MINUTES

Subcommittee on Environmental Carcinogenesis

National Cancer Advisory Board

September 23, 1982

The Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board (NCAB), met on September 23, 1982, in Conference Room 4, Building 31, National Institutes of Health, Bethesda, Maryland.

Members Present

Mr. Sheldon Samuels (Chairman), AFL-CIO
Dr. Tim Lee Carter (ex officio), Carter Clinic
Dr. Allen Heim, FDA
Dr. Philippe Shubik, Green College, Oxford University
Dr. John Todhunter, EPA

Dr. Richard H. Adamson (Exec. Sec.), NCI

Members Absent

Mrs. Angel Bradley, NCAB
Dr. Elliott Harris, NIOSH
Dr. William Powers, Harper Grace Hospital
Dr. Peter Preuss, Consumer Product Safety Commission
Dr. David Rall, NIEHS
Dr. Janet Rowley, University of Chicago
Dr. Irving Selikoff, Mt. Sinai School of Medicine
Dr. Gerald Wogan, MIT

Invited Guests

Dr. Donald Barnes, EPA
Dr. Arnold Brown, University of Wisconsin
Dr. Charles Brown, NCI
Dr. Kenny Crump, Science Research Systems, Inc.
Dr. David Hoel, NIEHS
Dr. William Nicholson, Mt. Sinai School of Medicine

Others Present

Mr. Jerry Boyd, The Cancer Letter
Ms. Marianna Bledsoe, NCI
Dr. Patricia Breslin, OSHA
Dr. Daniel Byrd, API
Dr. J.L. Festa, American Paper Institute
Dr. D.W. Gaylor, NCTR
Dr. Donald Heyward, Union Carbide
Dr. Peter Infante, OSHA
Dr. Morris Kelsey, NCI
Dr. Steven Lamm, CEOH, Inc.
Dr. Steven Lewis, Exxon
Ms. Mary Miller, BNA
Dr. Paul Okano, NCI
Mr. Timothy O'Leary, CMA
Ms. Jo Pelham, NCI
Dr. Ann Schluederberg, DRG
Ms. Maris Udey, NCI

After Mr. Samuels opened the meeting and welcomed the participants, Dr. Adamson announced that members of the public present at the meeting who wished to express their views regarding any items to be discussed could do so by contacting him within 10 days after the meeting. He added that any statements by members of the public would receive careful consideration.

Dr. Adamson then reviewed the Subcommittee's previous meeting, which took place on August 10, 1982, and summarized the contributions made by each of the speakers.

Next, Dr. David Hoel presented the report of the ORA Definition Committee, which met to develop definitions for several terms involved in the consideration of risks. After lengthy discussion, the group accepted the committee's definitions, with minor alterations, as follows:

Hazard Identification or Characterization (Qualitative Risk Assessment):
The determination of the toxicity of a test substance in experimental systems and the prediction of such effects in man.

Quantitative Risk Estimation:
Quantitative risk estimation is the process by which the risk of disease or death in a population exposed to a toxic agent is related quantitatively to the intensity and duration of exposure.

Quantitative Risk Assessment:
The assessment of both hazard and exposure information for purposes of estimating the likelihood that the hazards associated with the substance will be realized in exposed human populations or individuals.

The group also suggested that these definitions be preceded by an introductory statement that would tie them together.

Dr. Charles Brown then discussed the magnitude of uncertainty in extrapolation from high dose to low dose, presenting as an example excerpts from the document "Saccharin: Technical Assessment of Risks and Benefits Report #1" of the Committee for a Study on Saccharin and Food Safety Policy, National Research Council/National Academy of Sciences. Dr. Brown and Dr. Shubik felt it extremely important that some mechanism be built into the process of quantitative risk assessment whereby one judges which data enter the assessment and which do not. While the other members agreed, they also felt that a central and, at present, unavoidable element in assessment is the judgment of the individuals making that assessment.

Next, Dr. Kenny Crump discussed arsenic risk assessment, pointing out that he and Dr. Steven Lamm had each presented talks on this subject at hearings held by OSHA on the inorganic arsenic standard in the summer of 1982. Dr. Crump said that a major shortcoming of arsenic risk assessments carried out by several groups was that they were all based on the output of analyses which had been done for other purposes by other investigators. He stated

that ideally, risk assessment should be developed from the original data. Dr. Crump discussed the merits of various models of risk assessment and described the procedure of model fitting, pointing out that in considering the relationship of arsenic and lung cancer, he has found that an absolute risk model is more appropriate than a relative risk model. He closed with two questions he felt deserved consideration: whether the significant exposure for a determination of risk is peak exposure or cumulative exposure, and whether there is any evidence of a threshold phenomenon occurring in exposure.

Next to talk was Dr. Lamm, who was not originally an invited speaker but was invited by Dr. Crump and allocated time to speak by the Chairman. Dr. Lamm discussed his analysis of arsenic exposure data obtained from a study of a smelter in Montana owned by the Anaconda Copper Company (Dr. Crump had previously included this in the several studies he discussed). Dr. Lamm stated that in this analysis, the categories of heavy, medium, and light risk were best described on a qualitative basis by peak exposure. He also said that risk appears to be affected far more strongly by the level rather than the duration of exposure. With regard to a threshold phenomenon, Dr. Lamm stated that while workers having lifetime "ceiling" exposures of 500 micrograms/m^3 and above had elevated risk of respiratory cancer, those having exposures less than 500 micrograms/m^3 appeared to have no increased risk of respiratory cancer, except possibly for those with cumulative exposure of 12,000 microgram/m^3-years or greater. He concluded that the excess risk of respiratory cancer from arsenic in this study appears essentially to be attributable to individuals with ceiling exposures above 500 micrograms/m^3 and not to those with exposures below that level.

The last speaker was Dr. William Nicholson, who continued the discussion of the problems and limitations in quantitative risk assessment using the example of asbestos, which is one of the few materials for which there exists a substantial amount of human epidemiology. Dr. Nicholson pointed out, however, that in considering asbestos or other carcinogens, one must take into account the problems involved in determining exposure, mechanism(s) of action, and any additional biological processes that alter the dose-response relationships that are measured.

Dr. Nicholson said that most carcinogenic agents, including asbestos, demonstrate a linear dose-response relationship with no evidence of any threshold. Moreover, the carcinogenic effect of an exposure to some important carcinogens, such as asbestos, is to multiply a pre-existing risk at a given site by a factor relating to dose and to continue to multiply the risk in the absence of exposure for several decades. Manifestation of this multiplicative factor occurs in a short period of time, between five and ten years at most; however, since the "background" risk of cancer is low at younger ages, few additional cancers may be seen until older ages when the background risk which is multiplied becomes much larger.

Dr. Nicholson then presented various estimates of the number of individuals in the United States who are presently dying of cancer from past exposures to asbestos and discussed other estimates of the number who might contact the disease in the future. He stressed that since about 27,000,000

individuals--21,000,000 of whom are alive today--were exposed to asbestos between 1940 and 1980, the potential for litigation is enormous at present and may be expected to become even greater in the future.

At this point, Mr. Samuels had to leave the meeting on business. Assuming the Chair at Mr. Samuels' request, Dr. Adamson said that the Subcommittee's final task for the day was to consider five questions posed by Mr. Samuels:

I. The definition of quantitative risk assessment (QRA) as distinct from qualitative risk assessment.

Dr. Adamson pointed out that Drs. Brown, Hoel, Tardiff, and Wogan were considering this question and that they would submit their answer at the next meeting.

II. Which models or paradigms of QRA have been, are, or are likely to be heuristic in terms of data fit, testability, and predictive experience?

After extensive discussion of this question, the participants agreed on several points. First, all of the mathematical models for use in QRA are heuristic in a sense. However, there is at present little basis for choosing between them because of our lack of knowledge about the basic biological mechanisms underlying cancer. Consequently, the members suggested that it might be advisable to run a variety of models in each assessment and select between them by using the best possible judgment in analyzing the biological information that supplements the mathematics. As time passes and more is known about basic mechanisms, certain patterns will guide researchers to select different models in different mechanisms, but it is too early to select any model as being the best or to rule out others.

The second major point was that an important part of a carefully done QRA is an explanation of the assumptions which went into it and the uncertainties which were involved.

III. Is QRA practical in terms of data adequacy of both dose and effects?

Dr. Shubik and others thought society demands that QRA be done, almost exclusive of its practicality. But in any event, they felt that the answer to this question is similar to the answer to the previous question: QRA is basically practical as long as the assumptions and the uncertainties which underly it are explicitly stated, so that those who use the QRA are not misled into believing that it represents an absolute.

IV. Are the regulatory issues which involve QRA separable from the scientific problems of QRA? For example, should economic implications be used in the selection of a specific QRA method? Should QRA be used regardless of the level of uncertainty relative to the availablity of data? Can QRA be used by itself or in combination with other factors in determining a "significant risk?"

V. Who should do QRA: scientific organizations or regulatory agencies?

The members elected to consider questions IV and V together. Drs. Heim, Breslin, and Infante felt that the regulatory issues which involve QRA are separable from the scientific issues and that QRA should be carried out as a scientific exercise independent of economic considerations. Each pointed out that other factors--social, economic, and so forth--could be studied independently of and in parallel with the QRA and that the two could be balanced against each other when the studies were complete. They also felt that both scientific and regulatory groups should conduct QRA; Drs. Breslin and Infante pointed out that their agencies would carry out a QRA on a compound even if a purely scientific organization had already done so, to assure themselves that the assessment was done properly and that the assumptions underlying the QRA were consonant with the role and obligations of a regulatory agency. It was agreed, however, that scientific organizations could make a major contribution by carrying out research to improve the various areas of QRA and in acting as consultants to regulatory agencies. Several members also suggested that some mechanism be established for an external review of the QRAs conducted by regulatory agencies, although no specific mechanism was agreed upon.

Since there was no further business to conduct, Dr. Adamson thanked the participants for their efforts and adjourned the meeting.

Executive Secretary's Note: The following documents were provided at this meeting:

Agenda
Draft definitions
Testimony by Kenny S. Crump, Ph.D. at OSHA Hearings on the Inorganic Arsenic Standard
"Example of the Magnitude of Uncertainty in High- to Low-Dose Extrapolation" from Saccharin: Technical Assessment of Risks and Benefits Report No. 1, Committee for a Study on Saccharin and Food Safety Policy, National Research Council/National Academy of Sciences, November 1978.
"Arsenic Risk Assessment: Critique and Alternative," supplemental submission, prepared for the Arsenic Program Panel, Chemical Manufacturers Association by Consultants in Epidemiology & Occupational Health, Inc.
Nicholson, W., G. Perkel, I. Selikoff, and H. Seidman, 1981. "Cancer from Occupational Asbestos Exposure Projections 1980-2000." Banbury Report 9: Quantification of Occupational Cancer.
Nicholson, W.J. 1982. "The Dose and Time Dependence of Occupational Cancer" In: Prevention of Occupational Cancer: International Symposium, International Labor Office Occupational Safety and Health Series, No.46, Geneva.