that I and many of the same scientists attended the following week at Research Triangle Park, North Carolina, that dealt with genetic risk estimation in general. I am hopeful that the excellent discussions at these two meetings will stimulate real improvements in risk estimation. It seems that these discussions should direct much attention away from the doubling-dose method and toward the direct method of estimating genetic risk. If this happens, there should be more support for research programs such as mine that are designed to improve estimates of induced organismic damage in the offspring of exposed experimental mammals.

APPENDIX

Itinerary

March 20-21, 1987	Travel from Clinton, Tennessee, to Vienna, Austria
March 22, 1987	Weekend
March 23-27, 1987	UNSCEAR MEETING
March 28, 1987	Travel from Vienna, Austria, to Clinton, Tennessee

Persons Contacted to a Significant Extent

Sylvius Laboratories
Leiden, The Netherlands

Dr. P. H. M. Lohman
Dr. K. Sankaranarayanan

Gesellschaft fuer Strahlen- und Umweltforschung
Neuherberg by Munich, Federal Republic of Germany

Dr. U. H. Ehling

University of Stockholm
Stockholm, Sweden

Professor K. G. Luening

Medical Research Council
Harwell, England

Dr. A. Searle

Bhabha Atomic Research Center
Bombay, India

Dr. N. K. Notani

Literature Acquired

Rapporteur's reports for all sessions of the Genetic Sub-subgroup

Distribution

1-2. Assistant Secretary for International Affairs, DOE, Wash.
3. Charles DeLisi, Associate Director, OHER, DOE, Wash.
4. Director, Division of Safeguards and Security, DOE, Wash.
5-6. Director, Division of International Security Affairs, DOE, Wash.
7. J. A. Lenhard, DOE/ORO
8. Director, Division of Safeguards and Security, DOE/ORO (DP-82)
9. Herman Postma
10-11. S. V. Kaye
12. P. B. Selby
13. C. R. Richmond
14. J. T. Ensminger
15. R. J. M. Fry
16. F. C. Hartman
17. R. J. Preston
18. L. B. Russell
19. H. R. Witschi
20-21. Laboratory Records Department
22. Laboratory Records Department - RC
23. Laboratory Protection Division
24. ORNL Patent Section
25. ORNL Public Relations Office
26-27. Technical Information Center