MINUTES

Subcommittee on Environmental Carcinogenesis
National Cancer Advisory Board

August 10, 1982

The Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board (NCAB), met on August 10, 1982 at the Mt. Sinai School of Medicine, New York, New York.

Members Present

Mr. Sheldon Samuels (Chairman), AFL-CIO
Dr. Allen Heim, FDA
Dr. William E. Powers, Harper Grace Hospital
Dr. Irving J. Selikoff, Mt, Sinai School of Medicine
Dr. Gerald Wogan, MIT
Dr. Tim Lee Carter (ex-officio), Carter Clinic

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

Members Absent

Dr. Elliott S. Harris, NIOSH
Dr. Peter W. Preuss, Consumer Product Safety Commission
Dr. David P. Rall, NIEHS
Dr. Janet Rowley, University of Chicago
Dr. John Todhunter, EPA

Invited Guests

Dr. Donald Barnes, EPA
Dr. Patricia Breslin, OSHA
Dr. Charles Brown, NCI
Dr. David Hoel, NIEHS
Dr. J. William Lloyd, OSHA
Dr. Robert Tardiff, National Academy of Sciences
Mr. Paul White, Consumer Product Safety Commission
Dr. Philippe Shubik, Green College, Oxford, England

Others Present

Dr. John Festa, American Paper Institute
Dr. Nancy Hall, American Health Foundation
M. Karitodt, Mt. Sinai School of Medicine
Dr. M. A. Wolfram, Clairol

Mr. Samuels opened the meeting by thanking Dr. Selikoff for making the facilities at Mt. Sinai available for this meeting and stated that the subject of risk assessment was of importance for many reasons. He stated that bill H.R. 6159 entitled "Risk Analysis Research and Demonstration Act of 1982" had passed the House of Representatives.

(NOTE BY DR. ADAMSON SUBSEQUENT TO THE MEETING: Nine Federal agencies have been identified for participation in this program. They include the Food and Drug Administration, Environmental Protection Agency, Occupational Safety and Health Administration, the Food Safety and Inspection Service of the Department of Agriculture, Nuclear Regulatory Commission, Department of Energy, Consumer Product Safety Commission, Federal Aviation Administration, and the Department of Transportation. As noted in the bill, "this list is not inclusive but it is intended to bring into the program those Federal agencies with statutory bases for regulating risks to human life, health, or the environment.")

Mr. Samuels then asked Dr. Selikoff to make the opening remarks. Dr. Selikoff stated that the subject of quantitative risk assessment and the use of various models for quantitative risk assessment was both a timely and an important issue.

Mr. Samuels then asked for approval of the agenda and requested Dr. Carter, Chairman of the National Cancer Advisory Board, to make a few remarks.

Dr. Carter stated that it was a great honor for him to have been selected as Chairman of the NCAB and that he would work with all the members of the Board and its subcommittees in order to help reduce the incidence, mortality and morbidity of cancer.

The charge to the subcommittee, which was stated in Mr. Samuels' letter of July 22 (attached) was read and approved. Mr. Samuels also reiterated five questions which should be discussed by the members of the subcommittee and the invited guests.

Dr. Adamson stated that if any members of the public wished to make comments they should send them to him within 10 days after the meeting; all comments would receive full and appropriate consideration.

Following these remarks there were presentations by the invited guests.

Dr. David Hoel, Director, Biometry and Risk Assessment, National Institute for Environmental Health Sciences, discussed the outline which is attached. This outline is based on the draft report of the workshop on "Scientific Group on Methodologies for the Safety Evaluation of Chemicals," held in Rome, Italy on July 12-16, 1982. He stated that the draft reports were not yet ready for dissemination, but would be made available to this subcommittee as soon as the reports are ready. He discussed the various models that were available for quantitative extrapolation and Dr. Wogan stated that there was no basis at the present time for selecting one model over the other. There was a discussion of the various animal models and the necessity for defininina mechanisms of carcinogenesis and building

models from the mechanisms. It was felt that animal data might be useful to help build models but would have to be done on a case-by-case basis. He also stated that one of the papers summarized the difficulty in plotting mutagenesis vs. carcinogenesis and that the thresholds were discussed in regard to lab data not human data. It is hoped that the draft reports of this workshop will soon be available.

Dr. Robert Tardiff, Director, Board on Toxicology and Environmental Health, National Academy of Sciences (NAS), National Research Council, presented various risk assessment activities at the NAS and distributed an outline which is attached. Dr. Tardiff commented on the definitions in use which are summarized in his outline and he commented on the classical use of safety factors to determine "safe" occupational exposure for military personnel.

He reviewed the Drinking Water and Health, Volume 1, risk extrapolation which was done by the NAS in which they selected a multistage model for high- to low-dose extrapolation of cancer data. They also evaluated the problems of extrapolation including experimental design, toxicokinetics, thresholds, interactions and variability of models. He briefly discussed the saccharin risk assessment which demonstrated substantial variability in risk estimates from various models. He then discussed Drinking Water and Health, Volume 3, which reaffirmed the use of multistage models for cancer data and uncertainty factors for noncarcinogens. He commented on the assessment of pesticides, particularly where they were using seven pesticides for termite control in which they used a combination of low-dose extrapolation and potency comparison to recommend tolerable exposure limits for military personnel that were exposed.

He then discussed some ongoing and potential activities of the NAS-NRC which are outlined under numbers 8-12 in his handout (attached). He also stated that the NAS at present is doing a study for Congress on quantitative risk assessment which includes primarily a review of such questions as who should be doing it, whether there should be a new agency and whether the agency should be governmental or nongovernmental.

The NAS-NRC has been exploring various approaches for assessing risks to human health from exposures to toxicants other than carcinogens. Because there is no valid way to measure toxicity thresholds in the human population, the consensus has been leaning in the direction of replacing the "safety factor" approach with some form of quantitative risk assessment that would yield results in terms of risk of a specific toxic effect per unit dose. That approach is presently limited because there is little agreement on specific mathematical dose-response models that would be scientifically defensible for noncarcinogenic endpoints. Models, such as the probit model, are presently under investigation for such a purpose.

The presentation by Dr. Charles Brown, Biometry Branch, National Cancer Institute, was on high-dose to low-dose extrapolation and a complete copy of the slides he used and his conclusion are attached. A capsule summary of his presentation is as follows:

Quantitative risk assessment requires extrapolation from results of experimental assays conducted at high-dose levels to predicted effects at lower dose levels which correspond to human exposures. The meaning of this high- to low-dose extrapolation within an animal species was discussed along with its inherent limitations. A number of commonly used mathematical models of dose response necessary for this extrapolation was also descibed. Their dissimilar extrapolation characteristics, one of the major sources of uncertainty in high- to low-dose extrapolation, was also discussed. Other limitations in their ability to provide precise quantitative low-dose risk estimates included the existence of thresholds, incorporation of background or spontaneous responses, and modification of the dose response by pharmacokinetic processes. In concluding, he stressed three points:

(1) precise quantitative high- to low-dose extrapolations cannot currently be made with confidence;

(2) upper bounds for risk estimates, based on conservative assumptions, can be made with reasonable certainty but the true risk may be orders of magnitude below these bounds; and

(3) basic research on the biology of cancer must be accomplished before quantitative extrapolation can be made more precise.

Dr. J. William Lloyd, Director, Office of Statistical Analysis, Directorate of Technical Support, Occupational Safety and Health Administration, made a brief presentation and essentially made three points:

(1) that risk assessment should be done by scientists regardless of what agency they represent;

(2) he very briefly discussed the arsenic data and its relationship to cancer causation; and

(3) that the limitations of most studies, in his view, was due to poor quality of the data and inadequate exposure information.

Dr. Allen Heim, Acting Deputy Associate Commissioner for Health Affairs (Science), Food and Drug Administration (FDA), presented risk assessment activities at the FDA. Risk assessment, he commented, is a major component of the responsibilities the FDA has in assuring the safety of foods, drugs, and medical devices. The FDA is required by the Food, Drug, and Cosmetic Act of 1938 and its amendments to assure the safety of products it regulates. He stated that each risk assessement, fundamentally, should include (1) information on chemical and physical properties of the substance under review; (2) a hazard assessment including an analysis of the available toxicological data from animal experimentation or human epidemiological data or both; and (3) an exposure assessment which includes information on the production or occurrence of the substance, the level and form of

exposure, the potential for an extent of human exposure, benefits if they can be determined, and populations at risk.

To illustrate the difficulty of obtaining accurate measurements of competing values, Dr. Heim cited the following story, recounted by former FDA Commissioner, Alexander M. Schmidt.

> "I am reminded of the old story about how pigs were weighed on American frontier farms. The farmer found himself a long plank which he then put over a crossbar. Then he tied his pig onto the end of the plank. After a short rest, he next looked around for a stone that would balance the weight of the pig. After finding such a stone, he tied it onto the other end of the plank. If, in fact, the stone balanced the pig, that was all there was to it. Except, of course, to guess the weight of the stone."

Dr. Heim commented that in the absence of hard data it is necessary to assume that chemicals of similar structure will exhibit similar biological activity. It is also assumed that positive results from well-conducted animal experiments are useful for approximating effects in humans. Assumptions must be made at times concerning the extent of exposure for the general population or subpopulations. Other assumptions may have to be made concerning such factors as evidence from short-term tests, negative studies and others. In addition, he noted that there are some limitations influencing risk assessment:

> One serious limitation is the fact that the process is rarely quantitative. Additionally, risk assessment conclusions are often assumed to apply to every individual under all circumstances even though some subpopulations may have specific genetic, dietary, ethnic or other factors influencing the the level of risk in addition to those considered in the overall analysis.
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> A further limitation is the uncertainty of species to species extrapolation of data and the lack of procedures for extrapolating data from experimental dose levels to actual human exposure levels.
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> Epidemiological data have limitations because they are usually deficient in identifying interacting factors which may influence the observed effect. As an example he cited an attempt to estabish a causal relationship between the level of aflatoxin in the diet and parimary liver cancer for certain subpopulations in Africa and Southeast Asia that is complicated by the fact that hepatitis and the nutritional state of the individual also correlate postively and cannot be discounted.
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> The picture is made more uncertain because animal studies have demonstrated that protein deficiency increases the probability of aflatoxin carcinogenicity. Whether this is a factor in man is not known.

Dr. Heim stated that FDA's procedures for performing risk assessments utilize these fundamental criteria and are subject to the same kind of limitations mentioned. In the Bureau of Foods, for example, when FDA established the action level for a natural contaminant, aflatoxin, in milk at 0.5 ppb and proposed an action level of 15 ppb for aflatoxin in peanuts, the Agency attempted to quantitate the risk(s) associated with aflatoxin contamination in these products. The assessment included the factors previously discussed with particular emphasis on estimated human exposure levels calculated as µg aflatoxin/day/Kg body weight and the assumption that a given exposure level could result in the induction of primary liver cancer at a given rate in an exposed population. Primary liver cancer was used as the principal target for risk assessment because it was considered to be the most serious problem. Various routes of exposure to aflatoxin, such as direct consumption of the product or consumption of aflatoxin residues in animal-derived food products, were considered. In this latter situation, the formation of toxic compounds or metabolites in the animal still have to be avaluated. In an effort to estimate man's average daily exposure to the compound, assumptions had to be made concerning dietary habits of populations and subpopulations. In the analysis the Agency assumed that the toxic effect observed in animals would also be true in man. Resulting values are only estimations and compare relative risks upon which to base a decision.

Dr. Heim stated that epidemiology studies conducted in Thailand and several parts of Africa show a positive correlation between actual liver cancer incidence and estimated intake of aflatoxins. Utilizing the relationship derived by Peers and Linsell, risk estimates were calculated to range from 20.2 to 67.0 per 100,000 for estimated average and maximum aflatoxin intakes. How applicable such epidemiological studies are to the United States is not known, particularly since the liver cancer incidence rates in these areas outside the United States may be greatly influenced by the presence of pyrrolizidine alkaloids in herbal medicines and the existence of hepatitis B virus.

Dr. Heim stated that the risk assessment for cinnamyl anthranilate, which is used as a food flavoring and as a cosmetic ingredient, illustrates the fact that the same risk assessment may lead to different recommendations depending on the law and usage. In the case of cinnamyl anthranilate, the fact that it was shown to be carcinogenic in animals requires the FDA to ban its use as a food additive under the law. However, the determination that it poses little or no risk when used as an ingredient in cosmetics permits the FDA to allow its continued use for that purpose.

Dr. Heim stated that with cosmetic ingredients the requirements for risk assessment are similar to those for food additives, but the FDA has the burden of demonstrating potential harm. Consequently, the FDA is required to assess the potential risk to the consumer. Risk assessments of cosmetic ingredients are usually retrospective and most often include important information on actual use conditions. This information, when supported by laboratory animal data, provides reasonably accurate evaluation of what the harm or potential harm may be.

He commented that the situation with drugs is somewhat different. As with food additives, prior to approval the FDA evaluates anticipated uses and contraindications. This is essentially a risk/benefit assessment where the beneficial or therapeutic uses of the drug are compared to potential harmful effects. The FDA decision in regard to these assessments can vary significantly depending on the proposed use of the drug. As an example he stated that chemotherapeutic agents have been approved for the treatment of cancer because of the gravity of the illness despite known toxicity but would not be approved for illnesses of less severity. Nonetheless, the same kind of information concerning toxicity, proposed use, etc., which was discussed previously, is required for an assessment.

Dr. Heim noted that the FDA is required to assess risk for animal drugs, biologics, medical devices and radiation devices. With only slight modification the process is essentially the same as that described for foods and drugs.

He indicated that a requirement to be efficacious as well as safe is necessary to consider in an overall evaluation of many of the products regulated by the FDA. Drugs, biologics, medical devices and radiation devices are evaluated in order to balance safety and effectiveness. With food additives no risk of carcinogenicity is acceptable under the law, but margins of safety, based on estimated level of exposure and available toxicity data, are usually set at 100- to 1000-fold in considering risks to other kinds of toxicity. Dr. Heim also noted that the Bureau of Foods is now developing levels of concern based on available data, similar to the "uncertainty factor" used by the National Academy of Sciences.

This, Dr. Heim concluded, describes in general how the FDA assesses health risk and the impact of those assessments on regulatory decisions.

The next presentation was given by Dr. Donald Barnes, Science Advisor to Assistant Administrator, Office of Pesticides and Toxic Substances, Environmental Protection Agency (EPA), who made the following points:

> In its early days in the 1970s the EPA relied on scientific reviews conducted by different committees outside of the EPA. During certain legal proceedings EPA introduced "cancer principles" which drew considerable fire from various parts of society. In response the Agency issued, in 1976, a set of interim guidelines which described how carcinogenicity evaluations were going to be conducted.
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> An important feature of EPA's decision-making, which has become a part of some of EPA's legislative mandates and of many of its regulatory actions, has been the balancing of risks and benefits.
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> Dr. Barnes stated that Dr. Brown clearly and concisely presented the essentials of the risk assessment (hazard and exposure assessment) procedures carried out by EPA.

The qualitative determination made during the hazard assessment process is based on a weight-of-the-evidence approach. Human data, long-term animal data, and other information (short-term testing information, pharmacokinetic data, structure-activity relations, etc.) are carefully considered to determine the strength of evidence--in an individual study and in toto. Various methods have been used/suggested to express these results; e.g., categorization--strongest, substantial, suggestive.

An exposure assessment is conducted to determine if there is cause for concern in some specific instances.

Dr. Barnes stated that the details of the quantitative assessment are essentially those outlined by Dr. Brown, with an emphasis on the "upper bound" nature of the results generated by the multistage model used by the EPA.

The current approach has several useful utilities:

(1) It is useful in assessing whether or not a particular situation constitutes a risk that should be examined in greater detail. (Cf. EPA's evaluation of the emission of TCDDs from five municipal waste combustors.)

(2) It is useful in setting priorities in order to devote resources to addressing the most significant problems.

(3) It is useful in permitting more refined approaches to examining risks and benefits.

(4) It is useful in comparing control options by considering residual risks after application of various remedial measures.

The current approach, however, also has several limitations:

(1) It tends to analyze all carcinogens in the same way. In the quantitative part of the assessment there is little onportunity to utilize information on mechanism of action, to the extent it is know.

(2) It is handicapped in standard setting situations. The upper bound estimate is a statement that the risk is unlikely to be greater than this value. It provides no point estimate of what the risk is likely to be. Standard setters tend to use the upper bound as a point estimate.

(3) It generally limits the model used to the multi-stage model. In some cases it might be useful to use other model(s).

(4) It is limited in its ability to effectively project the strength of the qualitative case. The quantitative estimate often overshadows any statement on strength/weakness of the hazard assessment.

Dr. Barnes noted that the EPA is currently participating in the Office of Science and Technology Policy (OSTP)-directed effort to develop a consensus statement by various Federal Agencies on the science surrounding cancer and that the EPA is reviewing its own assessment procedures, which would fall under the umbrella established by the OSTP statement.

In summary, Dr. Barnes stated that risk assessment is an important activity at the EPA. It is a tool, but not the only tool, that is used in the decision-making process. As such, risk assessment has served the EPA well in the past and with the incorporation of science-based improvements over time, it should serve the EPA even better in the future.

In discussing risk assessment at OSHA, Dr. Patricia Breslin, Acting Director for Technical Support, Occupational Safety and Health Administration (OSHA), commented that OSHA's approach to setting worker health standards has been guided by recent court decisions interpreting the OSH Act.

She stated that the Supreme Court has ruled that the OSH Act requires that prior to the issuance of a new standard, a determination be made that a "significant risk" exists and that the new standard will reduce or eliminate that risk. The Court indicated, however, that the significant risk determination should not be a "mathematical straight jacket" and that OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty. The Court further ruled that a reviewing court should given OSHA some leeway when its finding must be made on the frontiers of scientific knowledge. OSHA is free to use conservative assumptions in interpretating the data, with respect to carcinogens, risking error on the side of overprotection rather than underprotection. The court acknowledged that, although they are mathematical estimates with some inherent uncertainties, risk assessments are nevertheless valid for determining the existence of a significant risk.

These findings by the Court mitigated some of the concerns that OSHA previously had about risk assessments and provide the framework for OSHA standard setting activities.

Dr. Breslin commented that OSHA's overall approach to setting worker health standards is a four-step process consistent with court interpretations of the OSH Act and rational, objective policy formulations:

(1) Risk assessments are performed where possible and considered with other relevant factors to determine whether

the substance to be regulated poses a significant risk to workers.

The Supreme Court gave some general guidance as to the process to be followed in making the initial determination of the existence of a significant risk. It recognized that "while the Agency must support its finding that a certain level of risk exists with substantial evidence, ... its determination that a particular level of risk is 'significant' will be based largely on policy consideration."

In order for such a policy judgement to have a rational foundation, it is appropriate to consider such factors as the quality of underlying data, the reasonableness of the risk assessment, the statistical significance of the findings, the type of risk presented and the significance of the numerical risk relative to other factors.

(2) OSHA considers which, if any, of the proposed standards for that substance will substantially reduce the risk.

(3) OSHA looks at the best available data to set the most protective exposure limit that is both technologically and economically feasible.

(4) OSHA considers the most cost effective way to achieve the objective.

In conclusion, Dr. Breslin commented that a Ninth Circuit Court remand provides that OSHA consider the issues in the first two as elements of the third step.

Mr. Paul White, General Health Scientist, Consumer Product Safety Commission (CPSC), made three points in his presentation:

(1) risk assessment is just one of the factors in the decision-making process;

(2) evaluation of the complete amount of evidence that is available on the compound in question needs to be done; and

(3) thus far the CPSC had not found that mechanism of carcinogenesis data was useful.

There was then general discussion on quantitative risk assessment and whether the definition as proposed by IARC in the Annex of their monograph (Volume 29) was acceptable. It was decided to establish a committee, to be composed of Drs. Robert Tardiff, Gerald Wogan, Charles Brown and David Hoel, whose charge would be to devise a new definition for quantitative risk assessment.

There being no further business, Mr. Samuels announced that the next meeting would be held on September 23 at the National Institutes of Health and adjourned the meeting at 3:30 p.m.

Richard H. Adamson, Ph.D.
Executive Secretary

Attachments

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

Agenda
Copy of July 22 letter from the Subcommittee Chairman, Mr. Samuels
Copy of Pages 391-394 of the Annex from IARC Monograph, Volume 29
Copy of Definitions Currently being used at the National Academy of Sciences
Outline of Risk Assessment Activities at the National Academy of Sciences
Outline of Workshop on "Scientific Group on Methodologies for the Safety Evaluation of Chemicals," held in Rome, Italy, July 12-16, 1982