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WORKSHOP ON PROBLEM AREAS ASSOCIATED WITH DEVELOPING CARCINOGEN GUIDELINES

Held at
Brookhaven National Laboratory
September 7-8, 1982

CHAIRPERSON
OTTO WHITE, JR.

COORDINATOR
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CENTER FOR ASSESSMENT OF CHEMICAL AND PHYSICAL HAZARDS
SAFETY AND ENVIRONMENTAL PROTECTION DIVISION

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PREFACE

The Center for Assessment of Chemical and Physical Hazards at Brookhaven National Laboratory (BNL) was requested by the Department of Energy (DOE) to develop guidelines on use of carcinogens by DOE and its contractors. As part of this task, the Center conducted a two-day workshop on September 7 and 8, 1982 at BNL to discuss problem areas associated with developing carcinogen guidelines. The format of the workshop included an oral presentation of their topics, and open discussion by all participants. Brief written comments or summaries of issues on problems were prepared in advance by the principal participants.

Principal participants included invited professionals in the field of chemical carcinogen research and carcinogen policy development. The Center's technical advisory panel served as the session leaders and the Center's technical staff participated and provided editorial support. Also participating were DOE staff from Washington, D.C.

Except for the brief prepared comments and summaries, the workshop proceedings were transcriptions, from tape recordings, of each session and discussion period. Because of its timeliness to this workshop, a special BNL seminar on the de minimis concept given in the Medical Department was included in this workshop with permission of the speaker, J. Newell Stannard. Transcriptions of the workshop sessions were edited for clarity and readability only and represent a sincere effort on the part of the Center to convey the actual discourse of the participants. Any error or misinterpretation of participants' statements is regretted and apologized for in advance. The conclusions and opinions expressed by the participants do not necessarily reflect the views of the Center, BNL, or DOE.

The workshop chairperson and coordinator thanks all workshop participants (see appendix) for their time and contributions to this important problem. We wish to especially thank Sandra Green (the workshop secretary), the workshop recording engineer, transcribers, the BNL Word Processing staff, and those who gave editorial assistance.

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PROLOGUE

Welcoming Comments
(Speaker - Victor Bond, M.D.)

Bond

It is my pleasure on behalf of our Director, Dr. Samios, and all of us at Brookhaven National Laboratory (BNL) to welcome you to the Laboratory. On such occasions I usually take advantage of having a captive audience to tell them something about the Laboratory. However, because most of you are from a national laboratory or know a good deal about them, I will spare you that and report briefly on new developments here that relate to biology and medicine and the subject matter of this conference. The first of these has to do with our High Flux Beam Reactor, which just last week went from a power rating of 40 megawatts to 60 megawatts. The significance of the increase is that a fair amount of experimental work at the reactor is devoted to determination of the structure and function of biological molecules. The upgrading in power substantially enhances the overall value of that facility, not only for people here at BNL but for the numerous users from other institutions as well. In a similar vein, the National Synchrotron Light Source is now going on line. It is a first-rate instrument with enormous potential in the field of structure and function of biological molecules. It is of substantial interest to biologists, within BNL and elsewhere, and the list of interested users is already formidable.

With respect to this conference, the importance of the subject matter is fully appreciated, not only within Brookhaven but generally. A number of programs within BNL are concerned with the subject matter, directly or indirectly. Otto White and his group are to be congratulated for putting together the program before us. The questions addressed are certainly forefront in this field, and we have an excellent group to address them. I wish you every sucess in the conference. Again, welcome to BNL.

Introduction
(Speakers - Otto White, Jr., CIH
James E. Brower, Ph.D.)

White

I have a few introductory remarks to place in focus the purpose of our being here. The Center for Assessment of Chemical and Physical Hazards (CACPH) has been charged with the development of a draft on a carcinogen policy which will be used as an internal guideline for the Department of Energy (DOE) and its contractors. We in the safety and health professions, especially those of us from laboratory facilities, have been concerned about carcinogen guidelines, since current regulations are focused toward production facilities. Our concerns are further increased as more chemicals are added to "carcinogen" lists, and as we find common chemicals such as saccharin and formaldehyde being identified as carcinogens. Do we treat them in the same manner as bis(chloromethyl)ether and aflatoxin B1? And, just what are the proper protective measures that should be used for the various types of materials?

We at BNL, as well as our DOE counterparts, have those concerns, and CACPH has been charged with assisting the DOE in developing an internal policy. Our efforts to date have been to canvass the DOE community and to prepare a model guideline. A questionnaire has been sent to each DOE facility and DOE contractor to determine what policy currently is in effect at their facilities. We have asked for identification of compounds that they treat as carcinogens and for the rationale that resulted in that determination. We have also developed a rough draft of a carcinogen guideline which takes potency into consideration. We do not expect much success with a carcinogen policy unless it takes the potency question into consideration. To that effect we have generated a first draft for which we received some discussion and comments from attendees at the 1982 American Industrial Hygiene Conference in Cincinnati.

With the results of the survey and discussions generated at that Conference, it became clear that there are a number of problem areas in which the CACPH staff needed some input. Therefore, we have asked you, distinguished members of the scientific community, who have expressed views in these problem areas, to join us to discuss your views, and to allow the CACPH staff and the BNL advisory panel an opportunity to hear those views as we try to formulate a policy for the DOE community.

Before we get into the formal presentation, Jim Brower, who is manager of the Center for Assessment of Chemical and Physical Hazards, will give you a brief overview of our program here.

Brower

Thank you, Otto. I would like to thank all of you for coming here and am pleased at the good turnout at this hour of the morning after the Labor Day weekend.

I want to tell you briefly about the Center for Assessment of Chemical and Physical Hazards. In the folders that you picked up at registration you should have an outline of the Workshop topics as well as a brief summary of what we do at the Center. We are under contract with the Department of Energy to assess the occupational health effects of chemical and physical hazards that workers in DOE, the DOE laboratories, and the DOE contractor community are exposed to.

We are currently heavily involved in assessing various chemicals that are potential health hazards in synthetic fuel areas. We are doing computerized literature searches, examining this literature, and assessing the health effects in summary reports. This information is then reviewed by our Advisory Panel which consists of members from Brookhaven National Laboratory and the State University of New York at Stony Brook. When the information is deemed sufficient and the problem significant enough, we will develop and recommend interim standards for that particular chemical. This standard is then reviewed by a panel of outside consultants who make additional recommendations or suggest revisions of the standard.

We have other areas where we assess chemical and physical hazards through a "hot-line" service. We may receive a request from a sister laboratory or a DOE contractor to review a potential health hazard at their installation. We then prepare a brief health effects summary on that problem.

That in general is what the Center does. We have several in-house staff who assist in preparing these assessments, and this is overseen, as I mentioned, by the technical Advisory Panel.

Next, I will give you some brief details on the Workshop. The format is basically that of a discussion. We have several people who will be key participants in each of the discussion sessions. Each of these people will present a short summary of their views on that topic. The topics listed on your outline are merely suggestions to give us some guidance and direction for the Workshop. I am sure other topics will come up in the discussion that certain speakers may want to address, and please feel free to introduce such items. We will then open up the rest of the period to all participants. The discussions will be coordinated by a discussion leader who is a member of the Center's Advisory Panel. Since we are transcribing these proceedings and publishing them, please identify yourself, speak clearly and succinctly, and minimize your use of technical jargon, or explain it clearly enough so that the transcribers will understand the complex terminology.

We will have one session this morning and two this afternoon. In the first session we will discuss the definition of a regulatory carcinogen. Dr. Robert Drew from Brookhaven National Laboratory will be the discussion leader for this session, and the first speaker will be Dr. Kim Hooper. Dr. Roy Albert will substitute for Elizabeth Anderson who is unable to be here. If there are no questions regarding the Workshop, then I'll turn it over to Bob Drew and Kim Hooper.

SESSION I

DEFINITION OF A CARCINOGEN FOR REGULATORY PURPOSES

Introduction
(Session Leader - Robert Drew, Ph.D.)

Drew

Ten years ago, and again about eight years ago, I visited the Soviet Union. I came away with a healthy respect for the scientists over there and a fair degree of skepticism with regard to the laboratories, facilities, and the research they said they were publishing. I mention this only because one of the things that impressed me was the fact that they are coming to grips with the problem of regulating carcinogens.

In general, I think the USA has had a "head-in-the-sand" approach toward the business of trying to regulate compounds which have proved to be carcinogenic in laboratory animals, and are suspect in man as well. For example, vinyl chloride in this country was regulated on the basis of detectable limit by an instrument. The regulation required that there shall be no vinyl chloride in the air as measured by an instrument which can detect 1 ppm. In my estimation that is a "head-in-the-sand" approach. Then we have the problem of saccharin versus cyclamates. Cyclamates are forbidden in this country and permitted in Canada; the reverse is true with regard to saccharin. Saccharin is used as a sweetener in this country and forbidden in Canada. These conclusions are pretty much based on the same data so it is clear that there are some problems

Finally, I have been engaged in research that defines carcinogens. One compound in particular, bis(chloromethyl)ether, has proved to be very potent and is now on the list of regulated carcinogens. I have also done research that clearly established that inhalation of SO_2 along with benzo(a)pyrene enhances the capability of benzo(a)pyrene to produce tumors. However, I would be very concerned if this country began to regulate SO_2 as if it were a carcinogen in the same kind of context that it regulates bis(chloromethyl)ether. It is to be hoped that this meeting will be able to address some of these questions.

Our first speaker is Dr. Kim Hooper, from the California Department of Health Services. His Ph.D. in biochemistry is from Harvard. He did postdoctoral study at Berkeley with Dr. Bruce Ames where he took part in carcinogenic potency projects. He is currently chief of the Hazard Evaluation System and Information Service in the California Department of Health Services.

Issues in the Development of California's Carcinogen Control Policy*
(Author - Kim Hooper, Ph.D.)

*Dr. Hooper requested that the following paper be substituted for the transcription of his presentation.

Hooper

Abstract

In a process that is unique to state government, the California Department of Health Services has been formulating a carcinogen policy for the past two years. Our experience may be useful to others engaged in similar local efforts to develop public health policies for control of carcinogens. Our policy focuses on the risks of exposure to chemical carcinogens; however, the principles discussed apply equally well to other major causes of cancer (e.g., cigarette smoke, radiation, viruses).

In an attempt to separate science from policy, the California Carcinogen Policy has been developed in three sections: (1) carcinogen identification; (2) risk assessment; and (3) policy considerations. Open workshops were held and public comments were invited on drafts of each section. The policy has been reviewed by scientists from academia, government, the regulated community, and labor and environmental groups. We have attempted to create a dialogue between these groups aimed at achieving concensus, wherever possible, and identifying principal areas of disagreement.

A carcinogen policy must make decisions on a number of controversial issues. In most cases, we have selected those options which we believe to be scientifically reasonable and consistent with a prudent public health policy. While our policy follows precepts set forth in the earlier Inter-Agency Regulatory Liaison group (IRLG) and Occupational Safety and Health Administration (OSHA) cancer policies, important differences exist which are discussed: (1) a positive result from a single, well-conducted animal bioassay defines the universe of carcinogens; (2) chemicals for which expert committees (e.g., International Agency for Research on Cancer or National Toxicology Program) have deemed there is "sufficient' evidence for carcinogenicity will be considered actionable carcinogens; and (3) risks are estimated for carcinogens without regard to their mechanisms of action.

Introduction

As this Workshop opens the day after Labor Day, it seems appropriate to dedicate this talk to the occupational health community of America which has contributed in large part to our knowledge of the carcinogenic effects of chemicals in humans. California's intention is to avoid the need for obtaining further information of this sort and, instead, to use animal test data, where possible, in efforts to control exposures to carcinogens. After describing an incident which illustrates the predictive value of animal toxicology data, I will discuss briefly how the California Department of Health Services has become involved in formulating a carcinogen identification policy for California and describe some features of this policy.

About five years ago in the rural town of Lathrop, California, male workers formulating commercial batches of several pesticides in an agricultural chemical plant realized that for several years none of them had fathered a child.

Their fears of apparent infertility were confirmed when, with the cooperation and assistance of their union, the company, and health professionals, semen analyses were conducted and the group was found to have an abnormally high prevalence of oligospermia (low sperm) and azoospermia (absence of sperm).[1] The frequency and severity of these effects correlated well with the duration of the men's exposure to the nematocide, 1,2-dibromo-3-chloropropane (DBCP). Marked effects on spermatogenesis occurred at exposure levels as low as 0.4 ppm (8-hour time-weighted average). These doses produced no other clinical signs of toxicity.[2]

Almost simultaneously, results of a National Cancer Institute (NCI) gavage bioassay were released which indicated that DBCP was a potent carcinogen, causing cancer in rats and mice of both sexes at doses very close to those that workers may have received.[3] Confirmation that DBCP was a potent carcinogen came six months ago with results from an NCI inhalation bioassay. DBCP was shown to be genotoxic in several short-term tests for mutagenicity using bacteria[4] or mammalian cells.[5]

The DBCP incident was the first documented example of workplace-induced reproductive failure in males, and illustrates that occupational exposures to chemicals can produce a broader range of toxic effects than previously imagined. Public concern was heightened by the discovery that DBCP had been found to cause a similar effect (low sperm count) in test animals and that these effects had been reported in the scientific literature eighteen years previously.[6] As with the carcinogenic activity, the testicular effects in animals occurred at dose levels close to those that produced similar adverse spermatogenic effects in the men. Had greater significance been attached to these results in test animals, the reproductive failure in workers at Lathrop might have been avoided.

Two lessons may be learned to help prevent similar episodes from occurring in the future. First, the release of information at the right place at the right time (e.g., animal toxicity data on DBCP to plant officials and workers at Lathrop) could be an effective part of a program of preventive occupational medicine. Second, greater weight may need to be given to results from studies in test animals as predictive of effects in humans. Data had been present for eighteen years that DBCP caused sperm damage in mammals. Only after effects were found in humans was action taken to control exposure to the chemical. Evidence that DBCP causes cancer in test animals is currently available. The question remains, "What is the likelihood that similar carcinogenic effects will appear in the future in these workers?"

The DBCP incident underlines the importance of communication between laboratory/medical scientists and the occupational health community. The practicing health professionals were not informed of the reproductive and carcinogenic effects that laboratory scientists had discovered, and labor and management were similarly uninformed. Shortly after the DBCP episode, the California Legislature moved to strengthen the State's resources in occupational health and medicine by establishing the Hazard Evaluation System and Information Service (HESIS).* HESIS communicates to California's workers, employers, and health professionals the results of published medical and scientific studies that point to new occupational health hazards. HESIS performs hazard evaluations on substances of concern and issues hazard alerts on high-priority risks (e.g., the carcinogens ethylene dibromide and ethylene oxide). Because of its

*HESIS is in the Toxic Substances Control Division of the State's Department of Health Services, 2151 Berkeley Way, Berkeley, California 94704, and is funded by a contract with Cal/OSHA in the Department of Industrial Relations.

evaluative function, HESIS was asked to assist in developing a carcinogen identification policy for California.

The development of such a public health policy on carcinogens faces several difficulties. First, the number of carcinogens is likely quite large among synthetic and naturally occurring chemicals. Indeed, the number of carcinogens may be so large as to overwhelm the limited capacity of government agencies to regulate them. This is contrary to the belief of the 1960s that carcinogens were few in number and might be regulated quite stringently.

A second difficulty arises because of the latency period of cancer. Most strategies devised to control exposures to carcinogens are based on predicted likely carcinogenic outcomes in humans. As the evidence of an effect in humans or test animals increases, so does the likelihood that the chemical will cause cancer in humans. As a matter of fact, the number of chemicals for which there is currently sufficient evidence for carcinogencity in test animals may number in the hundreds, whereas the number of chemicals associated with producing carcinogenic effects in humans is an order of magnitude lower. This large difference appears to be due to the difficulty of studying effects in humans rather than a greater inherent resistance of humans to the effects of these chemicals. It is difficult to locate an appropriately large human study population exposed to a single agent at reasonably high doses for a significant part of their lifetime and followed for a sufficient length of time (10-20 years) so that any carcinogenic effect, if it is expressed, can be observed. As stated elsewhere (see below), most chemicals which are demonstrated to be carginogenic to humans are carcinogenic to animals when adequately tested. Qualitative identification is a matter of accumulating sufficient evidence to produce concensus of opinion among experts that a carcinogenic outcome is "reasonably" likely. Our general approach is that as this likelihood increases, so should the stringency of our control strategy increase.

A third difficulty arises from the common situation that humans are exposed to carcinogens at much lower dose levels than those used in animal experiments. To predict risks for humans exposed to these low doses requires knowledge of the shape of the dose-response curve in the low-dose region. As with qualitative identification of carcinogens, we are bedeviled by not being able to confirm or deny the predictions that we make.

Thus, the latency period of cancer, the consequent need for extrapolation across species (animals to humans) and dose levels (from high doses to low doses), produces a degree of uncertainty with which most scientists are uncomfortable. After acknowledging this, we must proceed. Unfortunately, the uncertainties of animal-human extrapolation and estimation of cancer risks at low doses are not likely to be reduced significantly in the near future.

Cancer in the Modern Chemical World

Over the past 40 years, the production of synthetic organic chemicals has increased enormously (more than 300-fold[7]), and people are exposed to a much greater variety of chemicals than ever before. Few of these approximately 50,000 substances have been tested for their ability to cause such severe and life-threatening effects as cancer, mutuation, birth defects, or sperm damage. For those that have been studied, it has not been clear how animal test data, which provide most of the evidence, should best be used.

The long latency period of some human cancers (up to 20-40 years)[8] raises the possibility that past and present exposures will cause increases in cancer in the future. Although the cancer rate of the general population at present ap-

pears to be relatively stable, lung cancer has increased significantly over the last 80 years.[9] The major portion of this increase is attributed to increased cigarette smoking,[10,11] but the contributions of occupational/environmental factors are less clear.[12-14] What *is* clear is that significant increases in cancer have occurred in certain workplaces during this same period (e.g., exposures to bis(chloromethyl) ether, asbestos, 2-naphthylamine, benzidine, etc.) without causing visible changes in the cancer incidence in the general population, and that unacceptably high cancer risks have been experienced by individuals through exposure to carcinogenic agents.

Most of the known human carcinogens to which the public may be exposed have been identified by the high cancer rates observed among workers in specific industries: of the 36 agents for which there is strong or conclusive epidemiologic evidence of carcinogenic effect in humans, 26 were identified by occupational exposures; the remainder are mainly agents used in cancer chemotherapy (see Table 1).[15]

Cancer and reproductive disabilities are serious health hazards. They compel us to control exposures to toxic substances and to use animal data where possible to prevent such outcomes from occurring in humans.

The DBCP incident raises the important question: how can test results from studies of substances in experimental animals best be evaluated and communicated so as to protect public health? What is significantly reasonable and prudent public health policy for control of exposure to carcinogens?

Methods for Identifying Carcinogens

A carcinogen is generally understood to be a substance or agent that increases the frequency (age-specific incidence) of cancer in humans or in other animal species.[15-24] The identification of chemical substances that pose cancer risks to humans is complex and requires integration of information from several scientific disciplines. Evidence that a substance may be a carcinogen comes from four sources: epidemiologic studies in human populations; bioassays in experimental animals; short-term tests for mutagenicity and cell transformation; and similarities in chemical structure to known carcinogens. Procedures for evaluating data from the first three of these methods are reviewed briefly; it should be noted that they provide evidence of different strengths.

Epidemiologic Studies

Epidemiologic studies offer the overwhelming advantage of providing direct evidence for carcinogenic effects in *humans*. They are well suited to identify major causes of cancer in defined populations (e.g., cigarettes, asbestos, initial pregnancy late in life, etc.)[25] but are less suited to determining whether a *specific* chemical poses a cancer risk to humans. Even so, epidemiology identified several important chemical carcinogens (e.g., benzene, arsenic) before animal tests were performed.[15] At present, the International Agency for Research on Cancer (IARC) states that there is sufficient evidence for the carcinogenicity in humans of 18 chemicals, groups of chemicals, and industrial processes; and there is probable evidence of varying strengths for 18 others[15] (see Table 1).

In addition, negative results from well-conducted epidemiologic studies are useful in placing an upper limit of risk for a chemical exposure. They complement the more uncertain quantitative risk estimates made from data from animal cancer tests.

Table 1

Chemicals, Groups of Chemicals, and Industrial Processes That Are Carcinogenic to Humans

4-Aminobiphenyl

Arsenic and certain arsenic compounds

Asbestos

Manufacture of auramine

Benzene

Benzidine

*N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)

Bis(chloromethyl)ether and technical grade chloromethyl methyl ether

Chromium and certain chromium compounds

*Diethylstilbestrol

Underground hematite mining

Manufacture of isopropyl alcohol by the strong acid process

*Melphalan

Mustard gas

2-Naphthylamine

Nickel refining

Soots, tars, and mineral oils

Vinyl chloride

Probably Carcinogenic to Humans

Acrylonitrile

*Aflatoxin

Amitrole (aminotriazole)

Auramine

Beryllium and certain beryllium compounds

Cadmium and certain cadmium compounds

Carbon tetrachloride

*Chlorambucil

*Cyclophosphamide

Dimethylcarbamoyl chloride

Dimethylsulphate

Ethylene oxide

*Iron dextran

Nickel and certain nickel compounds

*Oxymetholone

*Phenacetin

Polychlorinated biphenyls

Tris(1-aziridinyl)phosphine sulphide (thiotepa)

*Evidence for effects in humans was obtained from nonoccupational exposures.
Source: Adapted from IARC, 1979.[15]

Epidemiologic methods are extremely useful tools; but, in general, they have low sensitivity. For example, when a cohort study population is relatively small (less than 1,000), the study may fail to identify an agent that increases the risk of a specific cancer by a factor of less than 5 to 10. Even large-scale studies may require an increase of more than 50% in cancer incidence before an effect is statistically significant. For this reason, negative results in studies of smaller size seldom provide strong evidence that an agent is not carcinogenic. To detect a carcinogenic effect, it may be necessary to have either a very large study population or a smaller-sized population that is exposed for several years to large doses of a potent carcinogen. In addition, such studies are often difficult to conduct, both because appropriate study groups and reliable information about past exposures are limited and because biases and confounding factors are difficult to eliminate. A recent review[2] reports that epidemiologic data do not exist (and are unlikely to be developed in the future) for the vast majority of industrial chemicals that cause cancer in experimental test animals and to which the public is exposed.

In addition, because of the 20- to 30-year latency period of many human cancers, epidemiologic studies are not suited to warn and protect people from the cancer risks from exposures to new carcinogens. If an early-stage carcinogen has been identified by an epidemiologic study as a cause of human cancer and the exposures are reduced or eliminated, the cancer risk among those previously exposed may remain appreciable over the ensuing 20-30 years. Limiting exposure to late-stage carcinogens or promoters can reduce the cancer risk more rapidly; e.g., cessation of cigarette smoking appears to modify the risk for lung cancer within five years.[27,28]

Thus, because of the insensitivity of epidemiologic studies, the long latency period of cancer, and the difficulty in obtaining an appropriate study population, we are forced to rely heavily on other means of identifying agents which have the potential to produce cancer in humans.

Assessment of Cancer Hazards: The Value of Animal Data

Fortunately, results from animal cancer bioassays appear to be reasonable qualitative predictors of carcinogenic effects in humans; and the laboratory animal bioassay is widely used to indicate the carcinogenic potential of a chemical. Bioassay procedures have been standardized in recent years and, except for minor details, there is now general acceptance of test procedures.[20,29-36] Most substances that are carcinogenic in one species of test animal are carcinogenic in a second when adequately tested;[37-44] and most substances that are known to be carcinogenic in humans, for which adequate animal data exist, are carcinogenic to animals (the chief exceptions being asbestos and arsenic).[15,42-44] For several recognized human carcinogens (4-aminobiphenyl, bis(chloromethyl)ether, diethylstilbestrol, melphalan, mustard gas, and vinyl chloride), the first evidence of carcinogenicity was found in test animals. Only afterwards were cancer effects looked for, and found, in humans.[44] From a scientific standpoint, it seems reasonable to consider substances for which there is evidence of toxic effects in test animals as likely to produce similar effects in humans. Thus, the International Agency for Research on Cancer (IARC) concludes that, "In the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity (i.e., a causal association) in animals as if they presented a carcinogenic risk for humans."[15]

Indeed, recent discoveries in the molecular biology of cancer would make it surprising if carcinogenesis in rodents is markedly different from that in humans. Cancer-causing genes ("oncogenes") and cell transformation maintenance factors have been isolated from rodent tissues and are virtually identical to those found in the corresponding human tissues.[45-51] These findings indicate that carcinogenesis in humans and test animals may be remarkably similar, and they strongly support the belief that test animals are reasonable and appropriate models for understanding the carcinogenic process in humans.

Sufficient evidence currently exists for the carcinogenicity in animals of about 200 chemicals. IARC considers there is "sufficient evidence" for carcinogenicity for 142 of the 422 chemicals it has assessed in its review process.[15] The National Cancer Institute (NCI) has concluded that there is "sufficient evidence" of carcinogenicity for 98 of the 190 chemicals evaluated in its bioassay program,[40] some of which are the same as those reviewed by IARC. As stated earlier, sufficient evidence exists for 18 chemicals that they are carcinogenic in humans.[15]

For most of the 200 animal carcinogens for which there is "sufficient evidence," it is unlikely that we will ever know with certainty whether they cause cancer in humans because of the difficulty in obtaining appropriate populations suitable for epidemiologic studies. Since it is unlikely we will ever confirm or deny the apparent carcinogenic potential of these 200 chemicals, it appears prudent in the interim to control exposures to them as if they had demonstrated effects in humans.

Short-Term Tests for Mutagenicity, DNA Damage, and Cell Transformation

Short-term tests[52-54] generally evaluate the ability of a substance to produce mutations, chromosomal alterations, or DNA damage in a test organism, or to induce transformation of cultured mammalian cells. Systems that are used in short-term tests include microorganisms (e.g., bacteria, yeast, and molds), cultured mammalian cells, and whole animals. These tests are comparatively inexpensive ($5,000-10,000 per battery of short-term tests versus $500,000 for an animal bioassay) and can be completed in a relatively short time. A number of these tests can, therefore, be performed with limited resources. They offer the potential for providing useful information on the two most intransigent problems in carcinogenic risk assessment--species differences between rodents and humans, and estimating risks at very low doses. Some short-term tests can be performed with human cells or tissues; and some effects, such as DNA damage, can be measured at very low doses.

Use of short-term tests to predict carcinogenicity is justified on both theoretical and empirical grounds. Many of these tests detect biological activities (mutagenicity and cell transformation) that are believed to be stages of carcinogenesis. Most known animal and human carcinogens have been shown to be mutagenic when tested in a suitable battery of short-term tests, while most noncarcinogens have not.[55-63] Because of this, a battery of tests can be a useful predictor of carcinogenicity. Such a strong correlation may exist because most of the chemical carcinogens tested this far act by mechanisms that involve DNA damage, though this has not been rigorously proven. The particular relevance of tests that measure cell transformation is based on the observation that transformed cells, when implanted into a receptive animal host (e.g., a "nude" mouse), will form malignant tumors.

There is a high probability that a chemical that is positive in an appropriate battery of short-term tests will prove to be a carcinogen when adequately

tested in animal cancer tests. Short-term tests can, therefore, be used to augment evidence for carcinogenicity from animal cancer bioassays that, for some reason, are not by themselves definitive. Short-term tests can also indicate the potential for carcinogenic hazard of chemicals not yet tested in animals. At present, short-term tests are not sufficiently standardized and validated to provide definitive information about carcinogenicity or noncarcinogenicity in the absence of other evidence.

Risk Assessment and Hazard Evaluation

Quantitative estimates of cancer risks in humans based on extrapolation from animal data are difficult to interpret but are routinely performed. What information needs to be developed to permit meaningful estimates of cancer risks from exposures to combinations of chemicals such as occurs in occupational settings? What is a reasonable health policy in the interim? Some principles are emerging. Although differences may exist among species in host responsiveness (e.g., differences in pharmacokinetics and DNA-repair efficiencies), in test animals the carcinogenic potencies of chemicals in different species (rats and mice) are generally similar.[64] Moreover, the responsiveness of test animals is reasonably similar to that of humans for those chemicals (21) that have been examined.[64,65] Clearly, the inadequacy of human exposure data limits the accuracy of such comparisons. Such interspecies differences as exist between rodents and humans must be viewed in relation to the presumed large variation among individuals (e.g., genetic heterogeneity and host-response differences) in the human population.

A Policy of Cancer Prevention

A first step in limiting cancer risks to individuals and the general population is to reduce the causes of major cancers (e.g., lung, colon-rectal, and breast) and control exposures to specific cancer-causing substances. The major identified causes of lung cancer include tobacco smoke and asbestos,[17] and diet is believed to play an important role in breast and colon-rectal cancer.[13] In theory, cancer may be prevented by modifying the diet, controlling the use of tobacco, and reducing exposure to cancer-causing substances (e.g., asbestos). As a practical matter, involuntary environmental or occupational exposures may be easier to control than has been the voluntary use of tobacco or improper diet.

While attention has been focused on assessing the relative proportion of present and future cancer incidences that are caused by either "lifestyle" or occupational and environmental factors[10,12] (with varying estimates that need to be resolved by future studies[12]), an uncertainty of perhaps greater public health consequence may be overlooked. The effect of simultaneous exposures to both factors, as is likely to occur in everyday life, is more relevant to an appropriate assessment of human risk. In two well-documented human studies of cancer risks from exposures to agents singly or in combination (cigarette smoking and exposures to asbestos or radiation), the cancer risks from the combined exposures are the product, not the sum, of the risks from separate exposures. Thus, prolonged cigarette smoking is associated with a 10-fold increase in the risk for bronchial carcinoma (lung cancer), while prolonged heavy occupational exposure to asbestos is associated with a 5-fold increase in risk. However, combined exposures (e.g., cigarette smokers exposed to asbestos) are associated with a 50-fold, and not 15-fold, increase in risk over that experienced by

nonsmokers with no asbestos exposure. There are data to suggest that a similar synergism exists between exposures to tobacco smoke and radiation.

Such synergistic interactions may be more common than is currently appreciated, but at present we cannot predict whether the effects of other interactions will be additive, multiplicative, or inhibitory. Thus, from a policy as well as a scientific standpoint, the dichotomy between "life-style" and environmental and occupational factors may be more artificial than helpful. A simpler view is that cancer has a multiplicity of interacting causes, including "life-style" and environmental and occupational exposures, and that these will only infrequently be disentangled.

Information is needed to improve the accuracy of quantitative estimates of cancer risk from exposures to combinations of agents. In the interim, carcinogenic risks to humans exposed to single chemicals or combinations of chemicals must be estimated by extrapolation from available bioassay data using suitable (e.g., multistage model) methods, while acknowledging that such methods will underestimate the true risks if synergisms occur. Compared to the population of test animals, the population is genetically diverse and is simultaneously exposed to a large number of chemicals. Suitable corrections for these differences also should be made in any appropriate risk calculations.

Conclusions

Research on cancer is continuing, and as our understanding increases, programs for prevention and control of these diseases will likely change. Prevention, however, can proceed without precise answers, and we must make health decisions based upon the best available evidence. Cancer risks to the general population can be reduced by a comprehensive program to modify the major identified determinants of cancer and to control exposures to specific carcinogenic substances.[13] Modification of health practices cannot be constrained to require absolute certainty when the consequences of inaction could result in serious effects on the health and welfare of the public.

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Issues in Carcinogenesis
(Speaker - Roy Albert, Ph.D.)

Drew

Our next scheduled speaker is not here, and Dr. Albert has agreed to pinch hit for Elizabeth Anderson. I'm sure most of you know Dr. Albert. Roy Albert has been active in the field of carcinogenesis for a long time. He is professor and vice-chairman of the Department of Environmental Medicine at New York University. He is also chairman of the Carcinogen Assessment Group of the USEPA. I hope that Dr. Albert will take a few minutes to address the issue of promoters versus initiators. Then we will open this meeting for discussion.

Albert

I'm sorry Betty Anderson is not here. The two of us have been working together for six years in relationship to the Environmental Protection Agency.

I might start by commenting upon Bob Drew's description of the field of carcinogen regulation as "head-in-the-sand." If that is consistent with contentiousness, then I would agree with that description. From my point of view, I've never seen any field whatsoever that has been as contentious as the regulation of carcinogens. Primarily because its basis is so flimsy from a scientific standpoint.

Bob mentioned the Russians and their approach to regulation of carcinogens, and I might tell you of just one example, which I became familiar with as a member of the USA-USSR cooperative program in environmental health research. The standard for benzo(a)pyrene in the Soviet Union was set at the Institute for General Hygiene in Kiev. Their approach to setting this standard, was to do an animal study in which they gave ten monthly intertracheal injections of benzo(a)pyrene at graded doses. They then determined from this experiment the highest dose which did not produce tumors. They translated this into the maximum lung burden after 50 years of breathing, and translated that into the air concentration which would accumulate in 50 years to that amount, ignoring clearance and so on. They then came out with a figure which they divided by a safety factor of 100, and it was too low. So they reduced the safety factor to 10 and it came out to be the exactly the average concentration of benzo(a)pyrene in the air in the city of Kiev, and that is how the benzo(a)pyrene standard in the Soviet Union was developed. That is an example of the depth of science in this field.

The EPA's involvement with carcinogens really came to a boil in 1975. The Agency was under attack from all directions because it was taking a very vigorous approach to the regulation of carcinogens, particularly pesticides. It had taken action against DDT, heptachlor, chlordane, aldrin, and dieldrin. So industry got on their war horses and were tilting at the Agency with ferocity, particularly attacking its apparently simplistic approach to what constitutes a carcinogen. They pointed out that the Agency was taking an overly simplified view in saying, for example, that anything that produces an excess of tumors in animals would be regarded as a carcinogen. For example, a high caloric intake in animals will increase the yield of tumors; so are calories to be called a carcinogen?

There was a tremendous degree of polarization in those days, which I think is still with us. There are the "smoking gun" folks who think an agent cannot be called a carcinogen unless there is concrete epidemiologic evidence that it

is carcinogenic. At the other end of the spectrum, there are those who think that any excess of tumors in bioassay animals should be regarded as evidence for carcinogenicity; furthermore, that one cannot go too far in quantitating potency because of the uncertainties in animal studies. The logic there is that if an agent is defined as a carcinogen, then it has to be regarded as nasty as carcinogens get. It was in this context that the EPA took a crack at setting guidelines, which were adopted in May 1976, for the assessment of carcinogens.

I believe we were responsible for the use of the term "risk assessment" and, by George, it's become a band-wagon. Our approach was not to make a black and white characterization of whether or not an agent is or is not a carcinogen, it was essentially to take the weight of evidence based on animal studies, epidemiologic studies, and short-term tests. The weight of evidence involves the scope of the studies, their quality, and, of course, the nature of the results. So, one can regard the weight of evidence as a signal for carcinogenicity which can be very strong, particularly if there is solid epidemiologic evidence, backed by animal evidence which pinpoints the offending agent, which of course may not be all that clear from the epidemiologic studies themselves. But it can range from that end of the spectrum to the other end where you simply have a positive result in one sex of one strain for a tumor which occurs pretty commonly in that bioassay animal (e.g., liver tumors in which one is not all that satisfied about the malignancy of that tumor).

Thus, in practice, one is dealing with a tremendous range of strengths of evidence, and the approach that the EPA took in its guidelines was to factor that into the judgment about the carcinogencity. Short-term tests were regarded as supportive evidence and not sufficient by themselves to warrant the characterization of an agent as a likely human carcinogen, and that position still holds.

On the quantitative side, it was recognized in these guidelines that one needed to be able to estimate, at least crudely, the magnitude of the impact of a carcinogen in quantitative terms. It was recommended that several extrapolation models be used, together with exposure data, to come out with estimates of the magnitude of the cancer impact. This can be done both in terms of "body counts" and by characterization of individual risk. And over the years, both approaches have been found to be desirable. It is possible to have a low "body count," but if there are people living close to a source their personal risk could be high, and this is undesirable. Conversely, the individual risk can be pretty low in a large population, and the "body count" can be disquietingly high.

Over the years, the practice of using a number of models has dropped out, and the linear extrapolation model has dominated the scene. The initial approach from a technical standpoint was to use the lowest statistically significant response and extrapolate down from that, on the grounds that it is the low level of response that is assumed to be linear, whereas in fact the dose-response relationships show an upward curvature at high doses. So the linearity was restricted to the low end. Since then, we have swung over to an approach developed by Kenny Crump, which he can talk about later. It is the use of the multistage model; forcing it to have a linear component at the 95% upper confidence limit. It is a lot more sophisticated--fancier--but it has not changed the general approach very much. Going back to 1976 this is the tack that the EPA has taken in the area of risk assessment, and it still prevails, at least ostensibly. At the present time EPA is undergoing a pretty substantial rethinking of some of these aspects.

The application of risk assessment will be discussed at a later session, but I think it is worth pointing out that the use of risk assessment in the regu-

latory framework has been a very difficult business. First off, the weight-of-evidence judgment leaves a lot of margin for regulatory action. Kim described one approach, but I think it is fair to say that in the early part of the Carter administration and the latter part of the Ford administration, there was a real gung-ho approach to regulation, such that relatively weak evidence was regarded as sufficient impetus to take regulatory action. Toward the latter part of the Carter administration and in the present administration, the situation has swung around rather dramatically. I think, for economic reasons, there is a considerably dimmer view taken about the regulation of carcinogens, and there is a push to get a better handle on the actual solidity of the data. What that translates into is the requirement for a higher degree of certainty about carcinogenic responses. The difficulty of translating animal responses into judgments about humans still remains. For example, one can see this in the case of formaldehyde which, in two independent studies, revealed a substantial yield of squamous carcinoma of the nasal mucosa. Nevertheless, there was a great deal of reluctance to do anything about it on the part of the EPA, although the Consumer Protection Safety Commission did take some action.

There has also been a great deal of difficulty on the quantitative side about the characterization of risks. The tendency on the part of the regulator is to take these numbers and treat them as gospel. The position taken by the people that produce these numbers is that they should be regarded only as upper-limit estimates. That is, the risk might be as high as indicated by these estimates but, alternatively, it could be considerably lower. I think there is a great deal of difficulty in handling numbers like that. If the argument is "Well if the risk can be anywhere up from the number on the linear extrapolation model, what does that mean? Can you do anything about it?" I actually think that one can from a regulator's standpoint. Namely, even with the linear extrapolation model, a very low level of risk provides a good margin of comfort. On the other hand, if risk is appreciable, a red flag is raised that the agent may be a public health risk.

At the present time, two things are cooking in the EPA. One is the adoption of the IARC scheme for stratification of the evidence from a qualitative standpoint. Over the years IARC has adopted a pattern of characterizing the evidence in terms of its being sufficient, limited, inadequate, or negative. They have used this scheme both for animal studies and for epidemiologic studies, and putting them together, they have made an overall judgment. I do not need to go into the criteria for these in both animals and humans, but the gist of it is that sufficient evidence in animals requires that the tumors be malignant, and that there is some element of reproduction of the results, either by separate studies or by a series of dose-response bioassays. Limited evidence is essentially a lesser degree of sufficient. That is, the criteria for sufficient are not met. And of course, inadequate can be generally insufficient quality of the studies. The overall combining of animal and human evidence comes out to essentially a gradation: I, being an agent which has sufficient human evidence; IIA, being good animal data with strongly suggestive human evidence; IIB, being sufficient with animal evidence; and III, being limited animal evidence.

We did formulate this and then got the opinions of about 20 outside experts, covering a range of point of views, from industry to the environmentalist side. There was uniform acceptance of the IARC scheme. I think that is going to have a very substantial impact on the regulation of carcinogens, because I think it will be very difficult to regulate agents in the limited category, on the basis of animal data. Now the rubric that describes this category is that one cannot make any judgment as to whether or not it is a

human carcinogen. I tried out a change in that by listing that category as possible human carcinogen, but that really got a Bronx cheer from virtually everybody--even the environmentalists. Perhaps they didn't realize what the implication was. In any event, a number of chlorinated compounds--pesticides and solvents--could very well fall in the limited category, and I think that characterization will probably not warrant stringent regulation at all. So I think the adoption of the IARC criteria is going to be important, and I would urge here that this particular approach be taken.

The other approach that we are trying out has to do with genotoxicity, or, more specifically, mutagenicity. Contrary to Kim's point of view, we have argued over the years (first) that the high correlation between carcinogencity and mutagenicity suggests their expressions of damage to DNA, which is supported by the evidence for interaction of carcinogens in their ultimate metabolic form, and (second) that the linearity for the dose responses for mutagens, coupled with epidemiologic evidence that is at least consistent with it, provide a reasonable basis for the use of the linear nonthreshold dose-response relationship. In addition, the matter of the add-on of the carcinogen to whatever is producing spontaneous tumors or tumors of unknown origin also supports the use of the linear extrapolation modal. The approach we suggested to a number of outside experts, where it was perfectly clear that the agent was not mutagenic, was essentially to not use the linear extrapolation model for estimating risks--to not estimate the risks since we don't know how to do it.

The approach that we have suggested was focused on the (EPA) water quality criteria. Water quality criteria concentration limits are suggested to the states by the EPA, and the states translate these into their own standards on the basis of local conditions. The approach that was suggested was to essentially define a range. The lower limit in concentration would be that derived from the linear extrapolation model pegged at a risk level of 10^{-5}. You may ask "Why 10^{-5}?" The answer is that there is nothing magic about the number, it seems a reasonable target risk to shoot for. The upper concentration limit would be the Russian approach that I just described; the conventional no-effect level with a safety factor. In that case, it would be a safety factor of 1000. We would provide guidance, an awareness range to shoot for depending on the evidence for mutagenicity.

The reactions to this approach, and admittedly it is a convoluted one, were mixed. Again, there were a lot of Bronx cheers on the very grounds that Kim Hooper raised. That is, we do not really know enough about dose-response relationships. The arguments are that we do not know enough about dose-response relationships for genotoxic and nongenotoxic carcinogens to be able to say that we should not use the linear extrapolation model. Some pretty formidable people took this point of view. Of course, the difficulty is that it not only pulls the rug out from not using the linear extrapolation model, but it severely weakens its use for mutagenic carcinogens.

Other equally distinguished individuals applauded the approach but called for more flexibility in terms of more evidence in, for example, the area of reversibility. One important distinction between a real "red-blooded" carcinogen and a promoter is the issue of reversibility. It has been demonstrated, in the skin at least, that if you give a carcinogen like benzo(a)pyrene, it does not much matter whether you fractionate the exposures, since you come up to the same level of response. But with a promoter, when you start fractionating it you begin to lose effect rather markedly. This issue of reversibility is possibly one of the single important aspects of promotion. Maybe this characteristic ought to be factored in, in addition to a number of other things, such as

pharmacokinetic evidence for a steeper drop-off in effective dose than would be predicted by a linear extrapolation from a higher-dose level to a relatively high-dose level.

So this approach is going back to the drawing board for reworking, and that is about where it stands. In effect, no distinctions are being made between complete carcinogens, or promoters, or partial carcinogens such as initiators, but there is a fair amount of talk about it. It may be that some scheme can be worked out in which such various factors as DNA interactions, mutagenicity, and pharmacokinetics can be factored in to essentially modulate the kind of risk approach from the linear extrapolation model.

Discussion

Drew

The room is small enough that there is no need to use a microphone. I would remind the commentators or questioners to mention their names first. I will now throw this morning's session open to general discussion.

Hooper

Roy, I would like to make a comment on restricting the use of extrapolation models with a linear term to those carcinogens that act by a mutagenic mechanism. My understanding is that an expression with a linear term is mathematically justified whenever the carcinogenic agent in question operates by a mechanism similar to those that are already contributing to the background incidence of cancer. The type of mechanism (mutagenic or nonmutagenic) is irrelevant. Perhaps, Kenny Crump could discuss this in the afternoon session. If the multistage model is equally applicable to carcinogenic agents which act by nonmutagenic mechanisms, I think it is really quite interesting and important.

In regard to the animal cancer data on perchloroethylene, I have a question on the application of IARC criteria requiring repeated results in test species. Perchloroethylene has been shown to be carcinogenic to male and female mice. Does this constitute "sufficient" evidence for carcinogenicity?

Albert

If the tumors were malignant.

Hooper

Yes, they were hepatocellular carcinomas.

Albert

I think if one takes the criteria literally, then the answer is yes. There are some people that do not like the mouse liver system. They are kind of close to home here, at least one of them. So that even with the working groups, such as in IARC, one gets differences in the way they come out.

I have one notable example. There is a monograph (and incidentally these working groups are international, and they cover a good spectrum of competent individuals) chaired by Norton Nelson that came out with a definition of "sufficient" for a number of the chlorinated pesticides and solvents. A later monograph, which put together a number of monographs, that was chaired by Arnold Brown, called the same compounds "limited." I think that this is really an expression of different views amongst scientists about the mouse hepatoma bioassay model. The adoption by IARC of a scheme for stratifying the qualitative evidence of carcinogenicity is not going to solve that problem. It simply means that some pattern will have to be established for the way an agency such as the EPA does its business. But if you take the criteria literally the answer is that it would be "sufficient."

Jones

I would like to ask a question about benign tumors. It is my understanding that often the conversion from a benign tumor to a malignant tumor occurs very late in the history of the tumor. Apparently, you have been looking at tumors in animal models with very short life-spans, relative to humans. There must be some concern about saying that a tumor which is benign in mouse is of no consequence to man. I guess the end result is that I would like to make a pitch for potentiation or promotion. Functionally, just how do you deal with benign tumors as opposed to malignant?

Albert

Well, with regard to the first point about the short life-span of the rodent, I believe that there is pretty good evidence that the timing of that tumor formation in response to carcinogen exposure is the function of the life-span of rodents, not the absolute amount of time. For example, we have done a follow-up study of children who were irradiated on their scalp for ringworm. There were about two thousand such individuals, and the follow-up time took about 30 years. The first scalp tumors began at about 14 years and have been increasing ever since. At least 60 individuals have one or more carcinomas of the scalp where they were treated. You take a look at rat skin, irradiated the same way at about the same proportion of age in the life-span, the timing of development is really right on the button in terms of their fractional life-span. So, I don't think that the point about the short life-span of a rodent being a consideration is valid. I think the response is a function of the life-span, not the absolute amount of time elapsed.

The IARC criteria for "sufficiency" distinctly talk about malignancy. This is a troublesome point because it is possible that tumors evolve from the benign to the the malignant given time, so that the tumorgenic response ought to involve both the benign and malignant. I think, though, that you have put your finger on a difficult point because there can be persuasive arguments made for taking the total yield of tumors as a basis for characterizing the response as statistically significant or not. So here again is another sore point or trouble spot.

Hooper

Just to add to that, in the NCI bioassay program, benign tumors are used to augment evidence for carcinogenicity. For example, if a particular tissue (e.g., liver) has a statistically significant increased incidence of carcinomas in dosed animals when compared to the control animals, benign tumors (adenomas) will be used to augment the evidence from the carcinomas. Dr. Hans Popper, an expert in carcinogenesis in liver, regards benign tumors as providing somewhat stronger evidence for carcinogenicity than do positive data from short-term tests, but not of the same importance as an increased incidence of carcinomas. In the Califronia policy, benign tumors are regarded as augmenting the evidence for carcinogenicity; not sufficient by themselves to conclude an effect as carcinogenic, but additional evidence for the effect.

Albert

Just a point about that. The National Toxicology Program is in the midst of trying to work out their position on this.

Crouch

I think one can get useful insight into what could happen in regulation by considering an extreme case. Let us suppose that somebody did a test and found 100% incidence of just benign tumors in all dosed animals. Now, what would you do about that? And I think you've got to answer that question right now, when you are deciding what is a regulatory carcinogen. I think I would take that to be a carcinogen, even though the tumors were benign.

Hooper

As an extension, a chemical negative in all short-term tests but producing benign tumors in 100% of test animals would also be considered a carcinogen?

Crouch

I think so.

Hooper

Yes.

Crouch

If you get a high response like that you're getting to think very hard about it, and once you've got that you're going to extrapolate it back so...

Albert

Is it better to ask why you think so?

Crouch

...I would say yes, that's the key. Furthermore I don't think that a given tumor in one species is predictive of a tumor, a particular tumor, in another species. So, it may be benign in one species and not in another. I was just pointing out that I think that in a regulatory position you've got to be reasonably consistent, so you have to think of extreme cases like this before you start.

Albert

Well, I think that's possibly a useful way of looking at it. But I don't think that I can recall any instance where that's come out.

Hooper

I think it is mostly a theoretical point.

Albert

Also if one looks at those agents which are known to cause cancer in humans, the tumors that are produced in animals are malignant.

Hooper

But I also think an important corollary is those agents which produce benign tumors in test animals usually, at least in all cases that I know, do produce a malignant tumor in some other species. That type of situation hasn't arisen, but it is interesting theoretically.

Perhaps I didn't make it clear where such a theoretical case might arise. If a chemical is positive in one species as described above but negative in short-term tests, it would be called a carcinogen. However, the control strategy might merely be to label it, instead of limiting levels of exposure. The regulatory response should be graded to the confidence placed in the experimental evidence.

Albert

Has this policy been adopted?

Hooper

No, we are thinking about it, and it may be useful to the discussion here.

Borg

My plea at this point is to introduce some mechanistic discussion which may be relative to what is implied here. I think it is important for us in this discussion to try to clarify what we mean by initiation and promotion. I think the distinction is important in discussing what we imply by "stage" or "step" in a multistage or multistep model, something we will be discussing later. I think it is also important in quantifying carcinogenic risk if, as some contend, we live in a sea of initiators, then the significance of a given exposure is largely a signal-to-noise one. It is also important in keeping our eye on the ball if promotion is largely environmental and potentially controllable.

As I see it, the question is to define the committed cell, associated as I see it with initiation. And then the stimulation of expression of the neoplastic phenotype which appears to be associated with what I call promotion. And promotion is, as you have already been reminded by Dr. Albert, apparently a multistep process that appears reversible in its earlier stages, at least in many cases. Now the classical view, as I would put it, is that promotion represents a stimulation of cell proliferation that gives rise to metaplasia--some benign tumors, perhaps--and ultimately to autonomous growth which is often invasive as well. No doubt a more contemporary speculation would seek to invoke recruitment of retrovirus-related transformation genes and would, in some fashion not yet clear, involve free radical reactive forms of oxygen and possibly lipid peroxidation. It would also invoke anticarcinogenesis (i.e., antipromotion) manifest by the enzyme superoxidysmutase in animal systems and by various compounds with the oxidizing properties such as retinoids. I think the confusion is illustrated in part, maybe I misinterpreted you, by Dr. Hooper's reference to DNA repair in what I thought he said was the context of promotion.

It is true that some very recent data cite clastogenic effects of promoting agents, especially those thought to produce reactive species of oxygen in situ. However, more traditionally, one thinks of DNA repair in the context of somatic mutation or cell commitment. That's what I think of as initiation. Now, with some thoughts on the matter and asking for others to discuss what I think is an important distinction between initiation and promotion, I will invite more comment.

Albert

I would like to point out that in the real world decisions have to be made where virtually none of this evidence relating to promotion or initiation is available. One simply has a few bioassays which are just routine administration of an agent to the animal and then defining the tumor response, maybe some short-term tests, maybe a bit of a look-see about DNA intereaction, generally not. There is just a striking paucity of detailed information on mechanisms available in the regulatory realm where decisions have to be made about agents. So my own feeling about this is that it's very important. We hope there will be enough tests to bring in the mechanistic information in terms of characterizing agents. But I must say, I'm skeptical about the extent to which this is ever going to come true.

Varma

I just wanted to comment on the interpretation of a high incidence of benign tumors. If one were to have such a high incidence of benign tumors, it is a strong indication that something is going wrong in the cell mutation, and we all know how often benign tumors are precursors of malignancies. So if one would observe such very increased significance in benign tumors, it should be interpreted, I would say, as an indication of potential carcinogenecity.

Albert

I would just like to point out that with regard to malignant tumors in the mouse liver, where this is one of the most contentious areas, the relationship between the occurrence of malignant tumors and benign tumors has not been worked out. One gets the impression in listening to these presentations that sometimes you have virtually all the tumors malignant and there are few or no benign tumors. Sometimes you have a reasonable mixture of the two. First off, it has only been relatively recently that the distinction has been made in large-scale bioassay studies. Also, nobody has analyzed the data. This is, as I understand it, being done in the National Toxicology Program which inherited the National Cancer Institute's Bioassay Program. So the patterns of response are not at all clear--whether or not a relatively mild carcinogen would produce mostly benign tumors and a few malignant tumors, and then a nastier carcinogen would produce mostly malignant and a few benign--so it seems to me that as with so much of this business, we're talking in a speculative mode.

Hattis

I have two comments. One is that, although we have been talking here mostly in technical terms about what should and should not be called a carcinogen for regulatory purposes, it is well to bear in mind that although this has

technical elements, it is not mainly a technical decision. What you call a carcinogen for regulatory purposes depends first, on what you are going to do when you call something a carcinogen, and that changes in different eras of history. Second, and most important, one must determine the costs and benefits of being wrong one way versus those of being wrong the other way. What are the costs and benefits of calling something a carcinogen on the basis of limited structural criteria if the likelihood of guessing "right" in some cases may be as little as 50%, and what are the costs and benefits of calling your 100% benign tumor agent "wrong" where the likelihood may be much less.

Borg

Can I get back in this? I don't really disagree with what Dr. Albert said, that regulators have to act in imperfect knowledge and that it is unlikely we will ever have perfect knowledge--if that's a summary of part of what you said.

Albert

I didn't mean perfect. I meant just a reasonable amount.

Borg

Nonetheless, I think we've already heard that our understanding of mechanism does make a big difference about what we do when we call something a carcinogen. As Dr. Hooper pointed out, we no longer have the picture that we will find a few dominant carcinogens in our environment that can be controlled, thereby reducing the carcinogenicity of our environment by very much. So mechanism really counts, and here I think it counts a lot. For instance, in the context of the cost/benefit of being wrong one way or another, let me be a devil's advocate. Say, as I do in fact believe, that promotion looks like a very important part of the story to the extent that many people, and I am one, are very impressed with cancer epidemiology which says cancer rates differ in different parts of the world and change with economic status. This suggests that something can be done. So the cost/benefit is not so much of being wrong as being preoccupied with the few initiators which may in some cases--let's say in the workplace, where you get a tremendous load--dominate the picture, and thus we don't pay enough attention to the promotional factors which are partly, perhaps largely, reversible. Intervention can occur, changes in life-style look important, and the cost/benefit would be huge. For the sake of being a devil's advocate, I'll say that's happening in part.

Hooper

I think your points are well taken. Richard Peto has made the argument that promoters may pose a significant hazard, but I think Roy's point is that we don't really have the means to identify such chemicals at present. The implication of your remarks is that we need more research on promoters. It is premature to devise a regulatory strategy to deal with them at present because we really don't know much about them (e.g., how to identify them). Results from animal cancer bioassays give a positive response without providing any knowledge about mechanisms. We really haven't developed sufficient sophistication in short-term tests to detect promoters. It's beginning to happen, and once such

tests are developed, they will obviously be very useful. What I mentioned about inhibition of DNA repair, enzyme induction, sister chromatid exchange, hormonal action, etc. is a mixture of promotion and cocarcinogenesis. Something can initiate, and if you inhibit DNA repair, you either "promote" that or have a cocarcinogenic effect. But again, we really don't know. Although we have these nice models at the biochemical level, we lack the ability to translate our bioassay techniques into that molecular mechanistic structure.

You mentioned oncogenes and we can theorize how chemicals can interact there. But I would say that, if you believe in those mechanisms, and if one mechanism is initiation, then another mechanism is "promotion"--whatever that is--and there may be a subset of mechanisms under those. If our new agent acts by one of those mechanisms, then isn't it additive? Isn't it that one would have a linear term? The ultimate social consequence may be that it will promote many, many agents and, in effect, may have more consequence than a simple initiator. It may promote many things that have happened. But we still haven't worked out in any sensible way a risk assessment methodology to accomodate all that.

One more thing. Bill is talking about cost/benefit. The way I see that, simply, is that there are costs to false negatives and costs to false positives. In the polarization that Roy spoke of, environmentalists vs industry types or whatever, it simply centers around these costs. As a public health person, I am very aware of the cost of false negatives. If someone tells me that something is negative (e.g., that perchloroethylene is a nonmutagenic carcinogen and would probably not have a great risk on the basis of some data they offer) I am very suspicious because I worry about false negatives, and I require quite a bit of evidence when something is negative. On the other hand, industry is worried about false positives, something that we call positive as public health persons, but which in fact is negative. Looked at this way our disagreement is reasonable: the evidence necessary to convince me of a certain outcome is different for them, and we are concerned about different outcomes. My business is health, and their business is selling chemicals, and that's reasonable. We're protective of false negatives and false positives in separate ways.

Hattis

I just wanted to support the point that mechanism is important. I must say that I'm much more optimistic about the potential for making reasonable statements in the basis of different kinds of mechanisms. We don't know everything there is to know about initiation and promotion, but we know pretty well what initiation is, and we know at least some plausible mechanisms of promotion including, in part, stimulation of cell division. Promoters may be important and a controllable element of carcinogenesis in society, but that doesn't mean we have to assess the risk the same way. Because the mechanisms of promotion may well be different, and are likely to be different, there is no reason for the dose-reponse curves for promoting activity to have the same kind of form as the dose-response curves for initiation. If, for example, you have a cell proliferation-type model, it is by no means clear that at low doses you get a straight forward linear increase in cell proliferation. With cell proliferation you clearly reach a maximum at some point. It is quite possible, depending upon the mechanism by which it increases cell proliferation, that you get a very steep decline. Also, it might matter a lot what the dose-rate effect is.

Albert

A number of people are convinced that promoters have a threshold, and that there are tests for determining promotion. The difficulty is in proving that the agent is not also an initiator, which basically is the difficulty of proving a negative. For instance, in trying to distinguish between mutagenic and nonmutagenic, when is an agent not a mutagen? Since you can't prove a negative, you have to set up arbitrary criteria. Everybody, I think, is reasonably convinced that complete carcinogens show a spectrum of differences in balance between promotion and initiation. So we have to talk about the issue of an agent which has promoting activity; for example, dioxin has some clear-cut evidence for promotion. But how do you know that it isn't an initiator? That's the difficulty from a regulatory standpoint. Even if you were set on treating initiators and promoters differently, some acceptable criteria will have to be established. And there's a lot of reluctance to do that sort of thing.

Crump

I guess I share some of Roy Albert's views about the issue of initiators and promoters. It's surprising to me how little information is available. It's not clear to me that we even have a common definition of what we mean by promotion, and I would concur with Roy that there is always going to be the question of does it do both, and those kind of questions. I am sort of pessimistic about how all this information is going to be incorporated into the regulatory process. The argument that Kim made earlier for linearity is one which I have also made and is, I think, the basic argument that people have used to support linear no-threshold models. But it is such a simplistic type of argument. It's been around for 6 or 8 years, and it is still the one that is being pulled out. I don't see all the information that we're getting on mechanisms being incorporated, and it's of concern to me that we aren't making more progress in that direction.

Borg

With regard to your pessimism, I don't know how increased understanding of mechanism will be reflected in regulation. I haven't much to say except we can't be like the drunk under the lamppost looking for the money he lost down the street because that's where the light is. If in fact the mechanisms of carcinogenesis and environmental carcinogenesis are complicated, then we have a more complicated problem. Let's try to get that understanding!

I would like to make a more detailed mechanistic comment with regard to thresholds. To the extent that there is some evidence coming out now that reactive forms of oxygen are important in promotion--not yet well documented, but strongly implied--I can make the flat-footed statement that if this is true, we can expect thresholds, and we can expect dynamic ones at that. Ones that show a strong dose-rate dependence. Because the reactive forms of oxygen are part of that big sea, at least of oxidant challenge, there are many body defenses that are maintained in a highly dynamic steady state that have to be overcome before one sees irreversible effects. So if that turns out to be an important part of mechanism, one can expect thresholds.

I would also say though, with regard to animal tests, that it seems to me the present protocols actually demand for an agent to look sensitive, that it be both an initiator and preferably a promoter. We don't expect either one to be

both an initiator and preferably a promoter. We don't expect either one to be pure. It is confusing to be sure, but there is no reason we must keep the same protocols forever. It may well be that we should test for initiation in animals that are known to be in a high promotional state. Inconversely, that instead of keeping whatever promotional level of a given regime as constant, we make that the variable for the fixed initiator. So, we could make animal experiments, I think, that reflect the promotion and initiation more carefully. It isn't a fixed thing forever.

Drew

We've heard from Dr. Hooper this morning how the California State Department of Health is going to approach the regulation of carcinogens. We've heard from Dr. Albert how EPA is approaching these problems. It's clear from the discussion that the question of initiators versus promoters is yet to be adequately addressed. I get the sense from the discussion that promoters are certainly to be considered carcinogens for most purposes. I'd like to hear a little more about the definition of a carcinogen for regulatory purposes, in that Dr. Albert told us that at least one Federal agency defined formaldehyde as a carcinogen to be regulated, and another one did not. With these remarks, we will bring this discussion to an end and reconvene at 1:30. Thank you.

SESSION II

POTENCY

Introduction
(Session Leader - Andre Varma, Ph.D.)

White

Session II, which covers potency issues related to carcinogens, will be led by Dr. Andre Varma. Dr. Varma is a member of the Advisory Panel for the Center for the Assessment of Physical and Chemical Hazards at Brookhaven National Laboratory and he is also associated with the State University of New York at Stony Brook.

Varma

I have only a few short remarks because we have an extra speaker this afternoon and I want to stay within our allotted time schedule.

A number of speakers this morning referred to the role of epidemiology in assessing the risk, or I should say the attributable risk, to chemical agents where cancer is the outcome. There are two kinds of epidemiological studies of human populations. Since prospective studies are really impractical for assessing carcinogenic risks, most of the time we use case control studies where we compare the antecedent factor (i.e., exposure to a chemical) in a number of cases and in a number of controls. I don't have to emphasize the difficulties we face. If the correlation is very obvious, e.g., smoking and lung cancer, or asbestos and mesothelioma and lung cancer, we have no problem. However, when the effect is marginal, problems may arise. For example, is coffee drinking an additional risk factor in pancreatic cancer? The choice of the control group and the assessment of the exposure then become very important and controversial. If there is consistency among the epidemiological findings, the animal studies, and the studies on cells, we again have no major problem. When the findings are inconsistent we can't comfortably resort to the extrapolation of the dose-response curves because we don't know if what we're doing is realistic for a human population.

This afternoon we will discuss the various aspects of carcinogenic potency, and I wonder whether we should restrict ourselves to cancer as the only response. Another aspect which we often overlook is morbidity. We study only one end point - cancer. Human cancer is not a homogenous entity. Some cancer patients die quickly whereas others may have five and ten-year survival rates.

We are also not considering the quality of life of the individuals afflicted by cancer. We are ignoring morbidity and noncancerous disease processes which might be initiated by an agent. In this context I am thinking of exposure to various fibers that trigger pneumoconiosis which can incapacitate a relatively young individual for 10-15 years, have a severe financial impact on the health care system, and cause suffering to the individual and his or her family.

However, in a short two-day meeting we cannot address all these various aspects. Therefore, we have decided to zero-in on one type of agent, chemical industrial agents, and to focus on one kind of response, carcinogenesis. In the total public health concept, however, I think we have to remember the broad complex issue. Only then can we properly assess the cost-benefit dilemma and, as

I said earlier, this tradeoff depends on whose ox is being gored - the industrial one or the environmental interest.

Our first speaker will be Dr. Harris Fischer who is an Associate Scientist with the Biomedical and Environmental Assessment Division, which is part of the Energy and Environmental Department here at BNL. He received a Ph.D. from Stony Brook in physics and a bachelor's degree from Swarthmore College. He has held a position in Suffolk County in the Environmental Department and was Acting Director of the Suffolk County Council on Environmental Quality. This position reminds me of one of our latest studies which concerns contamination of the groundwater table in the eastern part of Suffolk County with Aldicarb or Temik. A survey which we have recently analyzed seems to indicate that there is an increase in symptoms related to the peripheral nervous system, and also that there may be an increase in spontaneous abortion in the women exposed to the highest levels of this chemical. However, we are uncomfortable with the small response rate to our mail questionnaire. Here again we have another example of the effect of an agricultural chemical on the health of society. Dr. Fischer --

Definitions of Potency
(Speaker - Harris Fischer, Ph.D.)

Fischer

Just before we broke, Kenny Crump was cautioning us against simplistic interpretation of dose-response relationships, and I was very disappointed because everything that I have to say here is simplistic. I was asked to talk about "potency." Usually people who talk about something like that start by going to Webster's Dictionary and looking it up. I thought that in the case of this particular word, that procedure would be a bad idea--it could only lead us astray.

As I understand carcinogenic potency, the only way that its meaning can be visualized is in terms of a dose-reponse relationship, although that may only be an implicit relationship. For example, one interpretation of potency would be the TD_{50}, i.e., the dose required to give a 50% response, and presumably the inverse of this dose is a measure of the potency for an arbitrary dose-reponse curve. To me this is the slope B of a line drawn to a point in the middle of a dose-response curve (Figure 1).

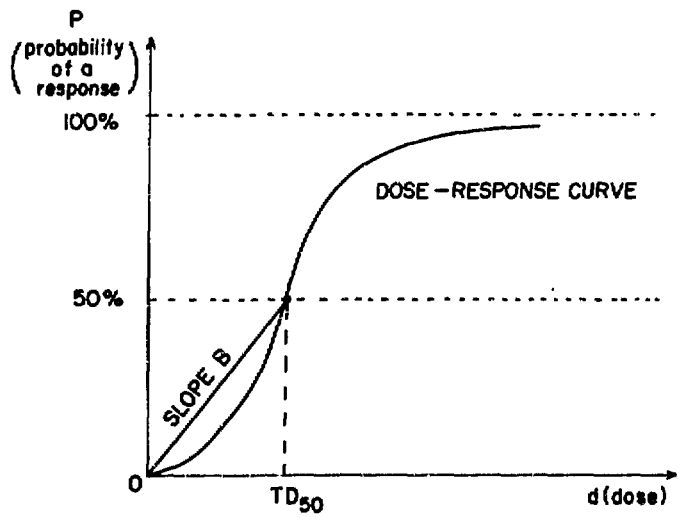


Figure 1

What we've been doing in a study that we're working on now has been to look at data in a manner similar to John Van Ryzin's work. I have to acknowledge our indebtedness to him for giving us a lot of clues as to how to proceed here. I don't have any data to show you, but Figure 2 is typical of the graph you get when you look at a variety of conventional models to fit dose response. Of course, you get a variety of answers, particularly at low dose. Since we are interested in very low incremental doses, we're consequently interested in differential effects. So our response was to take the derivative of the fitted dose-response curves; for our purposes this derivative curve (Figure 3) is what we would define as marginal or differential potency. For example, the slope of the dose-response function at any point (corresponding to a background dose) is a measure of the effect to the population of the United States at large from

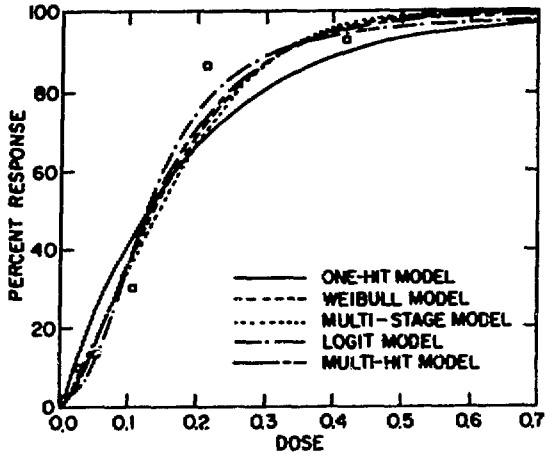


Figure 2. Fitted dose response curves and estimates of risk for benzo(a)pyrene based on five extrapolation procedures (dose mg/kg).

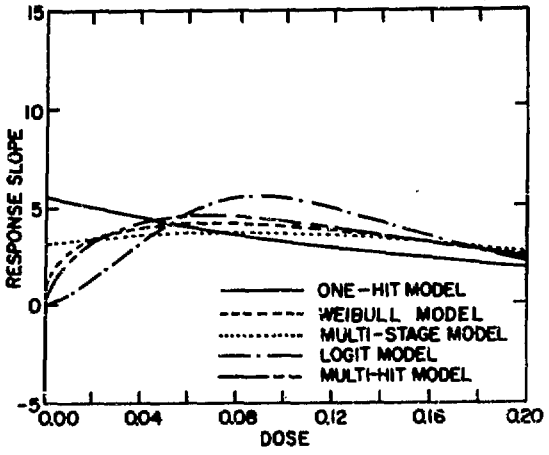


Figure 3. Estimated slopes of the five dose-response models for benzo(a)pyrene at different incremental exposures (dose mg/kg).

siting a power plant somewhere in the U.S., which would therefore add some small unit increment to an existing large background.

The point is that the way you look at potency depends on how you intend to use it. If you're interested in a large addition to an essentially nonexistent background, then you want to look at something like Figure 1--that is, the slope of a line to a point somewhere on the dose-response curve where you expect to be. If you are interested in doing incremental risk-assessment estimates, then you take the derivative; of course, in between these two extremes, there are other possibiliities.

It is of interest that in the case of the statistical models -- those that assume some sort of a distribution within the population of tolerance threshold --the differential potency is in fact the distribution of thresholds; i.e., if you're fitting a Logit or Probit model, you are by definition assuming a differential potency of a logistic form or a log normal form, respectively, and so on.

It seems to me that there is a potential problem in using any single definition of potency as a universal measure. For example, the low-dose problem of extrapolation is illustrated in Figure 4. Figure 4 may be a hypothetical situation, yet here are two different curves with the same potency according to the TD_{50} definition. In the low-dose region, hypothetically, these two curves could deviate from one another by arbitrarily large ratios, just as we find when fitting different models of dose response to a data set and then extrapolating to low dose. Therefore, you may need to worry a little bit about the appropriate definition of potency for specific applications. In other words, the definition of potency that is adequate and presumably best for occupational or other effects, where large doses are concerned, could conceivably lead to a reversal of potency rankings at very low doses. That means that rankings based on high dose experiments might be quite wrong when applied to public exposures. I don't know whether this hypothetical argument actually holds in real cases, but certainly given the status of our understanding of curve fitting to real data, i.e., the degree of uncertainty that's inherent there, this is a potential problem that needs to be considered.

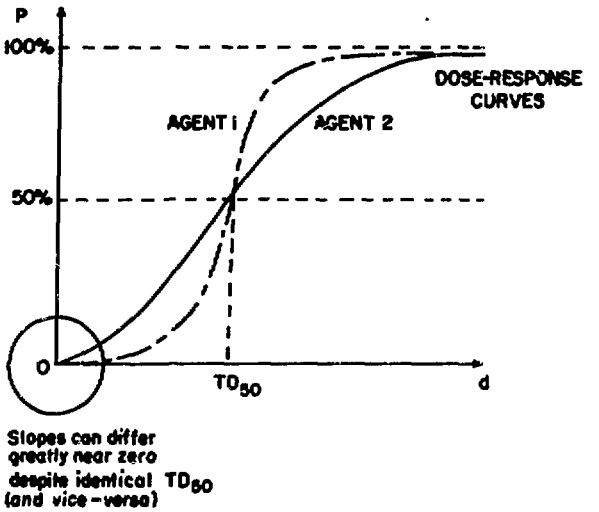


Figure 4

Along the same lines, you could also argue that background has a similar importance in defining potency for a particular application. Figure 5 illustrates a simplistic interpretation of independent and additive background: If, on some basis, you have derived a dose-response curve (Figure 5a) that starts at zero effect, and you want to make it fit to an existing spontaneous risk P_o, then from a purely graphical standpoint since it still has to saturate at a value of 1, you can either squeeze the curve up to fit between P_o and 1 (Figure 5b) or slide it to the left (Figure 5c). In both cases you can make the curve fit the spontaneous risk P_o at zero dose. Figure 5b corresponds to independent background risk and Figure 5c to the additive background model. From here it's easy to get a graphical picture of why you have low-dose linearity when you have additive background. You always get a nonzero slope at zero dose when you start sliding the curve to the left, so in a Taylor expansion you must have a linear term that will eventually dominate higher-order terms.

In any case, you affect the slope of the dose-reponse function by the addition of background of either sort, and therefore the effective background would have to be considered in defining low-dose incremental potency. In this case we would presumably fit the curve first and then look at the effect on the derivative.

I'm not sure I want to talk about the last view-graph (Figure 6). It deals with the old question of whether or not statistical models should be threshold models and the argument that you never see a six-inch-tall man. Therefore, why do you expect the tails of statistical distributions of biological variables--in a range that you can't even observe--to go down smoothly to the origin and not cut off at some finite threshold? That makes a lot of sense to me. The point of this figure is to show that even with a threshold (e.g., a log-parabolic distribution--which perhaps you might expect if, in fact, carcinogenesis were related to human height or, more seriously, to some other biological variable that also has a threshold), the previous argument of low-dose linearity from an additive background still holds. That is, if the way you have incorporated the background is to slide your original dose-response curve to the left as far as necessary to give a nonzero effect (i.e., by an effective dose

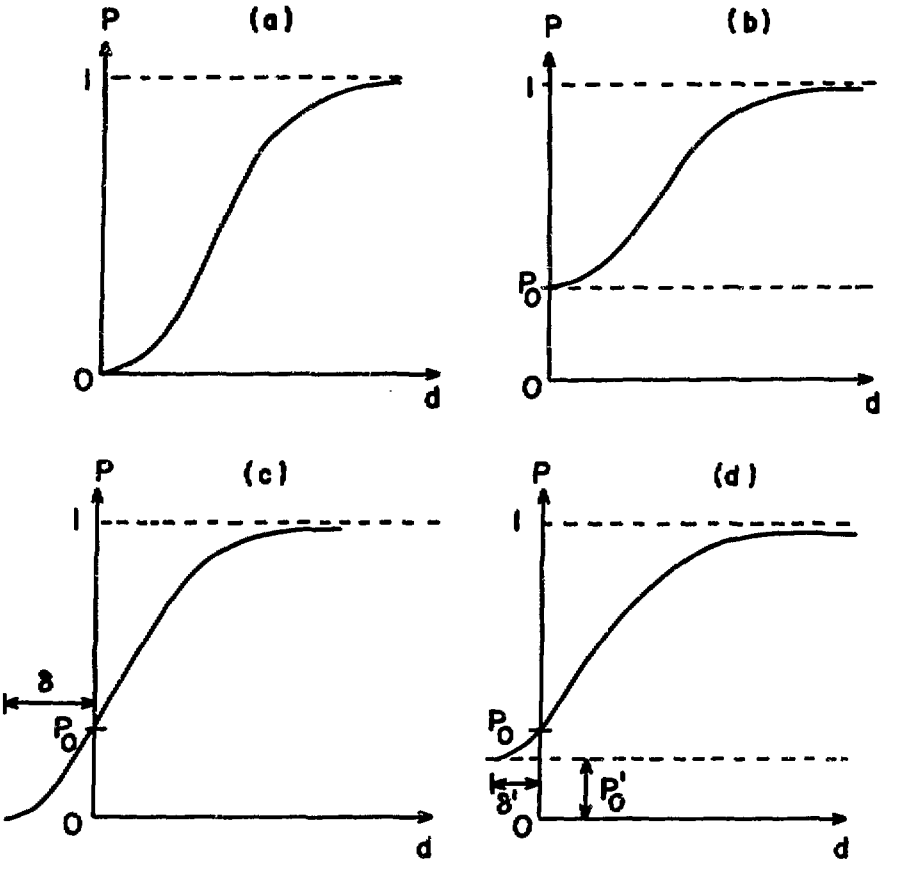


Figure 5. (a) Original dose-response function with no background rate. (b) Original function scaled vertically to fit between P_0, a background rate, and 1 (independent background). (c) Original function displaced leftward by an effective dose δ to intersect vertical axis at P_0 (additive background). (d) A combination of additive and independent background.

δ), then you necessarily have a linear term even though your original dose-response function had a threshold. Consequently, even for these threshold models there is low-dose linearity if spontaneous cancer incidence is attributable to additive background effects. I'm not sure that is central to the subject of this session, but I think it is interesting.

Finally, there's a question as to whether any of these considerations are important in the real world because in practice we can't distinguish between these families of dose-response curves (e.g., in Figure 2) except in a theoretical sense. So I'm not sure that these caveats I've presented really have a great deal of practical importance except to indicate the potential for a ranking system to give a wrong answer when doing risk assessment, for example, at low doses, if the ranking system is only appropriate to high-dose estimation--or vice versa. To me, this represents an important caution, even if a theoretical one. I expect that the only way we will resolve some of these questions in

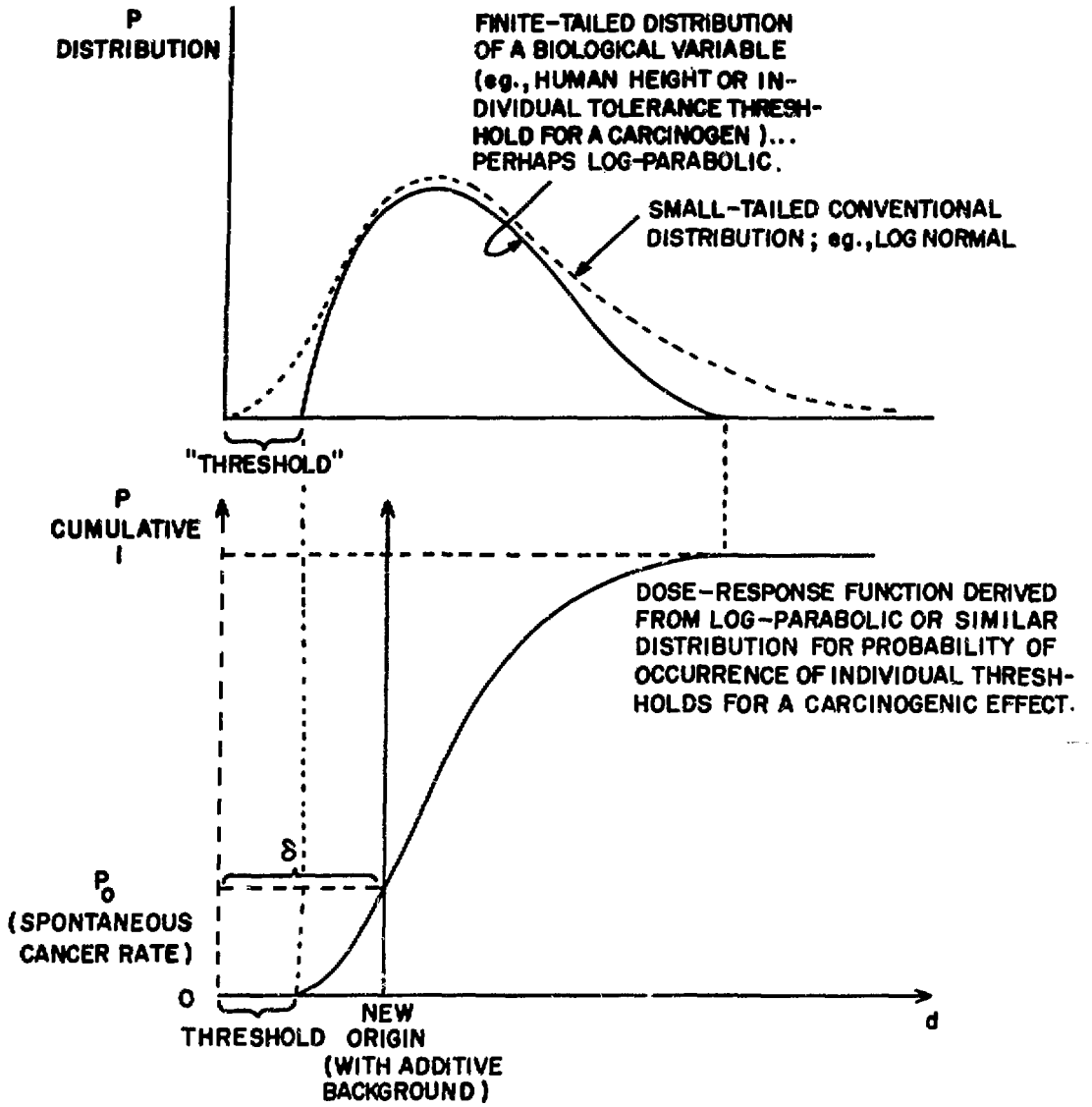


Figure 6

practice is through microbiology; we will determine whether background acts additively or independently not by contemplation of dose-response relationships, but by whether we find such mechanisms at work in biological experiments. Presumably, this is something that we can eventually get a handle on by looking at the actual microbiological processes occurring within the DNA molecule.

A Dose-Response Model That Provides an Estimate of Potency Factors for Neoplastic Potentiation
(Speaker - Troyce Jones, Ph.D.)

Varma

Our next speaker is Dr. Troyce Jones. He is an applied mathematician from the Health and Safety Research Division at Oak Ridge.

Jones

Being an applied mathematician, I'm going to rely mostly on my graphics. We have an expression that states, "A picture is like 2^{10} words," so I'm going to have a lot of figures. I'm probably going to move along very fast. Most of you have been in this business longer than I have, so you probably know more about it than I do. Actually, I will probably make only one or two points on many of the slides. Many of the slides will be similar to others I show, so if I go too fast or you want to look at something in more detail, give me the flag, tell me to slow down, speed up, or skip on, whatever. I'll try to adjust to the response, and that includes ducking.

A generalized dose-response model for neoplasia must consider initiation, promotion or potentiation, the cohort effect, time-to-tumor, and competing risk.

Question

What is cohort effect?

Jones

The cohort effect is the comparison of a treated group with a control group or an unexposed group. I think that the meaning of this term will be a little more apparent later on, but essentially you have treated animals and untreated animals, and basically that's all I'm trying to say. I'll elaborate just a little bit more later. If I don't say enough, then ask me again.

Varma

At some point will you please define incidence?

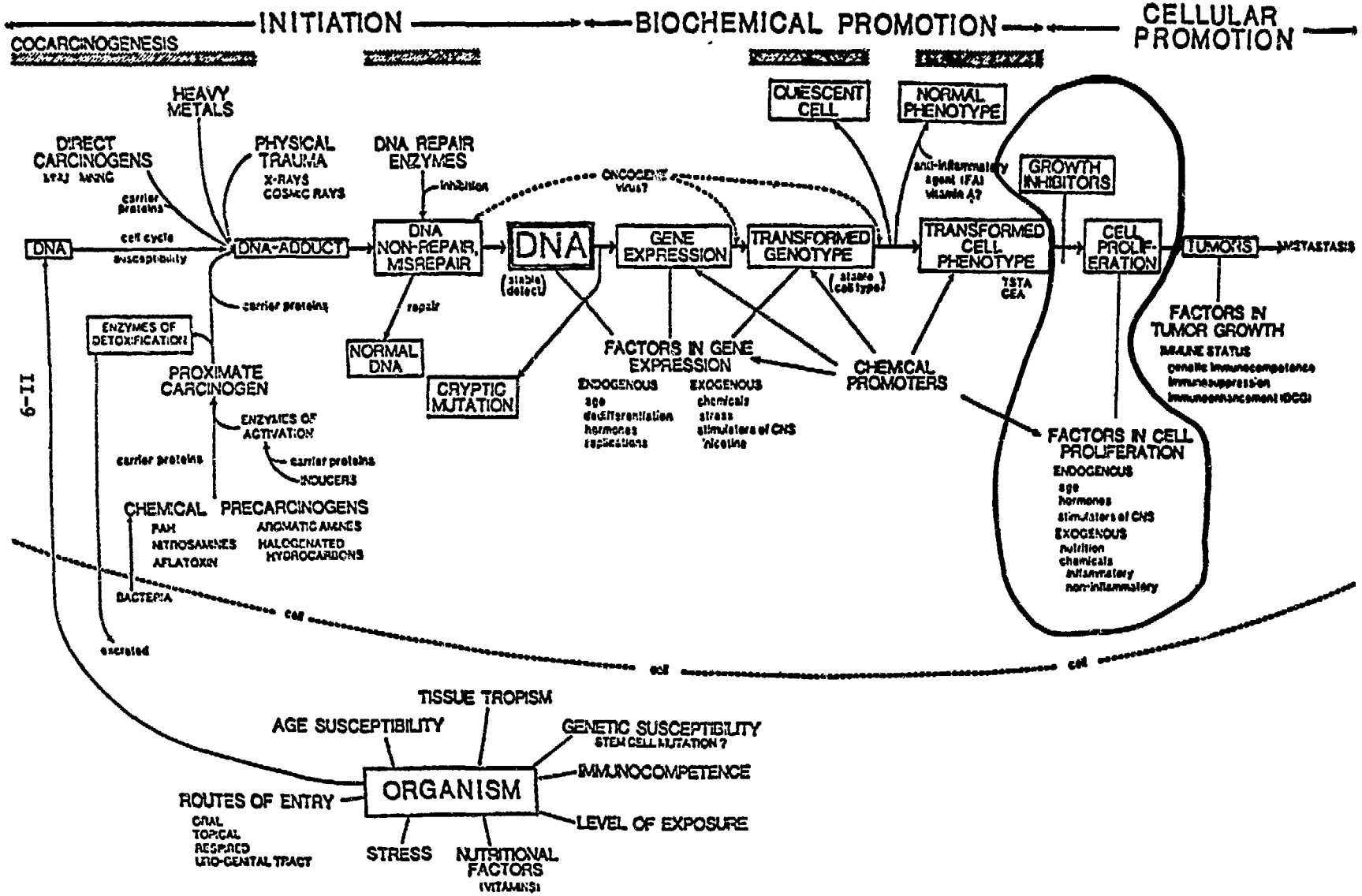
Jones

Yes, incidence refers to whether the role of the spontaneous tumor in dose-response studies is deterministic or insignificant.

Now, I think everybody agrees that carcinogenesis is very complicated, much more so than this simple little diagram (Figure 1). This figure was prepared by Carol Henry at Microbiological Associates, and I am using it to make one point. We talk a lot about initiation, biochemical promotion, and cellular promotion. Many researchers would like to break up both initiation and promotion into a lot of subcomponents. Now today I'm going to consider carcinogenesis as something more like a two-stage process, which is much like Berenblum's original description. I'm going to try to focus on this part that I've outlined here, and you can see that this outline falls under the broad heading of cellular promotion. Basically, I'm going to be analyzing data, and I'm

Figure 1

STAGES IN CARCINOGENESIS



going to be taking into account cellular kinetics, cellular promotion, cellular hyperplasia, etc.

This simple little logic diagram (Figure 2), which leads me to the treatment that I want to discuss today, concerns a biological stress acting on a biological model, mouse, or man. This insult can be either radioactive, chemical, physical, or whatever stress you prefer. Basically, the result of this stress seems to be described in three simple compartments. Some of the cells in the tissue matrix can die from the trauma. Some of the cells may be changed, but will remain reproductively viable. There's a broad spectrum of other changes. Some cells function normally, at least at low dose levels, i.e., they seem not to be affected at all. Now there are various transitions as a result of endocrine or immunologic control that can take place among normal, altered, or dead cells. Some of the cells that have been altered can die. Some cells are reproductively dead; they do not reproduce, and they do not go into cancer. Some of the cells that have been changed presumably have altered genotypes, or however you choose to categorize them. It is these cells that will eventually become manifest as papillomas, tumors, cancers, or whatever terminology or disease you are looking for in the end.

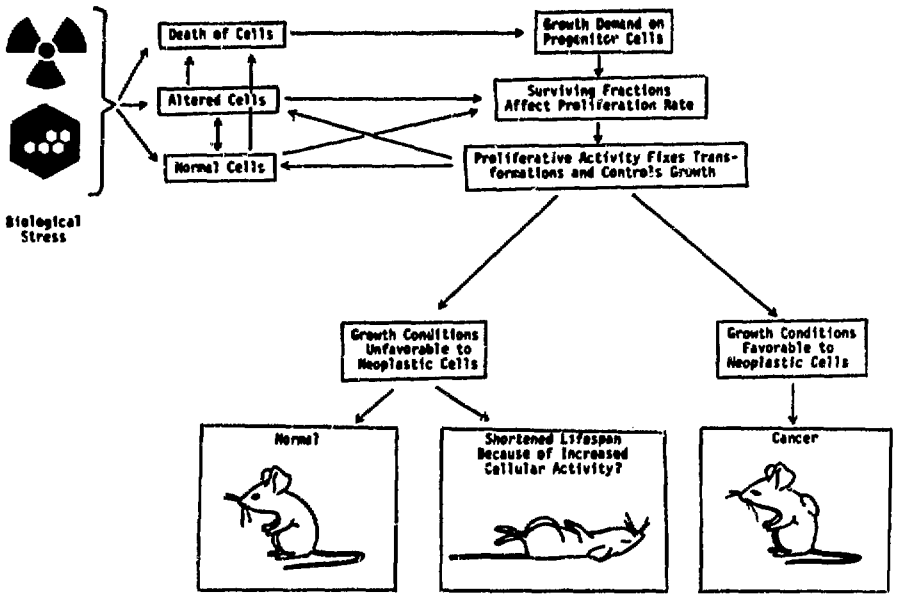


Figure 2. Simplification of systemic response to early biological effects.

But the basic component of the model that I'm going to describe today examines the death of cells. It tries to quantify that aspect for insults that induce cell death. Furthermore, there is a kinetic relationship among these three components. The surviving altered fraction plus the normal cells affect the proliferation stimulus, i.e., the healing response, and that brings us over into this kinetic-type loop here. We know that at least one round of cellular proliferation is necessary to fix the abnormal lesions in the cell (i.e., initiation). However, to get full expression in an organ, it probably takes more than one round of cell division. But, this is a kinetic process, and here it is simplified to the point of just showing the healing response. Once one comes out of that loop, you're essentially back to steady-state homeostasis. If the

growth conditions are unfavorable to the neoplasm, or the neoplasm is suppressed by the immune system, the following may occur: (1) The animal may be apparently normal throughout its life-span; (2) if there is a high-level chronic stress, the animal population may have a shorter mean life-span and die early from nonspecific causes; or (3) if the stress is conducive to autonomous growth, the animal may have excessive cancers.

The following equation tries to describe the generalized dose-response model for neoplasia in a little more detail:

$$\text{Response}\{D(\tau), T\} = \{\text{Initiation}\{D(\tau), T\} \cdot \text{Potentiation}\{D(\tau), T\} + R_o(T)\}\,(1 - \text{Competing Risk}\{D(\tau), T\})$$

At this point I'd like to consider the response as being a result of two variables, i.e., dose as a function of tau, where tau is some time parameter that describes the dose protocol, which is the temporal schedule of the dose. The T variable that I've used here can probably be thought of as the age of the test animal or human for this discussion. And so we put our model together. The response is a function of initiation, which is the result of applied dose, where tau is the time of treatment, and T is the age. This age contribution includes various heredity factors, viral, etc., and whatever is not encompassed in dose. It is very vague at this point. We've got potentiation that is a function of the same variables. The $R_o(T)$ is the natural tumor rate in the cohort group or the control group, i.e., the zero-dose group. For these tumors to be expressed in a study, the animals have to survive until the tumor is diagnosed, through either sacrifice or death. So we have a possibility of a competing risk-type factor.

At this point in our model, I'm going to consider that initiation is basically zero or one, like a step function:

Initiation = 0 or 1,

$R_o(T)$ available from experiment/or epidemiology,

Potentiation = $1 - e^{-\alpha D - \beta D^2}$,

Competing risk = 0, Kaplan-Meier, life tables, or from a mechanistic model, and

Time-to-tumor = T^N (currently) .

If we have promotion without initiation, we don't get cancers. We know that promotion is reversible, and all the discussions this morning led in this direction. My point is that if you promote an uninitiated system (i.e., a system that is not initiated through heredity, virus, an initiating dose, or some other method), then you should not find cancer. You may get hyperplasia, but you should not get carcinomas. Generally, the natural cancer rate, $R_o(T)$, is known from the cohort group or the control group. The potentiation factor is going to make the model that I use look like a two-stage model algebraically, but actually I'm coming in from left field. The two-stage appearance is due to only one stage which is promotion. I'm choosing this particular form which only looks like a two-stage model because it is quite a flexible expression and it fits cell survival data very nicely.

Question

Could you define potentiation, please?

Jones

Well, it's a term that I use very broadly. Actually, I'm thinking of a promoter, but the "mouse skin people" have very clear ideas as to what promotion encompasses. They tend to think of the biochemical characteristics of phorbol esters, TPA, or others. To try to avoid arguments and to use a term that can include chemical and physical wounding, I use the term potentiation. For example, if I have a population of initiated mice that has been given a "subcarcinogenic dose" of a chemical and if I hold the mice throughout their normal life-span, there will be no observable excess cancers in this group. You can repeat the study using some other chemical, ionizing radiation, or other agent. This feature seems to be organ specific. You can give very high initiating doses to the liver in the absence of carbon tetrachloride, or phenobarb, hepatectomy, etc. Usually, you don't see extra cancers in the liver without promotion. So basically I'm talking about the process of carcinogenesis that is somewhere past the initiation stage. If you return to Figure 1, the heavily outlined area is called cellular promotion.

Varma

Could you go back to the previous equation? It's a multiplication sign. Isn't it initiation times potentiation, where the initiation is a zero or one?

Jones

Yes.

Later on, I'm going to talk about initiation as if it is a binary thing, i.e., either you have it or you don't have it. In some animal studies, if everything else is held constant (i.e., the promotional schedule), the initiation dose can be changed by a factor of 2, or even a factor of 10, without changing the fraction of animals that get carcinomas. You can change the number of hyperplastic nodules in a given organ, but not the fraction of animals that get cancer. So that's going to be more or less implicit in the treatment that I'm going to show you.

Varma

Can we interpret initiation by a single substance, when viewing the total environment as an aggregate of risk factors? In public health we have to consider the relative importance before deciding what is socially acceptable. I wonder whether we will then find simple zero-one relationships.

Jones

I guess that I'm considering initiation to be some treatment with a carcinogen that does not raise the cancer incidence of the treated group above the cancer incidence of a control group. Now, if you do something else to express that treatment, for instance, feed carbon tetrachloride to the treated mice, then the incidence of liver carcinomas will be higher. If you feed carbon tetrachloride

to the control mice, you may make them sick, kill them, poison them, etc., but you should not get a higher cancer rate in the control group because they haven't been initiated, except for strains having a high natural cancer rate, such as Sprague-Dawley rats.

Albert

The data that we obtained are somewhat in variance with what you said. In the mouse, again, initiation does have a linear shape. Slaga got the same results.

Jones

But you're looking at the number of papillomas per mouse, aren't you, Roy?

Albert

Of both.

Jones

But generally the data that I've looked at, which I think also include Slaga's,† show that if you look at the fraction of mice getting carcinoma, then it is more or less independent of the dose of the initiator. It's not really critical to my presentation, and I'd be happy to talk with you later.

So back to the model (page II-11). The potentiation factor basically looks like a two-stage model. This factor is quite flexible. It can bend almost any way, depending on the values of alpha and beta.

Question

Can alpha and beta change signs?

Jones

The only time I have ever had any difficulty with the sign is for formaldehyde, which we should talk about in more detail. For all the other chemicals I have looked at, alpha and beta are both positive with a negative in front of them. Formaldehyde is different, but this is not the time to discuss those data.

The competing risk factor is generally taken to be insignificant or zero at low-dose levels. At higher-dose levels, it can be treated in several different ways.

So trying to put some of this together, let us examine the basic time-to-tumor model neglecting the competing risk factor:

†Added after meeting: For example see Tables 2, 5, and 6 from Nesnow et al. in Toxicological Effects of Emissions from Diesel Engines (Ed. J. Lewtas, Research Triangle Park). Remember that 10,000 µg/mouse of certain chemicals may contribute to promotion.

$$\text{Response}\{D(\tau), T\} = T^{N}\left(A(1 - e^{-\alpha D - \beta D^{2}}) + R_{o}(T)\right)$$

N, A, α, β = Evaluated from nonlinear least squares and $D = C \cdot \tau$.

If we define the parameters T as age and tau as some time unit that describes the administration of the dose, then in terms of serial sacrifice or life-span studies, this is a model that I believe describes the time onset of tumors. Here dose is taken simply as the concentration multiplied by the time the animal is exposed. We know that the pharmacokinetics messes this assumption all up, but generally in the practical applications, this assumption is compensated for in the alpha and beta. For instance, if we do a determination of alpha and beta from nonlinear least squares principles, then implicitly this treats the pharmacokinetics. The T^{N} factor is just the time profile factor of Druckrey's that I have put in here at least temporarily. It seems to work very well for some studies, but for others I have problems with T^{N}.

Question

What is the response?

Jones

The response is the probability of cancer, and I'll show you the result of that function in Figure 3, which is an evaluation of the previous model. It's tested against the ED_{01} study at the National Toxicological Lab at Jefferson, Arkansas. This is the way our model fits the liver neoplasia in that study. This figure is a three-dimensional plot. Liver neoplasia is a function of time and concentration in the diet. If you look at the zero-dose group or the cohort group, you see very few, if any, liver tumors. Whenever you look at the animals that live 33 months, there is some natural component of liver neoplasia that starts to appear. Now as you start to feed the animals different concentrations of the 2 AAF up to 150 ppm and monitor them for 33 months, you can see that it's a very steeply increasing function. On the flat part, I was going to say "practical threshold" and have decided against it. I will say that if you look at where these lines are parallel, you don't find any cancers (above background). For about 12 months, feeding the animals even 150 ppm of 2 AAF doesn't seem to cause any significant incidence in liver tumors.

Question

Do you feed the animals for 12 months and then keep them for their lifetime?

Jones

No. The animals are sacrificed at the end of 12 months on the diet. Now, of course, there are other components of that study where the mice are fed the 2 AAF for 15 and 18 months, and then are sacrificed. Of course, this is a very broad study with lots of data, and I'd like to talk more about these data at a

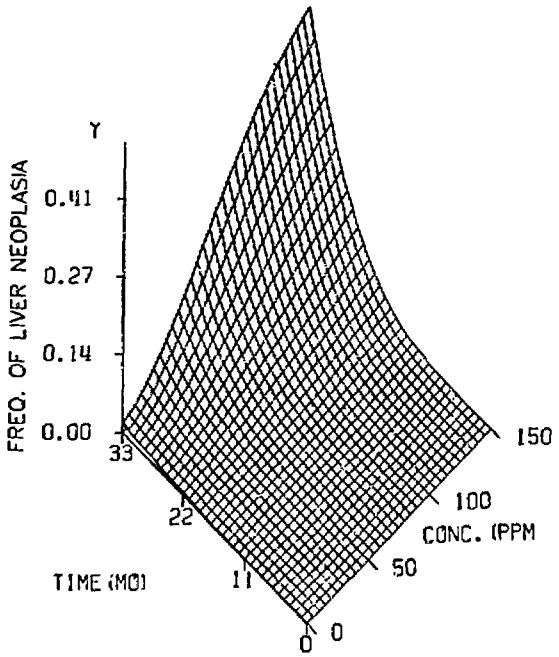


Figure 3

later time. We have also done this modeling treatment for bladder neoplasia in this same mouse study.

I know that everybody has models, and they're not very convincing without showing how well they fit. Anybody that is interested can check with me later and I'll get you a copy of whatever you request. Figure 4 presents the experimental and model data from the same study as Figure 3. The concentrations that were fed to the mice in this study are in the left column and across the top row is the time of sacrifice. The denominator is the number of animals treated in the group. The numerator outside the parentheses is the number of tumors actually found in the group. The number inside the parentheses is the result of evaluating the model that I just showed you. I think these data fit very well. Most of the cancers occur in the 24- and 33-month groups and the 100- and 150-ppm groups.

Drew

Could you explain that a little more? Are you saying, for example, in the left-hand column, that after 12 months on a diet of 60 ppm you sacrificed 279 mice?

Jones

Yes.

Drew

And at 12 months, not one of those 279 mice showed a tumor?

Dose (ppm)	Sacrifice Interval (Months)							
	12	14	15	16	17	18	24	33
0	0(0.98)/142	0(0.13)/140	0(0.13)/113	0(0.13)/88	1(0.32)/183	0(0.27)/128	1(2.3)/401	9(6.6)/383
30							17(24)/1573	55(59)/900
35						2(2.0)/389	7(14)/792	55(50)/639
45					2(1.4)/272	5(1.7)/264	7(9.3)/383	57(48)/445
60	0.(0.41)/279	2(0.77)/268	0(0.88)/224	1(0.96)/182	4(1.9)/265	6(1.9)/206	7(9.4)/268	71(66)/415
75	0(0.26)/139	0(0.51)/137	0(0.57)/110	1(0.65)/94	5(1.6)/174	5(1.6)/134	6(12.6)/267	62(66)/311
100	1(0.37)/142	3(0.74)/138	1(0.87)/117	4(0.91)/90	1(1.2)/90	1(1.2)/67	6(9.0)/131	47(47)/160
150	0(0.62)/140	1(1.3)/141	1(1.5)/114	1(1.6)/90	3(2.0)/86	0(1.9)/65	7(13)/121	56(52)/130

Figure 4. Incidence of liver neoplasia in sacrificed mice from the LD_{01} study of Staffa and Mehlman. The numerator (outside the parens) indicates the number of mice having liver neoplasia in total animals-at-risk, which is given in the denominator. The value inside parens derives from the cell proliferation model.

Jones

That was the outcome of the study.

Drew

And that you had 268 more mice on for 14 months.

Jones

Yes.

Drew

And 224 more mice for 15 months?

Jones

This was a very large study. There were 24,192 female Balb-C mice fed 2-AAF.

Drew

Well, if one assumes a latent period of more than a year, why should you expect that number to be anything but zero?

Jones

Well, I didn't expect it to be different from zero. I was just showing the result of fitting the model to these data, and the model suggested there would have been 0.41 mice out of 279 getting cancer. That is, you would need a significantly larger group to find it, even if the model were precisely true. This is the only case that I'm aware of where there is a tremendous amount of data, both as a function of concentration and of time. We have enough data to generate three-dimensional surfaces.

I feel compelled to test any model that I want to do an analysis with against these data because they represent very important data, and I just wanted to show you that this is the way this particular model fits the data.

Now, if one looks at simpler data, where the animals are all sacrificed at the same time and the control group is sacrificed at that same time, then that study represents a simpler situation than the 3-D plot we just considered. It is more like a one-parameter model; I call this a dichotomous model:

$$\text{Response } (D) = A \cdot (1 - e^{-\alpha D - \beta D^2}) + R_o$$

The function gets simplified here. It's basically just a function of dose where the A, the alpha, and the beta are evaluated by nonlinear squares techniques from the animal or human study.

The data that we have in Table 1 were taken from different species, different strains, different routes of intake, and different biological end points. Some people look at tumors, some at papillomas, some at cancers, and some at cancer in different sites. Other variables include the different numbers of treatments with the insult, the different time treatment schedules (such as one per week, two per week, or a one-time exposure), and the different follow-up periods. This is a very noisy system and very hard to analyze because we're trying to analyze all of the appropriate data (collected anywhere in the world) for a given chemical. We don't have a nice clean system like that in the megamouse study.

The first series is on benzo(a)pyrene, and I'm going to look at the effect of the different variables that I showed you in Table 1. Figure 5 shows the effect of species. First of all, we tried to standardize the dosimetry by computing the dose in terms of micromoles per kilogram bodyweight for the different routes of administration, i.e., inhalation, skin painting, etc. The y axis represents the percent response per unit dose. Most of you are used to looking at dose-response functions. The ordinate axis, then, is the dose response divided by the dose at that particular level. I don't have time now to discuss the rationale of this plot, but I'll talk later privately to anyone who is interested.

Question

What does the x axis represent?

Table 1

INSULT-RESPONSE DATA FOR B(A)P

OBS	RESPONSE (%/DOSE)	DOSE (MICROMOLES/KG)	REFERENCE	SPECIES	STRAIN	NEOPLASIA	ROUTE OF ADMINISTRATION	SITE	NO. OF INSULTS	TREATMENT INTERVAL (WKS)	FOLLOW-UP INTERVAL (WKS)
1	5.800	5.3	WETT77	RATS	FISCHER	TUMORS	PELLET	SITE	101	0	88
2	1.200	7.4	FCEI59	MICE	C57	TUMORS	PAINT	SKIN	312	3/WK	104
3	19.000	8.0	LEIT43	MICE	A	TUMORS	SUBQ	SITE	1	0	LIFE
4	17.000	10.0	LEIT43	MICE	A	TUMORS	SUBQ	SITE	1	0	LIFE
5	8.100	10.0	BRYA83	MICE	C3H-M	TUMORS	SUBQ	SITE	1	0	LIFE
6	18.000	13.0	LEIT43	MICE	A	TUMORS	SUBQ	SITE	1	0	LIFE
7	4.200	16.0	WETT77	RATS	FISCHER	TUMORS	PELLET	SITE	101	0	88
8	16.000	17.0	LEIT43	MICE	A	TUMORS	SUBQ	SITE	1	0	LIFE
9	1.100	19.0	POEL59	MICE	C57	TUMORS	PAINT	SKIN	312	3/WK	104
10	17.000	20.0	BRYA83	MICE	C3H-M	TUMORS	SUBQ	SITE	1	0	LIFE
11	9.700	22.0	WETT77	RATS	FISCHER	TUMORS	PELLET	SITE	101	0	88
12	8.500	32.0	LEIT43	MICE	A	TUMORS	SUBQ	SITE	1	0	LIFE
13	0.350	37.0	POEL59	MICE	C57	TUMORS	PAINT	SKIN	312	3/WK	104
14	6.700	40.0	BRYA83	MICE	C3H-M	TUMORS	SUBQ	SITE	1	0	LIFE
15	0.300	41.0	GROS65	HAMSTERS		TUMORS	IT	RESP.	13	1/WK	104
16	0.370	50.0	WYND60	MICE	SWISS	CANCER	PAINT	SKIN	.	1/WK	LIFE
17	0.370	50.0	WYND60	MICE	SWISS	PAPIL	PAINT	SKIN	.	1/WK	LIFE
18	0.060	83.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	186	1/WK	52
19	0.970	87.0	POEL59	MICE	C57	TUMORS	PAINT	SKIN	156	1/WK	52
20	0.097	100.0	FEPC73	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
21	0.190	110.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	.	1/WK	LIFE
22	0.087	110.0	HECH76	MICE	SWISS-F	CANCER	PAINT	SKIN	165	1/WK	52
23	0.510	110.0	WYND60	MICE	SWISS	CANCER	PAINT	SKIN	.	1/WK	LIFE
24	0.690	110.0	WYND60	MICE	SWISS	PAPIL	PAINT	SKIN	.	1/WK	LIFE
25	0.042	120.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	186	1/WK	52
26	0.065	120.0	POEL59	MICE	C57	TUMORS	PAINT	SKIN	.	1/WK	LIFE
27	0.028	130.0	KETK77	HAMSTERS	SG	TUMORS	IT	RESP.	1	0	LIFE
28	0.350	130.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	135	1/WK	52
29	0.076	130.0	HECH76	MICE	SWISS-F	CANCER	PAINT	SKIN	135	1/WK	52
30	0.340	150.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	105	1/WK	52
31	0.240	150.0	HECH76	MICE	SWISS-F	CANCER	PAINT	SKIN	105	1/WK	52
32	0.037	160.0	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	1	0	LIFE
33	0.830	160.0	WYND60	MICE	SWISS	CANCER	PAINT	SKIN	.	1/WK	LIFE
34	0.560	160.0	WYND60	MICE	SWISS	PAPIL	PAINT	SKIN	.	1/WK	LIFE
35	0.300	170.0	HECH76	MICE	SWISS-F	TUMORS	PAINT	SKIN	165	1/WK	52
36	0.450	190.0	WYND60	MICE	SWISS	CANCER	PAINT	SKIN	.	1/WK	LIFE
37	0.470	190.0	WYND60	MICE	SWISS	PAPIL	PAINT	SKIN	.	1/WK	LIFE
38	0.063	210.0	FERC73	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
39	0.420	210.0	HECH76	MICE	SWISS-M	TUMORS	PAINT	SKIN	135	1/WK	52
40	0.160	210.0	HECH76	MICE	SWISS-M	CANCER	PAINT	SKIN	135	1/WK	52
41	0.130	230.0	KETK79	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
42	0.096	240.0	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	30	1/WK	LIFE
43	0.039	250.0	KETK77	HAMSTERS	SG	TUMORS	IT	RESP.	1	0	LIFE
44	0.380	260.0	HECH76	MICE	SWISS-M	TUMORS	PAINT	SKIN	105	1/WK	52
45	0.270	260.0	HECH76	MICE	SWISS-M	CANCER	PAINT	SKIN	105	1/WK	52
46	0.310	290.0	HECH76	MICE	SWISS-M	TUMORS	PAINT	SKIN	75	1/WK	52
47	0.240	290.0	HECH76	MICE	SWISS-M	CANCER	PAINT	SKIN	75	1/WK	52
48	0.073	310.0	FERO73	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
49	0.070	430.0	KETK79	HAMSTERS	SG	TUMORS	IT	RESP.	14	1/WK	LIFE
50	0.150	440.0	KETK79	HAMSTERS	SG	TUMORS	IT	RESP.	28	1/WK	LIFE
51	0.180	450.0	KETK79	HAMSTERS	SG	TUMORS	IT	RESP.	57	1/WK	LIFE
52	0.029	460.0	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	5	1/25-DAY	LIFE
53	0.063	480.0	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	30	1/WK	LIFE
54	0.019	480.0	POEL59	MICE	C57	TUMORS	PAINT	SKIN	.	1	LIFE
55	0.079	410	KETK79	HAMSTERS	SG	TUMORS	IT	RESP.	1	0	LIFE
56	0.100	830	FERO73	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
57	0.016	950	SELL76	HAMSTERS	SG	TUMORS	IT	RESP.	10	1/WK	LIFE
58	0.041	950	SELL73	HAMSTERS	SG	TUMORS	IT	RESP.	10	1/WK	LIFE
59	0.040	950	SELL73	HAMSTERS	SG	TUMORS	IT	RESP.	10	1/WK	LIFE
60	0.041	950	SELL73	HAMSTERS	SG	TUMORS	IT	RESP.	10	1/WK	LIFE
61	0.065	950	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	30	1/WK	LIFE
62	0.036	960	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	30	1/WK	LIFE
63	0.013	1200	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	10	1/WK	LIFE
64	0.061	1400	WISL78	MICE	HYBRID	ADENOMAS	IP	PULM.	1	0	LIFE
65	0.045	1400	SAFF68	HAMSTERS	SG	TUMORS	IT	RESP.	15	1/WK	LIFE
66	0.045	1430	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	15	1/WK	LIFE
67	0.056	1700	FERO73	HAMSTERS	SG	TUMORS	IT	RESP.	52	1/WK	78
68	0.032	1900	SAFF72	HAMSTERS	SG	TUMORS	IT	RESP.	30	1/WK	LIFE
69	0.011	3500	HEMR73	HAMSTERS	SG	TUMORS	IT	RESP.	8	1/WK	LIFE

Jones

The x axis is the dose in micromoles per kilogram.

The M stands for mice, the R stands for rats, the H stands for hamsters. This plot represents all the data that I've found on benzo(a)pyrene. Benzo(a)pyrene is the only strong insult used in these studies. We didn't take the treatment schedules that involved TPA or some promotional stimulus in addition to B(a)P. We tried to retain a clean B(a)P system. Now from this graph it looks as if there is some type of dose-response behavior here. It appears to be decreasing, but there seems to be no clear-cut effect of the species as treated. The H's, M's, and R's all seem to be more or less vertically mixed together. This plot is on log-log paper, so it won't be a linear response. I'll show you how the response looks a little later on.

We have the very same data plotted the same way, but now in Figure 6 the symbols mean something different. The T's stand for tumors, C's represent carcinomas, P's mean papillomas, and A's mean adenomas. I was trying to determine if the papillomas were consistently higher than the tumors which were consistently higher than the cancers, and that didn't seem to be the pattern that came out of this plot.

Drew

When you say tumor, is it benign?

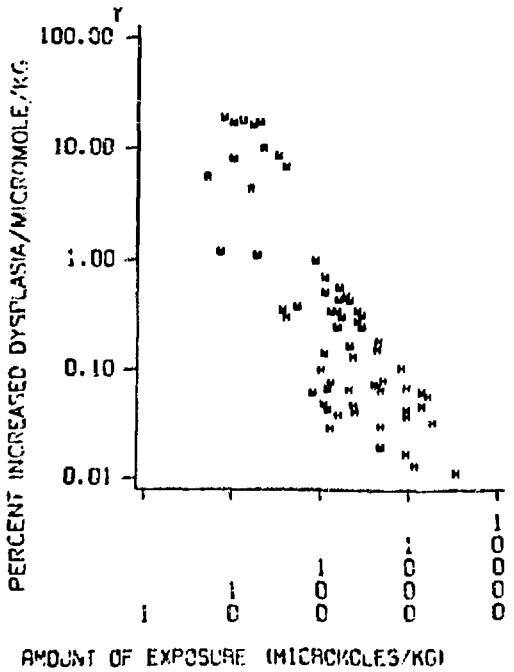


Figure 5. Insult-response behavior of the B(a)P database with respect to test species. Symbols: M = mice, R = rats, and H = hamsters.

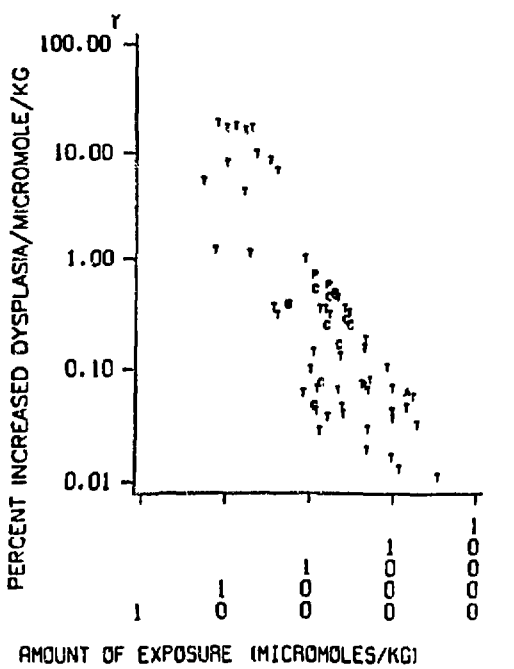


Figure 6. Insult-response behavior of the B(a)P database with respect to classification of neoplasia. Symbols: A = adenomas, C = cancer, P = papillomas, and T = tumors.

Jones

If the investigator in the original publication of the animal study called the response a tumor, then I called it a tumor. If he called it a cancer, I called it a cancer. In many studies the researchers did not try to assay metastatic potential. If the investigators sacrificed an animal and found a neoplasm there, they called it a tumor. Therefore, there are some cancers in those symbols that are marked as T.

Hattis

May I just ask if my interpretation of that negative slope is right? At the highest doses you get the least increment of tumors per unit of dose, which means that basically the dose-response slope is higher at low doses than at high doses.

Jones

Yes, and I have some more plots like this which I don't have time to show you. I have plots for formaldehyde, quinoline, benzene, 4-biphenylamine, and chromium. We looked at several different chemicals in this particular way. We see much the same pattern that we see here. Now I'll show you the bottom line from all of this.

There was a plot for different routes of exposure to B(a)P which you haven't seen. Then there was another plot to show the dose-rate effect from B(a)P which grouped the variables according to the number of treatments given. So essentially the ordinate and the abscissa stayed the same on each one of these four plots, but the symbols were changed to take into account the different parameters, e.g., route of administration, species, class of neoplasia, or whatever seemed to be important.

Hooper

I think you went through this once before in a meeting in Boston. Were the chemicals or the exposures that gave the highest increase per unit dose, the oral routes or the skin painting? Were you really looking at different efficiencies of routes of exposure to give an effective dose, rather than some quality of the dose such as high doses vs low doses, or were you really looking at the effectiveness of a lot of exposures?

Jones

One of the figures was to show that, and we'll talk about it later if you want. There seemed to be no pattern to route of exposure except for the pellet implants and the subcutaneous-type injections. They seemed to induce more cancers per unit dose. We have a dosimetry problem with pellet implants and subcutaneous injections. We know that the tumors generally occur near the site of implant or the site of injection. We don't know the retention time, (i.e., the residence time of the chemical), because it varies with both the enzyme system of the animal being tested and with the chemical being pumped in there. For instance, some of the hydrocarbons are detoxified and removed from the system in a very short period of time.

Basically, we went through a bunch of chemicals and searched the literature for the dose-response data. I fitted the model which we described previously to all observations for each chemical. In Figure 7 the percent increased dysplasia is the ordinate and the abscissa represents the dose in units of micromoles per kilogram body weight of the species. Then we can draw these dose-response curves. The solid line is B(a)P, the dashed line is benzene; then chromium, arsenic, 4-biphenylamine, benzidene, quinoline, dodecane, formaldehyde, and vinyl chloride are also represented. So these types of dose-response curves come from evaluating the equation with all available animal data. We are using <u>all</u> the data that we can find.

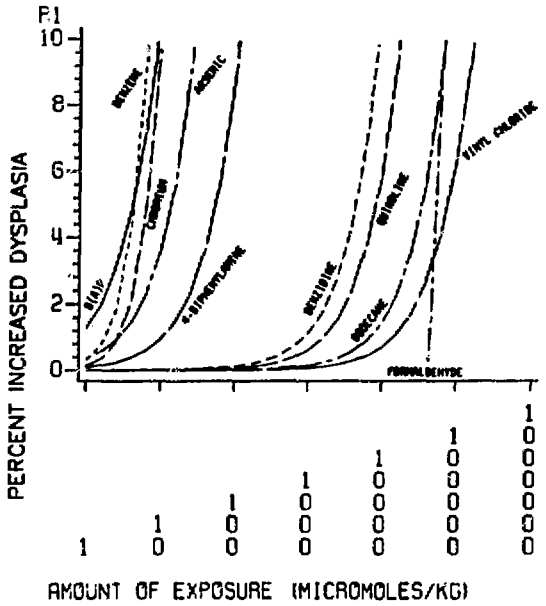


Figure 7

<u>Varma</u>

Can I summarize? We are looking at what you would call the attributable risk due to the cancer, and your response is any kind of tumor in any type of animal. It's an aggregate of what you could get from the literature.

<u>Jones</u>

Yes. Now, as you saw from the scatter diagram for B(a)P, the data basically scatters over plus or minus an order of magnitude, so you have to take these functions with some degree of uncertainty.

I just have one more slide (Figure 8). As you can see, these potency functions have different shapes. Note, the formaldehyde slope comes off very steeply. The model that we fitted suggested that there was a threshold for formaldehyde at 5.6 ppm. I think that the pharmacological studies over at CIIT suggest that there may be a threshold somewhere between 2 and 6 ppm. I'm not trying to say the model is right because it predicted the threshold. I'm just

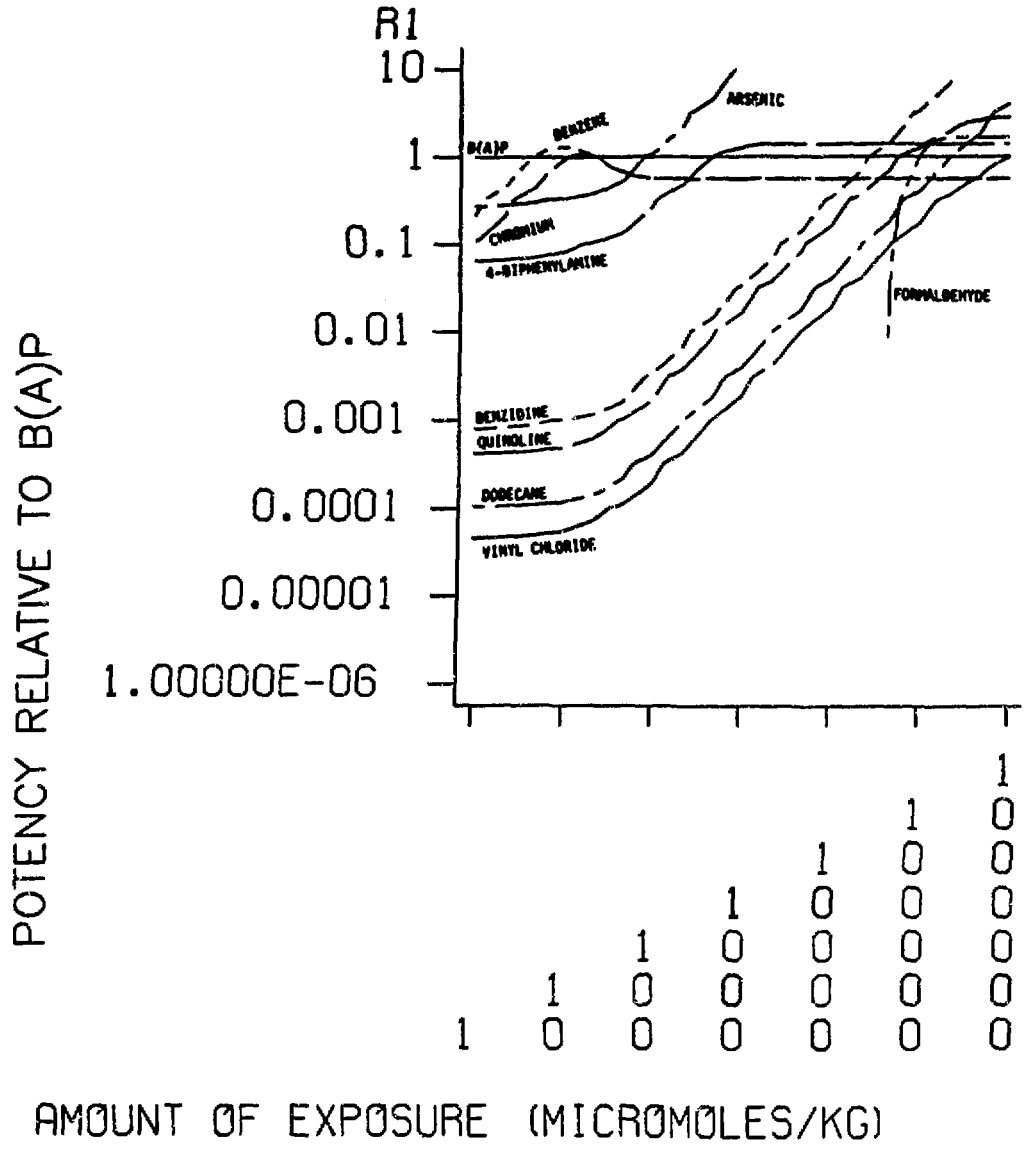


Figure 8

saying that in order to fit the formaldehyde data, the model had to have this characteristic.

Figure 8 shows the potency functions which compare these different chemicals to benzo(a)pyrene. These functions vary with dose.

That's all I have to say.

A Comparative Potency Approach for Estimating the Carcinogenic Response of Various Agents
(Speaker - Roy Albert, Ph.D.)

Varma

Dr. Albert will give the last presentation for this session.

Albert

I'll show you an approach to potency which has been used for a number of years by the Carcinogen Assessment Group (CAG) and the EPA to give a handle to the regulatory offices. When the unit exposure is known, one can multiply that factor by the unit risk to obtain an estimate of a lifetime risk of the individual exposed to that level. This approach is, in effect, a potency estimate because it really amounts to the slope of the assumed layer component of the dose-response curve at the low-dose end of the curve. I mentioned before that over the years this has been estimated two ways. The initial approach was to take the lowest significant data point and draw a straight line to the origin of the graph. More recently, we've used Kenny Crump's multistage approach with an upper-limit linear component.

Last week we put together the data that we have on 52 agents that the CAG has done (Table 1). We don't have this in tight form yet, but for each agent we show the slope as derived from the experiment itself in terms of milligrams per kilogram per day. This slope also gives the lifetime risk per milligram per kilogram per day which we have converted to a molecular basis in terms of the slope index in units of millimoles per kilogram per day-dose. For example, if one had a dose of one millimole per kilogram per day for acrylonitrile, the lifetime risk would be 10^{-2}. To look at the potency of these various materials we've just taken the power of the slope index. For example, if the slope index is 1.04×10^{-2}, we've listed the potency as 10^{-2}. The potency for these 52 agents fell in the range of 10^{-4} to 10^{-2}. In other words, for a millimole per kilogram per day, the lifetime risk would be somewhere between 10^{-4} and 10^{-2}. Table 2 shows that dioxin has the highest potency; aflatoxin falls here and saccharin is way down here. The curious thing I suppose is that the extremes are promoters. The most potent known carcinogen and one of the least potent carcinogens happen to be promoters. So that's another way of doing potency when you have the data.

When you don't have the data, then one can do things somewhat differently. For example, a problem arose when we had to estimate the risk from diesel exhaust particles when there was no information on the carcinogenic response from diesel particulates. We decided to use a relatively short-term bioassay to get the comparative potency to agents which are known to produce lung cancer in humans. For example, coke oven exhausts, roofing tar, and cigarette smoke are agents for which we have potency data in humans for lung cancer (Table 3). A battery of tests were tried to obtain comparative potency data for diesel particulates in comparison to these materials. Although a few of the tests seemed to work, the best was the mouse-initiation. Assuming a linear dose response of the human data, if you look at potency, then coke oven is 1, roofing tar is 0.4, and cigarette smoke is down at a thousandths of the roofing tar. Cigarette smoke is obviously very weak.

The relative potency for skin initiation in the mouse using phorbol ester as the promoter is remakably similar. Again normalizing the coke oven, roofing

Table 1

Relative Carcinogenic Potencies Among Suspect Carcinogens Evaluated by the CAG

Carcinogens	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Slope Index	Order of Magnitude (Exponent of Slope)
Acrylonitrile	0.53	53.1	1.04×10^{-2}	-2
Aflatoxin	2924	312.3	$9.36 \times 10^{+0}$	0
Allyl Chloride	1.19×10^{-2}	76.5	1.56×10^{-4}	-4
Aldrin	11.4	369.4	3.09×10^{-2}	-2
Arsenic	14 (H)	149.8	9.35×10^{-2}	-2
Benzene	5.2×10^{2}	78	6.67×10^{-4}	-4
Benzidine	234(W)	184.2	1.27×10^{0}	0
Beryllium	4.86	9	5.40×10^{-1}	-1
Cadmium	6.65 (I)	112.4	5.92×10^{-2}	-2
Carbon tetrachloride	8.28×10^{-2}	153.8	5.38×10^{-4}	-4
Chlorodane	1.61	409.8	3.93×10^{-3}	-3
Hexachlorobenzene	1.67	284.8	5.86×10^{-3}	-3
1,2-dichloroethane	3.70×10^{-2}	98.9	3.74×10^{-2}	-4
1,1,2-trichloroethane	5.73×10^{-2}	133.4	4.30×10^{-4}	-4
1,1,2,2-tetrachloroethane	0.20	167.9	1.19×10^{-3}	-3
2,4,6-trichlopherenol	1.99×10^{2}	197.4	1.00×10^{-4}	-4
BCEE	1.14	143	7.97×10^{-3}	-3
BCME	9300 (I)	115	$8.09 \times 10^{+1}$	+1
Chloroform	0.11	119.4	9.21×10^{-4}	-4
Chromium	63(W)	104	6.10×10^{-1}	-1

Table 1 (Continued)

Carcinogens	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Slope Index	Order of Magnitude (Exponent of Slope)
Dichlorobenzidine	1.69	253.1	6.68×10^{-3}	-3
DDT	8.42	354.5	2.38×10^{-2}	-2
1,1-dichloroethylene	1.04	97	1.07×10^{-2}	-2
Dieldrin	30.4	380.9	7.98×10^{-2}	-2
Dinitrotoluene	0.31	182	1.70×10^{-3}	-3
Tetrachlorodioxin	$4.25 \times 10^{+5}$	322	$1.32 \times 10^{+3}$	+3
Diphenylhydrazine	0.77	180	4.28×10^{-3}	-3
Epichlorohydrin	0.14(W)	92.5	1.51×10^{-3}	-3
EDB	8.51	187.9	4.53×10^{-2}	-2
EDC	1.44×10^{-2}	99.0	1.45×10^{-4}	-4
ETO	1.86×10^{-2}(I)	44.0	4.23×10^{-4}	-4
Formaldehyde	2.14×10^{-2}(I)	30	7.13×10^{-4}	-4
Heptachlor	3.37	373.3	9.03×10^{-3}	-3
Hexachlorocyclohexane:				
technical grade	4.75	290.9	1.63×10^{-2}	-2
α-isomer	11.12	290.9	3.82×10^{-2}	-2
β-isomer	1.84	290.9	6.33×10^{-3}	-3
γ-isomer	1.33	290.9	4.57×10^{-3}	-3
Nitrosamines:				
DMNA	25.9	74.1	3.50×10^{-1}	-1
DENA	43.5	102.1	4.30×10^{-1}	-1
DBNA	5.43	158.2	3.43×10^{-2}	-2

Table 1 (Continued)

Carcinogens	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Slope Index	Order of Magnitude (Exponent of Slope)
N-N-P	2.13	100.2	2.13×10^{-2}	-2
NEU	32.9	117.1	2.80×10^{-1}	-1
NMU	302.6	103.1	$2.94 \times 10^{+0}$	0
N-N-D	4.92×10^{-3}	198	2.48×10^{-5}	-5
PAH (B(a)P)	11.5	252.3	4.56×10^{-2}	-2
PCB	4.34	324	1.34×10^{-2}	-2
Toxaphene	1.13	414	2.73×10^{-3}	-3
Tetrachloroethylene	5.31×10^{-2}	165.8	3.20×10^{-4}	-4
Trichloroethylene	1.26×10^{-5}	131.4	9.59×10^{-5}	-5
Vinyl Chloride	1.75×10^{-2}(I)	62.5	2.80×10^{-4}	-4
Vinylidene Chloride	0.13(I)	97	1.34×10^{-3}	-3
Nickel	6.30(W)	58.7	1.10×10^{-1}	-1

Remarks:
1. Slope $(mg/kg/day)^{-1}$ are calculated based on animal oral studies except for those indicated by:
   I - animal inhalation study
   W - human occupations
   H - human exposure by drinking water
2. Slope index is defined as slope in $(millimole/kg/day)^{-1}$.

Table 2

Potency Index	Number of Carcinogens
+3 (TCDD)	1
+2	0
+1	1
0	3
-1 (aflatoxin)	6
-2	14
-3	13
-4	12
-5	3
-6 (saccharin)	1
	54

Table 3

Comparison of Relative Potencies of Emission Extracts in Several Bioassay Systems

Sample	Human Lung Cancer	Mouse Skin Tumor Initiation[a]	Mutation in L5178Y Mouse Lymphoma Cells[b]	Mutation in Ames TA98[b] (+MA)
Coke Oven Exhausts	1.0	1.0	1.0	1.0
Roofing Tar	0.39	0.20	1.4	0.78
Cigarette Smoke Condensate	0.0017	0.0011	0.066	0.52
Nissan Diesel Exhaust Particulates		0.28	0.24	12

[a]From papilloma multiplicity data (papillomas/mouse at 1 mg).
[b]With metabolic activation.

tar turns out to be 0.2 for the mouse compared to 0.4 for the human, and cigarette smoke condensate has a 0.001 potency value for both the human and the mouse. Incidentally, in using the mouse initiation tests the potency of diesel particulates turns out to be 0.3, which is in the range of roofing tar and coke oven exhausts. The mutation in the Ames test is somewhat less successful, for it tends to read high for diesel particulates, presumably because of the presence of nitroscaromatics which are potent mutagens but apparently not very potent carcinogens. The mouse lymphoma test is also not bad in terms of predicting potency.

This comparative potency approach has limited use for other systems, because you really need both human data and data that are associated with some exposure. But there are a number of agents (such as aflatoxin, vinyl chloride, ethinylestradiol, and mestranol) where we do have the human data for liver tumor response (Table 4). There are also a few bladder carcinogens for which we have human data, and I've already mentioned the data on a few compounds that are lung carcinogens. Additionally, we have data for ethylene oxide and benzene which cause leukemia. So it's possible to use this comparative potency approach for some agents where one has human data.

The mestranol situation is interesting because this comparative potency approach, as far as I know, provides the first approach in estimating the risk from a promoter. This method is independent of the use of extrapolation models because the risk from the use of contraceptive pills has been estimated. Mestranol is the major ingredient in contraceptive pills, and the risk is in the order of 10^{-4} and 10^{-5} for hepatocellular adenomas. Mestranol is a very powerful promoting agent in the rat liver. So, using this approach to estimate the risk from an agent, for example DDT (on the assumption that it is a promoter and indeed it does show up to be a promoter), it turns out that the mestranol is a thousand times more potent than DDT as a promoter. Therefore, one can use this risk that has been derived from mestranol to estimate the risk from DDT on the basis that it's one thousand times less potent. Thus, this method gives an interesting approach to risk estimates for agents which are promoters. However, you are never certain that the agent isn't something else in addition to being a promoter.

Varma

Thank you, Dr. Albert. We are out of time so we will have to defer discussion.

Table 4

Human Carcinogens Suitable for
Use in the Comparative Potency Method

Human		Test Animal	
Organ	Carcinogen	Organ	Species
Liver	Aflatoxin	Liver	Rat
	Vinyl Chloride	Liver	Rat, Mouse
	Mestranol (promoter)	Liver	Rat
	Ethinylestradiol (promoter)	Liver	Rat
Bladder	Benzidene	Bladder	Dog
		Liver	Rat
	Chlornaphazine	Local Sarcoma	Rat
	2-Naphthylamine	Bladder	Hamster
		Liver	Mouse
Lung	Coke Oven	Skin	Mouse
	Cigarette Smoke	Skin	Mouse
	Roofing Tar	Skin	Mouse
	Chromium	Lung	Rat
Leukemia	Ethylene Oxide	Bone Marrow	Rat
	Benzene	Lymphoma	Mouse

Prepared Comments

A Dose-Response Model Derived from Cytokinetic Considerations Provides a Means to Estimate Relative Potency Factors for Neoplastic Potentiation

T.D. Jones and P.J. Walsh

Cellular proliferation resulting from toxic hyperplasia and/or normal tissue-homeostasis is required to complete carcinogenic initiation. Also, cell proliferation is ubiquitous to carcinogenic promotion. Thus, an equation to estimate neoplasia as a function of cell proliferation has been described conceptually, approximated algebraically, and applied to radiation-induced leukemia in humans and to animal neoplasia resulting from both radiation and chemical treatment schedules. Excellent success has been achieved, and the model has been expanded to a "time-to-tumor" model by including the approximation of Druckrey. Druckrey's factor is reasonably accurate for treatment protocols which result in essentially steady-state cytokinetics but fails badly for interrupted or nonuniform treatment schedules.

Many factors influence the genesis of neoplasia. Most of these factors also impact either directly or indirectly on cell proliferation. It is impossible currently to model explicitly the general cancer problem as a function of all such stresses. However, the modeling approach described here estimates the composite amount of toxic hyperplasia resulting from a specific stress of concern relative to a cohort test animal or person subject to all conditions except for the stress of study.

For radiation-induced neoplasia, parameters of the model can be taken directly from human epidemiology and from experiments done in vivo (animals) and in vitro, so that the model becomes predictive in a complete sense. However, for treatment protocols involving chemicals, problems of estimating pharmacokinetic processes and dose-to-cells prohibit generality, and parameters of the model are evaluated by indirect means.

For B(a)P, benzene, benzidine, chromium, quinoline, 4-biphenylamine, vinyl chloride, formaldehyde, dodecane, and arsenic, the literature has been searched for all dose-response estimates in animals. The doses have all been standardized in units of micromoles of insult per kilogram-body-weight and the response has been expressed as percent-increased response (above the natural rate) per unit-dose. For each of these chemicals, a scatter-diagram is obtained, but a dose-response shape is defined clearly by the envelope of points. Obviously, many factors contribute to the scatter of these points. The factors include: dose-rate, interspecies variability, route-of-administration, sex, number of treatment fractions, pathological classificaton of neoplasia, carrier chemical, time-of-followup, age at first treatment, etc. Each of these factors may contribute significantly within a given dose-response study, but, nevertheless, the composite database for each specific chemical seems to be a much stronger function of treatment dose than of model-sensitivity parameters.

For NO_2, O_3, NO, SO_2, CO, and hydrocarbons not tested in animal-neoplasia studies, some parameters of the model can be taken from chemical homologues and other parameters may be taken from studies on a reference chemical and then corrected by using ratios based on molecular/cellular level studies. These different evaluation techniques have been used to derive the potency factors shown in Table 1.

Table 1

Tentative Relative Potency Factors for Neoplastic Potentiation From Synfuels Effluents

	Chemical	Relative Potency[a]	Biological Mode
1	Anthracene	0.01-0.05	Cytotoxicity[b]
2	Arsenic	4.0[d]	Neoplasia[c]
3	B(a)P	*1*	Neoplasia/cytotoxicity
4	B(e)P	0.05	Cytotoxicity
5	Benz(a)anthracene	0.01	Cytotoxicity
6	Benzene	4.8[e]	Neoplasia
7	Benzidine	0.005[d]	Neoplasia
8	4-biphenylamine	0.41[d]	Neoplasia
9	Cadmium	1.5	Cytotoxicity
10	Chromium	3.2	Cytotoxicity
	Chromium	5.3[e]	Neoplasia
11	Chrysene	0.007-0.03	Cytotoxicity
12	DB(a,h)A	0.08-0.02	Cytotoxicity
13	Dimethylnitrosamine	0.01	Cytotoxicity
14	Dodecane	0.00070[d]	Neoplasia
15	7-12-DMBA	2-3	Cytotoxicity
16	Formaldehyde (Neoplasia; model threshold at 45,000 µm/kg)		
	- 50,000 µm/kg	0.76	Neoplasia
	- 100,000 µm/kg	8.4	Neoplasia
	- 1,000,000 µm/kg	16	Neoplasia
17	3-MCA	1-2	Cytotoxicity
18	β-naphthylamine	2	Cytotoxicity
19	Phenanthrene	0.09-0.17	Cytotoxicity
20	Quinoline	0.004[d]	Neoplasia
21	Selenium	0.21	Cytotoxicity
22	Vinyl chloride	0.0010[d]	Neoplasia

Practical Threshold for Neoplastic Potentiation

	Chemical	Concentration, ppm	Model
(16)	Formaldehyde	√6 = Experimental	Neoplasia
23	CO	60	Cytotoxicity
24	NO	1	Cytotoxicity
25	NO_2	0.1	Cytotoxicity
26	O_3	0.2	Cytotoxicity
27	SO_2	2	Cytotoxicity

[a]Potency based on (mg/kg).
[b]Cytotoxicity of mammalian cells *in vitro*.
[c]Neoplasia in animals.
[d]Potency evaluated at √100 µm/kg.
[e]Maximum potency.

SESSION III

RISK ASSESSMENT

Introduction
(Session Leader - John Baum, Ph.D.)

Baum

I see by our outline that the next three sessions deal with risk assessment. Our hope was that during the session we are just beginning, we would be able to touch on some of the concepts that relate to acceptable risk, cost benefit, and cost effectiveness. Some of these concepts are very well known to those who have experience in the radiation protection field. In this area, we have a system of dose limitation that is promulgated by the International Commission on Radiological Protection, which is a three-phase, three-criteria system that includes, first of all, justification of the exposure; secondly, limitation of exposure to less-than-maximum-permissible exposure; and thirdly, optimization, which refers to an optimum balance between the dollars spent on reducing exposures and the estimated dollar value of the health effects being avoided by this expenditure. These, then, are concepts important in our setting of standards which we hope to touch upon in these sessions. Our first speaker will be Dr. Joseph Rodricks, a principal in ENVIRON, which is located in Washington, D.C. He is a specialist in risk assessment and previously spent about 15 years at the Food and Drug Administration, where he was the Deputy Associate Commissioner for Science. Dr. Rodricks has chaired the Interagency Regulatory Liaison Group which developed a carcinogen guideline and he has been a member of the National Academy of Science's Committee on Institutional Mechanisms for Risk Assessments. So we are looking forward to hearing from you Dr. Rodricks.

Risk Assessment And Risk Management
(Speaker - Joseph Rodricks, Ph.D.)

Rodricks

I agreed to come and talk about risk assessment, but when I got the program, I saw that risk assessment had under it a number of analytic processes that I am not very familiar with: cost-benefit analysis, risk-benefit analysis, acceptable risk, etc. My first reaction was that these are not what I usually conceive to be risk assessment. So I shall spend a few minutes talking about my conception, and I think the conception of others as well, of risk assessment. If a guideline is to be developed, we ought to be very careful of what we call what; how we organize that guideline is very important to our thinking. I take risk assessment to be largely a scientific activity, distinguished from activities which, for lack of a better term, I'll call risk management. I think that some of the problems that have arisen over the years come from a confusion between these two domains. It can easily happen that what we take to be science really isn't; it really requires certain policy decisions which go beyond the realm of science. I thought I would spend a few moments describing what I conceive a guideline for risk assessment would look like, at least in broad terms, and show how it is distinguished from risk management, and then begin to touch upon some of the issues that Dr. Baum mentioned; but I'm not able to go very far into them.

First of all, I think it's important that risk assessment be conceived very broadly. Many people refer to it as a problem of high-to-low dose extrapolation; I think that's only one of several components of risk assessment. I'm not alone in this view; the Committee on Institutional Means for Risk Assessment of the National Academy of Science spent a lot of time discussing these definitions. I'm going to give you what the committee agreed to call these different components of risk assessment.

The first component is Hazard Identification and Evaluation which is very similar to what Roy Albert said the EPA has been doing, although I have some differences with what Dr. Albert described. In Hazard Identification and Evaluation, we are talking about examination of epidemiologic and experimental evidence for not only deciding whether or not we have a carcinogen, but also going further than that in deciding what we know about the carcinogen; that is, what kind of carcinogen it is, what confidence we have in that characterization, and the degree of confidence we have that a material that produces carcinogenic responses under experimental conditions, or for which we have observed a carcinogenic response in a population, is likely to be a carcinogen under some other conditions - how strong an inference can be made from the conditions of observation to other possible conditions of interest? Here the importance of mechanisms comes into play, but I think Dr. Albert is right that we have very little information on this subject. However, I think it's also important that whatever information we have ought to be included in the evaluation - at least referred to and given some appropriate weight - so that the decision maker finally has some view of how confident you are that you really have a carcinogen. I think, and perhaps this is idealistic, that the problem of defining a regulatory carcinogen will disapear if you limit the risk assessor's role to characterizing the evidence for carcinogencity and to describing the strength of that evidence without drawing firm lines to define the point at which you have a regulatory

carcinogen. I think that is a separate kind of decision that would be one of the components of the risk management decision - how much confidence you need before you consider something to be a carcinogen. I also emphasize that I think it would be improper to decide at this point that you have something in need of regulation or control. This is only the first step, and one really ought to go through the rest of the operation before deciding whether or not you have a carcinogen and whether or not there is a risk of some importance.

The second component is Dose-Response Evaluation. I guess it's popular to talk about this as a potency analysis. My tendency is to favor Roy Albert's concept of the risk per unit dose at low doses, arrived at by the application of some model. I don't think that the TD_{50} Kim Hooper described is very useful for describing potency because it's not in the range of response that is of interest, and I think that despite all the other uncertainties about high-to-low dose extrapolation, at least we're in the range of the response of interest.

A subject which has received no attention here, and which is the most badly neglected area of risk assessment, is Exposure Evaluation (third component). The evaluation of exposure of the population you wish to protect is a critical element of risk assessment for which, I think, the data base is terribly poor. It's also an area in which, because of the poverty of the data base, a lot of assumptions have to be made. Exposure Evaluation is an issue that cannot be neglected if you're going to have what in my mind is a comprehensive assessment of risk.

Finally, these last two components (Dose-Response Evaluation, Exposure Evaluation) are combined to give some estimate of the Probability of Harm (fourth component) in the population group of interest. By the way, Exposure Evaluation would be concerned not just with duration and intensity of exposure, but also with the nature of that population and its size, etc. I take these four activities to be risk assessment and I think it is the role of the risk assessor to stop at this stage and say, this is what the information available reveals. Somehow risk assessment integrates all this information; in other words, it should not be reduced to probability estimates - it should indicate how confident you are that you really have a risk and that's very hard for scientists to do. I think we really haven't made much progress in describing scientific evidence, its character and its strength, to those who finally have to make a decision. But I think that once you have all of the information associated with risk, you can then look intelligently at questions of what I've called risk management.

Let me make a couple of more points about a guideline as it may relate to these four major components of risk assessment. At the Academy, we recently went through the Hazard Identification, Dose-Response Evaluation, and Risk Estimation components of risk assessment. For a fairly rich data base, containing epidemiologic and animal data, we counted 35 to 40 analytic steps during which one must make inferences and reach conclusions. I should think any guideline would have to consider all of those steps, laying out the scientific justification for each. In some cases the science is weak or at least it can only narrow the choices down to a few plausible choices: for example, high-to-low dose extrapolation models, or what you're going to assume about dose equivalency when you extrapolate between species. You have to lay out some process that helps you decide whether you're going to equate species on milligrams per kilograms body weight basis or unit surface area, etc. In high-to-low dose extrapolation, when you have several animal studies available that give apparently different

responses, the usual approach is to select the one yielding the highest risk per unit dose. That choice has been made primarily on policy grounds and may be wise public policy, but I'm not sure that it's necessarily the best scientific choice. Nevertheless, some choice has to be made. One choice might be to use all the data. If you've looked at a compound like carbon tetrachloride or others with a very rich data base, you have a great deal of data and the tendency has been to select one slice of the data and ignore the rest. I think, in developing a guideline, we ought to be very careful to note those areas where we cannot substantiate the best approach on scientific grounds alone. What do you do in those cases? Exposure Evaluation is particularly tricky here; because of the lack of data, it is often necessary to impose assumptions about how much people drink or breathe or eat, questions of absorption through the skin, the GI tract, etc. If you have data by one route of administration in test animals and you're worried about another route of exposure in humans, what are you going to assume about relative absorption between those two when you don't have data, which is the usual case. I think that any guideline should have to take into consideration those very important questions because they markedly influence the risk assessment.

Now in the risk management phase - as I said before, I don't know a whole lot about this - I can let you know a little about my experience in FDA. The first problem is that whoever must decide how to manage or control a risk should have a good notion of what an assessment says; that is, if it's reduced to a number, then it is very simple, although probably not a very wise thing to do for decision making. I think very little has been done, at least in the chemical area - perhaps more in radiation, that I'm not familiar with - to consider the degree of confidence we have in the quantitative and qualitative data in reaching a decision about whether the risk is "important." I should think that would be the first step and I leave "important" in quotes; by that, all I mean is that we are confident enough that the risk is such and such, that it is above something that we can refer to as a de minimis risk. Whether a risk is important may be ultimately a policy decision. But, there is no reason why some kind of objective analytic process can't be applied to that decision. I haven't seen this done yet in the chemical area.

I can talk about the experience I had at FDA 10 years ago. I must say, Dr. Albert, that we did propose risk assessment at FDA in 1972, which was 4 years before EPA. However, the regulation implementing that proposal is still not a final order, which is about average for FDA, an extremely slow agency. You may wonder why FDA, in the food area particularly, would be interested in quantitative risk assessment. Well, you all know about the Delaney Clause, which says that once you've reached this point (Hazard Identification and Evaluation) for a compound, the assessment stops no matter what the risk; you cannot intentionally add that substance to food. That's a policy stated directly in the Delaney clause. So you don't need to do all of that (Dose-Response Evaluation, Exposure Evaluation, Probability of Harm). It turns out that there are other materials which are added to food, but indirectly so, where the decision is not so simple. The problem arose in connection with drugs used in food-producing animals that might leave residues in the tissues of those animals that people could consume. That's an intentional additive in that one intentionally adds a drug to animals to get a certain effect in the animals and inadvertently there's a residue left in tissue - the classic example was DES. Congress modified the Delaney Clause in reference to these kinds of chemicals.

They said it's okay to use a carcinogen in food-producing animals as long as it was effective for the animal, didn't hurt the animal, and left "no residue" in edible animal tissues by a method of analysis that FDA approves. That law dates from 1960 or 1962, and up to 1972 FDA said no residue is 2 ppb. In other words, the decision was not based on the potency of the carcinogen; it was based purely on what was thought to be state-of-the-art analytical chemistry - 2 ppb, whether it was a fairly potent or weak carcinogen.

In 1971 we wrote a proposal which tried to change all that by defining the acceptable limit, which became the sensitivity or limit of detection of analytical methods that you would apply to tissues to determine whether a drug residue was present. We defined a virtually safe dose, which was a low-risk dose. We said that if you had a carcinogen, you did a bioassay, you applied a model - we proposed a probit model originally and then changed to a linear - you found the acceptable dose of the material corresponding to the lifetime risk of 1 in 1 million (or 10^{-6}) and then you converted that measure of dose to a residue level in liver, beef, eggs, milk, etc. I think it was the first time anyone had proposed the use of quantitative methods for establishing "safe levels of a carcinogen." It was an attempt to solve a problem so that although one couldn't be sure of the risk, one could at least put some degree of order into that regulatory process. The 10^{-6} was established in what I'd have to call a benefit/risk analysis; I don't know what else to call it. We assumed under the law that Congress wanted to allow manufacturers to introduce drugs into food-producing animals, and that the condition of absolute absence of a residue was simply unattainable, at least not demonstrable. So we wanted a system which would permit the introduction of some, but perhaps not all, carcinogenic drugs. We looked at the range of exposure levels that might result if you applied a 10^{-6} or a 10^{-7} or a 10^{-8} standard and when we looked at 10^{-6} it turned out that a large share of carcinogenic drugs then on the market would still be approvable; in other words, we attempted to narrow down the range so that it would be technically feasible to have a drug approval. You know, you could set that risk so low that analytical methods could never be developed to measure them. So it was a benefit/risk analysis; it was not explicit. If I went back and did that again, I think I would do it quite differently, but that's how 10^{-6} was arrived at originally and it has since been applied in several different contexts. That was initially the definition of whether a risk was important and worth controlling or not. As I said before, I would not make this decision now, based totally on the probability of risk, but would also include the nature of scientific evidence and the degree of confidence you had in it. I'm not sure what analytic process would be involved. Beyond that, once the decision is made that it is important and worth controlling in some way, one gets into another area of analysis that I'm not prepared to talk about: technical feasibility, the law, and many other considerations enter at this point.

Risk Assessment Methodology And Its Application
(Speaker - John Van Ryzin, Ph.D.)

Baum

Thank you very much Dr. Rodricks. That's a very important distinction you made between risk assessment and risk management and I hope as the discussion progresses we can discuss this distinction at greater length and further develop the risk management aspect of it. Our next speaker will be Dr. Van Ryzin who is with the Division of Biostatistics at Columbia University and with the Department of Applied Mathematics here at BNL. He formerly spent about 11 years at the University of Wisconsin. He has worked extensively on risk and dose assessment and on the effects of low doses of carcinogens, including detailed analyses for the Food Safety Council on the carcinogenicity of food additives and related regulations. He is also a member of the National Academy of Sciences' Nitrite Committee.

Van Ryzin

I first got into this type of work back at the University of Wisconsin where I was working jointly between the Department of Statistics and the Cancer Center. Some of the people from the Food Research Institute got me involved in assessing some possible contaminants in food. They were more interested in con-taminants than in food additives; for instance, we don't add pesticides to our food but pesticides do get in our food supply and they were interested in assess-ing the dangers. I then became involved in the Food Safety Council whose Scientific Committee put out an extensive report in 1978 which went through peer review, was revised, and came out in 1980. It's a good document and people ought to read it. In fact, I was interested in Dr. Rodricks' comment on exposure evaluation. There is a whole chapter on exposure evaluation in that report which turned out to be, as also on our NAS nitrite committee, one of the roughest questions: Who's exposed to what? In the final report, published in June 1982, the committee integrated scientific evaluation with social and economic concerns and made some recommendations for food safety regulation. You can get any of these reports from the Food Safety Council. My role in all this has been concerned primarily with the second point that Dr. Rodricks talked about, and that's dose-response evaluation. I want to talk a little bit about the low dose extrapolation problem and give you a few of my thoughts. I realize that there are many aspects to risk assessment. I'm going to talk mainly about using animal data for doing low dose extrapolation; so I'm confining myself to that aspect of the problem.

I'm going to talk about low-dose extrapolation and it's going to involve three notions: quantal response data, the dose-response curve, and the acceptable risk level. I want to define what I mean by these terms. By quantal response data (Table 1), I mean you have a control group, increasing dose levels, a certain number of animals on test at each dose, and a certain number respond with typically a tumor or some other end point; usually these are animals that have been carried for a lifetime or near lifetime. Using that sort of data, one then puts everything together with something called the dose-response curve, which I'm sure you all know about. The terminology I'll use is P(d) and this represents the probability that an animal on test at dose level d responds.

Table 1

Type of Data Available
Quantal Response Data

Dose level	Number of animals on test	Number of animals with response (tumor)
$d_0 = 0$	n_0	x_0
d_1	n_1	x_1
d_2	n_2	x_2
.	.	.
.	.	.
.	.	.
d_m	n_m	x_m

$0 = d_0 < d_1 < d_2 < \ldots < d_m$.

In the statistical sense, that means that on the average $[100 \times P(d)]\%$ of the animals will respond or have that toxic effect at dose level d. Now, a typical dose-response curve looks something like this (Figure 1). What I'm showing is a dose-response curve that comes down to 0. If there's spontaneous background, this needn't come down to 0 and also it needn't always go up to 1; it may level off below 1, but most of the models I'm going to talk about look like this. I will talk about incorporating background later on; it is a very important

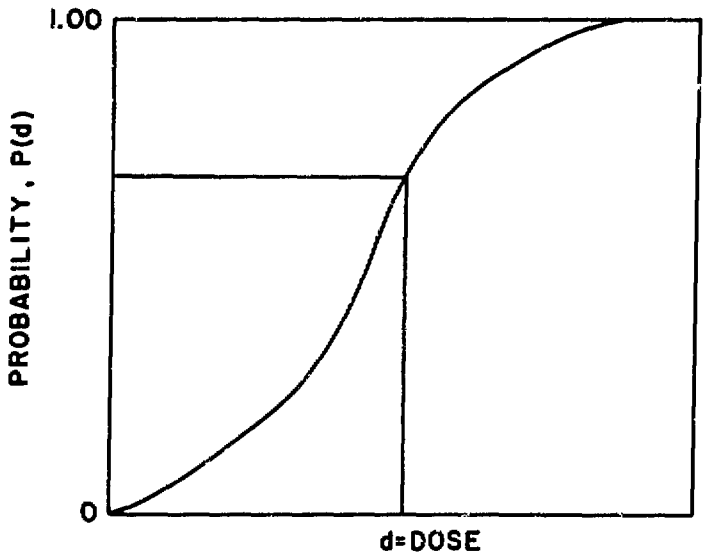


Figure 1. Typical dose response curve.

question as to exactly how one builds background into the model. Finally, there's the notion of acceptable risk level. The previous speaker referred to the number 10^{-6} and gave us a little history about it. I first came across the number 10^{-6} in the pesticide residue document put out by the FDA in the Federal Register; that's where they recommend 10^{-6} and I never knew how the number originated until today when the previous speaker told us how FDA arrived at that number. This number P_0 (Table 2) has been called the acceptable risk level. Roughly what 10^{-6} lifetime risk means is 3 deaths per year in the U.S. if the toxic response is death: if you think of 210 million people at risk with average lifetime of 70 years - or 220 million with average lifetime of 73 years, which is the same thing - that means that there are 3 million at risk per year, so it's 3 million times 10^{-6} which equals three deaths. I think people don't realize how small a number 10^{-6} really is. This assumes that everybody in the whole U.S. population is at risk for their entire lifetime. Now if it's a subset of the people, say only 20 million that are exposed, you have to divide that number by 10 in order to get the number of deaths per year that would result. I think this puts a little bit of perspective on what 10^{-6} lifetime risk means. It's a small number. In fact, there's been some interesting literature on the perception of risk. There was a conference at Brookhaven last November in which Vincent Cavello from the National Science Foundation talked on the psychological perception of risk. He gave some very interesting ideas about what level people perceive risk at, and people don't perceive 10^{-6} very clearly. So the problem of low-dose extrapolation is to put these three notions together by estimating a dose-response curve (Figure 2) by the dashed-line curve; the true curve would be the solid line curve. Then you pick an acceptable risk level (P_0), come across that to the dashed-line curve, go down to the dose axis, and get what is called the virtually safe dose; that is, the dose level that corresponds to the risk level that you picked. This, of course, is the terminology of virtually safe dose which lawyers tell us we're not supposed to use. I still tend to use it because Nathan Mantel used it originally and it really does convey what you're trying to shoot for; you're shooting for something which you consider virtually safe since we all know you can't actually talk about a truly safe dose - that's a number you usually can't get. With that in mind you can pose many different models and try this procedure.

Table 2

Acceptable Risk Level

P_0 = Probability of a toxic response over a lifetime

$P_0 = 10^{-6} = \frac{3 \text{ deaths}}{\text{per year in U.S. if toxic response is death}}$
(210 million people, average lifetime = 70 years
210/70 = 3 million at risk per year
3 million X 10^{-6} = 3 deaths)

$P_0 = 10^{-4}$ = 300 deaths/year

$P_0 = 10^{-8}$ = 0.03 deaths/year

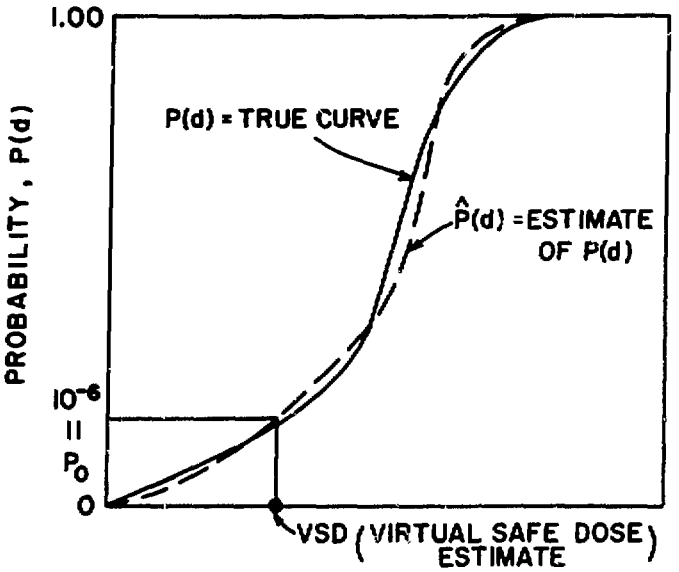


Figure 2. Low-dose extrapolation.
P_0 = prescribed acceptable risk level.

I'm going to give some data sets to which four different models have been applied - the one-hit model, the multistage model, the multihit model, and the Weibull model. I don't want to go into the origins of each of these models or the detailed equations for each of these models. Suffice it to say that the one-hit model is always linear at low doses and it is the one that the previous speaker referred to as being used by FDA. The multistage is

$$(1-e^{-(\alpha_1 d + \alpha_2 d^2 + \ldots + \alpha_k d^k)}).$$

The behavior at low doses is like the polynomial

$$(P(d) \doteq \alpha_1 d + \alpha_2 d^2 + \ldots + \alpha_k d^k);$$

if the leading coefficient is positive (i.e., if $\alpha_1 > 0$), then it's linear at low doses, and if it isn't then it could be quadratic (if $\alpha_1 = 0$, $\alpha_2 > 0$) or higher (say, cubic if $\alpha_1 = \alpha_2 = 0$, $\alpha_3 > 0$). The multihit model is a generalization of the one-hit model which postulates that it takes more than one hit to cause the toxic response. The Weibull model can be looked at from a tolerance distribution theory point of view or by considering a one-hit phenomenon except that the intensity parameter is not dose raised to the first power but dose raised to the m^{th} power. The character of these models at low doses determines the behavior of the extrapolation. At low doses, the one-hit model and often the multistage models will be linear; the other two models can be nonlinear at low doses because they both have a slope parameter. In low-dose extrapolation (Table 3), you select the model, estimate the parameters of the model by some

Table 3

Low-Dose Extrapolation

- Select model
- Estimate parameters of model by appropriate statistical procedure which accounts for background
- Put estimates of parameters in model to get estimated dose-response curve $\hat{P}(d)$
- Choose prescribed acceptable risk level P_0 of, say, 10^{-4} to 10^{-8}
- Solve $P_0 = \hat{P}(\hat{d}_0)$ to get

  $\hat{d}_0$ = virtual safe dose
  = dose level corresponding to risk level of P_0

appropriate statistical procedure - the one used in all the examples I am going to give is maximum likelihood - put the estimates of the parameters into the model to obtain the estimated dose-response curve $\hat{P}(d)$, choose some prescribed acceptable risk level P_0, and solve the equation $(P_0 = \hat{P}(d_0))$ for d_0, which is the estimated virtually safe dose. I went over that rather quickly, but it's easy to see if you look at Figure 2. All that I'm doing is fitting the dashed-line curve (estimate of $\hat{P}(d)$) to the solid-line curve (true curve) which you don't know and picking a point P_0 (your acceptable risk level) and coming across horizontally to $\hat{P}(d)$ and then down to d_0. The estimate $\hat{P}(d)$ depends on what model I assume. I'll give you three examples which I chose because they represent three different types of the low-dose behavior. First, consider vinyl chloride. These are Maltoni's data with liver angiosarcoma (Table 4). Zero out of 58 animals responded at 0 ppm, 1 out of 59 at 50 ppm, 4 out of 59 for 6.8% at 250 ppm, and 7 out of 59 at 500 ppm. There are parameters in each of the models. In the one-hit model the beta parameter is the slope parameter. In the multistage model the parameter k gives the number of stages involved and there are various coefficients in the polynomial in the exponent. The parameter k in the multihit model gives some idea of the slope of the dose-response curve; similarly, the parameter m in the Weibull model gives some notion of the slope of the dose-response curve. I picked this data set because if you graph these data, they increase in dose and then level off. The two models allowing for slope (multihit, Weibull) pick up a certain amount of "curvature" which would then carry down in a concave way to a low-dose range and you see that virtually safe doses at, say, 10^{-6} would give somewhat more conservative estimates than the one-hit and the multistage which are both picking up a linear term and carrying it all the way down. This is not typical of most dose-response curves, which rise in a convex manner. However, there are a few that behave in a concave manner like this example. Now I could talk about that more, but I bring this up only to illustrate that linear extrapolation needn't always be con-

Table 4

Vinyl Chloride Example

Data source:	Maltoni (1975)			
Species:	Rat			
Response:	Liver angiosarcoma			
Dose level (ppm)	0	50	250	500
No. of animals	58	59	59	59
No. of responses	0	1	4	7
% response	0	1.7	6.8	11.9

Extrapolation Results

Model	Estimated parameters	Virtual safe dose (ppm) at risk of 10^{-4}	Virtual safe dose (ppm) at risk of 10^{-6}
One-hit	$\hat{\beta} = 0.00027$	3.7×10^{-1}	3.7×10^{-3}
Multistage	$\hat{k} = 1$	3.7×10^{-1}	3.7×10^{-3}
	$\hat{\beta} = 0.00027$		
Multihit	$\hat{k} = 0.86$	1.2×10^{-1}	5.6×10^{-5}
	$\hat{\beta} = 0.00016$		
Weibull	$\hat{m} = 0.93$	1.6×10^{-1}	3.8×10^{-5}
	$\hat{\beta} = 0.00022$		

servative - that's one of the points I want to make with this particular vinyl chloride example.

Crump

Are the Weibull and multihit models redundant? If you've got one, does the other one give you anything?

Van Ryzin

Yes, they are redundant. In a paper by Dan Krewski and me in which we looked at these models plus the probit and the logistic model, this can be seen. The answer is that if you get one answer with the Weibull model you get more or less the same answer with the logistic and multihit. We looked at 20 different data sets in that paper and basically they all give the same answer with these three models to within an order of magnitude at least.

Crump

Even at low doses?

Van Ryzin

Yes, even at low doses. These three models (the multihit, Weibull, and logistic) are all very similar in their behavior.

Crump

I would prefer the Weibull just on the basis of simplicity.

Van Ryzin

Yes, even though I did a lot of work on the multihit and I have a program that does the multihit, my own feeling would be that if you do the Weibull you get more or less the same answers and it's much easier to handle mathematically. Let me just point out in the vinyl chloride example that there's no statistical test that will tell you that there is any difference between these models; they all fit the data quite well.

In the second example, DDT (Table 5), you have a slightly convex dose-response curve; that is, you have 4 out of 111 animals responding at 0 ppm, 4 out of 105 at 2 ppm, 11 out of 124 at 10 ppm, 13 out of 104 at 50 ppm, and 60 out of 90 at 250 ppm. You'll notice that the response goes along at a background rate, then rises and starts going up; there's a bit of curvature here. You can see from the model estimates that the one-hit model actually forces a linear curve as it has just one parameter in it; the multistage suggests two stages - a linear term $\hat{q}_1$ is the leading coefficient plus a quadratic term; and the multihit and Weibull models say there's a bit of curvature in the curve in the sense that the two parameters k and m are a little bit greater than one, which is an indication of a certain degree of curvature. This is what results in the experimental range. When you carry that down to 10^{-6}, the net result is that the one-hit and the multistage models, which have a linear term, will be

Table 5

DDT Example

Data source:	Tomatis et al. (1972)
Species:	Mouse
Response:	Liver hepatoma

Dose level (ppm)	0	2	10	50	250
No. of animals	111	105	124	104	90
No. of responses	4	4	11	13	60
% response	3.6	3.8	8.9	12.5	66.7

Extrapolation Results

Model	Estimated parameters	Virtual safe dose (ppm) at risk of 10^{-4}	Virtual safe dose (ppm) at risk of 10^{-6}
One-hit	$\hat{\beta} = 0.0038$	2.7×10^{-2}	2.7×10^{-4}
Mulcistage	$\hat{k} = 2$	6.4×10^{-2}	6.4×10^{-4}
	$\hat{\alpha}_1 = 0.0016$, $\hat{\alpha}_2 > 0$		
Multihit	$\hat{k} = 1.68$	7.6×10^{-1}	4.9×10^{-2}
	$\hat{\beta} = 0.007$		
Weibull	$\hat{m} = 1.58$	4.4×10^{-1}	1.8×10^{-2}
	$\hat{\beta} = 0.0003$		

fully two orders of magnitude higher than the multihit and Weibull models, which do not have a linear term. So the question of whether there's a linear term or not is very crucial. Now, what if you do a goodness-of-fit test? All the models fit the data here adequately, so you can't use the data to sort out the models in this particular situation.

Albert

Didn't you just say that the Weibull and the multihit and the multistage give about the same result?

Van Ryzin

No, I didn't include the multistage. I said the multihit and the Weibull and the logistic give more or less the same answer in order of magnitude.

Jones

Aren't you just getting the low dose data from these experiments? As from the vinyl chloride example?

Van Ryzin

I fit all the data that I'm showing you here.

Jones

But weren't there higher exposure levels in that study?

Van Ryzin

Yes, in the Maltoni data and in that data set it gets more severe if you put in higher doses in the sense that it bends over or levels off even more. I could talk about the fact that by using Ghering's correction for metabolism of vinyl chloride, the discrepancies between the models disappear (Van Ryzin and Rai, 1980). But I don't want to go into that now. I just want to show you the different dose-response curves and what troubles may arise when you extrapolate them to low doses.

Jones

I'm sorry to interrupt you, but I just want to make one comment. I've tried to fit all of the data with those models, rather than just the low dose data, and I didn't find them all to be equal; maybe it was my routine, but I didn't find them all equally good.

Van Ryzin

Which four?

Jones

The four you used plus logistic.

Van Ryzin

I didn't say that these (the one-hit, multistage, multihit, Weibull) would give similar answers. I said the logistic, the Weibull, and the multihit will give similar answers.

The last example I want to show is ethylene thiourea (Table 6). It begins over initial doses at a fairly constant background rate, somewhere around 2½-3%, and then shoots up very sharply. Now the three models which allow some curvature in them pick that up: in the multistage model, the linear coefficient ($\hat{\alpha}_1$) and the quadratic coefficient ($\hat{\alpha}_2$) would be estimated to be zero and the cubic coefficient ($\hat{\alpha}_3$) and the fourth-power coefficient ($\hat{\alpha}_4$) would enter; the estimated multihit would have a steep dose-response curve indicated by the parameter $\hat{k}$; and the estimated Weibull would have a steep dose-response curve indicated by $\hat{m}$. You will notice that when you extrapolate to low doses, these three models have virtually safe doses fully four orders of magnitude above the one-hit model at 10^{-6}. If one does a statistical test, does the one-hit model fit? If you test against any one of the other models, the answer is no - that is, the one-hit model does not fit the data. Now this, I think, portrays the problem even stronger than the other two examples. Within the observed data range, you say it's not linear. Furthermore, if that nonlinearity is carried outside of the experimental range, the virtually safe dose may be four orders of magnitude above what you would have if you do linear extrapolation. Now there are many ways for correcting this; one can put in conservative confidence limits or one can do some form of partial linear extrapolation. In other words, one could correct this by always linearly extrapolating beyond some intermediate risk level and going on down linearly from such a level. On the dose-response curve (Figure 3) you could cut off at 10^{-7} and then go down linearly from that. If you do this with the ethylene thiourea example - go down linearly from, say, 10^{-2} to, say, 10^{-6}, you'll notice (calculations are in parentheses in Table 6) that you change these estimates considerably for these three models at 10^{-6}; what you get out of the one-hit model which is naturally linear and out of the three models when you force the linearity from 10^{-2} don't differ quite as much, although the two models (multihit and Weibull) still allow a little bit of the curvature down to 10^{-2}, resulting in higher virtually safe doses at 10^{-6}.

Now, when we look at all this uncertainty, consider the last two examples. The DDT example said that you test for linearity and you can't rule out linearity. In that situation, it seems to me that you've got to do linear extrapolation. With ethylene thiourea, however, the data tell us that linear can be ruled out in the observed range, but then we don't know whether it can be ruled out in the low-dose unobserved range. In my view, we really have a problem here, and one possible solution would be to do something intermediate. Why should one do linear extrapolation in a situation like that when one can rule out data in the observed range? I think that goes back to what Kim Hooper was talking about this morning - there's a very strong mathematical argument for why we should always do linear extrapolation and that's called the additive background argument. There are two ways of putting background into the models

Table 6

Ethylene Thiourea Example

Data source:	Graham et al. (1975)
Species:	Rat
Response:	Thyroid carcinoma

Dose level (ppm)	0	5	25	125	250	500
No. of animals	72	75	73	73	69	70
No. of responses	2	2	1	2	16	62
% response	2.8	2.7	1.4	2.7	23.2	88.6

Extrapolation Results

Model	Estimated parameters	Virtual safe dose (ppm) at risk of 10^{-4}	10^{-6}	10^{-6}*
One-hit	$\hat{\beta} = 0.0019$	5.4×10^{-2}	5.4×10^{-4}	(5.4×10^{-4})
Multistage	$\hat{k} = 4$	20.8	4.5	(7.5×10^{-4})
	$\hat{\alpha}_1 = \hat{\alpha}_2 = 0$			
	$\hat{\alpha}_3 > 0$, $\hat{\alpha}_4 > 0$			
Multihit	$\hat{k} = 8.23$	60.0	33.5	(5.3×10^{-3})
	$\hat{\beta} = 0.024$			
Weibull	$\hat{m} = 3.33$	25.0	6.3	(1.1×10^{-3})
	$\hat{\beta} = 2.3 \times 10^{-9}$			

*Figures in parentheses calculated by linearly extrapolating from 10^{-2} to 10^{-6}.

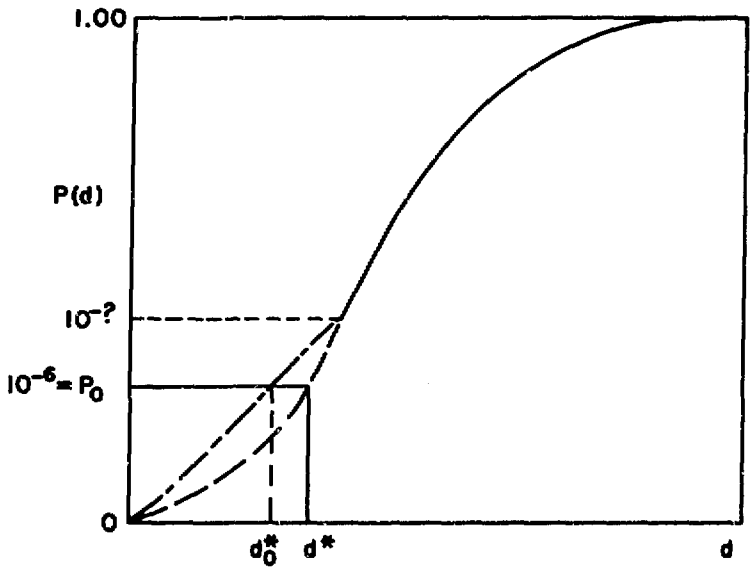


Figure 3. Linear extrapolation. d_0^* = virtual safe dose based on linear extrapolation; d^* = virtual safe dose based on model.

(Table 7). You can say the dose-response curves arise by a background response and also a response from the added dose alone. The independent background assumption would say that the probability of not seeing a response at the added dose is the probability of not getting it from background times not getting it from the added dose alone. If that independence assumption holds, the shape of the dose-response curve for any model would carry down to low doses. However, if the independence assumption does not hold and you have the additive assumption, which is that the true dose-response curve at the dose level you're observing is some "effective" background dose d_0 which adds to the dose you've added on, then a first-order Taylor expansion is applied to $P^*(d) - P^*(0)$ (the actual risk minus the background risk); you'll notice that that's approximately equal to the dose times the first derivative at the dose point d_0. In other words, what this says is that if this additive assumption does hold, then the added risk over background will be approximately linear, regardless of what the underlying dose-response curve was originally.

Because of this particular relationship, many people have said that one should always do linear extrapolation. Now there are two assumptions that are required: (1) the background is additive to the "effective" dose, and (2) $P'(d_0)>0$, which means you have to outlaw any possible threshold. The problem is, we can't test either of these assumptions and we don't know what the situation is in reality. We don't have much evidence on additive background - whether it's always additive - and we don't have much evidence on thresholds. So I think we're very much in the position that, although these dose-response curves suggest all sorts of different possible shapes, the only thing we can be absolutely sure of at this time is that going down linear outside the range is about the only thing one can do. I find that somewhat unsatisfying; when I see a steep dose-response curve and talk to various scientists who say you'd expect a steep one there because that isn't a very toxic substance or that's not a direct acting carcinogen, how do I build that into doing a low dose extrapolation?

Table 7

Incorporation of Background into Dose Response Models

1. Independent Background

$P^*(d) = \nu + (1-\nu)\, P(d)$ where $\nu = P^*(0)$ = prob. of response from background

Note: $[1-P^*(d)] = (1-\nu)[1-P(d)]$

2. Additive Background

$P^*(d) = P(d_0 + d)$ where d_0 = "effective" background dose

$P(d_0) = P^*(0)$ = prob. of response from background

Note: $P^*(d) - P^*(0) \triangleq d\, P'(d_0)$

Added risk over background = Linear function of dose in low-dose range if $P'(d_0) > 0$

One possibility would be to believe in the extrapolation a little bit, down to 10^{-2} or 10^{-3}, and then go linear from then on. But it seems to me that's a policy decision, not a scientific decision. There's nothing in the data that can tell you that; that is, if you have evidence of a steep dose-response curve and there's some biological evidence that there's a good argument for a metabolic break point and that break point seems to be below where this dose-response curve is coming down to, then you might want to believe in that dose-response curve for a little bit beyond the range of observation (below lowest positive dose) and then do some linear extrapolation beyond that. But it seems to me that those are not things that the data themselves can tell you - they must be corroborated by side experiments and by other sorts of judgmental factors.

In summary (Table 8), dose-response models allow for low-dose estimates of virtual safe dose at a variety of risk levels; they are extremely model dependent; and perhaps, for some regulatory purposes, we may want to extrapolate to some intermediate risk level and then linearly extrapolate beyond that. I personally prefer to run all the models and get some idea of the shape of the dose-response curve; the use of all the models does tend to give you that rather than just using one particular model. I still believe that models and low-dose extrapolation are preferable to safety factors because they make full use of the dose-response information and they can also be used in some form of risk benefit.

I give you one risk-benefit calculation (Table 9) that came from the Food Safety Council final report that was based on data from the Federal Register. This is a very crude risk benefit done by the FDA in order to look at PCB levels

Table 8

Summary

- Dose-response models allow for low-dose estimates of virtual safe dose at a variety of risk levels (P_0)
- Estimates are model dependent
- For regulatory purposes may want to extrapolate to risk level of say 10^{-2} or 10^{-4} and then linearly extrapolate to 10^{-6} or 10^{-8} if one cannot rule out possible low-dose linearity
- Models which involve shape of dose-response curve seem preferable (allow for linearity and nonlinearity) (multistage, multihit, and Weibull)
- Models and low-dose extrapolation preferable to safety factors because they make full use of the dose-response information from all dose data

Table 9

A Form of Risk-Benefit Analysis for PCBs in Food

Tolerance	Lifetime risk of cancer for heavy consumers of fish	Reduction in human risk	One-year cost (1974 dollars) of commercial fish (land value)	Increasing costs
5 parts per million	9.8 per 100,000 or 46.8 new cancers per year	Starting level	$ 0.6 million	Starting level
2 ppm.....	7.2 per 100,000 or 34.3 new cancers per year	12.5 new cancers	$ 5.7 million	$5.1 million
1 ppm.....	4.4 per 100,000 or 21 new cancers per year	13.3 new cancers	$16 million	$10.3 million

SOURCE: Federal Register, vol. 44, No. 127, June 29, 1979, p. 38333.

in fish. At the time this was being considered 5 ppm were allowed in fish; that would lead, if we use a one-hit model, to 9.8 per 100,000 or 46.8 new cancers per year. The current regulation cost $0.6 million a year in terms of how much fish was excluded from the market place. If you want to lower the allowable PCB level in fish down to 2 ppm, this is how the risk estimate would change: you would only have 7.2 per 100,000 or 34.3 new cancers per year and that would lead to a reduction of 12.5 new cancers and, at a cost of $5.7 million, the difference would be $5.1 million. If you went down to 1 ppm you would get it down to 4.4 per 100,000 with a reduction of 13.3 new cancers for a cost of $16 million, so the additional cost would be $10.3 million. On the basis of this risk benefit, the FDA concluded that it wasn't worth going from 34.3 new cancers down to 21 new cancers, a reduction of 13.3 additional cancers at a cost of $10.3 million, so they adopted the 2 ppm standard. Now that's a very crude risk benefit calculation, but I think the use of models to make these kinds of calculations is an improvement over the old convention of safety factors because when you divide by a hundred or you divide by a thousand you really don't know what you've done. I admit that what I am suggesting is very crude, but I do think dose-response models can play a role in these sorts of calculations.

Albert

What extrapolation model did you use?

Van Ryzin

This is taken from the Federal Register basically. At the time they did this, they were using the Mantel-Bryan procedure - that's the probit model with the imposed slope of 1. This is their calculation, not mine. But I'm saying you could use any model in this form and get some idea that if you reduce the dose so much, then you are saving so many new cancers, and you can weigh this against how much it is going to cost you. I think there is some benefit in doing that.

Discussion

Baum

I would like to suggest that we go back first to the question of risk assessment and risk management, since tomorrow morning we will be getting into dose-response modeling, and so we will again have time to discuss what John just presented if we do not get into it in this afternoon's discussion. I would like to focus our attention initially on the fact that both Dr. Rodricks and Dr. Van Ryzin have cited the 10^{-6} risk per lifetime of the FDA. That criterion can be compared to the 10^{-4} risk per year for occupational workers that is used in radiation protection. That number derives from the fact that 10^{-4} risk per year is characteristic of safe industries in general. The ICRP has reviewed the accident and health statistics data in the United States and concluded that it would be desirable that radiation workers be protected as well as workers in what are generally considered safe industries. So by adopting exposure limits that restrict the dose of radiation workers to a maximum of 5 rem per year, they conclude that the average exposure will be about 1 rem per year. This would provide a risk of cancer mortality of approximately 10^{-4} per year to radiation workers.

The question I would like to raise, then, is should we not adopt a similar criterion in the area of chemically induced carcinogens? Also, is the difference between the FDA number of 10^{-6} per lifetime and the radiation industry value - 10^{-4} per year x 50 years = 5×10^{-3} per lifetime - appropriate? The criterion for a radiation worker applies in an industrial occupational situation that has certain benefits for the worker that is so exposed, whereas the Food and Drug criterion applies where you have large numbers of people, the general population, etc., being exposed. So I welcome any thoughts anyone has on these criteria and whether they're applicable in the situation we are discussing here today.

Hattis

Let me first say that this is not a technical question; this is a policy question, and a bunch of experts sitting around a table should be expressing themselves purely as citizens rather than with any particular claim of being believed more than anybody else. But my particular policy view would be that 10^{-6} - three deaths a year for the population of the U.S. - is not a risk that should be undertaken without some demonstration that you couldn't avoid that without considerable trouble. The 10^{-4} figure is some average death rate for workers in the country and nobody ever said that it is an entirely acceptable level of risk that one shouldn't try to reduce. I think that a risk should be considered small or large, acceptable or unacceptable, in relation to the difficulty, effort, and competing risks that are required to reduce it. There really ought not to be a magic level of risk that is accepted regardless of how easy it might be to avoid.

Baum

I'd just like to amplify the question a little bit in that the 10^{-4} risk is actually an upper risk limit, as I tried to indicate in the introduction. In

addition, one has to reduce the exposure to as low as reasonably achievable. Presumably, the same criteria and concepts would be applicable in the chemical industry where you wouldn't expect everyone to receive the maximum exposure, and in addition you would try to optimize it in order to reduce everyone's exposure as low as possible within cost-effectiveness considerations.

Albert

I think it is a truism that there is no such thing as an acceptable risk in isolation because risk is only an impediment to action. Its only meaning is to hold us back, and we really only make judgments as to whether or not a risk is acceptable as a quid pro quo that the benefits make it worth while. So having said that truism, we're still over the barrel because in most cases we're dealing with risks and benefits that are incommensurable. If we're dealing with a pesticide, we're talking about corn production vs cancer deaths. Now how do you equate that sort of thing? In my own experience with risk-benefit balancing, I find it is fairly meaningless and what it really boils down to is that the administration of the federal regulatory agency does what it thinks the traffic will bear. If it's in a gung-ho era for regulations, it will push a regulation until political opposition develops. If it is in the anti-gung-ho era, it is very much attuned to the opposition to regulation and it may push hardly at all. I think it is pretty close to an insoluble problem.

Davis

Let me agree with both of you and say that I think Dale is correct to point out that this question you're posing is a policy question, but there are certain technical aspects to it I think we can discuss. One of those deals with the healthy workers that exist in industry - we should not mistake the fact that workers are, in fact, healthier than the rest of the U. S. population and that is one of the reasons why the 10^{-4} factor was developed. The general population, of course, includes a lot of people who cannot work, as well as children, the unborn, and those who are hypersusceptible. When FDA is setting its standards - except for PCB's and lead, as far as I know - it does not especially have children in mind. If one does an index, as my colleague Harvey Babich and I have done, of the TD_{50} of substances for adult animals compared to young animals, there is substantial evidence that the young can be more susceptible than the safety factors that FDA often uses. Scientifically, the evidence suggests that when it comes to protecting hypersusceptibles and children, one needs to have a risk factor that is more protective of them in terms of general environmental standards.

My other comment is that perhaps the chemical and radiation industries are different. Many industrial chemicals are ubiquitous; between 80% and 90% of Americans have detectable and substantial levels of pentachlorophenol in their blood. This is also an industrial substance. So I want to pose as an issue: does one consider that workers are exposed to chemicals to which they may also get double exposure in the ambient environment? Any of us who fills a gas tank with gasoline nowadays is exposed to benzene and a host of other things in that gasoline, depending on whether we stand upwind or downwind, or have a safety nozzle, or a number of other factors. And if you also work in a workplace, you're going to be exposed to benzene as well. So the fact that you get, in some

cases, double duty exposure may be a further argument for having again a standard of 10^{-6} when it comes to chemicals as opposed to 10^{-4}. Now that is a scientific question, even though I agree again with Dale that these are policy issues.

Baum

Do you suggest that 10^{-6} might apply in the occupational environment also?

Davis

One could make an argument for it if, in fact, many industrial chemicals prove to be ubiquitous. The Health and Nutrition Examination Survey (Hanes) at the National Center for Health Statistics examined blood and urine from a representative U.S. sample and found that Americans are absorbing chemicals on a very widespread level; food seems to be the only route. In the case of PCP, it appears that pentachlorophenol is added to plastic wrap because it is a very potent fungicide - so we can get our potato chips fresh without mold on them. That appears the likely reason why so many people have such levels of it in their system. Indeed, PCP may be far superior to mercury which was probably used in the last century for the same reason. Maybe when we talk about industrial chemicals we ought to recognize that exposure for some of them is so widespread that standards ought to be more like 10^{-6}. I'm posing that as a question, something for a discussion.

Crouch

I have two points which are related. The first is that to compare 10^{-4} safe industry risk or safe radiation risk with the FDA standards, you'd have to take the FDA thing as applying to total exposure. The radiation standard certainly is for total exposure, no matter how it arises. Then one would have to do a comparison with that. You would have to take exposure to all chemicals, giving a similar sort of risk - not individual chemicals, which I believe is what this is supposed to apply to.

Now the other thing is, how are we ever going to measure anything as low as 10^{-6}? For an individual chemical, the best that can be done in an animal study is to feed something like 10% to groups of 50 animals. The best you can get out of that - the most sensitive that you're ever likely to get - is a measure of potency such that to get 10^{-6} lifetime risk would require less than 15 mg per day human intake. That is, if you eat more than 15 mg per day, then you must necessarily exceed that risk level at our current level of testing. You can be sure, because our current test sensitivities are not that good. So that if you're going to demand 10^{-6} lifetime risk, then you necessarily limit any intake to 15 mg a day, and this raises problems of how to apply any sort of regulation uniformly. To do so, you've got to ban anything that is fed at any rate above 15 mg per day to humans, which is most foodstuffs, because you can't test them any better. If you're going to require that the sum of all inputs be less than 10^{-6} in a lifetime, then the same applies and the sum of all chemical inputs has to be less than 15 mg per day per human. It's even worse than that, because as soon as you allow uncertainty in any of these extrapolations to humans you're going to add another factor of 10 lower or so, and so you're not

going to be able to ingest any more than 1.5 mg per day per human of anything if you wish to maintain this standard uniformly.

Baum

Of any highly toxic substance, you mean?

Crouch

Of any substance. Any substance at all, if you're going to apply this standard uniformly.

Crump

I'm not sure what your basing this on. Is this irrespective of whether the substance has been determined to be a carcinogen or not? Or are you restricting yourself to something that is known to be a carcinogen?

Crouch

No. Suppose you test it as if it were a carcinogen and you wish to be sure of less than 10^{-6} risk.

Crump

You're not waiting for a positive result before you regulate?

Crouch

Suppose you had the most sensitive test and had only just gotten a positive result. Then the maximum you could allow would be 15 mg per day per human. If you got a negative result, you might be able to allow more, but you can't prove it. That is, the material may be a carcinogen, but tested negative because not quite enough was fed to the test animals. In any negative test there is no evidence to show that this has not occurred.

Bender

I'm sort of an advocate, I guess, of utilizing the radiation experience over the years as something of a model for considering the chemical question. A lot of questions you've heard about today are old, old questions, and I don't like to see us forget them. Several things have been said with respect to radiation carcinogenesis that I don't think are really true, and I think I ought to set us straight. In the first place, of course, we're all exposed to substantial ionizing radiation from natural background, and the natural background level to which we are exposed constitutes one way of looking at the question of acceptable risk. The fact is that the maximum annual exposure permitted to the general population under the old NRC regulations is of the general order of natural background; that is, it would constitute a doubling of whatever risk natural radiation constituted with respect to cancer and with respect to other effects as well. However, natural background is not all that we are exposed to. There

is an uncontrolled, or essentially uncontrolled, exposure source to most of the population that can be substantial, and that is the health-related utilization of radiation - diagnostic x-rays, nuclear medicine, and so forth. As far as I know, the basis for permitting this essentially unregulated exposure is that the benefits are believed to be far larger than the risks. So we get into the area of considering relative benefits on some basis vs relative risk - sometimes not sensibly, I feel, as in the case recently of whether or not to advocate large-scale mammography for breast cancer screening.

Another point I wanted to make, which is not related, is that we hear frequently numbers like 10^{-4}, 10^{-6} absolute risk; but I think it is important to keep in mind always what the natural risk is, just as it is important to consider what the natural background exposure is. I haven't worked the numbers out in my head, but an extra three cases per annum of cancers in the United States must be very, very small in relation to the number of cancers occurring, whether or not we accept these extra three cases. Does anybody know what that number is?

Audience

200,000? 400,000??

Bender

And that's deaths, not incidence, and I think we're talking incidence when we're talking about regulating, so that's another factor of 2 at least, I think.

Rodricks

I would like to repeat, in perhaps a slightly different way, something I said earlier. I don't think that the decision about acceptance, which is clearly a policy decision, is simply a matter of selecting a number and deciding that everything above the number is safe and everything below it is unsafe. There is more information in a comprehensive risk assessment that should influence that decision - most of it having to do, I think, with how confident you are that the risk is close to the number you're estimating. You take into consideration the uncertainty that appears throughout the risk assessment. I'm not sure what that analytic process is. Maybe it's too complex for day-to-day decision making in this area. I think it would be a mistake to reduce the decision simply to a number. I think the FDA decision, which I advocated 10 years ago, is basically incorrect. It's just too simplistic. The number should inform the decision, but it is only part of it. I haven't yet seen anyone develop or propose the tools to go much beyond that. Perhaps we're not ready to do that yet, but I think it is something that should be kept in mind. The data bases we're working from vary immensely from chemical to chemical. The quality and your confidence in those vary immensely, and I think that information ought to be incorporated in the decision-making process.

Albert

I certainly agree. If an agent is used as a purple coloring in bubble gum, and even if the risks were down to 10^{-6}, people would say get it out of the

bubble gum, who needs it? I suspect that the way things will eventually work out is that when there is sufficient evidence for an agent to be regarded as a carcinogen, then we will see how much it will cost to reduce the exposure and look at the associated risks. If we think the exposure can be cut down at acceptable costs and if the level of residual risk seems uncomfortably high, we'll try to push it down a little further. If it looks very low, we'll let it go at that. And it seems to me that things will begin to fall into a pattern and there will be classes of agents in terms of the kind of economic impact they have and a precedent will be developed. My guess is that the only way this will work out in the end is on the basis of precedent; that is, experience will develop with the regulation of carcinogens and association with certain risk levels, and once this begins to take hold it will probably form a basis for judgments about new agents as they come along. That's a personal view.

Baum

I didn't mean to exclude questions in the area of dose-effect modeling and so on, which Dr. Van Ryzin touched on. If anyone has any comments or questions in that area, please feel free to bring them up.

Borg

I'd like to make one value judgment on this last discussion, and then I do have a small detailed question for Dr. Van Ryzin. I talked this morning and used the phrase twice, I think, of keeping an eye on the ball. We're wondering what lifetime risks of 10^{-6} mean and how, even if those are for individual chemicals, that relates to the total cancer risk of 450,000 deaths a year. We know that other things are going on in our environment which have changed cancer incidence from one part of the world over the decades. For example, since I was a medical student, stomach cancer was the major cause of cancer death in men by factors of several times, and if you look at some of the upper GI cancers in certain parts of the world, by a couple of orders of magnitude. Now in the face of those enormous changes, which have something to do with what human beings do to their environment - you can call it life-style for the moment for want of knowing for sure what it is - I do sometimes think we are asking how many angels could dance on the head of a pin and I don't think we're keeping our eye on the ball. There are major factors out there that we're ignoring because we're preoccupied with numbers like 10^{-6} as opposed to something a little different.

Hull

Don has said most of it. I've had this experience in radiation protection, where I've been dismayed at trying to think about 10^{-6} risk levels. It produces a concern, as someone said earlier in the meeting, that we're searching around under the light when the real problem is out there where we can't see it. I'll make another comment with regard to this business about the fish. It's all very fine to get the number as far down as 5 to 2 parts per million. But I think if you do not wear blinders, you can extend the question very quickly to say - well, the cheaper the fish is, the more people eat fish, and if they eat fish instead of meat, from what we now know, they would reduce their cancer risk somewhat. So I think we tend to look at things in a very narrow way from our

own specialties and not to consider the overall global health risk within which we're operating. I keep saying to my fellow health physicists, it's time to put some health in health physics and look at the overall spectrum of health improvement in terms of how much money should be spent on radiation protection to avert the risk of cancer. I urge that as a sort of philosophic principle on all of you here who are involved in other specialties.

Crouch

No question, just a comment. 10^{-6} risk per life corresponds to approximately smoking one cigarette in your life.

Jones

I like what Roy says, but conceptually it gives me some problems. It seems that what you're suggesting always amounts to something like a three-way arm wrestle between politics, science, and industry. How would anyone ever go about balancing such a system?

Bender

I would like to comment a little bit on the modeling exercises. They, of course, are exercises that people interested in the effects of ionizing radiation have been going through for many years, and I think some of their experience would be helpful. In the first place, many of these models attempt to estimate a great many parameters, and they simply fail to give stable estimates of these parameters. The data sets are always limited, and I think the current thinking among those who do this sort of thing - as, for example, in looking at the Hiroshima/Nagasaki human data for cancer - is that you're duty bound to exclude some models in order to reduce the number of parameters. So, for example, when we fit the nonlinear quadratic to some of the Hiroshima/Nagasaki data, we seem to feel that it is much preferable to drop out a term that, as biologists, we really believe is significant, which is a sort of cell-killing saturation term, not because we don't believe it's real, but simply to get some kind of stability to the parameter estimates. The other thing which I think has happened is that there is some consensus that the models that are used and the way in which they are used ought to make some biological sense; that is, to fit both experimental observation and our perceptions - our current theories, etc. - about the processes involved. For this reason, for example, I think most of us would not fit certain models that allowed noninteger values for exponents. Just as an example, a multihit model which allows a single noninteger value for the number of hits just doesn't make any biological sense. I think we need to remember that sort of thing.

Davis

I can't resist, even though I want to keep my eye on the ball, making a comment about models used by the economists. For the most part they are fancy multilinear regression analyses that make a lot of assumptions about data, none of which any serious economist believes. But, nonetheless, they're models. I think that before Roy lets the horse out and then closes the barn door, we

shouldn't give too much away to the economists. We should demand of them the same examination of their models and assumptions that we're undertaking here with respect to cancer risk estimation. In particular, in a lot of the economic cost estimates that I saw when I was at EPA, and in others I've examined in work I've done at ELI and at Hopkins, what turns out to be the first best estimate of the economist about the cost of something often gets modified, usually down, sometimes by a factor of 100. Rarely is it modified up. That does not mean that industrial economists are lying when they first do their estimates. It simply means there are often a lot of unanticipated savings. The vinyl chloride emission cases may be one of the best examples. The so-called fugitive emissions were captured because of the required regulations. In doing this the industry became more productive and efficient instead of going under as originally projected. Now this is not to say that all environmental regulation is good economically, because that is obviously not true. But I want to make a point here that we should not just let the economic estimates stand as though they are set in concrete, and we are the only ones who are dealing with imprecise and uncertain terms.

Baum

I think, perhaps, we ought to call these discussions to a close at this point, and perhaps we will have a chance to bring up additional questions tomorrow. I certainly have some of my own that I haven't raised yet.

In summary, for this session I'd like to thank Dr. Rodricks and Dr. Van Ryzin for pointing out to us the basic elements in risk assessment and risk management, and for summarizing for us the various models which have been developed and pointing out their uncertainties and applications. I hope we'll hear more from both of them tomorrow on these subjects.

Prepared Comments

Risk Assessment

Joseph Rodricks

I take risk assessment to be a scientific undertaking, the chief goal of which is to describe and characterize the types of hazards associated with a substance or activity, and to estimate the probability that those hazards will be realized in populations or individuals under their conditions of exposure. Under this definition, risk assessment does not include questions of risk acceptance (or, as I prefer, risk toleration), nor does it include any of the types of balancing activities variously referred to as risk-benefit analysis, cost-effectiveness analysis, cost-benefit analysis, etc. I group activities of the last type under the general heading of risk management. These are by no means universally accepted definitions, but it appears that they are becoming widely adopted. It has also been suggested that the term risk analysis be used to encompass both assessment and management activities.

Risk assessment, under the definition I am using, is a broad activity, by no means limited to the uncomfortable problem of high-to-low dose extrapolation. It includes, as its first step, the problem of hazard identification and evaluation. In brief, this problem involves review and evaluation of various types of experimental and epidemiological information for purposes of identifying the nature of the hazards associated with a substance or activity. It is designed to answer questions such as: Is (substance x) a carcinogen? What type of carcinogen is it? What are the nature and strength of the evidence supporting this evaluation? The second step, termed dose-response evaluation, involves identifying the observed quantitative relationship between exposure and risk, and extrapolating from the conditions of exposure for which data exist to other conditions of interest. This step almost always involves high-to-low dose extrapolation and frequently extrapolation from experimental animals to humans. The third step is identification of the conditions of exposure (broadly defined to include intensity, frequency, and duration) of the human population group that might be at risk and for which protection is sought. The last step involves combining the information on dose response with that on exposure to derive estimates of the probability that the hazards associated with a substance or activity will be realized under the conditions of exposure experienced by the population group of interest. Risk assessment involves integration of the information and analysis associated with these four steps to provide a complete characterization of the nature and magnitude of risk and the degree of confidence associated with this characterization. A critical component of the assessment is a full elucidation of the uncertainties associated with each of the major steps.

I suggest this broad conception of risk assessment as a useful framework for the development of a guideline. I envision that a guideline based on this framework would set forth the scientific justification for the methods to be used in reaching conclusions in each of these four steps of risk assessment. It would also specify the bonds of scientific knowledge in each of these areas, and provide fairly specific guidance on what assumptions should be imposed in areas in which there are several plausible approaches, and selection among them can not be made on strictly scientific grounds. In the context of carcinogenesis,

at least the following areas require specification of policy, pending the development of additional data:

(i) Selection of data sets from a larger body of data sets for purposes of high-to-low dose extrapolation. The usual procedure is to select the data set yielding the highest risk, but such a procedure may not be scientifically justifiable.

(ii) Selection of models for high-to-low dose extrapolation.

(iii) Selection of interspecies scaling factors.

(iv) Selection of assumptions for exposure evaluation, when specific data are lacking.

(v) Selection of assumptions for extrapolation from one route of exposure to another, when specific data are lacking.

Completion of a risk assessment yields no view of whether the projected risks are important and require the imposition of controls. We here enter the realm of risk management, which is far less well developed than even the fragile domain of risk assessment. Some contend that risk management decisions are strictly matters of policy. I do not argue this point, but add that this does not mean they should be devoid of objective, analytic support. The problem seems to have two primary components. The first involves a decision on whether or not the assessed risk is important (i.e., not de minimis). This decision, I suggest, should not be based solely on the magnitude of the projected risk, but also on the degree of confidence that can be placed both in the data underlying the assessment and in the methods and assumptions used. The degree of confidence is a function of several aspects of the assessment, including the strength of the evidence supporting the conclusion that a substance or activity is indeed hazardous (e.g., that a chemical is a human carcinogen), the extent to which supporting data are biologically and statistically concordant, and the extent of variability in the risk when it is predicted under different assumptions and models. Some means is needed to permit systematic consideration of all these types of information in the decision-making process, but little analytic work has yet been done in this area.

Some agencies have defined negligible or de minimis risk for some carcinogens strictly in quantitative terms. This approach may be a reasonable place to start analysis, but it fails to recognize that the data bases for different carcinogens vary widely in quality and content, and that several other nonquantifiable factors (that I include as part of the assessment of "degree of confidence") influence the risk. In other terms, two substances apparently posing the same quantitative risk may, in fact, produce quite different risks. I suggest that the other nonquantitative information available in the risk assessment can serve as a guide to determining the likelihood of such differences.

If it is decided that a risk is worth worrying about, additional analysis is needed to decide how and to what extent control is necessary. This area involves questions of cost, technical feasibility, and law, all of which I leave to others.

Some Comments on Risk Assessment Methodology and Its Application

John Van Ryzin

The most common method of doing risk assessment with chronic animal toxicity data is to fit some mathematical model to the data and extrapolate downward to an acceptable risk level. By an acceptable risk level, we usually refer to a very low lifetime risk. For example, an acceptable risk level of 10^{-6} would mean about 3 cases per year in the U.S. if all 220 million persons were at risk, assuming the average person lives 73 years. That 220 million x 10^{-6} ÷ 73 years ≈ approximately 3 cases per year.

After this extrapolation downward is accomplished, one converts the animal dose to a human dose usually on the basis of either body weight or surface area.

Given that this is the method of risk estimation one is going to use, I would like to discuss a few of the issues involved.

Choice of Mathematical Model

A variety of mathematical models have been put forward. They include the one-hit, multihit, and multistage models as well as the conventional tolerance distribution models which include the Weibull, logistic, and probit models. A detailed review of these models is given in Krewski and Van Ryzin (1981). All of these models are possibly correct explanations of a specific carcinogenic response and no one of them is to be clearly preferred. It is true that the multistage model (see Crump, et al., 1976) appears to be a fairly plausible model. However, it does make certain assumptions on linearity in doses at all dose-related stages which may not be correct (see Van Ryzin, 1982). Thus, which model to fit is far from clear. Furthermore, typically all the more flexible parametric models with background included in them will fit the data adequately. For example, all models except the one-hit model fit all of the 20 data sets in Krewski and Van Ryzin (1981). Yet, when one does the low-dose extrapolations with these models, the answers concerning the virtually safe dose (VSD) at 10^{-6} risk are sometimes extremely different. The VSD is defined as that dose level over background giving an increased risk at the prescribed level. Thus, risk assessment cannot rely on any one model.

The main differences at low doses in the various models is how linear the extrapolation is at low doses. Thus, any model which is nonlinear at low dose can be altered by not extrapolating fully with the model and using linear extrapolation from any intermediate risk level (see, e.g., Van Ryzin, 1980). The multistage model with upper confidence limits and the one-hit model <u>always</u> do linear extrapolation and will lead to upper bounds on risk whenever the true dose-response model is convex. <u>Any</u> model can be used to do linear extrapolation beyond an intermediate range. Given this model uncertainty my preference is to fit a variety of models having different shapes, say, the one-hit, the multistage, the Weibull, and the multihit, and compare the various answers at 10^{-2} to 10^{-6} risk level. Then, the decision maker should decide how conservative he wishes to be, on the basis of:

1) biological factors (e.g., evidence of metabolic break points, whether or not carcinogen is direct-acting, etc.);

2) quality of data (number of animals, dose range of experiments, etc.);

3) other supporting evidence of carcinogenicity (short-term assays, etc.);

4) steepness of dose-response curve.

Having done this, the decision as to which intermediate risk level one wishes to extrapolate to with a model followed by linear extrapolation thereafter is primarily a policy choice. It must be judgmentally made on all pertinent factors since no model can guarantee a precise estimate.

Should Linear Extrapolation Always Prevail?

The fact that when a dose-response curve is strictly increasing and provided the administered dose is dose-wise additive to a background "effective" dose implies low-dose linearity has led some to say all low-dose extrapolations should be linear (see, e.g., Peto, 1978). However, this is not always true in practice if the background dose is small (see Krewski and Van Ryzin, 1981) and need not be true if dose-wise additivity does not hold (see Cornfield et al., 1978). Thus, again linear extrapolation becomes a policy decision and must be made on the basis of how conservative one wants to be.

Finally, linearity may not always be conservative if the underlying dose-response curve is concave in the low-dose range. For further discussion see Van Ryzin (1982).

Are Low-Dose Extrapolations Worth the Effort Given the Uncertainties?

Yes, because the alternative is to use safety factors which give no idea of risk levels. For example, if I divide by a safety factor of, say, 100, how much have I reduced risk? Mathematical models and low-dose risk assessment provide an estimate of this.

The second reason for using low-dose extrapolations based on mathematical models is so that one can do risk-benefit comparisons. For example, see pp. 72-74 of A Proposed Food Safety Evaluation Process (Food Safety Council, 1982).

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SESSION IV

UNCERTAINTIES

Introduction
(Session Leader - Donald Borg, M.D.)

White

As I pointed out yesterday in the introductory remarks, the purpose of the Center putting together this workshop is to give us an opportunity to hear from those of you who have expressed views on some of the areas that we have identified as problem areas in developing the carcinogen guidelines. You may recall that the OSHA 14 consisted of six human carcinogens and eight animal carcinogens. The original standards contained a special section that dealt with quality control and animal handling facilities. The OSHA document also specified a so-called de minimis quantity limit of 0.1% for solids and liquid mixtures of human carcinogens and 1% for animal carcinogens, indicating that those materials would not be treated under the standard if the concentrations fell below the de minimis values. These original standards, however, imposed no limits on air concentration. OSHA subsequently drafted a generic standard in which there are no compounds identified. However, they have taken the EPA CAG list and another group of compounds which they have identified as potential carcinogens and listed those as the compounds which they would expect to promulgate eventually into the generic standard.

In the meantime, we in the Department of Energy community are left without a uniform policy with respect to how we handle carcinogens throughout the community. The Center has been asked to develop an interim standard, and we have made some progress on this task. It might be best if I give a slide presentation which will give you a feel of what we have done to date and why we need some input at this point before we can continue (see Prepared Comments, page IV-34).

Current governmental cancer policies have drawbacks in their inability to distinguish the different levels of potency of a number of carcinogens. We propose a carcinogen guideline which consists of three safety programs based upon the nature of the exposure to the specific carcinogenic compounds. A Class I program is designed for use with low-risk carcinogens and requires only adherence to general laboratory safety procedures and the use of personal protective equipment. A Class II program designed for moderate risk carcinogens requires additional safe work practice controls and engineering controls in the form of containment systems, such as laboratory hoods and glove boxes. A Class III program for use with extremely potent, high-risk carcinogens would require maximum containment systems with sophisticated engineering controls and more recommended workplace controls.

We feel that in order to assign the compound to a program, we need to develop what would be identified as a carcinogen hazard index. Our initial approach was that the criteria for establishing the index would take into consideration a number of factors - carcinogenic potency of the chemical, chemical-physical properties (i.e., particle size, absorption mechanism, primary response route, potential for dispersion), use by worker (ways in which materials are handled), engineering controls, and environmental monitoring. Currently, we have eliminated engineering controls and environmental monitoring since, we feel that those aspects are included in the control program.

How do you estimate the carcinogenicity of the compound or its potency? We were aware that Bruce Ames and his associates have been ranking carcinogens using the criteria of the daily dose of each compound needed to produce an effect. In this system aflatoxin was at the upper end of the scale and saccharin was at the lower end. The American Conference of Governmental and Industrial Hygienists (ACGIH) has also put together a mechanism which allows us to define levels of potency for carcinogens. For our first cut we incorporated some of ACGIH's considerations, i.e., the lowest category would be all substances which produced neoplasms in at least one animal species (this is very similar to what Kim Hooper presented yesterday), and we gave some criteria as to the logic behind our choice. Our logic is an adaptation of the breakdown that the AGCIH used in their decision logic.

Category II would be those compounds which produce neoplasms in animals at levels lower than those placed in category I. And we had a third category for chemicals for which we said we really didn't have a loophole, i.e., for those chemicals for which there is currently a standard which by law the DOE community has to adhere to and be in compliance with (the OSHA-regulated carcinogens), and all industrial substances shown to be carcinogenic to man would be included in this category.

The topic areas scheduled for this workshop encompass problem areas that we envisioned from the first effort, and from the survey of DOE laboratories. There are a large number of compounds that could be labeled "carcinogens." Some of them are shown to be carcinogenic to man through epidemiological studies. There are more compounds implicated as being carcinogens on the basis of animal data. As you go throughout the logic system, there are even more compounds implicated by short-term tests and other schemes.

So, the purpose of this workshop is to obtain an approach that takes into consideration the potency of the carcinogenic compound, whether or not the linear concept or threshold concept is appropriate for these kinds of compounds, and whether or not a de minimis quantity is realistic. We would also like to get an idea of the pitfalls that we are likely to encounter on any legal regulatory carcinogen policy. If you have any views on policy setting, we would like to hear them. With this as a steering mechanism, maybe we can get information that the Center staff and advisory panel can use in developing a draft carcinogen policy.

Our leader for the morning session, which addresses a number of uncertainties, is Dr. Donald Borg, Chairman of the Medical Department here at Brookhaven.

Borg

I shall try somewhere toward the end of that discussion to elicit from the audience some consensus on whatever may be developing with regard to the more practical questions they are asking.

We have three speakers addressing the general topic area called "Uncertainties," although yesterday dealt with that, and perhaps Session V in yet another way. I would just like to make a remark myself before asking the first speaker to talk--one remark--having to do with uncertainty. There are two classes of uncertainties here, and they've not been completely unscrambled. One class of uncertainty really concerns the imprecision of our knowledge. We are uncertain as to what the facts are because we don't understand them well enough, although if we knew them, there might be no residual uncertainty. The other kind of uncertainty is the chancy or stochastic nature of certain events which,

no matter how good our knowledge, we cannot improve upon. And, it seems to me that the titles suggested to the authors here to which they addressed themselves, at this stage and probably for the foreseeable future, the way research goes has some content of the first class, that is to say, more research will improve our precision of understanding. The first two, dose rate and thresholds and dose-response extrapolations, may also run into the limit of stochastic uncertainty. The likelihood of a hit in a target volume which is referred to in the second talk we'll hear, that's uncertain just as in the macrocosm the likelihood of some catastrophic event like a meteor meeting the earth or a dam breaking, those things we probably can predict only to a certain level. There is a chance nature about them. I think it's important to keep the two kinds of uncertainty in mind, and perhaps we would use different strategies in approaching the limits of the two, and at the end I may ask for some consensus of clarification. As I see from the handouts that have been given by two of our speakers (and, by the way, I knew none of you one-on-one before this meeting, I know some of you by name, and I know the third speaker by name, reputation, and authorship), what we are going to be exposed to by the first speaker is an analytical presentation; he will be followed by a speaker who deals with mechanism and relates that to some extent to the analytical presentations. Last, I assume, from Dr. Crump, we are going to have another analytical summary with regard to the relevance of models. So with that prospect before us, I'll ask the first of our speakers, Edmund Crouch, to start. He is a research fellow at the Energy and Environment Policy Center at Harvard, which according to his address is actually housed in the Jefferson Physics Lab. As a good physicist, he is going start us off with an analytical approach.

Carcinogen Risk Assessments - Assumptions and Uncertainties Associated with Animal Models
(Speaker - Edmund Crouch, Ph.D).

Crouch

Well, I'm not really going to be analytical. What I want to do is to give a rough outline of what happens when you're considering a risk assessment for carcinogens based on animal data. The handout (see Prepared Comments, page IV-37) gives an outline of one realization of this. I want to address the topic generally and discuss where uncertainty may arise. It is useful to bear in mind the two sorts of uncertainty that were just mentioned. The use of animal results to estimate human risk is the basis of most current guidelines. In general, that's a species-one to species-two problem. You've got experimental results in species one, and you want results in species two. Now how are you going to analyze these experimental results? As they stand, they cannot be used directly. What we usually do is dream up some measure of dose, which I shall call D. D is usually something like a lifetime average dose. It may be a lifetime average weighted dose or an integrated dose rate. We don't know what the correct dose measure is for our purposes, but we expect any measure that we choose to be correlated with it. It may be that what we really want is the peak dose rate on day three of their age, but we don't really know that. We want to use some measure of response that will be useful to us, and the usual measure to use is the probability of a tumor. Perhaps we ought to be using the number of tumors or the tumors in a particular organ, or the sum of the tumors in all organs, or something like that. Then we want to use some dose-response form because we want to parametrize these data. Eventually we are going to extrapolate them somewhere. Again, we don't know what is <u>the</u> underlying correct dose-response form. We expect it to be of some functional form. It depends on the dose - it may depend on age. It's obviously going to depend on what we pick for our dose variable and what we pick for our response variable. But we are going to parametrize it by saying that response is some function of the dose, and assume parameters which I labeled α, β, γ, and so on. For convenience, think of α as the background rate, β as the potency (a slope, or something like that), and so on for higher-order terms. If we do this (which is what everybody actually does), we then estimate those parameters from the experimental results. Now in order to estimate those parameters we have to make a few more assumptions which are usually made implicitly, such as that animals act independently of one another, and that the results we see fit a binomial distribution. There are a few more implicit assumptions. In order to estimate the parameters we have to have an estimation procedure, which again is arbitrary, and which in most cases is the maximum likelihood. This has the advantage that we can get estimates for confidence limits and what not on all the parameters in a straightforward manner. We could also use least squares fitting instead, or almost any other estimation procedure. Plotting the data on a graph and fitting them by eye is also a well-defined estimation procedure, but one that's not often very useful. The output from our experimental results is actually going to be a set of distributions estimating the parameters in our dose-response model. That's in the first species. In the second species, which ideally will be humans, we are going to make the same assumptions as above. We've got to decide on a measure of dose, on a response measure, and on the form for the dose-response curve. Now in theory, any or all of those could be different from those in the first species, although in practice everybody always assumes they're the same. I certainly do

myself. Then we have a new set of parameters in that dose-response form, which I have labeled a, b, c, d, etc. Now in order to go from the first species to the second species, what is required is some model which relates the parameters of the dose-response model in species one to the parameters of the dose-response model in species two. We have a whole set of relations like that, relating the parameters, e.g., relating a in species two to all the parameters in species one; relating the dose levels chosen in species one to species two; relating the ages in species one and species two; and so on and so forth, using almost anything else you can think of, including calendar time.

It's usual to guess simple relationships. In fact it's usual to make the parameters identically equal in both species. However, that is an assumption, and it must be realized that it is an assumption. There is uncertainty involved in making that assumption. There is uncertainty involved in everything I have said so far. Any guidelines that you want to apply have to take into account the uncertainties with every stage of what I have just said, in choosing a dose-response curve and modeling the relations in species one and species two. Also, they have to take into account any exceptions you happen to find or you guess. I don't pretend, myself, to be able to do that. However, what I am going to point out is that these uncertainties can be large, and one has to estimate the size of them in particular cases. The handout (page IV-37) gives you a specific example of the procedure that I just outlined that tells you how big the uncertainties are, if you use the assumptions made in the example.

First of all I am going to ignore the uncertainties in choosing the dose-reponse model. I suggest that you try some other dose-response models in a similar sort of procedure and see what happens. I always think it is best to try the worst case first, and the worst case is generally agreed to be a one-hit-type model, linear at low doses. Take some sort of linear at low dose, one-hit-type model (you see a particular form of it on my handout, page IV-37); then parametrize the available data. Now typically when you do that, you estimate those parameters from experimental results and get a factor of uncertainty of 1.2 to 5, maybe 10, at 95% confidence limit. So, just by looking at the experimental results, you've already got a factor of up to 2 or more, or up to 5 or more uncertainty. You also saw that yesterday on the printouts that Kim Hooper handed around. The nice large confidence limits on a log scale were simply experimental uncertainties. What's more, they're not the only uncertainties in the experiments. They're actually minimum values for those uncertainties because, to get those confidence limits, you made a lot of assumptions which may not be true. There are actually further uncertainties in those experiments which are not included. For example, you've assumed that all the animals received the same dose; you've assumed that all the animals have the same dose-response curve; you've assumed that they all respond independently - that they don't respond group-wise by cage. These things may increase the uncertainties if you try to take them into account, although your best estimate is probably reasonably unbiased, I hope.

Now, suppose you make the assumptions of that model and suppose you also assume that in the second species you're looking at, the same model applies, therefore you can parametrize it in the same way. And suppose you expect there to be some sort of relation between the parameters, e.g., identity or near identity between the parameters in species one and species two. On the handout (page IV-37) I looked at the rat and mouse.

Even with these assumptions, you find an interspecies relationship is only good to within a factor of 5. I can show you that on this plot of potency (which is parameter β in this model) as measured in the B6C3F1 mouse in the NCI

series and in the F344 rat in this same series. Each point represents one chemical, each such point having a pair of confidence limits. The confidence limits represent those 95% confidence limits that I mentioned earlier based on assuming that everything is nicely binominal. However, you see that there is more uncertainty than that. There are items with small uncertainties from the experiment which are not identically equal; you don't get the same parameter in both species. In fact, you can represent these extra uncertainties by a normal distribution about that curve. It doesn't disagree with it anyway, so I shall assume that it is, and that's what I wrote down there. And the standard deviation is a factor of 5. That's a log-log plot, so the distance away from that line is typically of order of a factor of 5, or rather the difference in potencies in two species is typically a factor of 5. It seems to vary in no simple way from chemical to chemical. I mentioned that you have to take into account any exceptions. You know perfectly well that some of those NCI studies came up with a result in one species but nothing in the other species. What happens if you put such exceptions on a similar plot. Well it turns out that nothing startling happens. You can put confidence limits on the ones where you got no results, and plot those against what you actually observe in the other species. And you find that they could be simply statements of the uncertainty you saw before in the cases where you saw results in both species. So I don't have to think about uncertainties at the moment, not with this data set anyway, which is very fortunate.

So we have a factor of 5 for interspecies comparisons just between rat and mouse. Between a rat or mouse and a human, I would expect at least that factor of uncertainty. Now that's two uncertainty factors which add up to at least a factor of 5 or 6, say. Now, in general the procedure is to insert the estimators obtained from experiments in the first species into the relations you guessed in order to get distributions for the parameters for the second species. Then you add in the dose information that you have, to get a risk distribution. The risk here is measured in a way which is presumably related to the response that you are thinking about and that you are interested in extrapolating. Of course, you can do the extrapolation in two ways. You can extrapolate from the first species to the second species at high doses and then extrapolate down in the second species to low doses, or you can go the other way around, as in Figure 1. In the first case you need to know the dose-response curve to low doses in the second species. In the second case you need to know the dose-response curve to low doses in the first species and the parameters at either high dose or low dose. The thing I just showed you is the parameter relations at high dose. It was the relationship between potency in two species at high doses. If you are going to use something like this, the assumption you then make is that you know the dose-response relation in the second species in order to extrapolate down, ultimately to humans presumably.

The output of all this is going to be probability distributions for risk with certain assumptions, based on the assumptions that I mentioned. So you are going to have something that looks like Figure 2, a distribution for the probability of risk vs the value of risk, which is a probability density function of some sort. And you might have a δ function at origin just to take into acount the fact that you often get that sort of thing out of experimental results. The important thing to notice is that the distribution is wide in this context. The width is going to be a factor of 10 to 20 or so, where width is the distance between half power points or something like that. Furthermore, it's probably typically skewed toward high values. So wherever your best estimate may be (Figure 2), your mean value estimate or average may be substantially higher, (factors of

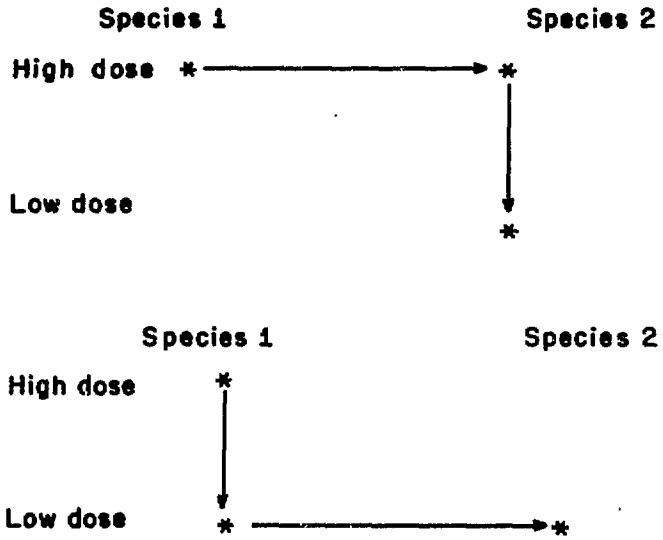

Figure 1. Ways of doing extrapolation.

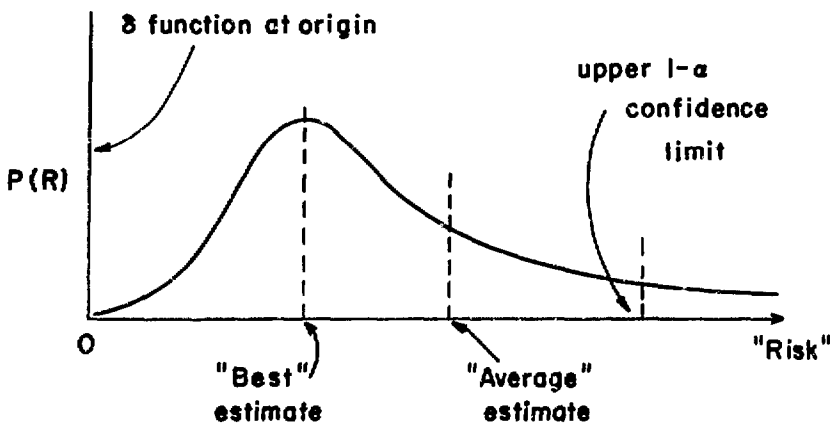

Figure 2. Probability distribution for risk.

5 to 10 or more), and the confidence limits may be much higher still. Any procedure that you use to estimate risk for basing your guidelines on has got to be able to take into account the possibility of getting input like this from your risk analysis and use that to set your guidelines.

Mechanisms of Carcinogenesis: Implications for Expectations About Dose-Response Relationships
(Speaker - Dale Hattis, Ph.D.)

Borg

Our next speaker, Dr. Dale Hattis, comes from the MIT Center for Policy Alternatives. He has been developing methodologies for assessing the health and economic impacts of different kinds of regulations, doing case studies, he says, on formaldehyde, lead, benzene, and contrast noise. Dr. Hattis is going to talk to us from the mechanistic point of view and, I trust, relating it to what we've heard and will hear later on.

Hattis

I just want to reinforce briefly the last point made by the last speaker. It is quite important to take into account the fact that these uncertainty distributions are likely to be skewed. They may often be distributed logarithmically. It may very well be that one's average estimate of risk may differ substantially from the best estimate of risk, and certainly one's confidence limits on risk may be orders of magnitude different from any central tendency one could hope to estimate. In decision making, it is important to communicate to the non-technical audience both your best estimate of how things are and also some idea of your uncertainties. Of course, the great tendency in dealing with uncertainties is to quantify the ones you can quantify and not to deal with the ones you can't quantify. There is some sort of a law that the uncertainties you can quantify are always (1) the least interesting kinds of uncertainties, such as statistical variability, and (2) nearly always a small fraction of the overall uncertainties that you might have as a result of uncertainties, in the selection of the basic dose-response models, etc.

Nonetheless, the thrust of what I am going to say today is that I think people are often more uncertain than they need to be about some basic features of cancer dose-response curves. We do know something about the mechanisms underlying carcinogenesis. What we know or what we can easily infer from basic principles has some nontrivial implications for cancer dose-response curves, although risk assessments must still be considered to have uncertainties of several orders of magnitudes in many cases. One thing we know is that at least one key step in most carcinogenesis is some change or rearrangement of information in DNA. I have outlined some of the evidence for this in the handout (see Prepared Comments, page IV-39). Basically, there are three classical lines of evidence. First, cancer seems to start in single cells, as observed in experiments where cells of a given tumor, in women who are heterozygous G6PD (an X-linked enzyme), nearly always have the same X chromosome activated in all the cells. This would not be expected if cancer arose independently in more than one cell. The second is the general association of mutagenic and carcinogenic activities in chemicals, and finally the fact that some well-characterized defects in DNA repair, like xeroderma pigmentosum, lead to substantial increases in at least some kinds of cancer risk. The new, and I think nearly conclusive, evidence comes from transformations in gene transfer experiments. You can transfer what some people call the transformed property with bare DNA in some well-characterized in vitro carcinogenesis transformation systems. I think that result is very exciting, and it's equally exciting that you can retrieve transforming genes from entirely normal cells as long as you break up the

DNA or strip some specific portions of the DNA of what might be normal control regions.

Now that we know that DNA is in some way involved and that some reactions between reactive molecules and DNA are involved, what does that tell us directly about the carcinogenesis process? If we had some way of directly adding to the nuclei of cells a DNA reactive material, we could guess pretty well that the rate of reaction would be a linear function of the concentration of the DNA reactive substance and the DNA. At low doses we certainly wouldn't expect to deplete the DNA, so at low doses you would expect the rate of generation of lesions to be proportional to the concentration of the active carcinogen at the active site. Now, of course, a lot of things can modify the linearity of that basic process, either between the time you get the chemical into you and the time that it gets to the active site, or after you generate lesions and before you get fully developed self-sustaining tumors.

I am going to talk about some of the quantitative implications of some of those different kinds of properties. Because, in many cases, people have rested claims that there might be thresholds on the action of some of these pharmacokinetic properties and other considerations.

One situation that has been postulated, which certainly does cause some nonlinearities in dose-reponse curves, is the idea of competing metabolic routes. Let's imagine that we have two pathways by which a chemical can be metabolized in the body. One of these produces a DNA reactive substance, and the other produces an entirely nonreactive and safe series of metabolities. Let's call the rate of the first reaction (the dangerous reaction), dR/dt. That is, dR/dt is equal to the rate of production of the reactive metabolite. If we believe that this is an enzymatic reaction, the ordinary presumption is that it should follow ordinary Michaelis-Menten enzyme kinetics. Let me illustrate what that means. Basically, the rate of the reaction is equal to some constant (k_1) times the substrate concentration (C), divided by some general enzyme constant (K_R) plus the substrate concentration.

$$\frac{dR}{dt} = \frac{k_1 C}{K_R + C} \quad ,$$

C = concentration of substrate,

R = reactive metabolite,

k_1 = Maximum possible rate of reaction,

K_R = Michaelis constant.

What that means is that at high doses, where C is very much larger than K_R, the C in the numerator and the C in the denominator essentially cancel out, and the rate of production of the reactive metabolite becomes constant no matter how high C rises. Physically, this means that basically all of the enzyme molecules are working as fast as they can. Their active sites are fully occupied with substrate, and you can't produce reactive metabolite any faster with the finite number of enzyme molecules present. At low doses, where C becomes much less than K_R, you can see that the rate of production of the reactive metabolite is going to be a direct linear function of the concentrations of that reactive metabolite:

$$\frac{dR}{dt} = k_1 C/K_R .$$

So our expectation is that where C is the concentration of the substrate, dR/dt is going to follow a saturation curve that is linear at low doses of C and comes to a maximum at high doses of C (Figure 1).

What if we also have in the same group another enzyme route that makes a safer metabolite?

$$\frac{dS}{dt} = \frac{k_2 C}{K_S + C} .$$

Well, it turns out that if you have the same kinds of expectations for the kinetics of that enzyme as you do for the first, the intrinsic reaction rate could be different, and the point at which it approaches saturation could be different. Let's say we're in such a concentration that the safe enzyme system doesn't saturate very much, you would find that again at low doses you have a relatively constant production of the safe metabolite as a function of carcinogenic dose, but at higher doses where you have saturated the dangerous metabolite route, you get an increasing fraction of the total material being handled by the safe pathway (Figure 2).

The effect of this on a cancer dose-reponse curve would be similar. This has been hypothesized as the cause for the famous dose-response curve for vinyl chloride found in the original Maltoni experiments in BT_1 rats. You see at low doses it tends to be somewhat linear, or at least close enough. At high doses it reaches a saturation level, possibly because the dangerous metabolite has been saturated, and more and more of the stuff gets handled by the safe pathway.

The other situation is where the safe pathway saturates first, and at high doses a larger and larger portion of the material is handled by the dangerous pathway. This would clearly lead to a situation where the curve turns the other way, the cancer dose-response function is contant at least at low doses (Figure 3).

But what happens at low doses? We can treat that easily mathematically by simply dividing the equations to calculate the ratio of the production rate of harmful metabolite to the production rate of safe metabolite:

$$\frac{dR/dt}{dS/dt} = \frac{k_1 K_S}{k_2 K_R} = \text{Constant}.$$

That gives us a ratio of the chemical that's handled by the dangerous to the safe pathway. (When you make the low-dose assumption, and perform this mathematical manipulation, the C's in the denominators become unimportant because they're very small relative to the Michaelis constant.) The concentration of the safe substances and reactive substances drops out and you wind up with a ratio of constants. That tells you that at low doses, the safe and the dangerous pathways each grabs some constant fraction of the total material. Therefore, at low doses the proportion of stuff going by the dangerous pathway and the expectation for tumors, or at least the expectation for the production of DNA reactive substance, has to be linear with concentration. You can't get a threshold out of the mechanism. In fact you can get a linear expectation.

The next kind of influence on dose-response curves that is often considered is DNA repair. Repair is also done by enzymes, and if we have no other information, it's not unreasonable to postulate that repair is also

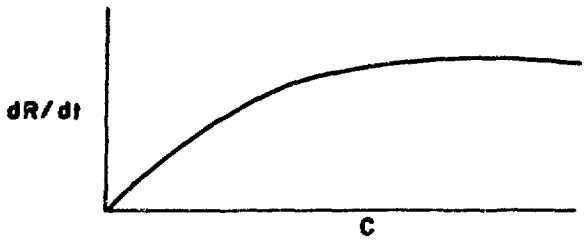

Figure 1 Relation between reaction rate and concentration from low to high doses.

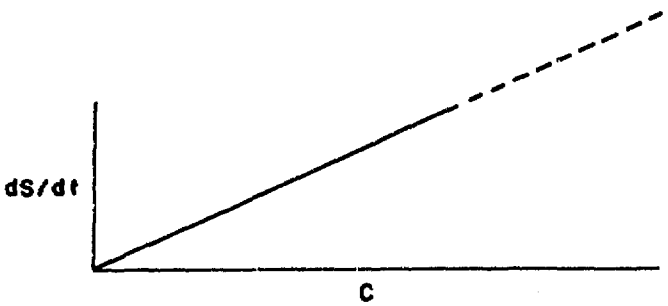

Figure 2 Relation between reaction rate and concentration in a safe metabolic pathway when the carcinogenic pathway is saturated.

Figure 3 Relation between reaction rate and concentration in a carcinogenic pathway when the safe metabolic pathway is saturated.

governed in some sense by Michaelis Menten enzyme kinetics. In this case, dL/dt, the loss of lesion with time, again should be some constant times the number of lesions that you have.

$$-\frac{dL}{dt} = \frac{k\,(L)\,(\text{Repair enzyme system})}{K_m + (L)} .$$

The following integrated equation can be calculated for the case of a burst of lesions generation at a particular point in time:

$$L_{t_1} = L_o e^{-kt_1}\,(\text{Repair enzyme system})/k_m .$$

There are two points to be made from that equation. First, the amount of lesions that persist at time t_1, whatever time t_1 is, will be a linear function of L_0. If you have a finite time to repair things, and I think you should expect that you do have a finite time to repair things before the next cell replication, or the next DNA synthesis, at that point it would be essentially reversible. If a lesion persists at the time of DNA synthesis, it has the chance of leading to a copying error and to some other breakage and rejoining event that would fix the damage in the genome. But assuming you have a particular finite time, and a finite number of enzyme molecules available for repair, you must get an expectation that the number of lesions persisting at low doses is to a first approximation linear with the number of lesions that you generate. On the other hand, of course, if you saturate your enzyme system to some degree, it's quite clear that a larger fraction of the generated lesions will persist to the time of the next cell division. So ordinarily you should expect that repair processes should give an exponential or concave shape to the dose-response curve for lesion persistence at the time of DNA replication. But at the limit of low dosage it is linear, albeit at a somewhat different and lower slope than at high doses.

Well, I see that I have a number of considerations yet to cover. One of the other implications of time, t_1, in the above equation is that if you increase the rate of cell division when you're also generating lesions, you would reduce that potential repair time, and you can vastly increase the likely persistence of lesions to the point of cell replication if ten times as many cells are dividing in a tissue. So this means that if you have overt toxic responses, cell-killing responses inducing cell proliferation responses in the target tissue, it's quite likely that you will vastly decrease the effectiveness of DNA repair and vastly increase the effectiveness of any mutagenic stimulus. I don't have enough time to go into this, but I suspect that this is what is going on in the case of formaldehyde. But, in any event, you still should get a linear dose response curve at low levels, albeit at a very much lower slope than at high doses.

There are a couple of other considerations, e.g., differences in individual sensitivity. Think of this as a series of populations. Say, you had basically a one-hit kinetics reaction in individual people, but you had vast differences among people, for whatever reason, in their individual one-hit kinetic reaction shapes. This would lend a convex graph or hyperbolic graph to the dose-response function because I had a small subpopulation here (say a tenth of the total population) that was ten thousand times as sensitive. (For them, the chemical was ten thousand times as potent as for the average.) Well, clearly you would saturate cancers in that subpopulation and then start to give cancers at a much lower rate with increasing dose to the larger fraction of the population

with average sensitivity. So that the composite population dose-response curve would look convex whenever you have a wide distribution of sensitivity among the population.

The last consideration that has been talked about a lot in the literature (I won't dwell on it in depth here) is of course the number of sequential mutations required for transformation. It has often been said that if you have one-hit or one-stage processes in direct competition with multistage or multi-hit processes, the one-hit process will tend to dominate at low doses. There are three lessons from this. First, there ought to be no general expectation of thresholds for DNA-reacting carcinogens that act in that way. I really think the threshold argument ought to be put to bed by this stage. Secondly, linear projections for low doses might often be closer to a best estimate than a confident upper bound. I mean there clearly are many ways in which you can get greater than the linear predicted risk if you happen to be unlucky in a particular case, either through wide distributions in sensitivity among the population, or by the saturation of the dangerous pathway before the safe pathways, as appears to have happened in the case of vinyl chloride. Thirdly, I would say that it's important not to try to load too much onto the multistage model in the sense of trying to explain the whole of possible departures from linearity in cancer dose-response curves. It would be much better to incorporate these other kinds of pharmocodynamic considerations into some more complicated models of dose-response curves. Make certain parameters that you can develop for these kinds of effects exogenous to the system, and let the multistage or other sorts of models handle only the residual curvature that cannot be explained on the basis of these other things. The other thing is that these kinds of considerations can be researched by little science in most cases. You don't need two-year carcinogenicity feeding studies. You can measure DNA adducts and their repair and how much of the material persists for how long in the system. There are fruitful areas for relatively little science type research that can contribute significantly to the overall quantification of expected cancer dose-reponse curves.

Borg

There is a quick question. Dr. Drew?

Drew

Why can't you postulate a safe pathway at low doses that predominates, and only until it becomes saturated do you then spill over to produce a dangerous metabolite.

Hattis

Well, let's consider two cases. If the safe and the dangerous pathways are both present in the same compartment, then there is no way to prevent the dangerous pathway from taking some of its share of the stuff at low doses.

Borg

But that "if" is very critical. I'd like to discuss it further during the discussion period. If they are sequential pathways, then what Bob has to say has a very different consequence.

Hattis

If you have more than one compartment, and the safe pathway is confined to the compartment that the chemical sees before the dangerous pathway, you still have an expectation of linear kinetics at low doses based on the following argument. Basically, the safe pathway has to capture all of the reactive substance before any gets to the compartment with the dangerous pathway in it, and if you think that diffusion between compartments is basically a linear function of concentration, then it's hard to arrange that. It may be that you can again have curves that look highly nonlinear, but you should still get linear behavior at the limit of low dosage. You should still get some diffusion across whatever barrier there is to the pathway that contains the system that makes the dangerous metabolite. Basically, Cornfield's model, which has this consideration in it, goes farther than I think the biology will take you, by assuming full equilibrium in the first compartment before any is allowed to get to the second compartment. I think that's what is wrong.

An Overview of Factors That Influence the Quantitative Risk Assessment of Carcinogens
(Speaker - Kenny Crump, Ph.D.)

Borg

The third speaker, Kenny Crump, is president of the Science Research Systems in Reston, Louisiana. He's been involved, as I think most of you know, with dose modeling and general statistics related to dose assessment for many years.

Crump

This session is on the uncertainty in quantitative risk assessment. I'd like to begin by listing five areas of uncertainty which I believe to be of major importance, most of which have been discussed already in this workshop. First is high-to-low-dose extrapolation; second is animal-to-human extrapolation (which Crouch discussed this morning). Additionally, there are other areas in which extrapolations are sometimes required. One of these is extrapolation from long-to-short exposures, or really from one exposure pattern to another, and this can be very important to understanding many of the human exposures which are short-term compared to the animal exposures. If something is an initiator it might have quite a different effect on the end result, depending upon the subject's age at the time the exposure takes place. You would think that very early exposures for an initiator would be more dangerous than exposures late in life. Frequently it is necessary to extrapolate from one route of exposure to another. We may want to know the risks to humans exposed to food whereas the only data that are available are through some other route. Another area which we haven't talked about very much, which is very uncertain, is the exposures to humans.

These are what I see as areas of major uncertainty, and the extrapolation from animals to humans embodies a number of things. The questions of whether to use data from benign tumors and which tumor site to use, I would classify as a subheading under animal-to-human extrapolation. There are some who tend to view risk assessment from animal data as totally different from risk assessment based on human data. When you work with human data, you are really doing something worthwhile, but work with animal data falls into a different category. I don't agree with that dichotomy. Not that I think you get very precise estimates from animal data. It's just that I view the estimates obtained from human data as also being imprecise in many cases. Of all of these sources of uncertainty, there is only one that you don't have with human data. Frequently, there is often a great deal of uncertainty concerning the measure of the dose in the human experimental group, whereas relatively speaking, the dose to the experimental animal is measured fairly accurately. I would place more confidence on risk estimates from good human data, but I think it's a question of degree more than anything else.

These are areas in which science does not give us unequivocal decisions about the choices that must be made. Yet when one does a risk assessment, one has to make some sort of decision about how to treat each of these areas of uncertainty. Because of this I feel it is very important that there be a unified approach to risk assessment. If, for example, you gave 10 separate groups the task of estimating carcinogenic risks from 10 different energy technologies and they came back with numbers such as the number of cancers you would expect from

each technology, I'm afraid that the results might not be useful. They would get different numbers, and unfortunately the difference in the range of magnitudes would probably reflect differences in their assessment methodology rather than in the true carcinogenic risk. One way to overcome that difficulty is to have some sort of unified approach. Even when the actual number is important as, for example, in regulation, I think a unified approach is important. There is a tremendous danger that a regulator will make a decision on how to regulate, totally divorced from the science, and then, after the fact, conjure up a risk assessment that will bolster the position he has already taken. I think that a unified approach to risk assessment would reduce this danger. I personally feel that the guidelines offer, perhaps, the best approach to arriving at a unified approach to risk assessment. There are potential dangers to guidelines. They may not allow you to take into account the latest scientific evidence. Some information, usually not available, may become available on a particular issue which the guidelines don't address, and then you might not be allowed to use this evidence. Perhaps the best way to overcome these problems is to have flexible guidelines which are reviewed periodically to determine if there is a need to update them.

Attempts have been made to quantify some approaches to the quantification of uncertainty; the most sophisticated one that I'm familiar with is the one of Crough and Wilson which Crouch talked about a few moments ago. I think that any attempt to quantify uncertainty should encompass all of these different areas of uncertainty. The most difficult one (perhaps they're all difficult) to come to grips with is the high-to-low-dose extrapolation. I would concur in what was said earlier about procedures for quantifying uncertainty in that we shouldn't ignore a major source of uncertainty just because it doesn't fit into our framework for evaluating uncertainty. A discussion of the carcinogenic mechanisms and some informal judgment on whether the mechanisms suggest linearity vs some threshold approach coupled with a range of risks - an integrated discussion - might be as useful as some formal procedure for incorporating uncertainty.

Yesterday, John Van Ryzin presented different models and showed clearly how, in certain situations, different models predict widely divergent results. I would like to add to that in the following sense. Not only do different mathematical formulations predict different results, but just take a single mathematical formulation which is fairly flexible. By that I mean any of the ones he presented except the one-hit model. They all fit all of the data sets resonably well. If you look at confidence limits based upon any of those flexible models, you would typically get a range of risks as great as, or possibly even greater than, the range John illustrated using the different models. So you get a wide variation in risk simply by using a single model and looking at the range of risks which are consistent with the data from that single model.

There has been considerable discussion about the linearity at low doses and evidence for linearity. Hooper and Fischer both presented the argument that low-dose effects are additive to background effects. Hattis just extended that to pharmacokinetic considerations and DNA repair. Van Ryzin gave a mathematical formula for linearity at low dose when you have an additive background. I would like to expand just a bit on what Van Ryzin said. If you recall, he mentioned that if you don't have complete independence or if you have some additivity, then unless you have a threshold, you have a low-dose linearity. This observation leads to the following conclusion. We've discussed the strength of the evidence for low-dose linearity. I can also conceive a situation in which a threshold might be the true state of nature. However, it seems to me the argument presented by Van Ryzin suggests that the intermediate models are far less plausi-

ble. That is, the multihit and multistage models show nonlinearity and nonthreshold and appear less plausible than either linearity or threshold. Unfortunately, I don't think that helps us very much in developing a cancer policy.

Another source of evidence for linearity, which hasn't been mentioned, is human data. There are some human data on dose response, and those I am most familiar with are on asbestos, arsenic, radiation, and cigarette smoke. None of these, as I recall, are radically inconsistent with just a pure straight-line-type response for the relative risk. The smoking data show something of an upward curvature, but are not dramatically inconsistent with a straight line. However, I would not give too much weight to this. There is always uncertainty as to the human dose, and I believe the effect is often to mask out any nonlinearity which might truly be present. Typically with human data, you have separated individuals into various dose categories, and you plot their relative risks. We have dose down at the bottom and relative risk on the vertical axis. Suppose the true response was threshold. What would happen to this true response if you took into account misclassification of employees as far as their dose is concerned? Well, some people belonging in one category would have been classified in another category and vice versa. Those that were misclassified in one category would tend to reduce this response artificially. Those that were misclassified in another category would tend to increase the expected response. Those that were misclassified in a third category would have no effect. So the net effect, it seems to me, would be to distort any threshold-like appearance and make things appear linear, so the linearity of the data could be due to these artifacts.

The EPA CAG uses a multistage model, takes the upper confidence limit, and calls that a plausible upper bound for risk. I'd like to make a case for that being more than just a policy decision. We've heard a number of arguments that linearity seems quite plausible in a number of situations. I think we can also argue that anything that gives a considerably higher risk than linear is fairly implausible. So I concur with CAG's approach of calling something based on linearity some sort of (but not well defined) plausible upper bound for what the risk might be. I view that as having some scientific justification, and more than just a policy decision. Now if a regulator decides to regulate at that upper limit of risk, then that is a policy decision. But expressing the uncertainty that way (as an upper limit, not necessarily what we might expect the true risk to be) seems to me to have some scientific merit. The true risk could be less than this, even considerably less. I think that Dr. Hattis addressed this when he showed the expected curvature upward or downward when you graph different models. I thought his presentation was quite instructive. Even if the arguments for low-dose linearity are correct, taking the upper limit based solely on the statistical evaluation of the data could still seriously overestimate risk. Yesterday we saw this in a graph of risk vs dose; if you have an additive background, you move out to where the curve shape is linear. However, if you have only a small component of additivity, simply drawing a straight line from the high-dose data could still seriously overestimate the risk at low doses. Even if the arguments for low-dose linearity are valid, that doesn't necessarily quantify how much linearity we would expect at low doses from the high-dose data.

I would like to conclude with just a comment about estimating risks from complex mixtures. From our experience with estimating risks from single chemicals and their uncertainty, I don't expect any precise estimates of risk to come from this endeavor. Typically, it will not be possible to directly test the mix-

ture in animals, not even pairs of chemicals for the most part. We will likely be forced to use an approach based only upon the data that we have from exposing animals to individual chemicals. I imagine we will eventually wind up with something very crude. I would like to suggest one such crude procedure and give at least some justification for it. That is simply adding the risks. The most famous example of a multiplicative risk is the risk from cigarette smoking and asbestos which multiplies a relative risk. You can get that from a model by assuming that the relative risk (RR) is some background risk (γ) times a multiplicative factor, $1 + \alpha d$, where d is the dose of asbestos, times another multiplicative factor, $1 + \beta x$, where x is the dose of cigarette smoking.

$$\text{Relative Risk} = RR = \gamma\ (1 + \alpha d)(1 + \beta x)\ .$$

So for each component - asbestos exposure and cigarette exposure - the risk is linear, which is pretty well what is observed. But when you put them together, the RR equals the product of the individual risks. This model expresses all of those observations. However, at low dose, when d and x are both small, the interaction term that involves the product dx will be negligibly small compared to the other terms,

$$RR = \gamma\ (1 + \alpha d + \beta\chi + \alpha\beta d\chi);$$

and if you neglect that term, then you have simple additivity. Therefore, even in the case of multiplicative response you can at least make an argument that at low doses the response might be approximately linear which would be one justification for simply adding the risk.

Discussion

Borg

We now have an opportunity for a general discussion in this area. Dr. Crouch?

Crouch

Ken Crump has just listed many uncertain areas in making a risk assessment for carcinogens. I think it has to be realized that for a risk assessment of almost anything you can write a similar list; even for very simple risk estimates it is necessary to make up a set of assumptions very similar to those listed on the blackboard. You can get differences of orders of magnitude in even very simple risk assessments just by changing your assumptions plausibly a little bit. The obvious examples are where you have to extrapolate in calendar time, or in geographical areas, or from one technology to application of that technology in another, or things like that. I think that one has to realize that any risk assessment is going to contain a similar set of uncertainties that is not unique to that carcinogen case.

Bender

I'd like to make some comments again based on experience with ionizing radiation hazard estimation, which is related to all three talks this morning. With respect to what Dr. Hattis said, the question often comes up of whether the human population is homogeneous with respect to sensitivity. This comes up with respect to ionizing radiation, partly theoretically, and partly because we already know of at least one rare genetic disease which confers a very high degree of sensitivity to ionizing radiation on the affected people, and that disease is ataxia telangiectasia. When you consider the arithmetic involved, and I think this must be true for the chemical case too, you find that the subgroups have to be fairly large and/or the degree of sensitivity quite a lot greater than the average in the population, and this simply doesn't seem to be true. That is, the cases we know of great sensitivity (and they're probably the greatest ones there are) are no more than ten times, probably more like 3 to 5 times, as sensitive, and their frequency in the population is very, very low - one in ten thousand, or one in one hundred thousand. So it seems to me, and I think it seems to other people who have considered this question for ionizing radiation, that such a distortion of the curve is going to be pretty trivial. Although it's a problem for regulators to decide on which level of sensitivity to regulate exposures, I don't think it distorts the curve shape.

One of the questions we've heard discussed this morning, and yesterday as well, is that of linearity at low dose. While I think this is probably true, it's also something which even if we thought there might be some thresholds, or something of this sort - I think we would have to assume it for practical reasons. The difficulty is what to do with the data we have, which very often are if not probably nonlinear, at least are plausibly nonlinear. One of the strategies for handling the problem of nonlinear data, which Dr. Albert referred to with reference to EPA's policy yesterday, is the practice of simply taking the lowest dose point for which there is a statistically significant increase and doing a linear extrapolation from that. I think that is in fact, as somebody said earlier, a sort of head-in-the-sand approach, and likely to lead

to errors of several sorts. In the first place, it throws away all the high-dose data. I think we can't ignore the shape of the curve. We've got to fit something, because otherwise we're fitting only that lowest point. The power of such extrapolation has to be low. The uncertainty is great; much greater than if we used all of the data set. I would suggest that a plausible thing to do, since it makes some biological sense and you can't rule it out in any case, is to apply the strategy which we have followed sometimes with ionizing radiation, to fit a quadratic expression to the data; that is to allow a dose square term. It may be very close to zero, but using the data to fit it, you get and use what is often called an alpha term, that is, the linear coefficient. It may be in error, but I think it's less likely to be in error than some of the other procedures. Another risk in taking the lowest dose point is that inevitably you tend to overestimate risk that way, because the lowest statistically significant point is the one that is, just on the basis of sampling error, likely to be higher than the true mean for that dose. One other final comment concerns the question of the effect of lumping dose categories. This is very often done with human data. The simple thing is to say we'll take 10 to 30 rad or mg/kg, whatever the dose is, but lump them together. This, of course, can lead to errors, in both directions; that is, you can, depending on how you lump the doses, take a straight curve and bend it either way, or take a bent curve and straighten it out. I think that most people are now coming to the view that the way to handle this is to make the best dose estimate you can for each individual and then do a grand regression of all the data on one model. At least this avoids the problem that you can fit any model you want to with much of the human data, provided you just stratify it right.

Borg

All right, Dr. Crump, you make a statement and I'll put myself next in line.

Crump

I want to respond to some of the comments just heard. The procedure that Roy Albert described yesterday is an old procedure, which is no longer used. I think you've outlined all the difficulties with it, and that's why it was dropped. The procedure now used is fairly similar to the one that you described. Higher-order terms are allowed, not just the quadratic term, but even higher-order terms. The estimate of the linear term is not taken, because that is often zero. What is taken is an upper confidence limit on the maximum value that that linear term could be. It is a procedure that does fit a model to all the data and is similar to what you described.

Borg

I agree in great depth with what Dr. Bender said, but there is one important caveat which, I dare say, he would accept as well. If we view the question of linear extrapolation at low dose from, as the physicists might put it, the frame of reference of the target, which presumably is the genome or perhaps DNA itself, I then accept much of what has been said regarding the stochastic or target-theory-oriented nature of things that does imply no threshold at low dose. On the other hand if we look at it from what the physicists call a laboratory frame, the situation is apt to be very different, and that applies to radiation

as well. What Dr. Bender had to say, correct me if you think I've put it wrong, is applicable to penetrating ionizing radiation that distributes itself, on the macro scale, uniformly in the body, and the stochastic nature of things has to do with it's lumpy distribution on the micro scale, but we don't have to concern ourselves with that. But take the case of an internal emitter plutonium, which distributes itself, because of physiological consideration, very unevenly in the body. Certain organs are affected by plutonium, and others essentially see, at least for a period of time, no plutonium. You really have, in terms of the distribution of that emitter with its short-range important emissions, a threshold in that it doesn't get to certain organs. So, in the laboratory frame, distribution counts and I contend with regard to Dr. Hattis's description of mechanism, there are some comparable kinds of things possible at the chemical level. Take, for example, the chemically very reactive compounds such as nitrosoamines; they don't need enzymes to react - they react spontaneously with many nucleophils. They react with olefins and form conjugates quickly and readily. For example, in a stomach that is reasonably full of ascorbic acid or olefins, the nitrosamines that we ingest may be completely scavanged (one can make other cases like that as well). Something associated with particles that get to the lung don't get anywhere else. The serial nature of some of the compartments is such, as in the case of chemicals, that at least some organs never see in any meaningful way a stress from some potentially mutagenic compounds. I don't think that's a trivial point. Having thrown it out, I see that Dr. Hattis wishes to respond.

Hattis

I would agree with everything you say if you substituted for never, very little. I think that's an important distinction. You surely don't mean that organs that don't get very much plutonium don't even see a single molecule. Probably they do, or at least there is some likelihood that they do, but nonetheless it's certainly true that the dose-response slope at low doses can be very very much lower than any dose-response curve you observe at high doses, if you do have highly reactive things, if they are very fast and efficient reactions, and if there is plenty of reactive agent. But I think that's a subject for experiment and modeling that you can use to amplify your direct ability to observe things and I think you can make some reasonable quantitative statements based on such models. Certainly in the case of plutonium you'd be silly not to worry much more about the organs where the plutonium actually sits. I have some other comments on things that Dr. Bender said. First, regarding the question of the dispersion of sensitivity in a population, I have a table that shows how much distortion of the dose-response curve you get for how much dispersion (Table 1). I despair of not being able to present those results simply, but if anybody wants a presentation of the results I'd be happy to give him a copy of the slide. (It is actually in my longer writeup, in case you want to examine it at length.) In fact, you do have a very substantial breadth of distribution of sensitivity in order to get large departures from linearity on the upside. On the other hand, you can postulate such things, it's not impossible, and I certainly would support this. Chemicals may be somewhat more complicated and more susceptible to this kind of problem than radiation because you have less of a problem with thte metabolic transformation, for example, in the case of radiation than in the case of chemicals, and that may be a source of some variance in the population.

Table 1

Relationship Between Median Risk and Overall Populations Risks for Populations with Log-Normal Distributions of Susceptibility Having Various Standard Deviations

"kd" for Median Person**	Median Risk***	Overall Population Risk*			
	LOG S.D.=0	LOG S.D.=0	LOG S.D.=1.0	LOG S.D.=1.5	LOG S.D.=2.0
$1x10^{-11}$	$1x10^{-11}$				$3.35x10^{-7}$
$1x10^{-10}$	$1x10^{-10}$				$2.75x10^{-6}$
$1x10^{-9}$	$1x10^{-9}$				$2.01x10^{-5}$
$1x10^{-8}$	$1x10^{-8}$			$3.77x10^{-6}$	$1.27x10^{-4}$
$1x10^{-7}$	$1x10^{-7}$			$3.46x10^{-5}$	$6.84x10^{-4}$
$1x10^{-6}$	$1x10^{-6}$		$1.75x10^{-5}$	$2.84x10^{-4}$	$3.09x10^{-3}$
$1x10^{-5}$	$1x10^{-5}$	$1.94x10^{-5}$	$1.72x10^{-4}$	$1.95x10^{-3}$	0.00116
$1x10^{-4}$	$1x10^{-4}$		$1.40x10^{-3}$	0.0106	0.0361
$1x10^{-3}$	$1x10^{-3}$	$1.93x10^{-3}$	0.0113	0.0441	0.0931
$2x10^{-3}$	$2x10^{-3}$		0.0196		0.119
$5x10^{-3}$	4.99x10-3		0.0399	0.100	0.161
0.01	$9.95x10^{-3}$	0.0188	0.0656	0.137	0.199
0.02	0.0198	0.0364	0.103	0.182	0.242
0.04	0.0392	0.0688	0.156	0.235	0.289
0.08	0.0769	0.125	0.224	0.296	0.341
0.16	0.148	0.216	0.310	0.364	0.359
0.32	0.274	0.345	0.408	0.436	0.452
0.64	0.473	0.505	0.512	0.511	0.510

* The overall population risk is the fraction of the total population that is expected to get at least one tumor.

** Where $P_{tumor} = 1-e^{-kd}$, "kd" represents the average number of tumors expected per person in a population of people with absolutely uniform sensitivity. At very low values of kd the ratios of the overall population risk to median risk become constant at approximately 2, 18, 380, and 34,000 for Log S.D. of 0.5, 1.0, 1.5, and 2.0, respectively.

*** Probability that a person of median sensitivity will get at least one tumor.

Jones

I think this whole session and the ensuing dialogue illustrate our concerns about thresholds and linearity. The arguments against thresholds, the arguments against practical thresholds, the arguments for linearity, all seem to revolve around a molecular-type argument. You're going back to very basic, perhaps rare, damage events, the events that change the phenotype of a cell. Now, it's my impression that when one finds a tumor in a mouse (maybe you can find it earlier by pathological investigation) it weighs about one-tenth of a gram. I think that's around 2^{20} cells. In man, a one-gram tumor might be diagnosed. I think that's about 2^{30} cells. It seems that it's very unclear what happens between that single cell of abnormal phenotype and the time we have 2^{20}, 2^{30}, or 2^{40} cells in a mass. I find it less than convincing that neoplasia is a linear process and that cancer is indeed linear at low dose.

Hull

As I was listening to the discussion this morning, I started to wonder about the role immune defenses may play. While I'm not arguing for a threshold as such, from what I read in the literature, immune defenses may act as a dike, if you will, which you must somehow get above in order to have an expression of a cancer. If this theory holds, it seems plausible that the dike has more possibilities of being breached with age, which is why one sees an increased expression of cancer with age. Perhaps Troyce or somebody else wants to comment on this?

Baum

One problem with that kind of concept is that 20% of the population is already over the threshold, wherever it is, and therefore for practical purposes, you might as well forget about it.

Borg

What threshold is that?

Baum

Whatever threshold exists.

Borg

For anything? Or are you talking about for radiation?

Baum

No, in general, 20% of the population is being stimulated above its threshold, whatever that is, by whatever agents they are being exposed to; radiation, chemicals, life style, and so on.

Borg

You mean that 20% of the population is dying of cancer? Is that where the number comes from?

Baum

Right, and assuming things are additive, if they are additive, then we are already over the threshold, for those people at least.

Davis

It's really not 20% of the total population that is dying of cancer, it's 20% of all deaths. I think that's an important distinction.

I have a question related to this 2^{10} number of cells as a detectable cancer. So what's 2^{10} cells mean? In other words, my question is directed to the question of benign versus malignant tumors. If you get 2^{10} cells, is that initiation? Is initiation 2^1, 2^2, I mean, when is "a cancer" a cancer? Does this not suggest, at least, with respect to the policy issue of how you interpret benign tumors, that you ought to interupt any oncogenic process as a likely carcinogenic process, especially in light of the recent molecular biochemistry of the oncogene work?

Borg

I'd say that they are not the same thing. Part of the phenotypic expression of a cancer, as opposed to a benign neoplasm, is that in addition to uncontrolled growth, it shows either invasiveness or metastasis, or both. That doesn't always follow inevitably; in fact the general picture of cancer biology, as I understand it, is that the preneoplastic lesion is common, and regression is not uncommon either. Although it seems along the path or on a branching and parallel path, an inevitable consequence of having a benign tumor is not that you will have a malignant one.

Hattis

The effect of immune surveillance and similar-type mechanisms on the overall dose-response shape is difficult because there really aren't the same sort of good models of what you should expect, in that case vis-a-vis DNA repair. On the other hand I would be surprised if the case were really qualitatively different for the following reason. Basically, you are going to have cells wandering around the body, attempting to detect new antigens that would signify a transformation. We're pretty sure that some fraction of the induced cells seem to go undetected in the ordinary case. Now you can postulate that that fraction is getting through because there is an unusual burst of transformations occuring several places in the body, which decreased, for the moment, the effective searchers. I don't know how to sort that out from the possibility that in fact, the system is just imperfect. Maybe it catches 99.9% of all the developing lesions. But if it has a reasonably consistent fraction that it misses, and unless you really have huge bursts of transformation, you probably wouldn't expect to overload the system. That would be consistent with the age consideration that you mentioned. You could simply view that as the fraction of things that go undetected, increases in some orderly way with age.

Jones

I guess that one thing that keeps nagging at me is the cell culture work and the animal studies whereby you need so many abnormal cells in a focus before growth becomes autonomous. For most of the work that I've seen (where tumors have been transplanted into athymic mice) there's been a tremendously large number of cells that had to be injected - I consider a large number to be 10^5-10^7 cells. In most systems you can inject 10^2 and 10^3 cells and nothing happens. Conceptually, I have a lot of trouble with believing that the immune system or any other system goes in and wipes out these abnormal cell phenotypes. I think that some of the mouse skin painting experiments indicate that many of these lesions are there, perhaps permanently. They're present for a long time and you can delay promotion for up to a year or even longer.

If you start the promotion as much as a year later, a significant number of these abnormal cells can be potentiated into papillomas and into skin cancer.

Davis

What are the implications of the hybridoma experiment, on the other hand, where you take cells from a cancerous mouse and grow a completely non-cancerous animal. That's the other side of the coin.

Borg

I think we're getting into an interesting mechanistic discussion, which I'd like to join in, but I do wonder how to relate it to the charge that we got from our conference Chairman.

Davis

Let me put it in a policy context. It is the question of the policy implication of the benign versus the malignant tumor issue.

Wambach

It just means that carcinogenicity and mutagenicity are not identical. It means that one cannot have absolute confidence in in vitro bioassays that look at mutagenicity instead of carcinogenicity.

Borg

You did not say that, even though not identical, they are not related and don't share some properties, that mutagenicity doesn't tell you something that alerts you. You didn't say that.

Davis

And therefore what is the policy decision on that?

Wambach

No, I think that everybody agrees that there's a strong correlation, but they're not identical, they're not the same phenomena necessarily in all cases.

One of the things that Otto put on the board when we started out this session was the ACGIH scheme, and it had an upper limit. It had certain dose levels in which they would say, "We're not going to consider these occupational carcinogens any more because the dose levels producing cancer in these animals were so high that they are not relevant to workers." I was wondering if some of you might comment here, because I think this is very controversial - something I'm not entirely comfortable with--and I'd like to hear some comments.

Hooper

I didn't understand his slide that way. I thought he was trying to classify chemicals in terms of categories.

Wambach

That's correct, it did do that. But one of the things it had was an upper cutoff.

Hooper

If the question is, whether it is reasonable to make some use of potency data from animal experiments to identify chemicals as higher risks than others, then what he was doing seems reasonable. If the implication is that high doses administered to animals make the data invalid, that's a totally separate question which I don't think we have addressed here, but I think it is incorrect. A situation in which high-dose experiments in animals are reasonably based on the limitations of experimental design is a totally different question. Do you seriously want to get into the question of the relevance of high-dose experiments? I'm not sure I understand your concern. Could you elaborate?

Wambach

Does everybody have a copy of excerpts of the committee guidelines for classification of experimental animal carcinogens from the 1981 TLV book? Notice the example there for dioxane. Now this is not TCDD, of course. Their conclusion is that the workers would not be exposed to levels of this chemical that would be of any health concern. Am I right?

White

I think he is speaking of the section beginning on page 41. The exception "no substance is to be considered an occupational carcinogen of any practical significance which reacts by the respiratory route at or above 1000 mg/m^3 for the mouse..." and so forth. Is that the section?

Wambach

Correct. I'm not very comfortable with that, for a lot of reasons. That is great from an operational point of view if we can say that exposure levels are so nonpotent that we don't have to worry about it (its carcinogenicity). If we can come to that kind of conclusion for some chemicals, that's a tremendous benefit.

Moskowitz

Doesn't part of that question revolve around what the relative exposure levels are? If you've got exposure, of course, admittedly those levels are really high. But if you've got an occupational situation with an exposure level equal to or higher than that, then it really deserves consideration.

Hooper

Or one-tenth of that. For dioxin that is quite common. Yes, I agree with what you are saying. I thought you meant the slide that you showed for DOE's categories: Categories I or II are different from ACGIH levels.

I would agree with Paul - I would disagree with the statement that it is not an occupational carcinogen of any practical significance. It depends on the case. The hazard it could be associated with would be, in a sense, the ratio of the human exposure to the effect of the animal effective dose. Here they are saying that they are just going to take the animal effective dose as an absolute cutoff. That isn't really appropriate.

Borg

Someone else?

Rodricks

There is some merit to the proposed scheme but I think it's fairly crude. I consider the ACGIH's scheme crude as well in that it really doesn't get at the question of risk as we have been talking about it here for the last two days. As in the last discussion, or as Roy Albert and John Van Ryzin talked about it yesterday, that risk should really include more than a consideration of whether or not it's a carcinogen and how potent it is. It has to include exposure as well. We also need, I think, some reasonable definition of potency. I think the ACGIH definition is fairly crude also. The type that John Van Ryzin talked about, I should think, would be a far more useful way to assess potency. We have also had a lot of discussion on the question of thresholds. I think that's not a very useful discussion. It's a very interesting scientific discussion but I think for purposes of deciding whether or not population thresholds can or cannot be detected or how to detect them, I don't think its very helpful. I think in systems which admit to uncertainties (saying we don't know what the risk is) that we can place some perhaps plausible upper bound on it at low dose. Let's admit that the true risk down to 10^{-6} or lower might be in fact zero, but, in fact, it could also be higher; that's the scientific uncertainty. That's a practical threshold in my mind. That's the area of insignificance, I don't mean 10^{-6} by itself without better information, but that notion leads to what I call a practical threshold and that, I think, is the best science can do. We shouldn't be forced into defining some population threshold. I don't know how we would ever do that except in some probablistic terms. So I guess my main point is that any guideline that the Department considers ought to go to the full question of risk, and not reduce it to some sort of simplistic scheme that ACGIH put out. Admittedly, a lot more work must go into a comprehensive assessment, but I think it's also likely to be scientifically far more acceptable to do a comprehensive evaluation before making important decisions on controls.

Jones

I'd just like to add that many areas of carcinogenesis seem to suggest that one of the main effects of a carcinogen or a potentiator or whatever term you prefer to use, is to accelerate tumors forward in time. In many cases you know the latency of a tumor, a silent period, or whatever you want to call it, may be long enough that it's of no practical consequences in the life-span of humans or animals that are being studied. I think it's important not to break this down into a cancer- or no-cancer-type situation. We have to consider the time profile of the possible onset of cancers.

Bender

That's an old notion, of course, and I think it deserves some practical attention, but my own view, and I think that of some others, is that there is not in fact a threshold latent period, but rather some distribution of times to appearance of tumor after initial insult. I think what that means is that although the probability will fall off rapidly as the insulted person gets older, the risk of a premature death from a tumor never gets to be zero. I think that's one reason for not considering this kind of practical threshold.

Jones

You mean the death from any cause or disease of one particular histological disease like bone sarcoma?

Bender

I mean tumors in this case in general. All I really mean by that is that while it is true that the average remaining life-span of the seventy-year old is not very much, what we generally say is that an ionizing radiation latent period for solid tumors generally might be twenty years. I don't think it's true that all the tumors, induced by whatever the insult was, appear after twenty years and that the competing risk would simply eliminate them all. I think what is true is that there is some kind of distribution of time to diagnose tumor. It might be a normal distribution or something else. What that tells me is that there is probably only a very short period, if any, following the insult during which the risk of developing a tumor and dying from it, as opposed to some other cause, is zero. It may be very small for short times but I don't think it's zero.

White

Could it then be considered a consensus at this stage of the workshop that a logic process similar to the ACGIH format or Kim Hooper's process of grouping or categorizing chemicals as a carcinogen or a noncarcinogen is a crude but useful protocol? The practical or recommended approach might be to evaluate individual chemicals on the basis of the toxological data, fit that to some model system (and I've heard the linear model being suggested as a worse case), and the involvement of a practical threshold concept.

Borg

You're not getting a direct answer. Should we have a show of hands? No, I don't think we can vote on science either.

I'm going to end the discussion. One of the charges of the session chairman is to make a take-home lesson or some kind of summary statement (that I probably get wrong in this case) from each of the speakers and ask him to either clarify or otherwise alter. With regard to Dr. Crouch's work on extrapolating carcinogenesis information from one species to another, he reminded us of the great number of uncertainties that underlie such a procedure. The question then is: Are the assumptions underlying the practical application of his approach reasonable? I jotted down and tried to make these direct quotes into several statements to indicate how much he questioned that himself. He said at one point, "There is uncertainty involved in everything I've said so far."

Another thing he said is "It's usual to guess simple relationships". I emphasize the word guess. Nonetheless, I think he did give us some practical guidelines on how to proceed through this morass. He said, with regard to dose-response relationships, "that we try some different dose-response relationships. Its generally best," he said, "to try a worse case first and usually (my emphasis) that's a linear extrapolation." Is it then fair to say that a sensitivity analysis, if you will, is worthwhile to give a feeling for the range of uncertainty?

Crouch

I don't think that's quite what I was trying to say. I tend to favor the simplest model for the situation which is, I think, the linear one-hit model here. I suggest that anyone wishing to advocate another model should try something similar to this before going ahead too far. That's the point I was trying to make there.

Borg

All right now, I'll take on Dr. Hattis, and again I may get things a bit twisted so be ready to straighten me out. I think you told us, at least in part, that mechanistic insight suggests that linear extrapolation from the high-dose regime to low-dose expectations may be wrong and is not necessarily even conservative when enzymatic and other metabolic considerations are taken into account. Nonetheless, in a practical sense and with much evidence to support it, the stochastic- or target-theory-oriented approach toward carcinogenicity at low doses that implies no threshold, does seem acceptable as a limit. Now I made some earlier comments on this as did others, and I shall not repeat them now, except to remind you that I think the question of thresholds with regard to promotion is much less clear. I shall not say more now. I will throw at you my understanding of one suggestion you made at the end in a challenging way. You said it could be useful in experiments that are not "big science" to look at DNA adducts their repair elimination limitation. But though it is not the field that I'm most expert in, it is my reading that the correlation of cancer in animals with DNA adducts is really not very good at present. Now would you like to respond to that?

Hattis

Yes, there is a lot we don't know about, for example, which adducts are really the important ones. Some people have suggested the more numerous adducts of not guanadine in some cases are much less important than the less numerous ones at oxygen positions. On the other hand, I think that one can do experiments on those and get a reasonable feel for how doses change things and how different dosage schedules change things. I think that it's likely to provide proxies for it if done correctly. It's likely to provide proxies for effective dose-response relationships in the long run. Every experiment is not necessarily going to lead to something that's directly related to tumor yield if you don't control for everything else in the world. I think there's a lot of hope for that. I think that you can do experiments with the pharmacodynamics. Instead of using the dose you feed the animal, you can use some estimate of the dose in time, or concentration, that reaches the target. Finally, I think some of these considerations have practical considerations for standard setting. For example if you believe, as in the case of formaldehyde, that there is a cooperation between the irritation cell-killing effects and the primary genetic action, then it becomes important that you set ceiling-type standards, in order to avoid that irritation stimulus which might, in theory, be synergistic with the genetic action, and you should probably also avoid other kinds of irritating stimuli that might stimulate the same tissue and also interact in that way.

Borg

Do you want to take on any of the other oversimplified generalizations or take home lessons I attributed to you?

Hattis

No, I thought they weren't exactly what I said but they didn't arouse my profound indignation either.

Borg

I would like to induce Dr. Van Ryzin to make, for the record and for the rest of you to hear, some comments that he made to several of us, I think on two occasions yesterday, regarding this target frame of reference that you and I have both discussed. Yesterday, you will remember, he pointed out that looking at the various models, the linear hypothesis seems to diverge in this extrapolation from the others (several of them pretty much operated as one set). However, when he took into account some of the things you brought into the discussion today, as have been brought forward at an earlier time by Gehring, he found an interesting result. May I ask you to speak about it?

Van Ryzin

I was very much interested in this question of linearity. I think that the question of linearity at the target organ or the site of the reaction is much more plausible and that a lot of the nonlinearities we see are due to saturation from some pharmacokinetic operation or something like that. This bothered me very much with the vinyl chloride data. I went back and did the corrections with the vinyl chloride data as suggested by Gehring in a separate me-

tabolism experiment. I then went back and applied them to the original data, and this wiped out the model differences tremendously and you do get a linear effect at the target site. But of course often we don't have that. I think your comments about possible dose-response shapes, a dose-response curve, and the implications of pharmacokinetics and how it acts at the target site were very good, and I really think this should receive more emphasis. Simply looking at response data for an overall animal bioassay will never resolve this question. I think that looking at how it works at the target site may help with some chemicals.

Hattis

It is important to make our models represent as closely as possible the biological system and we have to be creative. This, to some extent, makes it unrealistic to expect an absolutely uniform procedure to apply to all chemicals. For example, the analysis for formaldehyde with its considerations is not identical to the analysis for vinyl chloride, because different things appear to be influencing the shapes of the dose-response curves in those two different cases. Nonetheless, I think that the guidelines should be flexible enough that you do your best job pharmacodynamically and then you take the residual uncertainty and try to model that with the fundamental carcinogenic process. But your results may be misleading if you load all the burden of the nonlinearity onto the fundamental process when, in fact, you can, by introducing exogenous functions and exogenous parameters that you derive from other experiments, perhaps make a better guess.

Borg

I agree totally so I'll cut that discussion off at that point, and to be even handed, I'll give myself a chance to get Dr. Crump's summary a little bit wrong also. I think you said things like this to us, that "it's important that a unified approach to risk assessment be made." By this I assume that you mean an approach that takes into account the best scientific knowledge and that "rigid application of formalisms can be misleading." For example, different mathematical formulas, as referred to in Dr. Van Ryzin's work, can yield widely divergent results in extrapolating from high dose to low dose, especially when confidence limits are taken into account. Nonetheless, your position was that the question of linearity is not definitely answerable, although in the low-dose region you said there is much evidence to support it, including some data from human exposures. Scientifically it does seem to be a plausible upper limit to uncertainties at low doses based on extrapolation, at least in most cases. Finally, your operating guidance was that guidelines can be helpful in this context if we can't use rigid formalities, if they are endowed with reasonable flexibility, and if they are reviewed regularly in the light of current scientific knowledge. Do you want comment on that?

Crump

I would consider that a fair representation of what I said. I am aware of the tension between the guideline idea and the need to incorporate the latest scientific evidence and all the information which is particular to that chemical. I think guidelines should offer detailed guidance, while at the same time giving the risk assessor the opportunity to do something different with a clear

explanation of what he did and why. So I think guidelines should be fairly detailed in order to be useful, yet they need to allow for flexibility. It takes very careful thought to prepare such guidelines.

Borg

Thank you very much.

Prepared Comments

Practical Carcinogen Guidelines Based Upon Hazard Potential

M.G. Boundy, O. White, Jr., and D. Lillian (DOE)

ABSTRACT

Current governmental cancer policies and guidelines have a major drawback in their inability to distinguish and recognize the different levels of potency of the numerous carcinogens. The OSHA "generic" Cancer policy does allow for two separate listings of chemical carcinogens, but within each category all substances are regulated as though they presented the same degree of hazard. Factors such as comparative potency, physical properties, as well as situational factors relating to operational procedures and facilities are not adequately incorporated in existing criteria.

A carcinogen guideline is presented consisting of three safety programs based upon the nature of exposure to the specific carcinogenic compounds. A Class I Program (low risk) requires laboratory safety practices and the use of personal protective clothing. A Class II Program (moderate risk) additionally requires work practices and engineering controls in the form of containment systems such as laboratory hoods and glove boxes. A Class III Program (high risk) requires a maximum containment system with sophisticated engineering controls and more stringent work practices.

CARCINOGEN GUIDELINES

This guideline consists of three carcinogen safety programs (Classes I, II, and III) based upon the Carcinogen Hazard Index of the material.

Class I Program is designed for use with low-level carcinogens and recommends the adherence to general safety practices and the use of personal protective equipment (e.g., gloves).

Class II Program recommends additional work practice control and engineering controls in the form of containment systems such as glove-boxes and laboratory hoods.

Class III Program represents a maximum containment system with sophisticated engineering controls and recommended work practice controls for use with extremely potent carcinogens.

PURPOSE

To develop a practical gude for the use, handling, and storage of workplace chemicals to minimize any potential carcinogenic hazards.

CRITERIA

The following criteria will be considered in establishing a Carcinogen Hazard Index:

A. Carcinogenicity

B. Physical-chemical properties

C. Use by workers

D. Engineering controls

E. Environmental monitoring

Each factor will be assigned a numerical score indicating its likely contribution to the overall hazard. The criteria are presented in what we believe is the descending order of importance. Computer analysis will assist in the assignment of appropriate weighted values and the testing of this hypothesis on known and suspected occupational carcinogens. The summation of the scores will yield a carcinogen Hazard Index which will determine the appropriate Carcinogen Safety Program.

FACTORS IN HAZARD ASSESSMENT

A. Carcinogenicity

A chemical will be classified into three categories, depending on its known human carcinogenicity and its relative potency in animal systems. The categories are as follows:

Category 1. All substances that produce neoplasms in at least one animal species from doses administered in the following manner:

By respiratory route: (1) Elicity cancer from doses > 10 mg/m^3, 6-7 hrs/day for 12 months' exposure and 12 months' observations; (2) from intratracheal dose > 10 mg of material per 100 ml of animal minute respiratory volume.
Or by dermal route: Elicit cancer by skin-painting, twice weekly at > 10 mg/kg body weight per application for at least 75 weeks.
Or by oral route: Elicit cancer by daily intake via gastrointestinal tract $\geq$ 50 mg/kg body weight per day for the lifetime of the animal.

Category 2. All substances that are known to produce neoplasms only in animal species at exposure levels below those listed in Category 1.

Category 3. All OSHA-regulated carcinogens and all industrial substances shown to be carcinogenic in man.

Assumptions

1. There exists a qualitative and semiquantitative relationship between carcinogenesis in man and experimental animals.

2. Known human carcinogens pose a greater threat to workers than animal carcinogens with unknown human data.

B. Physical-Chemical Properties

The physical state of each material will be defined, i.e., gas, solid, or liquid. Emphasis shall be placed on such factors as particle size, volatility, temperature, and oil-water partition coefficient.

Assumption

The biological burden imposed by a chemical is dependent on its ability to reach the appropriate target site. Therefore, deep lung penetration and the ability of a material to cross biological membranes are critical to the ultimate carcinogenic activity.

C. Use

Any hazard is ultimately dependent on use. Thus, the amount of material and the way it is used must be considered. The three major subdivisions are storage, simple use, and complex use. Within each of these subdivisions, the amount of material and the potential for fugitive emission will be stressed.

D. Engineering Controls

Depending on the carcinogen category, the significance of factors such as ventilation, work practices, personal protective equipment, and containment will be considered.

E. Environmental Monitoring

The existence of a monitoring program to measure the carcinogenic material in the workplace is deemed an asset to minimize exposures.

CARCINOGEN HAZARD INDEX

The Carcinogen Hazard Index (CHI) of a material is defined as the summation of the numerical scores of each of the contributing five factors.

$$CHI = f(\text{Carcinogenicity}) + f(\text{Physical Chemistry}) + f(\text{Use}) + f(\text{Engineering Controls}) + f(\text{Environmental Monitoring}).$$

The actual assignment of numerical values to each factor (f) will be drafted and reviewed by a multidisciplinary committee of DOE consultants. The resulting index will be used to select the appropriate Carcinogen Guideline for the material in use.

An Example of the Application of a Linear at Low-Dose One-Hit Model for Experimental Data

Edmund Crouch

For pure chemicals, if one performs the following:

* Parametrize experimental data by fitting a dose-response curve:

$$P = 1 - (1 - \alpha) \exp\left[- \beta d/(1 - \alpha)\right] ,$$

where

p.....Lifetime probability of tumor

d.....Lifetime average dose rate - suitably defined

α :parameter - background dose rate

β :parameter - "potency" of chemical tested in species/strain/sex tested, for tumor site/type under analysis

* Estimate α,β from experiments - this requires explicit assumptions about sources of uncertainty

* Select only those results β which are statistically significant

* For each chemical/species/strain/sex select the largest value of

β obtained (amongst different tumor sites/types)

Then it is observed that:

* AVERAGED over all chemicals tested:

$$\log(\beta r) = K_{rm} + \log(\beta_m) \quad r{:}\text{rat} \quad m{:}\text{mouse} ,$$

where K_{rm} (of order $\emptyset$ but significantly different from it) differs for different rat and mouse strains.

* For INDIVIDUAL CHEMICALS we find:

$$\log(\beta_r) = k_{rm} + \log(\beta_m) \quad r{:}\text{rat} \quad m{:}\text{mouse} ,$$

where

$k_{rm} \sim N(K_{rm},\sigma_{rm})$ and $\sigma_{rm} \sim \log(4.5)$ for both comparisons so far possible.

(Note: the randomness is between chemicals.)

* There are no obvious exceptions to this. All apparent exceptions are within the uncertainty noted.

* This suggests that for pure chemicals we can write:

$$\log(\beta_h) = k_{ha} + \log(\beta_a) \quad h{:}\text{human} \quad a{:}\text{animal},$$

with

$k_{ha} \sim N(K_{ha}, \sigma_{ha})$, where $K_{ha} \sim 0$ if a = mouse or rat, by comparison of epidemiological observations with animal experiments, and $\sigma_{ha} \gtrsim \sigma_{rm} \gtrsim \log(4.5)$.

* A procedure for estimating risks to humans based on the above has been published (Risk Analysis, 1 (1981) 47-50). An animal experiment gives a probability distribution for the animal potency β_a, and hence we can get a distribution for the human potency by convolving this with the distribution for k_{ha}. Together with a distribution for human dose, this allows an assessment of the probability distribution for human risk.

* There are sources of uncertainty which are not explicitly taken into account in the above analysis, but which show up as part of σ in interspecies comparisons.

* Null results of animal experiments provide useful information, for they provide upper bounds on the possible value of β. The use of such upper bounds in regulation will lead to strong incentives for the best possible testing.

* All the above assumes lifetime testing by ingestion of the chemical tested. Further research is needed on other routes of exposure to see what relation, if any, there is to the ingestion route.

* The most sensitive experiments (mice, 10% of diet as maximum dose, 50 animals per group) might just allow measurements of potencies of $\sim 5 \times 10^{-6}$ kg-day/mg applied to humans, and demanding 1×10^{-6} lifetime risk then would require human intake of < 15 mg/day. This leads to the question: Is the regulation to be applied uniformly? If so then nothing ingested at a rate > 15 mg/day can be deemed "safe," on the basis of current testing.

* Doses are measured by reference to body weight. For the analyses so far, changing to a measure of dose referred to surface area simply changes some parameter values, but not the final results. Of more importance is the age weighting used for dose rates, and the methods used to extrapolate results of a partial lifetime study to a full lifetime.

Mechanisms of Carcinogenesis: Implications for Expectations About Dose-Response Relationships

Dale Hattis

The subject of dose-response relationships for carcinogens has been an area of great controversy in recent years. I believe that much of the controversy resulted from the clash of expectations between experts trained to examine incomplete available data with the perspectives of different disciplines who arrived at radically different expectations of what should occur in low regions of dosage where direct experiments were not feasible. This has been especially acute between people trained in traditional toxicology and people who received their training in newer molecular biological disciplines. It will be helpful for later discussion to clarify this particular disciplinary conflict at the outset.

A major theme, if not the central organizing principle of traditional physiology and toxicology, is the concept of the "homeostatic system." Biological processes are seen as part of a complex interaction web, exquisitely designed so that modest changes in any parameter will automatically give risk to compensating processes to restore optimal functioning. (For example, too much heat input automatically induces sweating so that temperature is kept within a normal range.) In this view, so long as a toxic material or any other disturbing stimulus does not push one or more parameters beyond a specified limit ("threshold"), adaptive processes will repair any damage which may have been temporarily produced and completely restore the system to its normal functional state. This paradigm has enjoyed great success in guiding the design and interpretation of a wide range of experimental findings on acute responses to toxic chemicals, heat, cold, and other agents where the mechanism of damage does, in fact, consist of grossly overwhelming a particular set of bodily defenses.

Another type of damage mechanism dominates thinking in molecular biology and genetics. At the molecular level, and some fundamental life processes are basically fragile--in particular, the integrity of the mechanism of inheritance depends on detailed accuracy in copying the massive amount of information coded within the DNA of each cell. An unrepaired error ("mutation") in copying will usually be passed on to all of the single DNA base, and massive adverse consequences may result if important genetic information has been altered in a way that affects its function.

For the molecular biologist it is intuitively obvious that even a single molecule of a substance which reacts with DNA has some chance of producing a biologically significant result if it happens to interact with just the right DNA site. For the traditional toxicologist, basic intuition leads to the opposite expectation; for any substance there is some level of exposure which will have no significant effect on a given biological system. Clearly, application of either intuition to a particular biological response is appropriate only to the degree that the causal mechanism for the response resembles the paradigmatic damage-producing process which is the basis for the intuition.

Up until recently there were three lines of evidence supporting the molecular biologists' somatic mutation theory of carcinogenesis:

- First, it appears that cancer originates within single cells. In women who are heterozygous for G6PD (a locus on the X chromosome), it has been found that tumors generally exhibit activation of the same X chromosome in all cells (Fialkow, P.J., 1977; Knudson, A.G., 1977, 1973).

If events within more than one cell line were usually involved in tumor production, it would be expected that different cells of individual tumors would be a mixture of cells exhibiting activation of both X chromosomes, like body cells in general.

- Second, some well-characterized deficiencies in DNA repair appear to lead to greatly increased cancer risk (Cleaver, J.E. and Bootsma, D., 1975; Vogel, F. and Motulsky, A.G., 1979).

- Third, there is a general association between mutagenic and carcinogenic activity in many chemicals (Vogel, F. and Motulsky, A.G., 1979; McCann, J. et al., 1975).

Very recently, a fourth and apparently conclusive line of evidence has been provided by gene transfer experiments (Marx, J.L., 1982; Cooper, G.M., 1982). Carcinogenic transformation has been produced by incorporating specific small lengths of purified DNA from any different lines of cancer cells into a standard strain of nonmalignant tissue culture cells. A low frequency of transformation evidently can also be accomplished by transferring DNA from normal cells, provided that the normal DNA has been broken up into small pieces by sonication. This latter result suggests that one kind of DNA change capable of inducing transformation is a breakage-and-rejoining event, in which a specific gene may be separated from its normal control region. (Recent experiments with cellular mos and ras genes (cellular homologs of two retrovirus transforming genes) reinforce this conclusion (Cooper, G.M., 1982). Removal of normal 5' flanking sequences for these genes leads to an increase in their transforming ability.)

Evidence available today, I think, clearly places most carcinogenesis within the molecular biological category. Given this, what can be said about carcinogenesis dose-response curves?

The basic expectation from ordinary bimolecular reaction kinetics is that the rate of production of DNA lesions by a reactive chemical intermediate should be a direct linear function of the concentration of the reactive material at the site of reaction. There are, however, a number of mechanisms by which the linearity of ultimate cancer dose response that one would expect from this fundamental process may be modified. These mechanisms include:

- dose-dependent changes in metabolic handling of the carcinogen (or precarcinogen)

- the properties of DNA repair systems

- contributions to cell division (and hence susceptibility to carcinogenic transformation) by overt toxic responses to carcinogens at high dose levels

- differences between individuals in primary sensitivity to carcinogenic action from numerous sources.

- the number of sequential mutations within a cell line required to produce carcinogenic transformation.

Space does not permit a full exposition of the influence that each of these mechanisms is likely to have on low-dose cancer incidence. In brief, I

can say that contrary to popular belief, the first two mechanisms can cause the rate of tumor production at low doses to be either higher or lower than that which would be expected by direct linear interpolation from high doses. The third mechanism will generally lead to a greater dose-response slope at high doses than at low doses where toxic responses do, in fact, accompany tumor production in experimental systems. On the other hand, under the fourth mechanism, wherever there is a wide diversity among individuals in susceptibility to carcinogenesis, one should expect that linear interpolation from high-dose data will underpredict the actual cancer risk to populations exposed to low doses. The fifth mechanism, like the third, will generally lead to a greater dose-response slope at high doses than at low doses, but where linear "one-hit" processes are in direct competition with those of higher order, the "one-hit" mechanisms will tend to make up an increasing percentage of total transformation at low doses. The take-home lessons for policy from this are:

- There should be no general expectation that dose-response relationships for genetically acting carcinogens will exhibit true "thresholds."

- Under some not-unlikely circumstances, linear projections from high-dose data may understate, rather than overstate, low-dose cancer risk. It may often be more appropriate to use linear projections as "best estimates" of low-dose risk, rather than "conservative" upper bonds.

I suspect that the field of carcinogenesis risk assessment has reached a turning point. It has been appreciated for some time that the inherent statistical limitations of carcinogenesis dose-response experiments in small groups of animals will generally prevent selections between alternative dose-response models on the basis of experimental data; many alternative models with vastly different implications for the magnitude of low-dose risk will fit the experimental data about equally well. Moreover, purely statistical techniques for curve fitting to the meager available data are now well developed, and it seems unlikely that further improvements along this line will markedly alter the confidence limits which can be derived from present procedures. It seems to me that the main hope of more accurate risk projections for individual carcinogens lies with more detailed quantitative modeling of the many individual steps that occur between carcinogen exposure and the eventual manifestation of clinically detectable tumors.

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Comments

Kenny Crump

The regulation of carcinogens should take account of the magnitude of the health effects, the effectiveness of the regulation in reducing health impairment, as well as the economic, political, and social implications of the regulations. The accomplishment of this requires not only information about whether or not a chemical is a carcinogen, but also quantitative estimates of both the dose response and human exposure--both current exposures and those resulting from various regulatory options. The making of these quantitative estimates is known as quantitative risk assessment. In most instances the knowledge and data base for conducting quantitative risk assessment are weak, resulting in considerable uncertainty in such estimates, which underlies the following comments.

1. Need for a Unified Approach

There is considerable uncertainty with regard to carcinogenic mechanisms and how our available knowledge relates quantitatively to the shape of the dose response curve. Typically, several dose-response curves will describe carcinogenesis dose-response data about equally well and yet predict risks which differ coniderably at the doses of interest in regulation of human exposures. There is also considerable uncertainty in other steps in carcinogenesis risk assessment, such as animal-to-human extrapolations, lifetime-to-brief exposures (or vice versa), and quantification of human exposures. This means that two different risk assessors, both using the same data and assumptions which are consistent with the data and current understanding of carcinogenesis, could arrive at considerably different estimates of human risks. Because of this I think it is vitally important that carcinogenic risks from different energy technologies be estimated using a common risk assessment methodology. Otherwise, differences in risk estimates are just as apt to reflect different assumptions made by the assessors as true differences in carcinogenic potential.

I can think of at least two ways of organizing risk assessment to promote uniformity: 1) having all risk assessments conducted by a central board or group or 2) using risk assessment guidelines that give recommended approaches for areas of major uncertainty in risk assessment. A central board would probably be overwhelmed by the amount of work and it would be difficult to get the needed range of expertise on a single board of moderate size. I believe that risk assessment guidelines are a better means of promoting consistency than use of a centralized board. Such a board could, however, be useful in developing and monitoring guidelines. Guidelines have the potential drawback of being too inflexible, which can result in prohibition of the use of new scientific discoveries or special information pertaining only to a specific issue. For this reason guidelines should be carefully written to balance detailed guidance and flexibility, and they should be reviewed periodically.

2. Need for Using Non-Human Data to Quantify Human Risk

If we accept the need for quantitative risk estimation, we must also accept the need for basing these estimates on non-human data. To wait until human data are available would be unacceptable; irreversible decisions regarding energy policies would already have been made, and irreversible harm to human

health would already have occurred. Some seem to accept animal data as a suitable basis for declaring a substance to be a human carcinogen but not suitable for making quantitative predictions of human risk. This strikes me as somewhat inconsistent. If results from animal bioassay experiments truly bear no quantitative relationship to human carcinogenesis, then animal bioassay studies are perhaps not worth doing; the knowledge that a substance might be carcinogenic in humans without any inkling of its potency is not very useful. It seems to me that when we accept tumor incidences from animal studies as providing useful information on human carcinogenesis, we are tacitly making the assumption that there is a quantitative relationship between animal and human carcinogenesis. Such a quantitative relationship would provide a scientific basis for predicting carcinogenic potency in humans from animal data.

3. Uncertainty in Dose Response

One of the most critical elements in a risk assessment, whether animal or human data are utilized, is the choice of a dose response curve for high-to-low dose extrapolation. Different models can fit data about equally well and yet differ enormously at low doses. Likewise, within a single model there are often sets of parameter values consistent with the data but which predict low-dose risks which differ by orders of magnitude. This uncertainty should be quantified insofar as is possible. One means of accomplishing this is to provide confidence limits for risk, rather than just a single estimate. It seems quite plausible that the dose-response curve might vary approximately linearly with dose at low doses. A more extreme dose-response shape than linear seems implausible. To reflect this, upper confidence limits on risk at low doses generally should be linear in dose. I can conceive of situations in which a linear dose-response curve might overestimate the low-dose risk by a considerable amount. This could happen, for example, when carcinogens are triggered by some gross physiological change such as organ toxicity or a change in hormone levels. A better understanding of carcinogenic mechanism is necessary before we can make definitive judgments about the shape of the dose-response curve at low doses. It seems possible that the shape of the dose-response curve is largely determined in many cases by pharmacokinetic mechanisms which convert the exposure dose to an active carcinogenic metabolite and transport it to the largest site. With current understanding it is difficult to rule out linear responses in most cases.

4. Measure of Risk

Most risk assessments have focused upon extra risk of death from a particular disease. Measures of risk which account for the amount of life, or the amount of life of a certain quality, lost might be more informative. Loss of life expectancy is one such measure. Such a measure would distinguish, for example, between death and an industrial accident at age 25 and death from cancer at age 75. I believe human concern would be more truly reflected in such a measure because most people are more concerned about length of life than cause of death.

Human data are, of course, the best basis for estimating loss-of-life expectancy. I question whether the time pattern of disease or death in experimental animal populations are very predictive of comparable patterns in humans. If estimates are to be made from animal data, it might be best simply to extract a crude estimate of carcinogenic potency from the animal data and to combine this

estimate with human mortality tables to estimate loss of life expectancy in humans.

5. Additivity Versus Interactions

Information for assessing risk from complex mixtures of chemicals is extremely limited. Perhaps assuming some form of additivity of effect is the best that can be done at present. There is a plausible argument which suggests that at low doses additivity might be approximately correct even for carcinogens, such as asbestos and cigarette smoke, which exhibit a multiplicative effect at high doses.

SESSION V

DE MINIMIS QUANTITY

Introduction
(Session Leader - Michael Bender, Ph.D.)

White

The leader for this session is Dr. Michael Bender, who is a member of the Advisory Panel for the Center for Assessment of Chemical and Physical Hazards, and a member of the staff of the Medical Department at Brookhaven National Laboratory.

Bender

Thank you, Otto.

One comment I would like to make before we start is that we've spent over a day now discussing some of the scientific problems involved in estimating risk. There is another side to the whole question, however, and I think this is the one that might be most valuable for the Center to get advice on. That is the question of what you do in a practical sense once you have risk estimates. Now the regulators perceive the public's perception of risk and what they may do about that. We're fortunate this morning to have Dr. Miller Spangler. Dr. Spangler received a B.S. in Chemical Engineering from Carnegie-Mellon University and a Ph.D. in Economics and Research Planning, which I think is of some significance, from the University of Chicago. His recent work experience has been related to risk-cost benefit assessment. For the past 10 years he has been employed by either the old AEC, Atomic Energy Commission, or, since 1976, the Nuclear Regulatory Commission, which you remember was split off from the AEC at that time. He's in the Division of Systems Integration and employed as Special Assistant for Policy Development in the Office of Nuclear Reactor Regulation which involves the assessment of risks, costs and benefits in the formulation of safety policy guidelines. With that introduction, I'll turn things over to Dr. Spangler.

Issues in Setting De Minimis Standards
(Speaker - Miller Spangler, Ph.D.)

Spangler

Thank you, Mike. This subject is unusually complex. You people have been talking about the scientific basis for decision making, which also has its own set of complexities. There are several clues in the session that we're addressing right now, in setting de minimis quantity standards, about what the workshop framers wanted. They talk about radiation equivalent chemical dose associated with acceptable risk. When I looked at those words, it appeared to me that there was a desire to have some sort of uniformity of policy development between different regulatory agencies and another aspect of how you decide what is acceptable risk. The term policy development is very different from the term policy analysis or scientific analysis. Let me explain by using an anecdote. During World War I, as in World War II, there was a problem with the German submarine menace, and the people debated what to do about it. Will Rogers finally, in his own inimitable way, came up with what he felt to be the perfect solution. He said, "It's simple! All you need to do is mount pumps on the Panama Canal and pump all the water from the Atlantic Ocean into the Pacific Ocean." And somebody asked him, "Where are you going to get all the pumps." And he said, "Don't bother me with details, I'm a broad brush thinker." Well, there's one crux of our problems. Policy analysts invariably tend to be broad brush thinkers. We have only so much intellectual energy to go around, and you can take your choice: either the knowledge to deal with the broad, interrelated analyses of the generalist or the depth of detailed knowledge of the specialist. Policy development, on the other hand, assumes both types of analysis, the generalist and the specialist. Science provides a factual basis which is very important for policy development. The policy analyst, on the other hand, deals primarily with the assessment of societal values in how best to organize these in a decision framework. I think that is the crux of that type of contribution as opposed to the scientific analysis. Unfortunately we don't merge these two disciplines or these two efforts very well in policy development. One can look around at different organizations and see how they choose types of people or skills for regulators. If a very complex set of scientific problems is involved or complex technological uncertainties or issues, the typical choice is a scientist or an engineer, rather than somebody who is strong on evaluating societal interests. For a very simple-minded technology, obviously the legal types or the social scientists or the generalists can step in very nicely. So we have those differences. Usually there is a very strong dynamic tension between scientists and policy analysts, and we don't need to deplore this. I think the controversy is legitimate and desirable. What we should deplore, however, is the tendency of these people to get into warring camps. Instead of having interdisciplinary analysis and integration of interdisciplinary points of view, which I think is what is needed, we tend to have multidisciplinary analyses. Each discipline presents what is viewed as a conventional wisdom in his or her own discipline and it's added like another patch to the quilt. You don't get the benefits of what I would call the unconventional wisdom that we seek in interdisciplinary analysis which distorts or converts the conventional wisdom of each discipline to some extent in arriving at a solution that's more beneficial to society. So much for that kind of background.

I don't have the time to go through the eleven issues one at a time, that I listed in the handout (Prepared Comments, page V-28). So instead, I would like to pose a different set of provocative questions, with some additional comments on these. We can then turn the session over to discussion and any of these eleven issues that you wish to discuss.

One problem in developing uniformity in decison criteria has been highlighted by the work of the Clark University, Center for Technology, Environment, and Development in their publication entitled "Worker/Public Protection The Double Standard." (Environment, Volume 23, No. 7, September 1981). They have an interesting table in here, "Comparison of Occupational and Environmental Standards." They list a number of undesirable health effects, or agents creating health effects. Then they give EPA standards and OSHA standards. The first agent is listed as carbon monoxide, the EPA standard is 9 parts per million for 8 hours and 35 ppm for 1 hour. By contrast, the OSHA standard is 50 ppm in 8 hours and ignores the 1-hour standard. You can go down that list. There is sulfur dioxide, e.g., 0.14 ppm in 24 hours for EPA vs 5 ppm in 8 hours for OSHA. Hydrocarbons are all lumped together: 0.05 ppm for the EPA standards as a guideline vs OSHA's 500 ppm. That's a very wide spread. There are also standards for lead, beryllium, radon, and noise. There is one on ionizing radiation, for example, that NRC is responsible for rather than EPA or OSHA. We have set a standard of 0.5 rem per year for the general population for maximally exposed individuals vs 5 rem per year for the occupational worker. The question this paper asks: Is that a proper standard? Should we have a tenfold difference? We have looked at standards in Russia, internationally, and within the U.S., between agencies etc., and find roughly a tenfold difference between safety standards for occupational workers and societal risks. Is this justifiable? And what is the explanation?

Well, there are such reasons as, for example, workers assume their risk voluntarily. One can examine that assumption and see that there are elements of duress in accepting employment, or after you get better information about risk, perhaps leaving one job for another. Nothing is wholly voluntary in a strict sense if you look at different elements of duress. Another argument is that oftentimes occupational workers receive extra pay for hazardous work. Still another argument is that, well after all, workers are not children or older people who have greater sensitivities to hazardous substances. Hence, workers' repair mechanisms presumably are more at peak condition. Also, they can manage a risk situation with some degree of control in reducing risk. And still another argument is that the common good of society more than compensates for the sacrificial risk imposed on workers.

We all have a stake in the common good of society. So, in a sense, when you get into the subject, for example, of Pareto optimality, we have a programmatic form of optimality. Regarding unequal situations where there are winners and losers in each kind of standard-setting decision (or societal choice of technologies), programmatic optimality can result only if different segments of society take turns in being winners and losers. Generally, we don't give this very much formal thought. But that is what philosophers call a "social contract theory," which many people more or less accept as justification for individual sacrifice. Maybe I should first define "Pareto optimality." In economic theory, Pareto optimality is achieved by a decision which results in some segments of society being better off and none worse off. But for risk-taking decisions in most complex technologies, that is not the case. A very basic question is

whether it is practicable or desirable to achieve perfect equity. This would impose very severe penalties on technological progress, I think, which in turn is a precursor to economic progress, which in its turn is a precursor to social progress. So, in terms of value systems, all of these things are interrelated in some kind of circular feedback mechanisms that we need to pay attention to when we think of the overall good of society.

However, let me say I think we should pay more attention to occupation risks than we do and not take it for granted that we should impose ten times as much risk on occupational workers as on society in general. In this regard, I would recommend the Toxic Chemicals and Public Protection Report to the President by the Toxic Substances Strategy Committee. They provide an estimate that about 20% of all cancers are caused by occupational exposure and suggest an uncertainty band for this number from a low of 5% to a high of 38%. Another reason for greater emphasis on reducing occupational risks of chemical carcinogens is that as we become short of certain kinds of nonrenewable resources, we shift more and more to chemicals and plastic substitutes. For example, in converting coal to synfuels, we may have a higher rate of cancer incidence than from our present use of coal or oil. There has been enormous growth in use of carcinogenic chemicals such as benzene and vinyl chloride: eight- or tenfold increases over the past decade or so. We can expect more and more proliferation of chemicals that are carcinogenic.

Another focus of attention in standard setting is the pathway and mechanisms by which occupational exposure to carcinogens is created. The greatest emphasis should be placed on controlling the quality of the air environment and the inhalation pathway. Liquid pathways such as impacts on drinking water or skin exposure may produce lesser risks and are easier to control.

Well, let me do what I promised and give a list of provocative questions.

First of all, what are acceptable risks? This invites the question of acceptable to whom, the equity situation.

The next question, how safe is safe enough? And that invites the question, how safe is too safe?

How does risk evaluation fit into risk management vs how does risk management fit into resource management and societal goals and interests? I think this is related to the previous question. If we attempt to make something overly safe, we can expend the resources of society very ineffectively and could perhaps achieve greater risk reductions if these resources were expended in other areas.

I remember that Professor Richard Wilson of Harvard, who was quite critical of the NRC--I think justifiably so--pointed out that one of our regulations led to a reduction of risk that was equivalent to $100 million per life saved. That's a bad bargain for society. I have a table appended to my issues paper which shows much lower cost estimates for various opportunities open to our society for life saving that could utilize these financial resources more effectively. When regulators impose risk-reducing measures, it isn't just industry we're penalizing. Generally, consumers bear the largest share of the cost burden. That's another myth that has evolved in the dichotomy between environmental interests and industry interests. What's good for General Motors isn't necessarily good for the country, if you recall the late Charlie Wilson's gaff. But it would be wrong to say that what's good for industry is necessarily not good for our societal interests, or what's bad for industry is not necessarily bad for our societal interests. There is quite a bit of overlap or parallelism

between the welfare of industry and the welfare of our society, which I think should be kept in view.

We discussed risk management yesterday in Dr. Rodricks' session. In the NRC we have focused on risk management; but I don't say we are necessarily an example to imitate. I think we're fumbling a great deal, although we're on a learning curve. I would really not claim that what we are doing is a model for general application. Yet some of our methods and policies are worthy of discussion. We've been pressed to get into some of these risk management issues, I think, ahead of the occupational regulation of chemical carcinogens. We have three sources of pressure on us. One is the National Environmental Policy Act, of 1969, which imposes certain analytic for decision options. Another set of requirements is our own Atomic Energy Act, or Energy Reorganization and Development Act of 1974. The third pressure came with the Three Mile Island accident, which was followed by the Kemeny Commission report, recommending that the NRC develop safety-cost tradeoff criteria and explain them to society.

NRC has its Federal Code of Regulation, as does EPA and other agencies. Numerical guides for reactor design objectives and limiting conditions for plant operations, called ALARA, are found in 10 CFR, Part 50 (Appendix I). The term ALARA means "as low as is reasonably achievable, taking into account the state of technology and the economics of improvements in relation to benefit to the public health and safety and other societal and socioeconomic considerations and in relation to the utilization of atomic energy in the public interest." Now those are a lot of good words, but they don't give detailed guidance. But now with our safety goal effort, NRC is going into these matters a great deal more carefully. We are inviting public input and discussion, and we now have proposed trial safety goals which are more in the nature of safety guidelines.

Previously there wasn't much interplay with the public in trying to distill what the public values were. I think that is a real dilemma. The public, as we know, is poorly informed on many things. But, of course, they're better informed on their own value systems than are regulators. There is an interaction between information and values in determining how society arrives at its risk-benefit preferences. Preferences and attitudes would probably change a great deal with improved scientific information. Thus, there is some justification for a kind of scientific elitism whenever society remains poorly informed. But there also is, I think, a travesty when regulators do not give very much serious thought to the variety of risks, costs, and benefits, along with the uncertainties that affect their assessment. Value assessments are perhaps even more uncertain than scientific assessment. Societal values are not stable over time, and perhaps this is desirable. Our sociey needs to be adaptive to changing circumstances.

Another question is whether it makes sense to set <u>de minimis</u> standards when the information base on which to set them is still inadequate. Should we wait a while for impending fresh knowledge, or should we go the route that Dr. Crump suggested in setting guidelines. NRC uses this approach in some areas of safety regulation by establishing interim guidelines. We have proposed trial cost-effectiveness criteria, which entail a very narrow scope of societal interests. These criteria require estimates of only the safety benefits of a technological fix to weigh against the dollar costs of the modification. We have suggested an interim guideline for ALARA set at $1,000 per man rem which some have estimated to equal $5 million per life saved. In the appendix to my issues paper, many examples of opportunities for life saving fall under half a

million dollars. If one uses a half million dollars, then the above standard is roughly 10 times higher than these other opportunities. Is this justifiable? We've been talking so far about risk in terms of hazards like mortality and morbidity, or benign tumors vs malignant tumors. But risk in the public mind seems to have additional dimensions. For example, there are anxiety costs with regard to certain ways that people might die. Nuclear risks have the blemish of catastrophic potential, and they're more dreaded by the public than other energy risks. Coal risks, for example, have some catastrophic potential with regard to the Greenhouse effect, but that's a little more distant in people's thinking and doesn't come out quite the same. I would say that it has been an observation of many people who do value analysis in the health field that people, in general, seem more fearful of cancer than of other ways of dying. Perhaps that's the reason why one might advocate a tighter standard for cancer risks than noncancer risks that affect mortality. But certainly with the morbidity aspect, if there is a long period of illness, enormous anxieties are created. Aside from the physical pain and activity limitations of disease, the treatment of disease can also be very painful. So those are additional risk elements to be considered. Another policy issue is the claim that benefits suffer neglect in the development of safety standards. In my experience, I think that benefits aren't the proper focal point. I think net benefits is. In our safety goal development we have wrestled with different approaches to setting safety goals. Among these are risk/risk comparisons, the cost-effectiveness approach, and the benefit-cost analysis (defined in dollar terms). However, the National Environmental Policy Act, or NEPA, requires analysis of consequences beyond dollar in benefit-cost analysis. Other analytic methods include the no-risk approach, technology base standards approach, and the risk net-benefit balance framework. The last is described as follows in the NRC REPORT (NUREG-0880, February 1982) on Safety Goals for Nuclear Power Plants: "A risk/net-benefit framework balances the benefits less the costs against risk. This framework resembles benefit-cost analysis except that all factors would not necessarily be translated into a common unit (i.e., monetary terms) as in cost-benefit analysis. Rather, the risk would be considered one factor in reaching a regulatory decision. Though quantification is sought to the extent practical, not all factors may be subject to precise quantification; some may necessarily be place in a so-called display and discuss category."

We heard yesterday a comment that the use of risk/net-benefit balance in policy development was in a bad state because of the incommensurablity of risks, costs, and benefits. That's so true. And yet to neglect a reasoned discussion of certain incommensurable attributes of decision making in a risk/net-benefit frame work is, I think, inviting serious political costs. Although I have tried to directly address the question of how to put political cost into our decision-making processes, I have not been very successful. We all know that they're put there, in regulatory decisions, but it's sort of a back door method. In order to focus attention on political costs I have attempted to find precursors or, if you will, suitable surrogates for political costs. I've tried to focus attention on things like social costs, or psychic costs and benefits, as unmarketable effects. Social costs, if they're left unattended, lead to political costs, obviously. Equity considerations is another focal consideration for reflecting political consequences. Regulatory decision makers historically have been pretty well schooled on examining the balance between total costs, total risks, and total benefits from societal standpoints. But that isn't where polit-

ical costs come from. They come from situations of inequity, where the risks and costs benefits aren't borne uniformly by different segments of society. Nor are they perceived the same, even if competent regulatory assessors would assess them the way society assesses these things. Individuals in society, or groups or subgroups within society, assess these things quite differently from the way experts assess them.

Maybe, that's a good breaking point, or we're not going to have much time for discussion.

Discussion

Bender

Thank you very much, Miller.

I will exercise leader's prerogative to comment a little bit. A great deal of what you said is brought home in the context of radiation exposures by my own personal experience. Years ago I did licensing hearings frequently for the Regulatory Commission. As a matter of fact, Don Borg and I in that period both worked for the Atomic Energy Commision, and I, in fact, attended some of the ALARA hearings, so we go back a long way. In the course of talking to intervenors etc. about their perception of what the risks of some nuclear power plant was, I was often faced with "a little old lady in tennis shoes." Having perceived that she had lost the argument on scientific grounds, she would usually stamp her foot and say, "Well, how would you like to live next door to one?" And I never had an answer until I moved up to Brookhaven when I proceeded to build my house next door to the as-yet unfinished Shoreham Nuclear Power Station. That's my perception of risk. I have not had the opportunity to respond, retort to the little old lady, as yet, incidentally. But there's a little vignette that's associated with my decision which I think illustrates the real problem. Often I pass by the construction gate of this nuclear power station, and from time to time there is a small band of dedicated citizens demonstrating outside this gate. The vignette I have is a picture of one such bedraggled man standing out there in the rain and the cold, dressed in a Halloween skeleton suit and carrying a sign reading "Radiation Causes Cancer," while at the same time he was chain smoking cigarettes. This seems to illustrate a great deal of the problem.

One of the questions you brought up, Miller, that I think is part of the problem is that of: risks borne by whom for benefits achieved by whom? I think this, as well as the perception of risk, goes to the question of whether we should set de minimis standards for chemical carcinogens, and if so, how? My background is in genetics, and the hazard estimation I most often do is for genetic hazards. And here I think this difficulty is spelled out almost to the ultimate. In this case, we argue that workers ought to be allowed to assume extra risks. As you point out, this is roughly a tenfold increase in risk, we believe, certainly in dose, because, after all, they're compensated for it and it's their choice. But if the hazard is genetic, and we believe there are genetic hazards, the cost is borne not by these people who may benefit from the extra pay, and not even by their immediate descendants who may also benefit in some way, but by as yet unborn generations who may pay a penalty perhaps 1,000 or 2,000 years into the future. We have a very complex situation. To throw the whole subject open to general discussion, I would like to emphasize, not only the questions raised by Dr. Spangler, but those that are raised, at least tacitly, by the subtitles in the program. One practical consideration relating to carcinogen standards is the question of de minimis quantities. Here, we mean quantities, exposures, not risk, although this has to be based on our perception of risk. And two questions are raised by the subtitles. One of them is the question, as I read it, of whether it is proper to have a radiation equivalent for chemicals. My own view is that it is probably not. The second is the question of dose associated with whatever the acceptable risk is. With that I'll just throw the subject open to general discussion.

Baum

Yesterday Dr. Rodricks outlined for us very nicely the two aspects of the problem; namely, risk assessment and risk management. Today Dr. Spangler has given us some very interesting numbers in the area which relate to the risk management part of the problem: in particular, your table about the costs that society is willing to pay to save lives, for example. Now, these can be compared to the $5 million per life saved that the NRC has more or less been using in some cases and also to the million dollars that came out of the data that you, Dr. Van Ryzin, showed yesterday that the FDA analysis uses. Apparently, they were using about a million dollar per cancer avoided in deriving their 2 ppm limit. So the question I think I'd like to pose is, where in this range should we be thinking? If NRC were to come up with a number today, would it be closer to a million dollars per life saved, or would it still be in the range of $5 million? Perhaps other people have thoughts on this question.

Spangler

We are reexamining all these things. I think these limits were set originally without much deliberation in terms of the various important aspects of policy setting that we now realize need consideration. There is a feeling, however, among a lot of top level people in NRC that the thousand dollars a man-rem may still be justifiable despite the fact that with the use of the same monetary resources, you can get better bargains in saving lives elsewhere. Not all the costs are included in our analyses of proposed safety modifications. We have deliberately excluded, for example, anxiety costs, except in the case of Three Mile Island, where the U.S. Circuit Court has ordered us to consider it. We have not dealt adequately with property damages from a serious nuclear accident and many other questions. There is a kind of crude proportionality between accident risks involving death and these other harms to society. I should mention that the Commissioners have emphasized that this is still a trial number which may be altered after a period of time. Also, and this is perhaps even more important in the thinking of a lot of people, there is a recognition of the need for an extra margin of conservatism for the deficiencies in the state of the art in quantitative risk assessment. In NRC this is referred to as probablistic risk assessment, or PRA. This is not a very rigorous science. It is full of all kinds of iffy assumptions and challengeable aspects in terms of accuracy. Hence, the need is felt for a margin of conservatism.

However, looking at the problem from an equity standpoint, if you assume a margin of conservatism in setting one risk standard, you may be denying a different group in society who would prefer a different technological solution. What is conservative for one interest group may go against the interests of an opposing interest group. Another argument for conservatism is public trust and confidence in regulatory decisions. This is not a problem just for NRC. I dare say that OSHA and others have that problem too. If one doesn't use margins of conservatism, one risks losing public trust and confidence should scientific information be developed that proves "best" estimates of risk to have been in error. That, too, is an ingredient of political cost. Of course, the cumulative effects of numerous safety adders justified by unwarrantedly high margins of conservatism could price the technology out of existence. For example, it is believed that the best scientific estimates support the view that nuclear energy

is safer than the use of coal for generating electricity, then society may be denied the net life-saving benefits of using nuclear instead of coal. This could happen if we use too large a safety margin in setting these cost-effectiveness criteria and the technology loses its market competitiveness. I think there are some who feel this may have happened as a result of technological fixes after Three Mile Island. And if the loss of economic advantage is added to the adverse public perception of risk associated with nuclear energy, then the whole game may be lost.

Beall

In the light of what you had been discussing and of the general tenor of the conversation, it may be worth emphasizing Roy Albert's point yesterday and bringing up another area for discussion. Roy Albert said that as decisions are made, precedents are set. As they are set, we develop a history of risk assessments and decision making which will guide future assessments and decisions. It seems to me that we've heard a lot about mathematical models, a lot about numbers that are acceptable, and a lot about social costs. I haven't heard much discussion about what we've learned from our history of risk assessment and decision making. What have past risk assessments taught us about making risk assessments in the future? Let me put this into a policy context. Is it appropriate for DOE or other agencies to use history lessons on risk assessments in developing new assessments? An example of what I'm talking about involves the benzene standard. OSHA established a lower exposure standard for benzene. The Supreme Court set it aside because OSHA failed to demonstrate that the lower exposure level would, in fact, significantly improve or enhance human health.

Spangler

I am currently a member of an advisory council to a study project of the Midwest Research Institute and the Impact Assessment Institute sponsored by the National Science Foundation. This project is looking into methodologies of comparative risk assessment using different technologies as case studies. This will further advance the notion that you have presented. While I'm on the subject of the study being done by Edward Lawless and Martin Jones for the NSF, I might point out that the definition of risk assessment they're proposing is quite different from the one given by Dr. Rodricks. They prefer the term "risk evaluation" for the list of items that Rodricks put on the blackboard. Their definition of "risk assessment" is more in the framework of a decision analysis, as the Office of Technology Assessment would practice, using estimates of risks, costs, and benefits in a comparative mode of analysis. I think they want to do that precisely because people who work in the risk field tend to focus on risk assessment to the neglect of other costs and benefits that are decision consequences. Sometimes risks may be very miniscule relative to the benefits, or the loss of potential benefits, at stake. Also, Otto White mentioned that, in setting de minimis safety standards, if risk is below a certain level it can be forgotten. Risk/net-benefit analysis is a way of establishing more carefully what is important and what isn't. What is important to one agency in its regulatory responsibility for a certain chemical carcinogen does not necessarily have the same importance to another agency which must deal with another set of technological options. I think that in part accounts for the differences be-

tween OSHA and EPA, as well as other agencies, on some of these matters. So I think this is something we should be paying a lot more attention to.

Wambach

Just one comment on the worker vs the general population. I don't think the difference is in risk estimation. There is no difference, really, on how you estimate risk. The difference is in risk management. One way to manage risk is to set exposure limits. But there are a variety of other methods of managing risk. With the worker population you have an identified population of people, 100 people, 200 people, and you have their names and their social security numbers, and you can haul them into a clinic for medical exams and do a lot of other things to manage that risk. That's usually the reason there is a big difference between worker exposure limits and general population exposure limits.

Spangler

That's a very good point and let me enlarge upon it. In NRC we use the term risk management in a fairly broad sense although with certain detailed aspects. Risk management includes one segment which might be identified as accident prevention or exposure prevention. Another is accident or exposure management. There are cases in which something untoward is happening and it takes a certain amount of time before developing into an accident with serious consequences. In these cases you can manage the risk while it is in process, and you have decision options. Another aspect of risk management is consequence mitigation. Consequence mitigation, you know, has many aspects. Some of it can be built into technological design, and some into, say, evacuation procedures. Some of it can be built into medical practice or medical research that may mitigate the societal consequences of morbidity or mortality. So there is a whole gamut of things under risk management that are interrelated.

Bender

In the context of this question of worker vs general population, I think one thing should be kept in mind. You asked Miller, I believe, whether the tenfold difference between worker-permitted exposure levels and general population levels was reasonable. I think, in fact, that multiplier is far higher. In the first place, the 500 millirem (mrem) per year is an unmeasured value. The practice is to limit the average exposure to, roughly, a third of that 167-170 mrem just because the reasoning is that the maximum won't be more than three times the measured dose. But then with the creation of ALAP and ALARA, the Regulatory Commission is at least taking the view that general population exposure should be as low as possible. I think from the numbers I've seen in the nuclear industry it's somewhere of the order of 1 or less mrem/yr. That's a big factor.

Spangler

There are several frameworks involved. One is the framework of setting a standard for a maximally exposed individual which is what ALARA does. Now, in NRC's proposed safety goals, we're dealing with a different kind of standard.

We're talking about the average risk, and we've had a lot of discussion about what those words mean. The Office of Policy Evaluation developed this proposed statement with a lot of interaction with the staff and the public workshops that were held. Let me refer to the language of several of these what we call provisional numerical guidelines. The Commission proposes the following provisional numerical guideline: "The risk to an individual or to the population in the vicinity of a nuclear power plant site of prompt fatalities that might result from reactor accidents should not exceed 1/10 of 1% of the sum of prompt fatality risk resulting from other accidents to which members of the U.S. population are generally exposed." Notice that both the individual and the population have the same safety standard. However, when you do calculations of risk, you find that the individual is the controlling factor. If you develop measures to serve that goal for the individual, you far exceed the safety guideline for the population. Now the key question is this, does "an individual" mean a maximally exposed individual, or are we dealing with the concept of an average individual? What we seem to be coming up with (and this hasn't been fully resolved) is that we don't mean "maximally exposed." What we should be focusing on is the average individual risk within one mile of a nuclear plant where the acute fatalities are greatest. Dose-response curves are used to determine this. Such an average is based on a much higher level of exposure than, say, between one and two miles, or five and ten, or any other greater radii that you might go out to. But it's still quite a bit lower standard than the maximally exposed individual standard. You would probably bring all technology to a halt if you had this great protection standard for just a single maximally exposed individual.

Bender

I think something else needs to be noted here. In radiation protection in the NRC's business, what one does very frequently is in terms of population man/rem, at least for late effects, and this has the effect of averaging, I think. But implicit in doing that kind of averaging is the idea that the dose-response curves are going to be linear and that it doesn't matter very much, within certain limits, whether a few people get all the dose, or whether it's evenly distributed. I think the same question arises in the case of chemical carcinogens. Do we take average risks? Is that a fair thing to do? What is the basis? And that has to hinge on the notion of the dose-effect kinetics at low dose, and again some definition of what we mean by low dose is needed. This often comes up in discussing radiation hazards, and there is a fairly general agreement among many radiobiologists that what we mean by low dose is that region of the dose curve where linearity does, in fact, pertain, which is often difficult to establish.

Spangler

One concept of low dose that I've been working on is the idea that, if the dose is quite low, then the incremental risk of cancer is quite low. However, the personal anxiety produced by even quite low radiation exposures from a nuclear accident would be considerable, leading to the promotion of risk-compensating mechanisms. For example, exposed persons are likely to have more frequent medical checkups and better medical care. There is a real possibility that this would increase life-span much more than the risk of cancer incurred by

these very low doses. So there are mitigative options open to society, and I think the evidence on Nagasaki and Hiroshima support this view. So that's another consideration in comparing decision options.

Bender

I think you're correct in many respects, but I would point to some recent experiences, as you have done. In the first place, I think the Kemeny Commission came to the conclusion that the only demonstrable health effect of Three Mile Island's accident was anxiety among the people, and that anxiety persists. Several of the agencies that were involved in the government's handling of that crisis came to the conclusion, as did health effects people in the Kemeny Commission, that offering certain kinds of medical follow-up was scientifically unsound, in that it was unlikely to contribute anything worthwhile to our scientific knowledge, but it would very likely increase, not decrease, the anxiety of these people. So there is a problem there. Again it is partly, I think, a matter of perception of risks, and the perceptions are different among people whose livelihood economically depends on some hazard, and people who don't see it that way. I think that's illustrated by the various crises we've had in New York State--at Niagara Falls at the Love Canal area. The people up there, a lot of them, work in the chemical industry. The whole area is clearly polluted. EPA's recent measurements of levels of nasty chemicals demonstrate that. And yet the demonstrations, the emotion, all of the pressures are not to clean up Niagara Falls. Not to clean up those chemical plants. There may be some pressure, but it's not notable. The pressures, rather, are to do something about Love Canal where no hazard has as yet been substantiated statistically. Not only is there anxiety, but those people are convinced, many of them, that they have suffered ill health, that this will continue, and there is very little that can be done about it. But they want some real economic advantages. They don't want the government to buy the inner ring of houses, or two rings of houses; they want it to buy a very much greater number of houses surrounding the canal. It's almost implausible to me at this point to think there ever was any real risk, and there certainly is none now. This would cost, I don't know what the estimates are, but probably approaching a billion dollars. So we have a problem of how people perceive risks. How differently they perceive them, depending on whether they're workplace risks that they presumably assume voluntarily, or whether they're something "they" are doing to us. Something they are involuntarily forced to assume the burden of. Fortunately, in the context of the Center and the DOE's requirement for recommendations, what we have to do, I think, is consider the workplace standards and, consequently, workers' perception of risk.

Spangler

Yes, I quite agree with you. Perhaps now would be a good time to mention that I have a number of publications that view the various aspects of the issues I've been discussing this morning. I'll be happy to send them along to you.

Bender

Thank you, Miller. I'm sure that many people, myself included, will take you up on your kind offer.

**Are We Ready to Apply the De Minimis Concept to Standard Setting--
A Historical Approach***
(Speaker - J. Newell Stannard, Ph.D.)

*Presented at a BNL Medical Department Seminar on September 17, 1982.

Summary

This seminar discussion of the pros and cons of de minimis concept applies to both radiation and chemical exposures. However, most of the examples are from the radiation field.

It begins with a quick review of the multiplicity of hazards to workers identified and described by Bernadino Ramazzini in his classical book published in 1713, De Morbis Artificum. One reason for reaching this far back in history is to conclude that with so many diseases and so few qualified people to handle them there had to be circumstances where the exposure or the effects were regarded as trivial, i.e., de minimis.

This is followed by a brief history of radiation protection philosophy divided arbitrarily into "Eras." These are, respectively: the era of empiricism, the tolerance dose, the maximum permissible dose, ALAP and ALARA, and the challenge of the '80s. It is pointed out that until the concept of a threshold disappeared there was little need for any other "floor" or any de minimis level. During the era of the maximum permissible dose attention centered on the growing evidence that cancer, as well as genetic effects, should be regarded, for the sake of prudence, as being linear to dose with no threshold. The philosophy focused on the idea that there was no completely "safe" dose. With the coming of ALAP and ALARA, a very meritorious concept as originally conceived, came the tendency to push acceptable levels lower and lower, sometimes with very large expenditures to produce a marginal biomedical gain. Especially when ALARA was given regulatory significance in a quantitative sense, the recognition of the need for some restraint on the ever lower values gained momentum. This was the de minimis dose. In the '80s with the strong movement to use risk as a basis for both radiation and chemical standards, the need for adding the concept of a trivial risk has taken hold.

The balance of the seminar considers examples of possible de minimis levels, some of the problems not fully addressed as yet, and some of the current activities. Since the purpose was to generate discussion the original question "Are we ready to apply the de minimis concept to standard setting?" was left somewhat open. However, it was concluded that some sort of floor is highly desirable.

Finally it is pointed out that historically we are coming full circle in the sense that any de minimis level, if adopted, would have to have an empirical basis just as did the original upper limits.

Text

Thank you, Dr. Carsten. The last time I visited Brookhaven, except for a quick "in-and-out" meeting or two, was the year you were responsible for the summer practical training of students from Rochester and several other schools in the Northeast. (Rumor has it that the Rochester students did not always lend tranquility to the Brookhaven summers. I am sorry about that!) We are very

proud of our students, in general, and especially proud of people like Dr. Carsten who have gone on and done many important things.

The prime purpose of my visit to Brookhaven has been to conduct interviews with members of the Medical and Health Physics Divisions on the historical development of various facets of research with radioisotopes, pertinent to a book I am writing on "Radioactivity and Health - A History." Partly it is to seek new information and partly it is to see if I got things right in some chapters which have already been written.

This afternoon's seminar is a very informal offshoot of those matters and is done at the request of Dr. Carsten. It also has an historical approach. Since it was something of a last minute decision to do it, the format will be more to stimulate and lead a discussion than to attempt a polished lecture. Nevertheless, I do happen to have some slides along pertinent to the subject - "Are we ready to apply the de minimis concept to standard setting? -- An historical approach," which were used for an unpublished symposium of the San Diego Chapter of the Health Physics Society.

We will start in 1713 with Bernadino Ramazzini who was, I suppose, the first occupational or industrial physician. We will review the amazing breadth of his coverage of all aspects of worker health by looking at the chapter headings in his book De Morbis Artificum. This book was translated from the original Latin of 1713 by Wilmer Cave Wright, emeritus professor of Greek at Bryn Mawr College, and was published by the University of Chicago Press in 1940. (Several slides were shown giving the extent of the coverage in the 43 chapters of De Morbis Artificum, ending with Ramazzini's dissertation on the "Diseases of Learned Men." These are not reproduced here to save space.)

A somewhat more detailed review of this and other early approaches to occupational medicine can be found in a review by Stannard ("Breathing is an Old Habit" In: Pulmonary Toxicology of Respirable Particles, DOE Symposium Series 53, 1980).

The purpose of showing you all of this is first to indicate how long ago many of our common occupational hazards were recognized and second to conclude that with a handful of people to worry about all of those situations there just had to be exposure levels that were essentially trivial, i.e., de minimis. Indeed, Ramazzini and others proposed minimum levels of exposure in some instances and did much to protect workers.

I would like now to trace very briefly some aspects of the history of radiation protection which bear on our subject. (Note that I do not propose to review the history of the standards themselves, but only the philosophy of radiation protection.) This has been done many times by many people. Yet, another review may be useful to our discussion. This will be done with a series of slides dividing the historical progression somewhat arbitrarily into eras. The first slide summarizes the five eras I propose to discuss:

Eras in Radiation Protection

Empiricism
The tolerance dose
The maximum permissible dose (exposure)
ALAP and ALARA
The challenge of the '80s.

The second slide considers the era of empiricism:

The Era of Empiricism

Rollins - photographic plate (1901-1903)
CA 10-20 R/day
Russ - World War I experiences
Mutschuller - 1/100th of threshold erythema dose (TED)/month (1924).

This era began, I suppose, with the first formal attempt to limit radiation exposure. I will choose to say this happened when Rollins suggested that x-ray exposures of a duration that darkened a photographic plate of the era in a given time or less, were excessive. In retrospect, this translated to a dose of about 10 to 20 roentgens per day. Another pioneer was Russ who suggested limits based on experiences with radiology and radiologists during World War I. Probably the most substantive of the empirical formulations came from Mutschuller. He produced many publications and his contributions were summarized masterfully by Lauristen Taylor at the Health Physics Society's Silver Anniversary symposium (Health Physics 41, 571-576 (1981)). Mutschuller's recommendation related to the erythema dose, as shown on the slide, and was published in 1924. This assumed a threshold.

The probable dose in roentgens associated with a "Threshold Erythema Dose" as proposed is shown in Slide 3:

The Threshold Erythema Dose in Retrospect

"Grenz" Rays	100 R
100 KVP x-rays	350 R
200 KVP x-rays	600 R
1000 KVP x-rays	1000 R
Radium Gammas	1500 R

Energy would be reduced by scattering.
e.g., Failla took 600R for radium gammas
American Committee on X-Ray Protection used Mutschuller's work with rounding factor of 2 to arrive at T.D. of 0.1 R/day (1934). (Adapted from Cantril and Parker.)

Note that with a bit of rounding this led to the figure of 0.1 R/day which was used for many years.

Note particularly that all the ideal of this era assumed that a threshold existed. In a sense, any doses below the threshold for damage might have been regarded as trivial and thus "de minimis," but the term was not applied.

The era of the tolerance dose for both external radiation and for radioisotopes can be considered to have begun roughly when the roentgen was defined in 1928. Obviously it was based on the idea that there were doses that were tolerable. However, they might or might not be "threshold" in type. If there was an

effect, it was simply assumed that it was of negligible importance to the organism or the race at the levels chosen for the standards.

Slide 4 indicates a few major events in this era:

The Era of the Tolerance Dose
External Radiation

Definition of the roentgen in 1928
Work of American Committee on X-Ray Protection
(Later the NCRP)
Work of the International Commission on Radiological Protection
Retrospective analyses of "safe" x-ray and radium installations and their personnel.
Animal data, including genetic

Radioisotopes

Radium in man 1941
Radon in mines and industry 1941.

All but the animal work was based on retrospective analyses of doses under conditions where significant harm had or had not been detected. In general, the methods applied, even the interpretation of the animal data, were closely similar to those used in industrial hygiene, industrial medicine, and chemical toxicology in general. Each of the items in the slide can be reviewed in depth in the writings of L. Taylor, G. Failla, and R.D. Evans. It was only in the genetic experiments with animals that the ideal of a tolerance level began to be questioned. Hermann Muller insisted that any increase in the load of genetic defects was not tolerable.

The tolerance dose was not as likely to be regarded as "trivial" as was the threshold dose. Hence, this second era moved away rather than toward the implications of having a de minimis dose.

The next major era, the era of the maximum permissible dose, is shown in slide 5:

The Era of the Maximum Permissible Dose

First Tripartite Conference - Chalk River, Ontario, 1949
Second Tripartite Conference, Harwell, England, 1950
Third Tripartite Conference, Harriman, NY, 1953

NCRP and ICRP used these together to issue recommendations of the 1950s.

Critical organ
Acceptable risk to individual
Genetic risk
Secondary standards
$(MPC)_A$
$(MPC)_W$
Separate system for bone-seeking radionuclides.

This era can be regarded as beginning with the tripartite conferences in 1949. These involved Canada, the United Kingdom, and the United States. Many of the numbers and the system we operated under for many years came from here. The primary difference from earlier philosophy was a negation of the idea that there is a dose which can be tolerated indefinitely without effect. Instead the ideal grew that some risk had to be assumed and that a maximum permissible dose could be developed which was acceptable in terms of risk, but not negligible, or at least not zero. The full bloom of this system came in the reports of the NCRP and ICRP in the 1950s, particularly those issued in 1959, and in the U.S. Code of Federal Regulations as applied to atomic energy. A few details of the components are shown in the slide.

As you all know, as research penetrated further and further into the realm of low doses of radiation and of low dose rates, and as information on dose-response relationships for induction of cancer accumulated, ideas were modified still further. It appeared that there was no threshold at all and that the only prudent assumption was that effects were linear to dose clear to the origin of the dose-response curves. A natural corrollary of this was the view that there was no safe dose, if "safe" meant without any effect at all. (We could have another seminar on whether or not any biological effect is to be considered an injury.) This took us still further away from any idea that there could be a trivial dose, i.e., a de minimis dose.

Partly as a result of these developments, another layer was added to radiation protection philosophy. That was the admonition to keep all doses as low as possible (ALAP). This was first formulated by the NCRP in 1954. Thus it began not too long after the concept of maximum permissible dose took hold.

Slide 6 lists some of the features of this development:

ALAP and ALARA

The linear, no-threshold hypothesis
The system was intended to be flexible
ALAP becomes ALARA
ALARA gets quantified and the figure given regulatory significance.
"If you can do it you must do it."

I have called it an era for convenience, but it is really only a facet of the era of the maximum permissible dose. Because of abuses in application of the "as possible" feature of ALAP beyond reasonable economic limits the terminology was changed. Toward the late 1960s it became "As Low as Reasonably Achievable" (ALARA).

Let it be emphasized that the original intent of ALAP and ALARA was flexibility. What might be ALARA for one installation might not be for another, even of similar design, but built at a different time, etc. To my mind it was a great mistake ever to attach a single number as the ALARA number for a given type of activity or installation, and especially to give it regulatory significance. ALARA was intended to be idiosyncratic for each installation. Soon the creeping paralysis voiced so well by Hoyt Whipple (whom your John Baum worked with) all but ruined the concept. This is shown at the last item on Slide 6. "If you can do it, you must do it." Levels considered to be ALARA crept steadily downward.

One result of these trends was the idea of balancing risk and benefit. This actually began fairly early in NCRP work and in the philosophy espoused by the Federal Radiation Council. But it was articulated most completely in the ICRP reports 26, 27, and 30 issued in the mid-to-late 1970s. I am including these in the final era labeled "The Challenges of the '80s" (Slide 7):

The Challenges of the '80s

The ICRP mixed risk-rem system
- ICRP 26
- ICRP 27 (all prospective)
- ICRP 30

NCRP "pure-risk" system
Problems of application
- Assessment
- New reports in preparation

Revision of 10CFR20
Concept of de minimis dose.

Since all of this is current, I will not belabor the details. Even though the concept of risk and acceptable risk arose much earlier, I am choosing to label the flowering of the use of risk systems, either pure or mixed with dose calculations and the concept of rem and the balancing of risk and benefit as occurring primarily in the current era.

Along with all of this has come a crescendo of interest in placing some sort of floor under the protection philosophy. The concept of a de minimis dose or a de minimis risk was heard more and more frequently. As you know, the term had been used in the legal profession for many years to characterize those things that were trifles (Slide 8):

De Minimis

De minimis non curat lex
"The law does not concern itself with trifles."

The reasons for this growth of interest are many. The crescendo of papers on the subject of de minimis, even talk of adding it to the revision of 10CRF20, attest to this growth. I will discuss two possible reasons.

Firstly, the abuse of ALARA and the need to engage in ever more lengthy and expensive survey and investigations to prove that a given operation was ALARA must have had something to do with it. Secondly, some events in chemical toxicology entered the picture. One of the expected benefits of a risk system for radiation protection is the possibility of adding risks from several sources to get a composite picture. This would include combining not just radiation sources, but other occupational risks, especially those from chemicals in the workplace and the environment.

The concept of a threshold dose persisted in chemical toxicology much longer than in radiation biology. However, work with the chemical carcinogens and chemical mutagens jolted this idea considerably. These seemed to show linear dose-response curves with no threshold, much like those for ionizing radiation. The chemical toxicologists could no longer hide comfortably behind the

threshold dose idea. Yet zero dose was even less possible than with radiation. Therefore, the idea of a de minimis dose took hold also in the possible regulation of exposure to many toxic chemicals.

What criteria might we set up to delineate a de minimis dose? Slide 9 lists a few:

Possible Criteria for De Minimis Dose

Risk is lost in the "noise"
Latency of effect is beyond life span
(≯ practical threshold)
Relation to background radiation
Expense of further reduction is unacceptable
Further dose reduction is absurd.

If the concept is adopted we can expect hefty polemics around what value or values to choose.

In Slide 10 are listed a few of the possible consequences of adopting the de minimis concept:

Consequences of Adopting
De Minimis Dose Concept

ALARA stops here
Has effect of a practical threshold
Zero risk is impossible

Probably the most important is that any dose at or below the de minimis level would automatically be ALARA. This does not mean that ALARA and de minimis would be coincident. ALARA levels might frequently be higher than the de minimis level for a variety of reasons. However, ALARA would stop at the de minimis level and go no lower.

In a sense, adoption of a de minimis dose concept and level has the effect of introducing a practical threshold. This differs from the practical threshold introduced in the radium data in that cancer induction times are longer than the life-span. It would simply be the de minimis level and it is there for all practical purposes regardless of what the theoretical dose-response relationship is.

Obviously, if a de minimis level is adopted, a situation with zero risk is virtually impossible. However, this is an academic point since zero risk is essentially impossible anyway. If some of the lower values for de minimis are adopted, the risk might approach zero for all practical purposes!

Further ramifications of the concept are listed in Slide 11:

Ramifications of the De Minimis Dose Concept

Is background dose rate de minimis?
If not, what fraction is de minimis?
De minimis sources:
Airplane travel
Television viewing
What if more than one de minimis source is present?
De minimis collective dose
What of time of exposure to de minimis source?

Opinions have already been expressed on some of these. There have been suggestions that a de minimis concept might be tied to the levels of background radiation. It is unlikely that the normal background could be adopted. It is too high. There is more and more indication that it is not biologically trivial. It is just something we can do little about. But that is not sufficient reason for proposing to double it. Some fraction of background might become a viable figure.

The slide lists some other sources that we treat as if they were trivial. These might become a basis for a figure.

Of greater concern is the problem of the multiplicity of sources. Can we devise a system and choose a level that will be useful in the case of only one or a few sources, yet not be dangerous if circumstances led to a large number of separate de minimis exposures? There are those who think this is very unlikely to become a problem, yet situations can be visualized where it could occur, especially in some routine manufacturing operations.

What of the collective dose in person-rem from the summation of individual de minimis doses? Do we need to set a collective de minimis dose? I believe we should. How could such a figure be implemented and by whom?

Furthermore, none of the current discussions of de minimis sources say anything about time of exposure. Presumably, any source low enough to be labeled de minimis would be trivial even for lifetime exposure. However, this might place such heavy restrictions on the acceptable level for daily use that the concept would end up having little utility.

A final ramification is not listed in the slide. This involves the possibly unnecessary use of de minimis sources as an easy way out. Even if the source is de minimis, there is probably no excuse for using it if a substitute contributing a markedly lower dose can serve equally well.

Enough of these detail problems. They are being discussed very fully around both radiation and chemical standard setting. Does our discussion so far lead you to conclude we are or are not ready to adopt the de minimis concept?

There are currently many probings. The upcoming revision of the Code of Federal Regulations 10CFR20 is one. The November 1981 draft of that document takes a positive view on the need and indicates consideration of 1/10th of a millirem per year as an acceptable collective de minimis dose. At 1/10th millirem per year, chances of suffering a radiation-induced disease would be about one in one hundred million. Over a lifetime the chances would still be less than one in a million. Is this low enough? Is it too low? Is it susceptible to implementation? Remember that background radiation levels are in the 100 to 200 mrem/yr range and we would thus be dealing with levels much lower than "the noise."

In chemical toxicology the Delaney Act has stimulated the FDA to consider that one chance in a million of damage may be acceptable over a lifetime. Sources providing less risk than this might be considered de minimis chemical sources. If a single risk value were adopted, radiation and chemical risks could be equated relatively easily.

The 1982 versions of the 10CRF20 and of the FDA codes have been modified in response to comments. The provision for having a de minimis level has remained in 10CRF20. A proposed level of 1 mrem/yr for an individual in the population has been added.

Others, for example the NCRP, are giving thought to incorporating some sort of floor in their revised radiation protection recommendations, but no firm decisions have been made as yet. Many individuals are looking seriously at the matter. The Atomic Industrial Forum meeting, scheduled for this October in New Orleans, includes a session "Exploring the Uses of the De Minimis Concept in Radiation Protection." The speakers include many of those who have been actively discussing the topic; Morton Goldman from NUS Corporation as Chairman, Saul Harris from Union Electric, Joyce Davis from General Physics, Guy Cunningham from NRC, Floyd Galpin from EPA, etc.

Let me conclude this discussion with a general comment. Historically we have almost come full circle. As we saw, originally the ceilings were set empirically. We have now developed protection to the point where tradeoffs between expenditures for lowering levels still more and for other important activities are becoming urgent if we are to avoid being absurd. Can we improve the situation by adopting the de minimis approach? I am not one hundred percent convinced that we are ready to embrace it fully, or that it is the only answer. Yet the need for some sort of floor to the regulatory process seems evident. If we do adopt the de minimis concept I can guarantee that the levels will have to be determined empirically, just as the ceiling levels were determined originally by empirical means. No acceptable level would be one at which any measurable damage could be detected. The circle is thus to a degree completed.

Thank you very much.

Discussion

Carsten

We have time now for discussion on this. Any comments?

Meinhold

You wouldn't want to get away that easily, Newell? I guess a little problem that most of us who are concerned about de minimis have is does the time when we're asked to accept as the most reasonable estimate of risk for low level radiation a sort of $y = mx + b$ relationship, that has to equal zero, which means that small doses for large numbers of people produce real deaths. How do you justify the de minimis concept with that sort of an end point?

Stannard

I think you put your finger on one of the reasons it has not been adopted. There are many who feel that if you can establish a reasonable occupational model, within occupational exposures standards, there are often levels below which it's not reasonable to go because few people are involved. But as soon as it is applied to collective dose, we're in trouble, and I don't see a way to make a decision out of context of the whole problem of acceptable risk for everything. This requires the kind of effort that has been discussed in many quarters; that of bringing in people from outside science to help decide acceptability. From the standpoint of moral obligation or from the standpoint of the law, what is an acceptable risk? My answer is, I don't know.

Carsten

At the same time you have the point where the costs become unacceptable. Who's going to define the costs as being acceptable?

Stannard

The sponsoring agency.

Carsten

That's right. But if you start, I think, to deal with the business of how much it may cost to take care of individuals who suffer under a situation like that, you get back, I think, to the concept that if you think medical education is expensive, try disease or something like that. Any other, questions? Charlie Meinhold. You see, Charlie's another student of Dr. Stannards, so now he's using this chance to get back.

Meinhold

Well to return what you said, I think you can come to numbers using exactly those techniques that you mentioned. I think you can locate the costs of the effects on society using other techniques that measure the effects of ill-

ness in the human population and come to some upper limit of the value of a man-rem, if you like, or a man-Sievert. I love to hear that Sievert in there, marvelous stuff. But you can come up with that value using some acceptable societal technique. Society is going to come up with that value, and once they do, the differential cost benefit will have to be evaluated. Weighing the risks and the costs of reducing that risk through whatever kind of protection you're going to provide, whether its stronger shields, or whatever, you can do it in a logical way. It seems to me that eventually we're going to move in that direction.

Carsten

I think your problem there would be when they would say, looking at it from outside, when you can't decide on the shape of this curve, how well can you decide that the risk is one in a million, and on that basis how can we make a decision as to what is acceptable or not? Dr. Borg?

Borg

I think you are arguing about a world which we don't live in. Richard Wilson and others have tried to see what kinds of judgment people have made about other perceived risks and use those as acceptable guides. But what we know is that there are all kinds of strange phenomena that many people do not view in this large context. In the first place, the uncertainty of cancer can be viewed differently from the uncertainty of an automobile accident, or a dam breaking, or other major accidents. It's a matter that certainly weighs heavily on decisions. That's one of the concerns of looking at the risks of radiation. It is a fact, but how can we get up here and talk about how we ought to have a consistent scheme? We ought to evaluate traffic light crossings, the amount of money we put into different projects, but we don't do that. We just don't do that. It's asking too much.

Stannard

I find it easier to conceive of a system where you decide that it costs too much than I can conceive of a system of uniform agreement on what is an acceptable risk for what sorts of activities within what population.

Member of the audience

It's absolute that to try and put any number on a cost-risk-benefit analysis type of thing is almost impossible as a generalization because within different societies we are faced with a very different set of orders, values, etc.

Carsten

Life has different meanings in different places.

Stannard

That's a very interesting point. I think Charlie Meinhold will recall that ICRP very clearly indicated in both reports 26 and 27 that their recommenda-

tions were general ones and that each individual nation should take them under advisement and apply them to their own situations. I don't know very many nations that have done this, but I believe that this was partly to allow for discussion of difficult points of view about risk and about cost. Is that true?

Meinhold

Absolutely, and that's the whole question, that the values for man-rem are going to be very different in different cultures with different needs. After all, a nation which doesn't have enough electricity to support its hospitals will be silly to accept a much higher value for man-rem than a nation like the United States which can afford increased protection. There are obviously going to be societal values on those types of things, and those have to be determined by the individual societies. ICRP feels that those should be the same at each national level, however. We probably don't have different values for human life in New York than we have in Southern California, wouldn't you say?

Hull

I would make an observation and ask a rhetorical question. It seems to me that we wouldn't even be here listening to you today if it weren't for the fact that the dangers of cancer from a millirem or a fraction of a millirem of radiation from nuclear power has become a convenient surrogate issue for this whole argument on the policy of energy and energy sources. We wouldn't be here if that weren't the case, because nobody previously paid any attention to this issue except us professionals. Now that brings me to the second question which is: as scientists and health professionals, how do we deal with the fact that no risk is the greatest risk of all? How do we point out the foolishness to society and special interests of pursuing just one type of risk, whatever it is, and ignoring all other risks. There are tradeoffs. Until people start looking at tradeoffs, we're just going to be in this morass of single-issue risks.

Stannard

Well, I thought there was an indication that de minimis can be applied to risk other than radiation, although it may need to be modified.

Hull

That would be a lot easier, although I think many people would not agree.

Carsten

At first when you said we wouldn't all be here, I thought it might be because of the level of radiation.

Hull

It wouldn't be an issue.

Carsten

I know.

Borg

Do you think it would be possible to bring a measure of rationality into the level of what is meant by absurdity even though different people in society may put different values on the risks we're talking about. If one could show the public at large the range of fluctuations of the hazard, whatever type it may be, chemicals in one's diet, radiation from the environment that come from everyday life. What happens if you decide to live on the 17th floor of a building, rather than in a stone house. If you could get an understanding of those fluctuations then it might seem rational to people no matter what their absolute values were that some tiny fraction of that kind of fluctuation is not worth going very far to avoid. Other things will bring it to you anyway. Somewhere in one of your early lists you have the word absurd and, of course, that's a value judgment. I think that by bringing to people information on a comparative basis about the same class of risk you can finally get a more informed public.

Carsten

I think coming back here I remembered something that bothered me some years ago, hearing lectures from Dr. Stannard and others when they talked about this. What were the standards at that time? There was a concept at that time and I don't know if it still exists, about emergency exposures which were permissible if inaction might result in loss of life or significant loss of property. Here, again, people were asked at that time to make value judgments on what was significant. And I think we're still faced with this question. This may or may not be an issue, but I think there are big differences in different countries because of different concerns regarding general health. For example, in certain areas of the country or in the world the people eat grain that may have aflatoxin in it because they're going to starve to death if they don't eat the grain, even though it's been stored and gotten wet. I think this is a very real current difference.

Drew

It seems to me that the real problem is one of educating the public rather than educating the scientists. And one way to do that is to develop a unit of risk cig rem or something like that, or perhaps person miles traveled in an automobile, so that we can compare risks in a way that people who take risks every day can relate to, rather than the somewhat esoteric values currently used, particularly for rather widely perceived risks as opposed to actual.

Carsten

Jones suggested back in a series of lectures in 1958 that the rem per pack etc. might be useful and I agree. But to play the devil's advocate, what they always come back with is, but it is my choice to smoke or drive a car. I want my choice whether or not I'm exposed to radiation which we know is ridiculous be-

cause the individual takes the choice to turn on the light and use the air conditioner. They've got to get it from somewhere, and I couldn't agree with you more. I think the education part will not work, because in spite of the cigarette thing, people smoke. In spite of the car statistics, people drive cars.

Member of the audience

There's a major problem with this kind of attempt at normalization of risks. The risks are not weighed against the benefits. If you want to fly somewhere in an airplane, the risk you accept in flying the airplane is very closely wound up with the fact that you want to get there. If there is no other way to get there, you know, you're going to go in the airplane. And that's not the same as driving to work every morning. Those kinds of risks, compared to eating a peanut butter sandwich, you order or whatever are not comparable. Some things are easy to avoid if you want to avoid them. And other things are difficult to avoid. Then you have the same risks. But it's not independent.

Another member of the audience

People believe what they want to believe. Clearly, the statistics with regard to safety belts show that not using them is a significant risk that people choose to take for no benefit whatsoever other than not having to reach around and put the belt on. It's not clear in black and white.

Carsten

We have time for one more question.

Hull

About ten years ago in the National Safety Journal there was an article by John Zirr, in which he proposed a new unit the millimart, a risk of 10^{-3}. It seems to me something universal like that has a lot of appeal. Very simple. So I think the comment has a lot of appeal when you get something that people generally recognize.

Carsten

Do you have a last comment?

Stannard

I would say, besides "thank you very much," that just as I had hoped, the audience contributed much more than I did. But I would like to say to those of you who have not read yourself to sleep with Ramazzini that the dissertation on the diseases of learned men is especially interesting reading. If you read the book, I think you will be amazed at the clarity with which the symptoms and the complexities of what happens are described. He goes way off base on causation, of course, but you have to take your hat off to these folks, Ramazzini in particular, for being able to describe, and we should not discount their abilities.

Prepared Comments

Policy Issues in Setting De Minimis Standards for Latent Cancer Risks of Radiation and Chemical Carcinogens

Miller Spangler

In the fuel cycles for the development and utilization of alternative energy resources, the risk of latent cancer arises from a number of sources. Included are ionizing radiation and the carcinogenic potential of polluting chemicals present in certain fuels or in materials associated with the construction, operation, maintenance or waste treatment processes of nuclear power, fossil fuels, synfuels, biomass, and other sources of energy. One aspect of developing a carcinogen guideline policy for a consistent and effective regulatory regime to use in dealing with these assorted carcinogenic risks is the setting of de minimis quantitative standards. In this summary paper, 11 policy issues related to the setting of such regulatory standards are identified and a brief commentary is provided.

Issue 1. Should quantitative de minimus safety standards for carcinogenic risk be established using absolute or comparative risk assessment?

Commentary: Arguments for and against the use of comparative risk assessment were presented in Cogressional hearings on the Ritter Bill (HR 4939) which was recently passed by the U.S. House of Representatives.[1] Without the use of comparative risk assessment to serve as a basis for standard setting, it is difficult to see how available societal resources for protecting health and safety could be effectively and equitably allocated. A drawback is the difficulty of achieving the legislative or administrative reforms to promote the objectives of comparative risk assessment.

Issue 2. If comparative risk assessment is used in setting standards, should it encompass a wide range of related and unrelated risks or should it be restricted to a comparison of alternative choices of technologies that could accomplish the same or similar societal benefits?

Commentary: Both types of comparative risks have been used in the proposed safety goals and provisional numerical guidelines issued for public comment by the U.S. Nuclear Regulatory Commission in seeking to establish standards for acceptable risk.[2] If comparative risk assessment is to pursue the inclusion of benefits, costs, and other associated adverse impacts beside safety risks (see below), it would appear essential to limit the scope of comparative assessments to a realistic set of related decision options.

Issue 3. Should quantitative risk standards be established that allow for differences in net benefits of alternative technologies, thus permitting risk/net-benefit tradeoffs?

Commentary: Technologies are developed principally for their intended societal benefits with costs and other unintended adverse impacts being deducted to arrive at net benefits. Without inclusion of differences in net benefits and the concept of risk/net-benefit tradeofffs, the singular focus on risk-risk comparisons could be prejudicial to the net benefits available to society through the acceptance of certain technological options.

Issue 4. Should, or under what circumstances should, a more limited cost-effectiveness criterion of safety-cost tradeoff be used as a basis for setting acceptable risk standards?

Commentary: The expected dollar cost per life saved as in decrements of risk versus increments of costs with increasingly more rigorous de minimis standards under consideration is one such approach. A suggested consideration in its use is that there is no likely major loss of net benefits other than the increased dollar costs involved.[3]

Issue 5. When cost effectiveness is used in setting de minimis standards, how does one treat the ethical issue of appearing to put a price on human life?

Commentary: A proper perspective for such a decision process would appear to be that of achieving an equitable allocation of scarce societal resources for alternative opportunities for risk reduction or saving lives.[4] Some examples are provided in Table 1.

Table 1

Illustrative Examples of the Cost of Life-Saving Opportunities in Alternative Uses of Financial Resources[a] (in dollars per life saved)

	Item of opportunity	Estimated cost (dollars)
1.	Improved medical x-ray equipment	3,600
2.	Improved highway maintenance practices	20,000
3.	Screening for cervical cancer	30,000
4.	Proctoscopy for colon/rectal cancer	30,000
5.	Mobile cardiac emergency unit	30,000
6.	Road guardrail improvements	30,000
7.	Tuberculosis control	40,000
8.	Road skid resistance	40,000
9.	Road rescue helicopters	70,000
10.	Screening for lung cancer	70,000
11.	Screening for breast cancer	80,000
12.	Automobile driver education	90,000
13.	Impact absorbing roadside device	110,000
14.	Breakaway signs and lighting posts	120,000
15.	Smoke alarms in homes	240,000
16.	Road median barrier improvements	230,000
17.	Tire inspection	400,000
18.	Highway rescue cars	420,000
19.	Home kidney dialysis	530,000

[a]Source: Selected from a list of similar items as cataloged by E. Siddall, "Risk, Fear and Public Safety," Atomic Energy of Canada Limited, April 1981, pp. 39-42.

Issue 6. What should be done about the problem of discount factors and other considerations in comparing risks of early versus latent deaths?

Commentary: Reduction of life expectancy is a quantitative consideration if discount rates are to be applied. Other considerations are the longer period of anxiety, cost of medical treatment, morbidity discomfort associated with latent versus early deaths.[5]

Issue 7. Should safety standards for occupational workers differ from those involving risks to the public? If so, what criteria should govern such differences?

Commentary: A prevailing view is that extra pay for hazardous occupations and the voluntary nature of occupational risk acceptance should account for some difference in standards. Countervailing considerations might involve a much lower level of risk for workers than the public, large uncertainty of risk assessment, and the sources of duress in seeking alternative employment.

Issue 8. When wide ranges of uncertainty accompany the estimation of risks or verification of actual safety performance, should a standard be stated quantitatively or qualitatively? If quantitatively, should the numerical guideline of acceptable risk be administered as a mandatory requirement or as a design or operational target (or goal) with permissible variations? What guidelines, decision criteria, or administrative procedures should control permissible variations?

Commentary: The problem of treating uncertainty in risk assessment has been widely discussed.[6-8] Dose exposures by occupational workers and the public are often more accurately determined for radiation than chemical carcinogens. However, dose-response estimates of latent cancer morbidity and mortality (especially for low dose rates) have broad ranges of uncertainty for both types of hazards due to inadequacies of data and scientific methodology.[9,10] The cost, delay, and degree of uncertainty reduction of extended research to provide an improved basis for de minimis standard setting are important decision criteria.

Issue 9. When the setting of de minimis safety standards is known to be highly controversial among antagonistic interest groups, how are equity considerations and public input to enter the decision process?

Commentary: This is generally a more important policy issue for standards involving public exposure to radiation or carcinogenic chemicals than for occupational hazards, except when the two are closely linked. Various approaches include Congressional hearings, public workshops sponsored by government agencies, the publication of proposed policies, rulemakings, or standards in the Federal Register inviting public comment, adversarial hearings associated with the issuance of Generic Environmental Impact Statements, or special scientific committees or panels commissioned by the government to make recommendations.

Issue 10. In the setting of de minimis safety standards, how are gaps to be resolved between how experts assess and treat risk in decision making contexts and how the public perceives risk and decides on their acceptability?

Commentary: Various studies have explored this subject, revealing that the gap is wide, involves a complexity of attributes and attitudes, and will not readily be resolved.[12-15] Nevertheless, this gap has influenced the character of legislation and regulatory practices in a number of questionable ways affecting both the short- and long-term public interest. Strategies to alleviate this gap could be an important adjunct to the successful setting of de minimis standards of socially acceptable risk.

Issue 11. Should, and how should, procedures be established for periodic review and change of de minimis safety standards in view of the possibility that: (i) substantial improvements may occur regarding scientific rigor in assessing risk or in validation standards compliance, (ii) technological progress may reduce the cost of risk reduction or enlarge the net benefits of the technology, and (iii) changes may occur in societal values, perceptions, and attitudes toward the risks, costs, and benefits of technological options and their social acceptability?

Commentary: Regulatory instability too frequent changes in standards that penalizes inflationary costs of technological applications or deters their utilization need to be balanced against the benefits and other costs of regulatory change. Institutional rigidity in making desirable changes is also a problem to be reckoned with in setting de minimis standards in the face of an uncertain outlook for their future change.

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SESSION VI

LEGAL AND REGULATORY ISSUES

Introduction
(Session Leader - Samuel Morris, Ph.D.)

Morris

Some of the laws which govern regulatory processes require risk assessment. Others interestingly forbid it. The EPA people I know complain about that all the time, because they need to regulate both sorts of laws. To further complicate the issue, either risk assessment in the past decade has become sufficiently ingrained or else people so seriously regard it as a tool for rational decision making, that even when a regulatory agency is itself forbidden to do risk assessment or to take into account cost-benefit analyses as part of their regulatory decisions, other people or other agencies will, on their own, promote risk analyses for some of these decisions. In fact, I think what happens is that many of the risk analyses are not so much aimed at the specific decision maker in the regulatory process but at influencing the general public's feeling about some risk which indirectly then influences the regulatory process. So that a session on risk assessment in the regulatory side of things is a very appropriate way to bring together some of what we have talked about so far. So without any further digressions I'll introduce Dr. Devra Davis who is with the Environmental Law Institute and is an epidemiologist interested in cancer epidemiology currently working at Johns Hopkins University.

Regulatory Policy Propositions
(Speaker - Devra Davis, Ph.D)

Davis

There are a diversity of laws that require risk assessment. It's important to keep in mind that the whole field of risk assessment really is created by the laws. We've been at this in some systematic fashion for more than a decade. I'm going to take Otto White's opening to heart and try to suggest some consensus propositions here. I'll start with those that I think will arouse relatively little argument and then proceed to others which may be more controversial but always my focus is not on what is scientifically correct or valid but on the policy questions involved. One of my handouts details more than 14 different laws that regulate toxic substances in the environment. This authority is parcelled out to EPA, DOT (which regulates hazardous materials in transport), OSHA (which is supposed to regulate hazards in the workplace), the Food and Drug Administration (which has a variety of responsibilities for regulating hazards in consumer products of a medical nature), and the Consumer Products Safety Commission (which is supposed to set standards for hazards in consumer products). In addition, let me comment briefly on the most recent law enacted to protect against toxic hazards, the so-called superfund law which was passed after the last election, in December 1980. This law, I think, typifies what has happened most recently in that it requires some kind of balancing of economics and health, but it is still very much oriented towards health.

The handout summarizes these laws and what "triggers" them into action. In some cases, you have laws which consider health only. Section 112 of the Clean Air Act is not at all concerned with the economic consequences of regulations. If something is a toxic air pollutant as defined under the act, it is supposed to be banned. It is noteworthy that until recently only a handful of substances have been regulated under that law; the average length of time required to regulate a substance as a toxic imminent hazard is four years. There is another type of law which requires no compliance but offers general guidance. That will be indicated in the chart as well. A third type of law gives very specific factors which can be triggered into action, for example, TSCA, the Toxic Substance Control Act, passed in 1976, which has yet to be fully implemented. That law stipulates that things can be regulated if they cause carcinogenic, mutagenic, teratogenic, behavioral, or other synergistic effects. That law and some others are what I call <u>basic science forcing</u>; they presume that we know those things scientifically, in spite of the fact that we often don't have quantifiable information that we can use. Another handout, which is a string diagram, shows the multiple nature of health effects associated with chemicals. Next I want to offer some propositions (Prepared Comments, page VI-23) which I'll now briefly go through.

The first issue that I'd like to address is actually a continuation of the discussion begun this morning, on the matter of animals versus humans. I want to suggest that animal studies are much more readily available than are human studies (Issue 1.1, page VI-23). Human studies document past risks not current or future ones (Issue 1.2). There is a kind of catch-22 in that. When you do a case control study and document a relative risk for pipe fitters as has recently been done, the immediate reponse of the industries which are large enough to engage in control strategies is to reduce exposures. Subsequent attempts to validate the relative risk get into a catch-22, because the exposures have, in fact, been reduced. But most important, one of the biggest limits of

epidemiological studies is that they can only tell you the past. They cannot tell you anything at all about the future.

It is possible to consider past exposure history of damage done, such as with coke oven workers, when a new potential hazard appears, such as synfuels, which seems to share many of the same effluents, both fugitive emissions and otherwise. One can see an approach being adopted to set up what are called risk assessment units, that considers past occupational exposures, to project what new occupational exposures may bring based on the past. So, the statement that only past risks can be documented by human exposures at least needs modification.

Rodricks

I want to suggest a similar kind of modification. If you mean we can't use past experience, past documentation of human risk, to project risk in the future, let's say under different exposure conditions for the same material, then I disagree. OSHA did that recently. For example, for arsenic, in which there is documentation of risks in the past, and workers are now exposed to much lower levels, they still use that to project risks in the future.

Davis

Yes.

Rodericks

I guess you mean just to discover the risk?

Davis

Right, I think that's a very good modification. Andy?

Hull

To give a quick example of your point, not only has the nuclear power industry achieved the environmental emission limits designed for their reactors, but current levels are practically below the limits of analytical detectability, so I think your point is well taken.

Morris

I think, particularly since we only have one speaker, that we should let her go through her presentation and then have the discussion afterwards. Otherwise we won't be able to keep to our schedule.

Davis

I'll try to limit my own comments then, and I'll present them in a straightforward fashion and aftewards we can get to a discussion of the issues. But I'm inclined to say after Joe Rodericks and his comments, "that's what I meant." Epidemiological studies can identify exposures that resulted in certain levels of harm. In the case of synfuels, where you are able to characterize the nature of the ambient pollution and either its chemical structure or its exact

name, as in the case of benzopyrene or polycyclic aromatic hydrocarbons and coke oven-type emissions, then obviously it is instructive. In situations where we have the unknown, as in many chemical processes, or industrial processes where there's a manufacturing process going on, like pipe fitting or isopropyl alcohol manufacturing, you're not sure exactly what are the caustive agents. Let me try to move right along here, to short-term versus long-term questions. Concerning animal studies, more short-term and acute tests are available on new and existing chemicals than long-term or chronic tests (Issue 2.1), and I have recently reviewed the premanufacturing notification data provided to EPA under Section 5 of the Toxic Substance Control Act. There are few data and those are all short-term and acute. For many substances there is nothing. As you may know, EPA is moving toward a strategy of exempting wide categories of substances from any premanufacturing data whatsoever, which is interesting and noteworthy.

Issue 2.2. Almost all chemicals which cause cancer in humans cause cancer in animals.

Oncogenes or cancer-causing or cell-transforming genes are virtually identical in mammals and humans. Therefore, agents which transform mammalian genes should be regarded "as if they presented a carcinogenic risk for humans."

Issue 3. On the question of thresholds and linearity.

Issue 3.1. Thresholds may exist for individual chemicals in individual organisms. In heterogeneous human populations some hypersusceptible persons exist.

Issue 3.3. The unborn, neonates, and the immunologically young are more readily compromised and have more sensitive metabolism than do adults. There are some things that can have a half-life in the fetus that is four times as long as that in the mother.

Issue 3.4. Therefore, given the population distribution of susceptibility and the vulnerability of the young, thresholds have no practical policy implications, and linear interpolations or extrapolations should generally be performed. I offer that as a consensus.

For potency, threshold is a valid concept but not practically useful. For a single health effect such as cancer, chemicals can be logarithmically ranked as to potency. This looks like a useful exercise. Now on the very last page of the handout is a string drawing. It shows that there is no single chemical among those my colleagues and I looked at which causes only cancer. If it causes cancer or mutation, it does something else as well. You can see with DBCP: it presents reproductive hazards and also causes cancer. Now, there are largely animal data, but in some cases there are human data. Nickel causes respiratory hazards and is also a carcinogen. I would make the general case that most chemicals can have multiple health effects.

Issue 4.3. Most people are exposed to multiple low-dose carcinogens and mixtures of toxins in the ambient environment.

Issue 4.4. A weak carcinogen may be a potent neurotoxin, etc. Carcinogenic potency and other health effect potencies are not necessarily directly correlated. Think of cadmium or lead. Therefore, given the multiplicity of effects and exposures, carcinogenic potency is of limited policy value.

Issue 5. Limits of cost-benefit analysis. Ordinarily, economic benefits and cost assessments rely on bottom line toxicological estimates of health risks. This is changing, but that's been the way they have proceeded for the most part. These assessments involve numerous economic and toxicological assumptions. Therefore, cost-benefit analyses, like risk assessments, are at best <u>tools</u> for decision making as opposed to <u>rules</u> for decision making. This may, in fact, be obvious to many of you but some may disagree. There is always

this appeal of trying to discover some sort of algorithm that could scientifically determine policy.

Issue 6. There can be no scientific regulation of carcinogens. I distinguish regulation from identification. Diverse basic science-forcing environmental laws and regulations exist, as witness the chart. They cover things in different media, at different times of their life cycle, from their generation to their transport to their disposal, to their consumer product use. Some of these laws require health-only considerations in triggering regulatory action. The famous or infamous Delaney clause has actually been used only three times in its almost thirty-year history. That's a very important point. I don't know what you want to call it, perhaps its artful regulation, but in fact it has been invoked only three times. The other law with a health-only consideration theoretically is the Resource Conservation Recovery Act known as RCRA. As originally enacted RCRA did not allow for any economic consideration, but it has subsequently been substantially amended. One effect of this part of the law was that soon after it was first enacted the oil interests got a whole bunch of oil drilling mud and sludge exempted from being categorized as a waste.

Issue 6.3. Most laws require some balancing of health benefits and economic costs. TSCA, the Toxic Substance Control Act, FIFRA, the law regulating pesticides, all require some consideration of economic and health effects. No law that has been passed yet requires a strict cost-benefit procedure. However, the Carter administration had an executive order, and the Reagan administration has an executive order, which requires cost-benefit analyses of all "major" regulations. Major regulations are defined in terms of their economic not their health impact. These major regulations in fact constitute almost all regulations. Although the laws themselves may not expressly require it, most regulations are in fact subject to some sort of economic cost-benefit analysis. Therefore, carcinogen regulation remains an issue for administrative discretion. Science can determine how best to identify carcinogens but not how best to regulate them. I don't know if there's much disagreement on that, but I'd be very interested to discuss it if there is.

Issue 7. Cancer policy documents. Cancer identification policies have been under development throughout the past decade. I think it's important for any conference such as this, which is addressing cancer policy, to appreciate that there's been a lot of water under the bridge when it comes to this issue. Being a bit of a bug about history, I would just point out that this goes back into the late '60s. In fact if you want to look at something fascinating look at the hearings for the original Delaney amendments. The hearing started in 1948. At that time concern over the widespread use of DDT spurred interest in chemicals in food. There were some people saying that such broad use might not be a good idea. For now I simply want to call your attention to the fact that there have been a lot of different professional groups, international groups, that have considered cancer policy issues. Specifically, the International Agency for Research on Cancer issued its Volume 20 Appendix which rationalized treating animal data on carcinogenesis as if a substance was carcinogenic to humans in the absence of negative evidence. The Organization of Economic Cooperation and Development (OECD) chemical's group in 1979 in Europe also issued guidelines for carcinogen identification from a number of expert groups. The Interagency Regulatory Liaison Group, the IRLG, now deceased, finally developed its own carcinogen identification guidelines in 1980. Joe Rodricks might be willing to talk a little bit about that process. The State of California issued its own guidelines in draft form in 1982. These efforts all generally concur on major issues of carcinogen identification.

I did not include the American Council of Government Industrial Hygienists (ACGIH) policy statement on carcinogen standards, as I have not reviewed their proposal. I am concerned with the issue that Mr. Wambach raised about ACGIH. My understanding of the MTD maximum tolerated dose is that the dose should be derived separately for each substance and no automatic cutoffs can be employed. I looked at those numbers and couldn't think of too many things for which the MTD was not exceeded. On the other hand, if you exceed the MTD you have dead animals and you can't do the study. I would just say there may be enough of a difference between what the ACGIH does and what the other groups have done on cancer policy issues. The ACGIH addresses the question of what you do with something that causes cancer, how you regulate, how you set a standard. These other efforts concentrate on how to identify carcinogens. Therefore, I would suggest that these concurring cancer identification documents should remain the major point of departure for discussion for cancer policies to identify carcinogens.

Earlier I was talking to Kim Hooper and I got this idea. We have all talked about time to tumor as an important indicator of potency at one point. We need also to talk about time to regulation. This is strictly a policy issue, but we need to think about this when it comes to asking how we identify a carcinogen. OSHA has set standards for less than 20 carcinogens in over a decade of existence, no matter how you call it. It depends on whether you want to say OSHA set a standard for benzene or not. They tried to; in fact, they were instructed by the Supreme Court in the benzene decision to review the data, and I understand that they are still thinking about it, although some companies report that they are well under what OSHA proposed. Again, identification and regulation are distinct activities.

Issue 8.2 EPA has set standards for a handful of toxic air pollutants and for toxic water pollutants only after protracted litigation. All of this takes time, lots of time, and lots of money.

Issue 8.3. IARC, ACGIH, and other such groups proceed slowly to build scientific consensus in identifying carcinogens. A case in point is a table that shows more than 20 epidemiological studies published in the past two years that identify more than 19 tumor sites as carcinogenic. Most of these industrial processes or substances have not yet been reviewed by IARC. The IARC list that we all talk about was made up in 1979; it is now 1982. There are a lot more data now than there were then. Yet, IARC is not proceeding at any great pace nowadays. Those of you who may have followed their recent deliberations on benzene have probably found them noteworthy. I think it's a mistake to let some of these lists seem as though they are the final statement, because ours is an evolving science when it comes to health risk assessment.

Issue 8.4. Since regulation proceeds so slowly, decisions must necessarily rely on incomplete, best available evidence as to health and other risks. You have to start the process of thinking; is this a risk, how much of a risk is it, and what to do? You cannot wait for "better evidence" all the time. You have to think about issues which we have not talked about at all. We have been talking almost exclusively about toxicity here, but exposure, it seems to me, is a very valid concern. Something that is used as a floor wax and is also an ingredient in lipstick ought to be considered a little bit differently than something which may be a very potent carcinogen, but which is a used in a completely contained industrial process. Exposure considerations are very tricky. It's extremely important that the process of assessing exposure begin in a deliberative fashion and not be held up while we wait for always better evidence, even though that is to be desired. We need good science but we

ought not to let the demand for good science hold up the beginning of what is often a long process.

There are some other issues which I've not addressed and I just want to mention some of them: what are the policy implications of the fact that essential micro nutrients are high-dose carcinogens; background versus added doses; benign versus malignant tumors; and the notion of a central board review versus guidelines versus "creativity." Those are real policy issues, but as I'm sure you're aware, there is a definite move in this administration toward some kind of central board. I think it would be appropriate for people here to comment on whether they think that's a good or bad idea and how, in fact, it would work.

I think Mr. Chairman what I would suggest is that I'll put up these propositions in the order in which I presented them and people can comment on whatever they would like.

Morris

Let me just interpose that Dr. Rodricks is going to give us a short discussion of the OSHA standard he's working on and so what we'll do is to allow about fifteen or twenty minutes for questions and discussions on this paper first.

Discussion

Davis

On the first page, then, let's discuss these issues.

Bender

On the first page, I would comment that experience, at least my experience, says that although in a sense those things are true, that is with the caveat that you can predict the future risk if you know what the agent is. My experience is that human data, if and when they do become available, drive out all the animal data, and then it becomes very difficult to persuade anyone to agree to use the animal data. Witness the difficulty with radiation cancer risk estimation, which has plagued us for some time. Early on, we knew from human data that radiation caused cancer in humans, but we had to rely on animal data almost exclusively for our numbers. Now that there are several bodies of human data, notably the Hiroshima-Nagasaki study, it is very frustrating to try to get anybody in the cancer estimation business to pay any attention to the lessons that the animal data, in my opinion, show. They just want to look at the human data and throw out the animal data.

Davis

I think that's most unfortunate because if you look at some of the so-called human data, let's take DDT as an example, some of the early studies performed and published in '68 and '70 on DDT took little snapshots of exposed workers. Let me give you an example of one that I looked at in some detail. The study looked at workers in Montrose Chemical Company and excluded from the study population all workers with any liver disease. It then proceeded to find that there were no effects. And this study, done by a very reputable toxicologist whose name I will not mention, was cited for years as evidence of the safety of DDT. This was not that long ago. As an epidemiologist I am very wary of that sort of development, although I think you make a very important point that this is what tends to happen. I think we need to be very careful about so-called negative studies because of that.

Rodricks

Just a question: Is there some hidden meaning behind issue 2.1? I don't find that surprising, but what is the point?

Davis

There is no hidden meaning.

Rodricks

What is the point of the statement?

Davis

Simply that there are some who say that short-term tests are of no value at all for identifying carcinogens. I've heard some people in Washington nowadays saying that. That liver homogenates differ, that all rats get breast cancer, that we have to rely on humans, and that we have to rely on long-term studies, and we need good solid science and it's going to take a long time to get it.

Rodricks

All right, I don't disagree with that, but I don't think the statement says that. I guess that was my question. Just that more are available.

Davis

That's right and I said more data and implicitly valid data. They are not more valid but they are also valid. That's all; there's no hidden agenda at all. Simply that they exist.

Hooper

I think the point is that epidemiology is not an effective screening method for carcinogens. Once a chemical has been identified as a carcinogen by an epidemiologic study and exposures to the carcinogen are controlled, cancers will continue to develop and be expressed over the ensuing 10-20 years because of the long latency period of human cancer. Human evidence of carcinogenicity is a poor end point from a public health standpoint.

Davis

It's very definitely the case that epidemiology is a crummy end point for a safety measure.

Bender

Regarding the question just raised about point 2.1: if that's meant to apply to quantitative risk estimation, as opposed to risk identification, you do have a problem there, no question.

Davis

Yes, you're right.

Bender

Even with the human data, we worry, for example, as to whether the fact that Japanese females are not subject to breast cancer to the same extent as Western women - Caucasian women - whether that invalidates the utilization of the quantitative data from the Japanese studies for radiation-induced breast cancer. There are all kinds of problems of that sort. I don't mean just short and long term.

Davis

Yes. A related problem is the Japanese cultural acceptance of early abortion. The rate of abortion very early in pregnancy is much higher, which calls into question survivor studies there. Let me go on to the next page. Agents which transform mammalian genes should be regarded as if they present a carcinogenic risk to humans. That is what a number of different groups have said over and over again, although the Heritage Foundation wrote a report to the president in which it was suggested that this particular policy needed to be looked at again.

Bender

At the risk of monopolizing things, I think that points 2.3 and 2.4 imply something I'm not sure I'm prepared to accept, which is that we know something more than I think we know about the origins of cancer and the mechanisms involved. Oncogenes may be important, but that may well not be the only thing that's important.

Davis

Indeed, this week's Science has an article on the retrovirus, and I'm sure that is the case. The argument made here is simply that if there is something which all mammalian organisms have in common, and that this thing appears to cause cancer or transform cells in all of them, then it would seem to strengthen the case for conclusion 2.4 which is the validity of extrapolating from animals to humans. That's all. Now, as a group of scientists, you may think this is a finished issue, but it's really not finished politically. I would just like to mention that, to call it to your attention.

Borg

This is just to say I don't think it is a finished issue scientifically. There was some discussion this morning without identification of the source. They may have been thinking of Mensing's work of a few years ago about epigenetic mechanisms, and I think scientifically the issue is alive too. That's enough for the present discussion.

Wambach

Obviously, we're bent on pathways that are different in different animals.

Davis

Yes. Now on to part No. 3, thresholds and linearity. I think the issue of thresholds is scientifically fascinating. There is no question, it really is very intriguing and I think they probably do exist. But I do not think that they have very many implications for policy purposes. When you consider that most standards are not set with hypersusceptibles, the young, or the unborn in mind. For the most part, we don't have toxicological data on these groups. These data are being developed now, but it's a neglected area. Dale?

Hattis

Yes, I tried to make the case earlier that for carcinogens, which are thought to act by way of the primary genetic route at least, one probably ought not to expect thresholds. I would really like to see that word not used in the context of policy for carcinogens in whatever derivative form, because I think it derives from an earlier notion (that is still valid for application to some kinds of toxic effects of chemicals), but I think is not fundamentally appropriate to genetically acting carcinogens. I think that probably it creates more confusion to use the word threshold, much more than it's likely to be worth, and it calls to mind the whole set of associations with some overwhelming of a body compensatory mechanism that I think is unfortunate and likely to be confusing to people.

Borg

At the risk of sounding like a broken record, I think we have gone back to concerning ourselves primarily with initiation when we refer to carcinogenesis, and as I say, like a broken record, I think the story on promotion is much less certain and the likelihood that we're dealing with a more traditional kind of pharmacological behavior there where thresholds are still an open issue.

Hattis

I entirely agree that uncertainties about the mechanism of promotion leave open that possibility.

Bender

I agree with Dr. Hattis about the likelihood for thresholds for chemical carcinogens; never mind the promotion aspect. But it's the old story; people keep bringing up the issue. I don't think we can forbid them to; that's the history of setting radiation standards. Those with vested interests say "yes, but you can't prove there isn't a threshold: maybe there is no effect"; and you simply can't disprove that statement. You can sometimes prove that there is a threshold, but nevertheless you're still stuck with this generic problem, and I think the answer has to be not so much mechanism or theory, as simply saying that although we can't prove it, it is nevertheless prudent to act as though there cannot be one, and just let it go at that.

Crouch

Could you tell me who has measured a Gaussian sensitivity to carcinogenesis?

Davis

Who has measured it? I don't think anyone has measured it. The assumption is that you have a Gaussian distribution in a population.

Crouch

I don't think you can state there's a Gaussian distribution anywhere.

Davis

All right, thank you.

Borg

Everybody says its log normal.

Davis

Let me ask a question, however, on that last issue and the issue that Otto mentioned in the morning. For workers, there are threshold limits values and the whole concept of threshold limit value is derived from the assumption of some kind of a safety factor. There is also HLA typing and some genetic screening going on in the workplace now, based on animal studies. They are screening workers and assigning them to certain jobs and not to others on the basis of an assumed susceptibility because of an enzymatic repair depletion in them that mimics one in a mouse that gets more cancer. This is happening now and it calls into question the whole concept of threshold limit values which I think is what you were trying to talk of before.

White

How would you describe the concept of threshold versus nonthreshold when you decrease the homogeneity of a population such as by going to a working population?

Davis

Well, I prefer not to think about it. We have a tradition of regulating chemicals on a chemical-by-chemical basis in this country. We set standards one at a time. In 1980 the General Accounting Office issued a report in which it said that at the current pace of regulation it would take OSHA one hundred years to regulate known occupational hazards. That tradition of regulating chemicals one at a time, setting standards one at a time, it seems to me could be changed. And if it were changed, I would suggest that it be an environmental control strategy at the source. So that instead of regulating levels in the environment, you would focus on developing control technologies in the first place that would reduce all emissions to, the "lowest feasible levels." Feasible is a word in the OSHA statute which is only getting its own case law definition now, like many of these terms, like acceptable risk or unreasonable risk that are defined in the law as cases are brought into court. Lawyers file briefs and the judges make decisions and they define these terms. But the approach that I would like is that workplace standards not be set on a chemical-by-chemical basis, but be addressed by an environmental source control approach. This is what is done in some European countries. I have not thought it through, but that is the sort of thing I'd rather see us do. I would also rather see us do categoric regulations, by which I mean allow for exemption and regulation of whole classes of substances, so that we do not have to go for each substance, for each medium.

White

It's not clear to me that that would result in a reduction of risk to workers. It might reduce overall the exposure to the population in general, but you could still have extremely high exposures to the work force.

Drew

I'm concerned with the implications of this particular slide. I agree that carcinogens exert other kinds of toxicity and that certain compounds which are potent neurotoxins may be weak carcinogens. But to then imply that carcinogenic potency is of limited policy value is of great concern to me. Are you saying that, to use my analogy at the beginning of this meeting, you're going to (and we'll take for granted that SO_2 is a promoter and therefore a carcinogen by definition) regulate SO_2 with the same degree of rigor that you're going to regulate bis(chloromethyl)ether?

Davis

It depends on the exposure. Risk assessment, if you boil it all down, has two parts. One is toxicity and the other is exposure.

Drew

Toxicity is, in part, potency, but potency isn't toxicity. Potency is, however, deeply entwined in toxicity.

Davis

Yes indeed.

Drew

But you say here that potency is of limited policy value.

Davis

Yes, that's right.

Drew

I think there is a dichotomy here that I don't quite understand.

Hull

I'm not sure of what you're saying. Let me take the analogy to radioactivity; clearly in protection against radiation (which I suspect is not that far ahead of other carcinogenic agents) the preferred approach is by means of time, shielding, and distance. You'd like engineered shielding and containment and thus not to have to put somebody in a mask or to limit his time. In this sense, it is a far more positive solution. But if you're saying this should be done generically, for example for all nuclides, then I might have a

problem. Tritium is potentially carcinogenic, but the body burden is a millicurie. To be expected to treat it in the same way as plutonium, for which the body burden is a few nanocuries, seems unreasonable when there is almost an order of 10^6 difference just because they're "carcinogenic."

Davis

You made that category, I didn't.

Hull

Oh, all right.

Davis

I didn't make the category of nuclides.

Hull

But I was using analogy.

Davis

Yes, I understand what you're saying. In this workshop, the possibility of generic regulation is an idea we might discuss. Kim, I thought you had a comment?

Hooper

I think we should consider it a misnomer to state that there are "threshold limit values" for carcinogens. The definition of a TLV is that a worker may be exposed to a substance eight hours a day, day after day, forty hours a week, over his work life without adverse effect. For carcinogens, this simply isn't true.

Borg

For most workers, there is a big difference.

Hooper

In contrast to common acute toxicologic end points, which may have a "no-effect" dose level, even low doses of carcinogens have some probability of producing an effect. There's no guarantee of no adverse effect. The definition of TLV doesn't seem to work for carcinogens.

Davis

That's a very interesting issue of whether a TLV is inappropriate for carcinogens. I guess that's a much better way of saying what I was trying to say.

Rodricks

I want to comment on issue IV. I'm not sure what definition of potency is used here. If it's something like an LD_{50} or, a minimum effective dose, I agree that's not very useful. However, if it's the type, for example, that Dr. Crouch described or that Roy Albert has described that EPA uses, that is, unit risk at low dose, I think that combined with some exposure estimate gives some quantitative measure of risk which although uncertain is still useful, taken together with other information. I would just not throw it out. I think that's terribly useful information. So if we have a definition of potency that somehow reflects the likely low-dose response for human exposure, then I disagree with what you have said here.

Davis

So, when one refers to a single health effect, such as cancer, the unit risk analysis that they have been doing and the Clement scoring system that was developed take multiple health effects and develop a score for a number of health effects to try to develop a unit risk dose. That's what this is trying to suggest that that's a good idea and let's see how far you can go with it, although I have reservations on how far you're going to get when you start thinking about mixtures. But I do agree that for single health effects, potency is of limited value. Something that would indicate the combination of effects and give a true measure of unit risk per unit exposure would be invaluable. But again, it's limited because no one is ever exposed to only one chemical.

Bender

May I just comment? If I can collect my thoughts, the problems associated with establishing a TLV are very similar in many ways to those that have been associated with establishing acceptable daily intakes of food additives or pesticides. The procedures are very similar: that is, they have relied on animal data, in some cases human data, for establishing so-called "no effect levels," and then applying some safety factor, usually fairly large in the case of the general population; larger than has been applied for worker populations generally. For example, for pesticides and for food additives, the usual safety factor is 100. That's based on a no-observed-effect level from chronic toxicity studies. The most sensitive end points are used as the determinant to derive an ADI, acceptable daily intake. No one has ever claimed that ADI's or TLV's are without risks. I don't think so, for we can't know that for sure. That procedure has not been applied for carcinogens, at least until ACGIH recently undertook to do this for some classes of carcinogens. I'm not sure we are positive that no matter what safety factor we use for carcinogens, there will not be some finite risk, no matter how large the safety factor, whereas for other kinds of toxic hazards, we can somehow feel assured there won't be a risk. I don't think there is a very clearcut distinction between the two, although people have made that distinction. I personally don't favor safety factors of a no-observed-effect level for anything; I think that system tends to overlook all the dose-response data. But I don't see why there has been this sharp distinction between carcinogens and other kinds of toxic effects in the setting of TLV's or ADI's.

Morris

Let me interject that I'm afraid we are going to have to cut off this interesting discussion in another minute or two.

Bender

I think the answer to that question has to lie in our perception of which effects are stochastic, and therefore unlikely to have real meaningful thresholds, and which are not. I think that it's perfectly possible to theoretically set a TLV for a particular effect, let's take ionizing radiation. Let's say that it's acute death, bone marrow death. Nobody dies of bone marrow death until you get up into the hundreds of rads range. It tapers off, but there is a real, very large threshold, and, consequently, we do not regulate radiation exposures on the basis of such an effect. It doesn't matter that radiation has multiple effects or that chemicals may have multiple effects. We will regulate on the basis of the one which concerns us most, very largely because it is the one that is bound to be dominant as far as human health goes. We don't really worry about ozone in the environment because there is some weak evidence that it's a mutagen and so forth. We worry about it because when you get up to certain levels, people begin to get sick and die and they don't get sick and die for genetic reasons or because of cancer: their hearts and lungs go. So I think this is an important difference and that it bears some on the question of whether it's possible, and if so on what basis, to set a TLV for something believed to be a carcinogen. I think it is possible myself but the basis must be carefully stated and the basis will not be zero risk. It will be some acceptably low risk.

Davis

Let me ask a question. Where do you think the basis should be for occupational standards, developmental embryology, or some other field? I guess my contention is that cancer is not the most sensitive indicator of the hazard of a substance. Cancer takes a long time to develop and is a multistage process with multiple causes. It is not just due to chemicals. It is due to life-style and genetics and a whole host of other factors. And if you were looking for, say, the most sensitive health effect to regulate, the one that would really maximize your health protection, it might be neurotoxicity or it might be immunocompetence or it might be reproductive effects. In my view, it would be something of a short-term nature which would cause morbidity and for which we now have very few data systems in place to collect the data, animal or human. We have this legacy of a tremendous amount of data and money that have gone into creating cancer risk assessment models. This has eclipsed equally valid concerns with other chronic effects, some of which are very short in gestation. Reproduction, even in humans, takes only nine months. We ought to think about the implications of focusing this tremendous energy and intellectual talent on carcinogen risk assessment and identification onto more subtle reproductive or behavorial effects. The recent studies on lead poisoning published in the New England Journal of Medicine in the last two weeks are probably a very good case in point.

Morris

Is there any comment on that?

Setlow

I'll make a response. Since there are no good dose-response data on any of the effects you're discussing, you have no guarantee that there is not a threshold. What we are really worried about is what is happening at low doses. There are good theoretical and experimental data, that have been quoted, to indicate that there is a linear component at low doses, i.e., as Mike Bender said, it is a stochastic kind of a process and the other ones may not be.

Davis

The other ones may not be?

Setlow

May not be this random process. They may be an accumulation of damage such as would lead to death. That is a great end point for radiation. It takes only how many days? Thirty days?

Bender

It depends on the dose range.

Setlow

Yes, but any way, you could get a death end point in thirty days but you're not going to use that as an end point, even though it's faster than a carcinogenic process.

Davis

But you could use fetal wastage if you had data on it.

Setlow

But what's the dose-response curve for that?

Davis

That's what I think we need to develop. But I do think with respect to neurotoxicity on lead and some very interesting neurotransmitter inhibitions, there are data emerging now. It's ironic because lead as you all know has been around for a long long time, and its neurotoxicity has been known since the ancients. Yet we have invested this tremendous effort in cancer.

Morris

A final word, Dr. Bender?

Bender

To amplify on what Dick said, there are other reasons as well for not using an end point such as fetal wastage. One reason for not using fetal wastage in humans is that humans tend to produce more fetuses than they really want anyway and as long as they are lost decently early in pregnancy, nobody is aware of them. Which also makes it very difficult to determine the effect. In fact, there is good reason to think for a number of agents, of which radiation is one, that fetal wastage is not a stochastic process, but rather has a threshold. Furthermore, in many cases where the admittedly sensitive fetus or embryo is exposed, the problem becomes one of what are the important doses. We know that mice in the fetal stages are more sensitive to the production of genetic changes than in the adult stages. But it really has no great pertinence to the question of environmental or occupational exposures, because the bulk of the exposure is nevertheless accumulated by the adults, since the sensitive fetal stage is so short a period in the life-span.

Davis

Actually, I was not thinking so much of necessarily monitoring animals. Really, we do have a lot of children in this country. It would be possible, it seems to me, to look at the kinds of consequences to them of the effects of the levels that are in the ambient environment right now and we are not doing that. Only now are we starting to look again at the whole set of behavioral and cognitive decrements associated with lead where one in five poor black children in inner cities appears to be affected with a level sufficient to cause an IQ decrement. This is fifteen years after the raging controversy about IQ began.

Borg

But those data in themselves are creating another raging controversy.

Davis

They ought to.

Borg

But the validity of the data is what I'm referring to.

Davis

I understand that and they ought to. Those kinds of findings ought to be subject to very fine and detailed review and discussion. Having recently reviewed some of that literature, however, I think that in general the issue will be resolved in favor of the findings of Needleman and Goldberg and Silbergeld and those who are saying that lead has much more subtle neurotoxicological effects than we have ever thought of in the past; and that there probably is not a threshold for some neurotoxicological effects.

Borg

I have not seen the data personally, but I have heard an awful lot of criticism about Needleman specifically.

Davis

Yes, I understand that.

Morris

Well, thank you very much. Now, Dr. Rodricks?

OSHA'S Carcinogen Policy
(Speaker - Joseph Rodricks, Ph.D.)

Rodricks

Most of you probably know that OSHA went through a rule-making process beginning back in the early days of the Carter administration. They wanted to develop a generic policy for identifying and then regulating carcinogens in the workplace. I was not involved with that policy, although at the same time, a beast was formed in Washington called the Interagency Regulatory Liaison Group, IRLG. That was to serve many purposes. It brought four major regulatory agencies together, the FDA, OSHA, EPA, and the Consumer Products Safety Commission, and it established a whole set of tasks that the agencies were going to undertake together to try to coordinate activities, not necessarily the regulatory activities, but some of the ancillary activities that were central to regulation but not regulation itself. One of the committees, for example, chaired by Jim Beal, was on toxicity protocols. The agencies got together and decided that they really could develop toxicity protocols for all kinds of studies that they could use jointly, and they decided to develop those protocols so that there would be a common set that industry would have to follow in dealing with any of the regulatory agencies. One of the other committees was called the Committee on Risk Assessment, and I chaired that committee for about two years. We produced a document called Identification of Carcinogens and Estimation of Risk, the purpose of which was to say that the regulatory agencies could indeed identify carcinogens in some consistent, uniform way. It really didn't matter whether it was food or pesticide, or water contaminant, etc., or an occupational carcinogen, the basic science was identical. It also talked about quantitative assessment of risk, although at the same time we were developing this document, OSHA was going through a rule making in which it considered quantitation of risk but at the same time wanted to reject it for regulatory purposes. So we had that problem in OSHA. They had really decided during the course and after the rule making that they did not want to include quantitative risk assessment in the process of regulating occupational carcinogens. So the IRLG document really had to go softly in the area of quantitation to accommodate all the views. It simply said it may not be appropriate for all regulatory purposes, but if it is done, here is our recommendation on how to do it. We basically promoted models of the type that you've been hearing about here for the quantitative aspect. That IRLG document, did deal with all four aspects of risk assessment I described yesterday, and it became a document which the agencies accepted for a few months, until the Reagan Administration came to town and ended all IRLG activity. The IRLG, by the way, also had undertaken to do a similar kind of analysis of reproductive hazards. They spent a year and a half gathering a lot of basic information but didn't get to the point of putting it together in some coherent form before the IRLG was disbanded, and all that work, I think, has so far gone to waste.

The OSHA cancer policy is, as I said, a huge record, about 250,000 pages. Some of you may not like what OSHA did finally and how it treated the science. A major criticism is that its treatment was far too rigid and inflexible. It set up minimum criteria for the acceptance of certain kind of data which many people thought were just too demanding. It elminated too much information. But that record is invaluable. It contains an enormous amount of information and very useful analysis. All of the same issues we have been talking about here came up in that record, including quantitation of risks. OSHA rejected

quantitation of risk in that regulation but it has an extensive discussion of the problem of quantitative risk assessment that I think you would find terribly valuable here. I also should mention what Devra said about the history here. There is a long record of what I call guidelines for carcinogen assessment. Most of the guidelines do not get to the question of quantitation, but there are reports, produced during the mid- and late '60s, from the Department of Health, Education, and Welfare, concerning pesticides that are carcinogenic and the kinds of evidence appropriate for assessing such hazards. There is a long record, reflected in the work of the National Cancer Advisory Board, the IRLG, and the IARC which, although fairly limited in scope, all point in the same direction. So we're not working new ground here at all.

I think, however, improvements can be made. OSHA is now attempting to do that. Their carcinogen policy regulated no carcinogen at all, but rather set up a scheme which said that once you identified a carcinogen and you had a certain degree of experimental or epidemiological evidence, it became a Category 1 carcinogen. Once you had established that, then the goal was to reduce exposure in the workplace to what OSHA called the lowest level technically feasible. In other words, the OSHA scheme did not go beyond identification of the carcinogen. OSHA applied that idea in the case of benzene, and was challenged by the American Petroleum Institute (API). The Supreme Court finally agreed with the API and said that it wasn't enough for OSHA to say that if something was a carcinogen and if you could find it in the workplace, you had to reduce exposures to the lowest level technically feasible. They had to go beyond that and make some attempt to show that whatever exposures existed presented a "significant risk." The Supreme Court did not define this term. I think the record suggests that "significance" is certainly a matter of quantitative risk but not only that; other qualitative factors could also be used in the determination. The Court talked about ranges of sigificance and insignificance. Risks of one in one thousand are clearly significant, they said, assuming you have strong evidence that the chemical is a carcinogen. The Court also said that one in one billion is perhaps insignificant, but they refused to say anything about the millionfold difference between those two extremes of risk. So OSHA now has to reconsider its carcinogen policy in light of that benzene decision and will be going through another rule making. The OSHA policy now will come to grips with the problem of dose-response evaluation (or potency), exposure evaluation, and risk estimation, and will make some specific proposals on how OSHA proposes to perform these evaluations. Then OSHA has to answer the question of significant risk. The two demands on OSHA are to show that under a current standard, a significant risk exists, and that if you then reduce the standard to some lowest feasible limit, there is a significant reduction of risk.

As far as I know that is now the only activity concerning carcinogen policy in Washington, except what Roy Albert described concerning these policies and the group the White House put together under Keyworth to replace the IRLG. They were going to reevaluate the IRLG's work, but they have been silent so far.

Discussion

White

How familiar are you with the proposed benzene standard? More specifically, with the de minimis quantity section and how that level was ascertained?

Rodricks

Well, which standard are you talking about? They proposed to reduce the exposure limit from 10 to 1 ppm.

White

Under the scope of the proposed benzene standard, mixtures that contain less than 1% were excluded from its provisions.

Rodricks

I'm not familiar with that. I can't talk intelligently about it. There are many others here who can.

Hattis

I think that the 0.01% idea is really arbitrary. I mean I do think that there is a need to make some determination in particular cases of what component of a mixture is likely to significantly affect your regulation of it. But if you told me that there was 0.01% of tetrachlorodioxin in, say, something made from trichlorophenol, I'm still worried about that. Because that 0.01% of very potent stuff might well dominate the reponse to the mixture. So I think that basically the cutoff of what you regulate has to be some product of the concentration times the relative potency of the component.

Prepared Comments

Suggested Propositions for Concensus at a Workshop on Problem Areas Associated with Developing Carcinogen Guidelines, September 7 and 8, 1982, Brookhaven National Laboratory

Devra Lee Davis

I. Animals vs Humans

1.1 Animal studies are more readily available on existing chemicals than are epidemiological or other human studies.

1.2 Human studies only document <u>past</u> risks, not current or future ones.

1.3 Therefore, as to <u>future</u> risks, animal studies must be relied on exclusively in most cases.

II. Short Term vs Long Term

2.1 Concerning animal studies, more short-term and acute tests are available on new and existing chemicals than are long-term or chronic tests.

2.2 Almost all chemicals which cause cancer in humans, cause cancer in animals.

2.3 Oncogenes, or cancer-causing or cell-transforming genes, are virtually identical in mammals and humans.

2.4 Therefore, agents which transform mammalian genes should be regarded as "if they presented a carcinogenic risk for human." (IARC, 1979)

III. Thresholds? Linearity?

3.1 Thresholds may exist for individual chemicals in individual organisms.

3.2 In heterogenous human populations, some hypersusceptible persons exist.

3.3 The unborn, neonates, and the (immunologically) young are more easily compromised and have more sensitive metabolisms than do adults.

3.4 Therefore, given the normal distribution of susceptibility and the vulnerability of the young, thresholds have no practical policy implications, and linear interpolations should generally be performed.

IV. Potency: Valid but Not Useful

4.1. For a single health effect, such as cancer, chemicals can be logarithmically ranked as to potency.

4.2. Most chemicals cause multiple health effects.

4.3. People are exposed to multiple low-dose carcinogens and mixtures of toxins in the ambient environment.

4.4. A weak carcinogen may be a potent neurotoxin etc.; or carcingogenic potency and other health effect potencies are not necessarily directly correlated.

4.5. Therefore, given the multiplicity of effects and exposures, carcinogenic potency is of limited policy value.

V. Limits of Cost-Benefit Analysis

5.1. Ordinarily, economic benefit-cost assessments rely on bottom line toxicologic estimates of health risks.

5.2. These assessments involve numerous economic and toxicologic assumptions.

5.3. Therefore, cost-benefit analyses, like risk assessments, are, at best, tools for decision making, as opposed to rules for decision making.

VI. There Can Be No Scientific Regulation of Carcinogens

6.1. Diverse, basic-science-forcing environmental laws and regulations exist.

6.2. Some require "health only" considerations in triggering regulatory action.

6.3. Most require some balancing of health benefits and economic costs.

6.4. Therefore, carcinogen regulation remains an issue for administrative discretion. Or, science can determine how best to identify carcinogens, but not how best to regulate them.

VII. Cancer Policy Documents

7.1. Cancer identification policies have been under development throughout the past decade.

7.2. IARC, 1979, OEDC, 1979, IRLG, 1980, and the State of California, 1982, generally concur on major issues of carcinogen identification.

7.3. Therefore, these documents should remain the major point of departure for discussion of policies to identify carcinogens.

VIII. Time to Regulation

8.1. OSHA has set standards for less than 20 carcinogens in over a decade of existence.

8.2. EPA has set standards for a handful of toxic air pollutants, and for toxic water pollutants only after protracted litigation.

8.3. IARC, ACGIH, and other such groups proceed slowly by scientific consensus to identify carcinogens.

8.4. Since regulation proceeds so slowly, decisions must necessarily rely on incomplete best-available evidence as to health and other risks.

Other Issues Not Addressed Above.

- Essential micronutrients as high-dose carcinogens
- Background vs added doses
- Benign vs malignant tumors
- Central board review vs guidelines vs "creativity"

SUMMARY

Introduction

White

Dr. Richard Setlow is going to summarize what has occurred over the last two days. I have asked him if he could make his comments with respect to the needs of the Center in terms of developing a carcinogen policy. Dr. Setlow is the Chairman of the Biology Department at BNL and is a member of the Center's Advisory Panel.

Summary Comments
(Speaker - Richard Setlow, Ph.D.)

Setlow

You must remember that this workshop was called together for a particular purpose. It wasn't really aimed at solving the general problem of carcinogenesis in the world from exposure to all sorts of chemicals. The primary purpose of this two-day workshop is to assemble key members of the scientific community with the Center staff and its advisory panel, thereby providing a forum for addressing some of the fundamental issues which serve as major drawbacks for current regulatory guidelines on occupational exposures to carcinogens. So, the major emphasis is to get some guidelines to help set occupational exposures. But first let me make some rather general comments. Some of them have to do with what we know of a fundamental nature which is really all that I know about this subject. That is the question of why we concentrate on carcinogenesis and not on other end points, and again the best place to draw some of this information is from ionizing radiation studies where, as has been pointed out, there are real thresholds for killing people by ionizing radiation. Once you get over that threshold, in a rather narrow dose range, the probability of death approaches 1. At these doses, somewhere over 500 rad, the probability of getting cancer is negligible in terms of this probability of 1. The number of cancers made by radiation at these doses is really very small compared with the number of deaths that you might get. So if one were to plot such dose-response curves, for lethal affects a curve such as Figure 1 would be obtained.

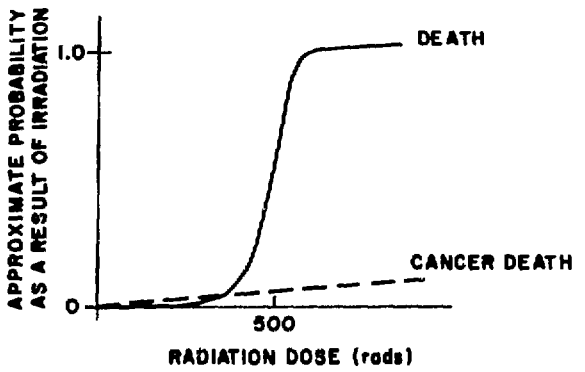

Figure 1

Actually, the best kinds of data that we have for human epidemiology come from radiation fields. One of them is ionizing radiation and those of you who follow these fields know that even in that case the dosimetry is uncertain at the moment. So this is a problem that is peculiar, not just to chemicals, but also to ionizing radiation. Dosimetry is uncertain. In the case of ionizing radiation the best kind of theoretical fit for the available data is that for acute doses. The kinds of response that we're talking about, the probability of getting cancer, goes as some constant background rate plus linear and higher-order polynominals.

$$\text{Excess Probability} = \alpha D + \beta D^2 + \ldots .$$

If you went to high enough doses, there are other killing factors, and our job, therefore, really is to know how the coefficients alpha and beta vary. It's important to recognize that such coefficients, which are evaluated for acute exposures, are also functions of the dose rate. When one gets very low chronic exposures, which is really what we are concerned about in these cases, the coefficients decrease. We don't really know how they decrease. We really don't know very much about the functions. Certainly not in the chemical case. For ionizing radiation and at low doses, there is a predominant linear term. There are good theoretical reasons for that linear term and all that I want to say is that alpha, the slope, decreases as the dose rate decreases to some minimum value, not necessarily 0. So that's ionizing radiation.

The other case for which we have a great deal of human epidemiological data is also a physical carcinogen. It's the only one that I know anything about. It happens to be ultraviolet radiation and its production of skin cancer. It's not a lethal disease, but it is so prevalent in the United States white population that it is rarely counted. There are of the order of 400 or 500,000 new cases per year of skin cancer in the United States. Skin cancer incidence follows a law in which the log of the cancer incidence is equal to some constant plus another constant. I'll call it A, times the average yearly exposure. So in this case, we know from the epidemiological data that skin cancer incidence increases exponentially with exposure. It's the log of the incidence that's proportional to the average yearly exposure, and the only problem with the interpretation of such data is that you don't really know how much an individual is exposed to. Bob Drew obviously has had a reasonable exposure recently, and others of us have had apparently little. It's averaged over the world and not necessarily people. It's exposure at the surface of the earth and it depends on whether you have gone outside and it depends on your complexion and so on. There are tremendous numbers of data of that type.

The only reason for talking about this is to indicate another case in which everyone presumably is primed and well above such a threshold, if one exists. This again is the same kind of problem that we have for chemicals. We don't necessarily know what an individual receives. You don't have an ionizing radiation dose meter on such people. You know what's in the atmosphere and the surroundings. That was just to set my sights as to what I'm going to try to say. We have discussed such things as cumulative doses. Most of the effects of some of these stochastic processes depend upon the accumulative insults and in the case of ionizing radiation, by the mere fact that we call it ionizing radiation, we mean that we agree with one another that after putting in certain correction factors we can add up the doses so you can use a dose meter and even though there may be what we call different relative biological effectiveness, we can add them up. The same is true to a certain extent for ultraviolet radiation. We don't know what to do about chemicals.

We speak about chemicals as damaging DNA and that this is an initiation event, but most chemicals damage DNA in different ways, unless you take very very narrow classes of chemicals, and even there they make different kinds of products in DNA. For example, one of the classes that is most studied is the nitrosamines. But there are nitrosamines that alkylate DNA with methyl groups or with ethyl groups or with propyl groups, and these could all be very different and the different nitrosamines can give rise to chemicals that alkylate different groups on DNA. It isn't apparent how one should do the dosimetry from sums or mixtures of agents and perhaps that's why it's wise to be a little conservative and speak about ionizing radiation since everything you know is commensurate. You can have one standard for chemicals, but maybe we should be a lit-

tle more careful be cause they are liable all to be additives. We don't have a good dosimeter that averages all those things.

The question of background came up and was discussed. How should one treat background cancer risks or any other risk? It's not very clear how to do this. The usual argument is to make the assumption that the kinds of changes that result in background are similar to those that might result from chemicals. There's no good reason to make that assumption, but that's usually what's done. There is no reason why it's the same kind of damage to DNA. If one looks at the kinds of damages to DNA that we are experiencing as we sit around in this room, they are probably very different from what you would find in the occupational workplace. Completely different kinds of damages result from our existing at 37°C and sitting here and drinking coffee than being in some other place and it's not clear that those should be added in the same fashion. We don't really know what to do. It brings us back to the point that we have to know how these various agents work before we can make rational estimates other than wishing that we knew what the shape of dose-response curves were. We have to make such rational estimates if we are to get some kind of estimates, but we don't really have a lot of the background information necessary to do this.

Lastly in this summary, let me elaborate on a point that has come up before and that is the variations among people. In the response of different individuals, we like to think of ourselves as homogeneous. Obviously we are not. There are two kinds of responses that we know a great deal about, but we do not know what influence they have on the response of individuals. One of these aspects is the metabolism of various chemicals. Most of the chemicals we are speaking about are not direct-acting carcinogens and if they were, they would be too reactive and wouldn't do anything. So they must be metabolized and it depends upon what your metabolic pathways are compared to mine, as to whether you have damage or not. There is no indication that they have to be identical or whether, if you're primed to make more agents, this is good or bad. In any event there are lots of data indicating that individuals differ in their metabolic activities. We don't know how to take this into account except that this would be expected to broaden the variance, if anything, in the normal population. A second aspect which again is focusing on the initiation aspects has to do with the repair of damage that's made to DNA. We know, at least from the extreme cases, that relatively small changes in the capacity to repair DNA might produce very large changes in response.

The only ones we know of very clearly are some of the genetic-defect diseases. One of these that's been alluded to is xeroderma pigmentosum, in which the individuals are constitutionally defective in their ability to repair ultraviolet light damage. These individuals, among other things, get skin cancer at a very early age. Their risk to sunlight-induced skin cancer is in the neighborhood of 10^3-10^4-fold greater than normal. Luckily, they are a small fraction of the population so they don't really appear in any population effects. But we do know that the genetic defect in these individuals that results in defective repair, and increases their risk by, let's say, a factor of 10^3 or 10^4, is not a 100% defect. It's hard to get estimates for populations, but this defect, let's say, just to average it crudely, is not 100%, but is around a 70% defect. There aren't very many other data of this sort, but what I'm saying is that a defect of 70% could give rise to changes of the order of 10^3- to 10^4-fold in risk from a carcinogen that everyone is exposed to -- sunlight. Most of us do not have this disease and we repair the damage. That means, unfortunately, we don't really know too much about the dose-response curves, that smaller defects could account for perhaps 10-fold changes in the

amount of susceptibility. Hence a big variation in the population may come from variations that you would usually describe as normal. We do know that there are repair variations which exist between normal individuals. How much of this is experimental, how much is life-style, and how much is some physiological or genetic background are not known, but there exist differences in the normal populations of the order of 2-fold in the ability to repair DNA. This is another big variation. We don't really know how this varies from one individual to another.

The last thing I should say about repair systems is that in all instances known, the repair systems are not saturated for chronic exposures. They are always probably operating at their maximum speeds and the doses to people that we're speaking about are always nonsaturating ones. The difficulty in extrapolating dose-response data from animal studies to humans is that in many instances the doses to which animals are exposed are probably saturating doses for some of the repair systems or for various metabolic activation systems. That really raises problems in extrapolation, especially because for several of the repair systems that have been looked at, rodents are defective compared to humans. That's an extrapolation problem that has to be put in perspective.

Now the question is, How can we apply everything that we've heard of to the questions that Otto has raised? How can we help to set the stage, advise the Center for Assessment of Chemical and Physical Hazards how to develop carcinogen guidelines for the Department of Energy for its workforce (which is really what the Center is supposed to do) not make carcinogen guidelines for the whole world or the United States population. For most of the chemicals that the Center deals with, we find that there isn't a tremendous amount of carcinogenic data. They have really been chosen, in a sense, for this reason. If there were a tremendous amount of carcinogenic data, they would have been handled by some other occupational procedure. So most of the chemicals the Center deals with have very few data available and where there are data there are certainly negligible human data. Where there are some animal data, how should one deal with them? I have no answer for that question. Really, Otto, maybe you should ask particular questions of the assembled group, since this is the last crack that you will get at them. Maybe you'll get some specific answers.

Discussion

White

In the remaining few minutes that we have, I think there are some key questions that would be worthwhile for the Center staff to have answered as we go about our tasks. One question is the importance of a potency parameter. One critique that we have had within the DOE community and at Brookhaven is an expressed need to categorize these carcinogens in terms of potency. Whatever control process that you would hope to incorporate in terms of safety protection must also reflect the potency category. For example, aflatoxin B1 is certainly in a different category than, say, formaldehyde or paradioxane. So as a first attempt, we have tried to put together a potency matrix which in this case is identical to the ACGIH breakdown. This matrix has been described today as a crude mechanism for trying to establish a ranking system for these compounds. However, there are probably several hundred compounds which need to be so classified. One suggestion has been that we take the individual compound and go through an evaluation and apply various dose models and make some prediction and find what could be characterized as a practical threshold or an acceptable level of risk.

Setlow

Let's not use threshold. Let's use another word.

White

We'll leave it at the acceptable level of risk then. To characterize on an individual basis several hundred compounds, I don't think is a practical approach for us as a way to generate policy or protective measure for the Department of Energy community within the near future.

Drew

Otto, are you saying that you have several hundred compounds that are unique to the Department of Energy, that have not been considered by other agencies?

White

No, that's not quite true. Generally the Center would be addressing compounds that are unique. However, in the absence of a carcinogen guideline or policy for federal agencies or the general public, DOE is putting forth a forward posture in deciding that it will provide a safe work environment in the absence of some general policy. We would develop an interim policy until OSHA or some other regulatory agency promulgates a more uniform standard. The only thing that really exists in terms of regulating exposure to carcinogens is the original OSHA 14 and some 6 or 7 additional compounds. Asbestos, for instance, is an additional carcinogen which has in effect a threshold limit value of two fibers per cc, whereas the 14 have no acceptable "airborne levels." Given the unsuccessful attempt to reduce the current threshold limit value for benzene based on the fact that it has been shown to be carcinogenic, there is an absence

of sufficient regulatory information and guidance needed by DOE to protect the community and their workforce.

Morris

It seems to me from your standpoint it would be much easier to look at things from the other way around and ask in a practical way what are the DOE contractors that are working with these materials going to do? It seems to me that all they can do is to treat the exposure to the chemicals in some ordinary careful way, just as you would treat anything you thought might be toxic with good industrial hygiene controls and clinical monitoring of the people and what have you. Or they can treat them in some heroic way where they either don't use that compound at all and take, you know, inordinate costs to find replacement materials or only work on it in glove boxes or something like that. It seems to me those are the two general ways that you have to deal with things. If you can separate things into those two categories, that may solve a practical problem for how people do it.

White

That's basically what we have proposed. That is, we would break down those chemicals which have been identified as carcinoganic on the basis of some toxicity or carcinogenicity or potency as we have been discussing for the last two days. Traditionally, the control mechanism that you develop for a specific chemical depends upon its overall toxicity. We would set classes of chemicals, some that would be safe to work with on a lab bench, others that would have to be used in laboratory hoods, and still others that would require the use of even stricter containment. Basically, that's what we're saying in respect to these chemicals. Now one of the problems is how do you differentiate levels of potency or toxicity or carcinogenicity?

Setlow

Suppose they're plus, suppose they're carcinogenic. Things differ in carcinogenicity from aflatoxin to formaldehyde. You have to have some means of accommodating those extremes.

White

What we have done is use the ACGIH criteria. Now it would be of value to the Center to have some feedback on that. That's in the handout I gave out this morning as to whether or not that is a valid mechanism. At one point today it was described as an extremely crude process.

Morris

But your process is bound to be extremely crude. I mean you describe the whole way that we set regulations as being pretty crude and you're talking about setting DOE standards on the things that are not yet developed to the level where people are ready to set regulations on them. So, I mean the whole premise has to be, that whatever you do is going to be incredibly crude.

White

The problem areas that we have identified and are trying to address are just that. They are problem areas and represent concepts for which more development is required and maybe the prudent approach for the Center is to take these crude measures such as the ACGIH and try to develop some mechanism for suggesting regulations for carcinogens. It is a step above what is currently available and what is in the process of being proposed (i.e., OSHA is proposing criteria for classifying a substance as a carcinogen, but not taking into consideration the potency of the compound). So it's likely on the basis of whatever data base exists to have highly potent carcinogens and fairly weak carcinogens classified as an OSHA category 1 carcinogen. What we would propose is somehow establishing a ranking system for those materials which would be an improvement as far as workers at Brookhaven are concerned.

Setlow

To me that seems like a rational way to proceed. If you think of something as a carcinogen, then you want to know whether it's in a very dangerous, or intermediate, or not very dangerous category. And on that basis set what you agree is a sort of crude estimate of potency. You know what the general exposure is in the DOE facilities and that can be used to accommodate data for suggested guidelines for reducing exposure or not.

Barancik

But do we know the corollary health affects on the DOE employees?

Setlow

Of course not. There are no data in most of these cases. There are no data on human health effects. There are animal data from which one might extrapolate.

Barancik

One point that is very clear from the last two days of discussion is the need to have adequate surveillance of the occupational groups, and we still do not have that. There are efforts to improve this throughout this country, but the restrictions on access even to existing human data for epidemiologists are great and increase each year. In other words, the availability of even existing data is becoming more restrictive so that epidemiologists' use of such data potentially is going to become more limited. So it would seem that one factor to be considered here along with all aspects of risk assessment that have been discussed is that we all have to go back where we started working with organizations and discuss it with our epidemiologic colleagues. We need to design studies that include elements that are useful in risk assessment as defined here. The epidemiological community uses a different jargon in describing the same problems. The term accident is used here which, in epidemiological circles is a term that we're not very comfortable with.

Setlow

I think one of the problems that arise from the cases that I have come across in the Center's analysis is that the number of individuals exposed to some of these chemicals is relatively small. I don't remember what some of the numbers for some of the chemicals are, but they are very small in epidemiological terms. The probability of obtaining any meaningful epidemiological data from those is negligible. It's useful to follow them for perhaps toxicological reasons, but for a carcinogenic risk, I don't think you would get any data.

White

I think it is possible that we may get some guidance from this and that we take the approach that we are going to use, say, a crude mechanism in developing some ranking of the carcinogens and develop some safety guidelines based upon the category that the chemicals fall into. Through the surveying of the DOE community, it is possible once we have that ranking to couple it with potential exposure data because we did ask in a survey that was distributed for the number of workers that were likely to be exposed to various compounds and the quantity that existed at that time within that DOE facility. So that may serve as a combination of those two elements may serve as guideposts for identifying compounds that the Center will want to address in more detail and develop specific standards which are based upon some lowest practical risk considerations.

Fischer

Here's a suggestion that's only partly in jest: if the guidelines the Center is developing are meant to serve DOE as interim standards until final standards can be promulgated, then the permissible range of "error" in setting standards might be greater; for example, five years of exposure to an interim standard which was then lowered by a factor 10 in the final standard for the rest of the person's life would result in his total lifetime exposure being of the same order of magnitude, because of the relative shortness of time over which an interim standard is intended. I don't know how far you would want to seriously push something like that, but it is a consideration.

Drew

Given the examples that we were given this morning with regard to how long it takes to regulate, I don't think that is a very practical approach. I have a feeling that if we set standards then, at least for DOE, they're going to be cast in concrete and copied for quite some time.

Fischer

It only makes sense if you're really convinced that this is an interim standard. If you have any suspicion that it's not, then of course you wouldn't do any such thing.

Drew

Well, I think that it would be nice to have an interim effort, but other agencies are going to take one look, and they're either going to agree or disagree. If they disagree, it's going to take a long time to begin to make them more rigorous. And if they agree, that's as far as it's going to go. I think it would be a mistake to consider these interim standards, unless you define interim in terms of decades.

Baum

The three-category system you're speaking about already has quite a wide range of containment capability to cover this problem that Dr. Setlow was referring to with the wide range of potencies we have to consider, even if something has been classified as a carcinogen. You could further extend that range of coverage, however, by requiring additional containment of some sort, depending on the potency, so that if it is a carcinogen and a highly potent one, then not only do you have to have it in a glove box, but perhaps double containment in a glove box or limited quantities in a glove box, or additional precautions could be built into this system you're speaking about.

White

Well, we have three levels. It may be a useful exercise to show what we have at a later time to the panel and get some feedback in terms of whether or not the three levels of protection have built into them sufficient elements of protection to cover the broad range of toxicity.

Hull

I don't disagree with John completely, but it seems to me the desire in whatever schemes you need to arrive at regulatory limits should be to keep the basis as simple as possible. It seems to me that if you have three categories, that ought to be enough. If it's not enough, rather than to superimpose fine structure on these categories, you ought to have another category. That's what you're doing de facto if you're tailoring individual categories. To me, radioactivity, particularly internal burdens which are inside the body, provides a fairly good analogy, except that you don't have a rad equivalent for other carcinogenic agents. Therefore, you have to go back to a surrogate for potency. The point is that you're basing your limit on a risk number and radiation standards are based on risk numbers, imperfectly known as they are. Obviously I realize there is a big problem in terms of most of these agents. You don't have human data, therefore you have to go to animal data. In fact, we haven't good animal data for all nuclides. When they're not available, you generalize from an analog and try to have something consistent with it.

Bender

It seems to me that we have arrived at some sort of consensus about some features of this. Some number of categories of carcinogens are going to be created and they will be treated differently. Perhaps it's three, perhaps it's four, but some number, and in assigning compounds to that set of three or four categories, certain elements are involved. One of them, apparently, is confi-

dence that the material really is a human carcinogen, and ways have been proposed to handle that, rating them 1, 2, and 3, or something like that, depending on the nature of the evidence. Then there is the question of potency. There doesn't seem to be a lot of agreement on exactly how you rank them as to potency, but something surely can be done that is reasonably good; it doesn't have to be perfect. Then I suppose there is something of the notion of a de minimis quantity, i.e., what is the risk, that is to say if I have a milligram of something that is a potentent carcinogen, and I swallow it all, what is my risk? It's clearly different than if I have a box car load of it, and this is the third thing. There are probably some others. The decision on which box to put this in as far as regulation goes is some function of all those things. Maybe it's simple, maybe you add them all up and divide by three, or something. I don't know exactly what it ought to be, but it seems to me that a consensus agreement could be arrived at that would allow you to proceed with this process at this point.

Borg

The previous two speakers have covered part of the ground I wished to cover, so I'll make my remarks brief and make a plea that in considering carcinogens, whether it be in three or four ranks, you also set up your guidelines, as I think was suggested by both Hull and Bender, to look at the hazard. You didn't want to classify them according to the amount of material available for exposure but as to the procedures to be followed, but you should, if I understand what Dr. Bender said, fold those things together. We used to have here at the Laboratory a safety standard that gave some consideration to the concentration of the putative carcinogen and the amount, and you treated, at least at the laboratory level, the material differently depending on it. I think that was good advice, that should be now backed up by the dose equivalent, the potency of the material, so that you don't treat the same amount of potent material in the same fashion as one that is less potent. But in addition you gave us useful guidelines then, and they were practical. I hope that you will continue to consider those same factors. One of the other sets of factors you considered then was volatility or particulate nature, in short, how difficult it is to contain something. A dilute solution in small amount is one thing. A highly volatile material of high potency is another. Those are factors not to lose sight of, that's all.

Bender

I suppose that's exposure potential, that might be a factor D in this some kind of equation.

White

I think it might be worthwhile to show the first overhead I used this morning. In categorizing a carcinogen on the basis of its potential hazard, we are suggesting taking into consideration the carcinogenicity, which has wrapped up in it potency, the chemical physical factors which take into consideration not only volatility but to some degree its potential for dispersion, and the third factor, the operational activities which will enhance that dispersion capability (see IV-36).

Drew

Your concept of exposure combines the second two of those three.

White

Exposure is wrapped up in those two, right.

Bender

Exposure potential, I suppose. I'm not sure I understand what you mean by use. If I put it in a petri dish, then you worry about it more than if I keep it in a serum bottle with a stopper.

White

And whether or not you're spraying it vs painting it or transferring it from a weighing device, considerations such as that.

Bender

I guess what Don and I are proposing is to feed more things into it and see if you can't make something workable out of it. I think some of these things have to be questions such as, how much is there going to be around anyway, even if I was exposed to all of it, for the risk to be acceptable? I would accept something like that myself, such as glove box etc. regulations.

Hull

I have a little problem with the last term in that equation. To me it's a controllable one either through engineering, administrative practices, or what not. So, it's really a function of what you think about the first two terms, isn't it?

Bender

I think it is more than the first two. That's just the point. The concern of those of us in the laboratory is that our milligrams or micrograms of some potent carcinogen, no argument about it, are going to force us to do things that are impossible, such as weigh out micrograms in a glove box, which I've never been able to do. It's just as simple as that. The maximum hazard, there, if I've got a milligram or a few milligrams in a bottle, and it's diluted, for example, down to nanograms per milliliter, of which it is unlikely I could ingest or inhale very much without deliberately trying, just has to be considered.

Setlow

But these aren't at the moment aimed so much at the laboratory, are they, as they are at processes -- industrial processes?

White

These guidelines are intended to include laboratory applications as well as production facilities; it's the entire DOE structure. So whatever the laboratory concerns are, they ought to be included in the criteria for the guidelines.

Bender

That's just what I'm getting at here. I think we run the risk that what is practical for nonlaboratory production facilities is going to end up a millstone around our neck. This question of the maximum quantity to be handled, for example, is very important to us on the laboratory end of it. If we can get an exemption for less than a gram, say, or less than 100 milligrams, I'll be very happy.

Borg

Just in this context, and you've heard me say many times before, let's also not lose sight of things to the point where we treat laboratory hazards differently from the way we treat cigarette smoke and smokers. We don't dress up in white suits when we come into a room in which someone smokes etc. So let's have some level of minimum hazard that doesn't mean we have to turn the world upside down, and it ought to compare with the environmental hazards we face all the time such as cigarette smoking and the exhaust out in the parking lot.

Spangler

I haven't yet determined where you're factoring in cost benefits in this thing. It seems to me that since what you're proposing is extremely crude, as you put it, you ought to propose anything that you do as a guideline and have a sort of escape hatch clause that would require anyone who believes a hazard to be too costly to eliminate to then begin to study cost and whether there are substitute technologies. I think we have to allow some sort of relief for unreasonable expenditures to save a life. If I tried to say anything in my talk today, it was that as a very minimum you would want to have a cost-effectiveness standard because that isn't very complicated.

Hull

I was just going to say, addressing myself to Mike's question with regard to radioactivity, the NBS handbook has some rough guidance in a few categories. It has limits for how much you can have open on the bench, what quantity necessitates containment in a hood, and at what quantity you should utilize a glove box. It's obviously different for tritium on one hand and plutonium on the other. It seems to me this same conceptual thing could be folded into carcinogenic chemical guidelines.

Setlow

I'm going to make only one further remark and let Otto have the floor for the other two minutes. You have to remember that we don't really understand the carcinogenic process. I've spoken and other people have as if we do. That's

not true. We know what happens in single cells, but when you come to whole animals a very complicated process is going on. Radiation happens to be a very simple case, the chemical ones are much more complicated. We don't really understand that. We don't understand these long latent periods.

White

I will just close by saying that we hope to get some cost-benefit feedback as the draft of these documents is presented to the various components of the DOE community. I think one problem in cost-benefit analysis that cuts across the board in terms of different types of activity, laboratory vs operational activity, is that often the chemical which you are addressing has different cost-benefit values as you apply it to the various operations in which it is used, and it is hard to start off on a regulatory basis or on a guideline basis for controlling that one chemical unless you have all the input from the various operations to which it is going to be applied. So we hope to get that kind of input from the review process, but certainly we can take a look at those operations where we are aware that the compounds are going to have some major impact, and that should be available to us from the survey which we conducted.

I will close by saying that we thank everyone for participating and presenting their views, and the Center and the staff will take these comments into consideration in continuing the development of the DOE carcinogen guidelines. Thank you.

APPENDIX

A Workshop on Problem Areas Associated With Developing Carcinogen Guidelines

September 1982

Berkner Hall - Room B
Brookhaven National Laboratory
Upton, N.Y. 11973

Working Agenda

	TOPIC	PARTICIPANTS
9/7		
10:15-10:30	Prologue	Victor Bond Otto White James Brower
10:30-12:00	Session I. Definition of a Carcinogen for Regulatory Purposes	Kim Hooper Roy Albert Leader: Robert Drew
1:30-3:00	Session II. Potency	Harris Fischer Troyce Jones Roy Albert Leader: Andre Varma
3:15-4:30	Session III. Risk Assessment	Joseph Rodricks John Van Ryzin Leader: John Baum
5:30-7:30	Banquet	
9/8		
9:00-10:15	Session IV. Uncertainties	Edmund Crouch Dale Hattis Kenny Crump Leader: Donald Borg

Working Agenda (Cont'd)

	TOPIC	PARTICIPANTS
10:30-12:00	Session V. De Minimis Quantity	Miller Spangler Leader: Michael Bender
1:00-2:30	Session VI. Legal and Regulatory Issues	Devra Lee Davis Joseph Rodricks Leader: Samuel Morris
2:30-3:00	Summary	Leader: Richard Setlow

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