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Workshop Report on EPA Guidelines for Carcinogen Risk Assessment

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Workshop Report on EPA Guidelines for Carcinogen Risk Assessment

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EPA Contract

for the

Risk Assessment Forum
Technical Panel on Carcinogen Guidelines

U.S. Environmental Protection Agency
Washington, DC 20460

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WORKSHOP ON CARCINOGEN RISK ASSESSMENT

January 11-13, 1989

Virginia Beach, Virginia

INTRODUCTION

On September 24, 1986, the U.S. Environmental Protection Agency (EPA) issued guidelines for assessing human risk from exposure to environmental carcinogens (51 Federal Register 33992-34003). The guidelines set forth principles and procedures to guide EPA scientists in the conduct of Agency risk assessments, to promote high scientific quality and Agency-wide consistency, and to inform Agency decision-makers and the public about these scientific procedures. In publishing this guidance, EPA emphasized that one purpose of the guidelines was to "encourage research and analysis that will lead to new risk assessment methods and data," which in turn would be used to revise and improve the guidelines. Thus, the guidelines were developed and published with the understanding that risk assessment is an evolving scientific undertaking and that continued study would lead to changes.

As expected, new information and thinking in several areas of carcinogen risk assessment, as well as accumulated experience in using the guidelines, has led to an EPA review to assess the need for revisions in the guidelines, particularly in the areas of classification of carcinogens and the decision logic for when and how to apply quantitative risk estimation methods. On August 26, 1988, EPA asked the public to provide information to assist this review (53 Federal Register 52656-52658) and on December 12, 1988, the Agency announced that a workshop for analysis and review of these issues would be held in Virginia Beach, Virginia on January 11-13, 1989 (53 Federal Register 49919-20).

The Workshop was part of a three-stage process for reviewing and, as appropriate, revising EPA's cancer risk assessment guidelines. The first

stage began with several information gathering activities to identify and define scientific issues relating to the guidelines. For example, EPA scientists and program offices were invited to comment on their experiences with the cancer guidelines. Also, the August 1988 Federal Register notice asked for public information on use of these guidelines. Other information was obtained in meetings with individual scientists who regularly use these guidelines.

The Virginia Beach Workshop completed this information-gathering stage of EPA's preliminary review of the guidelines. For the Workshop, EPA assembled experts in various aspects of carcinogen risk assessment to study and comment on the scientific foundation for two general aspects of the guidelines. As outlined in the Workshop agenda, workgroups studied "qualitative" issues bearing on the classification of chemicals as potential carcinogens and "quantitative" questions on extrapolating data from test animals to human populations.

EPA emphasized that the agenda had been deliberately limited in two important ways. First, although the Agency recognized that many issues were ripe for discussion, the Virginia Beach Workshop was limited to the specific subject matter areas outlined in the agenda. EPA plans to study other issues in later stages of its review. Second, EPA stressed that the Agency was not expecting consensus on, or resolution of, all issues. Rather, the Workshop was an information-gathering exercise -- a scientific forum for objective discussion and analysis among the invited panelists. Background issues papers were developed to help focus discussion on technical questions, and the Chairman of each workgroup session prepared a brief summary of each discussion for presentation at the closing plenary session (Section 3 of this Report).

In the second stage of the three-stage guidelines review, EPA will analyze the information described above to make decisions about changing the guidelines, to determine the nature of any such changes and, if appropriate, to develop a formal proposal for peer review and public comment. EPA's analysis of the information collected so far suggests several possible outcomes, ranging from no changes at this time to substantial changes for certain aspects of the guidelines.

In the third stage of this Agency review, any proposed changes would be submitted to scientific experts for preliminary peer review, and then to the general public, other federal agencies, and EPA's Science Advisory Board for comment. All of these comments would be evaluated in developing final guidance.

MEETING AGENDA

WORKSHOP ON CARCINOGEN RISK ASSESSMENT

Virginia Beach, Virginia
January 11-13, 1989

TUESDAY, JANUARY 10, 1989

7:30PM - 9:30PM	Early Registration/Check-in	

WEDNESDAY, JANUARY 11, 1989

7:30AM - 8:30AM	Registration/Check-in	
	Continental Breakfast served in the Horizon Lounge	
8:30AM - 11:30AM	**PLENARY**	
8:30AM	Welcome and Introduction	Dorothy Patton
8:4[illegible]	Perspective on EPA's Carcinogen Guidelines	
	- Environmental Protection Agency	John Moore
	- Public Interest	Frederica Perera
	- Industry	James Wilson
	- European	Kees Van der Heijden
10:00AM	Logistic Announcements	Kate Schalk
10:10AM	BREAK (20 minutes)	
10:30AM	Participants Discussion	Moore, Perera, Wilson, Van der Heijden
11:15AM	Workshop Overview; Directions to the Work Groups	William Farland
11:30AM - 1:00PM	LUNCH	

WEDNESDAY, JANUARY 11, 1989 (continued)

WORKSHOP SESSIONS

Qualitative Issues - Virginia Room

Two Sessions: Animal Tumors, Weight-of-Evidence

Participants

Roy Albert
Margaret Chu
David Clayson
Marilyn Fingerhut
Gary Flamm
John Graham
Richard Hill
Kim Hopper
Eugene McConnell
Colin Park
James Popp
Peter Preuss
Ellen Silbergeld
Thomas Slaga
Robert Squire
Raymond Tennant
Kees Van der Heijden

Quantitative Issues - Chesapeake Room

Three Sessions: Scaling, Mechanisms, Additivity/Independence

Participants

Melvin Andersen
Carl Barrett
Linda Birnbaum
Murray Cohn
Robert Dedrick
William Farland
Michael Gallo
David Gaylor
James Gillette
Daniel Krewski
Arnold Kuzmack
Frederica Perera
Christopher Portier
Richard Reitz
Lorenz Rhomberg
Stephen Safe
Robert Scheuplein
Thomas Starr
James Swenberg
Curtis Travis
James Wilson

GENERAL: John Moore, John Ashby

1:00PM - 5:40PM

Animal Tumor Work Group*
Chair: Eugene McConnell

Scaling Work Group
Chair: Melvin Andersen

3:00PM — BREAK (20 minutes) — BREAK (20 minutes)

5:00PM - Observer Questions/Comments

5:20PM - Chair's Summary

*This group continues on Thursday.

6:00PM - 7:30PM

RECEPTION
Cash Bar and Hors d'oeuvres
in the Horizon Lounge

THURSDAY, JANUARY 12, 1989

8:00AM - 12:30PM	**Animal Tumor Work Group (continued)**	**Mechanisms Work Group** Chair: Michael Gallo
9:20AM	Observer Questions/Comments	
9:40AM	Chair's Summary	
10:00AM	BREAK (20 minutes)	BREAK (20 minutes)
10:20AM	**Weight-of-Evidence Work Group** Chair: Gary Flamm	
12:00 NOON		Observer Questions/Comments
12:20PM		Chair's Summary
12:30PM - 1:45PM	LUNCH	LUNCH
1:45PM - 6:00PM	**Weight-of-Evidence Work Group (continued)**	**Additivity/Independence Work Group** Chair: Daniel Krewski
3:30PM	BREAK (20 minutes)	BREAK (20 minutes)
5:20PM	Observer Questions/Comments	Observer Questions/Comments
5:40PM	Chair's Summary	Chair's Summary

FRIDAY, JANUARY 13, 1989

8:30AM - 12:00 NOON	**PLENARY**	
8:30AM	Introduction	Richard Hill
8:40AM	Work Group Reports	
	- Animal Tumor	Eugene McConnell
	- Weight-of-Evidence	Gary Flamm
	- Scaling	Melvin Andersen
	- Mechanisms	Michael Gallo
	- Additivity/Independence	Daniel Krewski
10:15AM	BREAK (15 minutes)	
10:30AM	Participants' Discussion	McConnell, Flamm Andersen, Gallo, Krewski
11:30AM	WRAP-UP	John Ashby
12:00 NOON	ADJOURNMENT	Dorothy Patton

QUALITATIVE EVIDENCE ISSUES

- **Relevance of Tumors in Animals to Human Carcinogenicity**
  - **Pre-meeting Issue Paper**
  - **Work Group Summary**
- **Weight-of-Evidence Classification**
  - **Pre-meeting Issue Paper**
  - **Work Group Summary**

PRE-MEETING ISSUE PAPER

WORKSHOP TOPIC

RELEVANCE OF TUMORS IN ANIMALS TO HUMAN CARCINOGENICITY

GOALS:

1. To further develop the list of factors (Attachment 1) that should be considered in making evaluations about the significance of tumor findings in animals to human carcinogenicity.

2. To analyze in detail some of the identified factors as to whether various outcomes tend to strengthen, weaken, or void the presumption of human carcinogenicity based on animal tumor data.

ISSUE:

Tumors in chemically treated animals generally signal that a chemical may be carcinogenic to humans. However, a careful review of all relevant information can strengthen or weaken a final judgment about carcinogenicity in humans.

In the late 1970s both IARC (1977) and NCI's National Cancer Advisory Board (NCAB, 1977) stated that carcinogenic responses in animals signaled potential effects in exposed humans. Later, an OSTP (1985) cancer principle gave deference to the IARC language, "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 in animals as if they presented a carcinogenic risk to humans." for the use of animal tumor data to predict human carcinogenic risks. Even given this, Sir Richard Doll stated in a symposium organized through IARC (1985; p. 5-6) that

> . . . chemicals with 'sufficient' evidence for carcinogenicity [in animals] have generally been accepted as posing a potential hazard to man, even in the absence of detailed knowledge of the mechanisms by which they exert their effect. . . . More recently, however, it has come to be realized that carcinogens with 'sufficient' evidence for carcinogenicity [in animals] may act by different mechanisms and that even for these substance reasons may be found that make extrapolation from one species to another inappropriate. It seems, therefore, that experimental toxicological data on carcinogenesis can forewarn us of potential hazard to man, but that our final decision must rest on a full assessment of our total knowledge. . .

To this end, the OSTP report stated that the presumption should be reviewed in light of other information in reaching a final position on human carcinogenicity. The EPA guidelines (EPA, 1986) also expressed this position in its weight-of-evidence approach.

Therefore, the question is how to determine the degree of human relevance of animal tumor observations and how to determine what are the factors and analyses that can be used in answering the question.

DELIBERATIONS AND OUTPUTS:

The present workgroup is to perform two tasks. The first is to identify those generic factors (attributes) that one sifts through in evaluating the relevance of tumors in animals to human carcinogenicity. A short list of potential factors (Attachment 1) is attached for workgroup consideration and modification. The second task is to analyze some of the identified factors in more detail as they, alone or in combination, apply to the determination of human carcinogenicity. The workgroup discussions should not be distracted by debates on issues such as "What is a 'promoter'?" but rather should focus on the use of information on promotion characteristics in making a judgment of human carcinogenicity.

Two sample data configurations are included to help identify factors for Attachment 1 and to begin the discussion on the relevance of the various factors. Data configurations in one case (Attachment 2) suggest increased confidence and in the other case (Attachment 3) suggest decreased confidence of the relevance of animal findings to humans. Some of the attributes are components of a given or of several long-term animal studies; others are mechanistic, pharmacokinetic, or other biological information on the substance; still others reflect structure-activity relationships (SAR). Some of these factors may stand alone in diminishing/increasing the significance of animal tumor data to human cancer hazard but many need to be considered with additional factors to determine the impact on the question of human relevance.

ATTACHMENT 1
SAMPLE FACTORS:

1. Bioassay factors:

a. Route of administration to animals significantly different/similar to human exposure.

b. High/low background incidence of tumors at specific organ sites.

c. Presence/absence and extent of cellular toxicity where tumors occur.

d. Presence of evidence for or against the progression of preneoplastic and early neoplastic lesions to malignancy.

e. Degree of consistency of tumor outcome in repeat bioassays.

f. Number and sex of animal species affected.

g. Dose-response characteristics.

h. Organ or tissue sites of tumors and existence of analogs in humans.

2. Metabolic, toxicologic, mechanistic factors:

a. Differences/similarities in toxification/detoxification pathways (comparative metabolism).

b. Differences/similarities in absorption, distribution, excretion, as well as rates of metabolism (qualitative and quantitative pharmacokinetics).

c. Ability of parent compound or metabolites to bind covently with cellular macromolecules.

d. Outcome in genotoxicity tests for a range of end points.

e. Presence/lack of promotion activity.

f. Findings on the influence of the chemical or metabolites on physiological adaptive mechanisms (e.g., presence or lack of hormone disturbance, oxidative stress, glutathione depletion).

3. SAR factors:

a. Nature of evidence of carcinogenicity of compounds chemically related to parent chemical/metabolites.

b. Electrophilicity/biological alkylating ability of analogs/metabolites.

c. Knowledge about the toxicological effects of analogs/metabolites.

d. Mechanistic insights on analogs/metabolites.

ATTACHMENT 2

Configuration of experimental data that strongly suggests the tested substar is a human carcinogen.

I. Bioassay factors:

1. A clear dose-response effect.

2. The induction of tumors is seen at doses below observed acute, subchronic, or chronic toxicity.

3. Tumors are induced in multiple animal species and/or at multiple sites a species.

4. Preneoplastic lesions and benign tumors are induced early and rapidly progress to malignancy in a dose-related fashion.

II. Metabolic, toxicologic, mechanistic factors:

1. Tumors occur at doses with no evidence for disruption of homeostasis.

2. The chemical and/or its metabolites are shown to induce DNA damage/repa and form covalent adducts with cellular macromolecules.

3. The chemical and/or its metabolites are found to induce gene mutations and/or structural chromosome aberrations.

4. Pharmacokinetic data help explain why certain organ/tissue sites develo tumors and others did not.

III. SAR factors:

1. The parent chemical is expected to be metabolized the same way in humans as in the test species.

2. The parent chemical and/or metabolites belong to a class of human carcinogens.

ATTACHMENT 3

Configuration of experimental data that suggests the animal findings may not be relevant to human carcinogenicity.

I. Bioassay factors:

1. Induced tumors in animals found only at doses where substantial tissue and cellular injury occurs.

   i) Such injury is observable soon after administration of the chemical.

   ii) Nature of the injury is known or found to lead to cellular proliferation and hyperplasia.

2. Induced tumors show little progression to malignancy.

3. Induced tumors arise from tissue for which there is no human analog.

4. Tumor tissue/cell type occurs with high and variable incidence in the test species while it is very rarely seen in humans.

II. Metabolic, toxicologic, mechanistic factors:

1. Chemical appears not to induce mutations and DNA damage/repair.

2. Significant differences exist in pharmacokinetics and metabolism between test species and humans.

3. Doses that induce tumors are either non-physiological or clearly disrupt homeostasis.

III. SAR factors:

1. The parent compound and/or its metabolites are not members of a class of human carcinogens.

References

*EPA (1986) U.S. Environmental Protection Agency, Guidelines for carcinogen risk assessment. Fed. Reg. 51:33992-4003.

IARC (1977) IARC Technical Report 77/002, Preamble. International Agency for Research on Cancer, Lyon.

IARC (1985) Interpretation of negative epidemiological evidence for carcinogenicity (Wald, N.J. & Doll, R., Eds.). IARC Scientific Publication No. 65. International Agency for Research on Cancer, Lyon.

**NCAB (1977) General criteria for assessing the evidence for carcinogenicity of chemical substances: Report of the Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board. J. Natl. Cancer Inst. 58:461-5.

OSTP (1985) Office of Science and Technology Policy, Chemical carcinogens: a review of the science and its associated principles. Fed. Reg. 50:10371-442. (*Reprinted, Env. Health Perspectives 50:201-207 only, 1986.)

* Enclosed for all participants.
** Enclosed for qualitative workgroup.

Chair Summary of Work Group Session on the Relevance of Tumors in Animals to Human Carcinogenicity

WORK GROUP REPORT HUMAN AND ANIMAL TUMOR DATA
January 11-12, 1989
Chair: Ernest E. McConnell

The animal tumor workgroup met Wednesday afternoon, January 11, and Thursday morning, January 12. The workgroup was divided into two parts. Dr. McConnell lead the discussion on various factors that impact on the relevance of the animal bioassay to human hazard evaluation. Dr. Popp followed by leading a discussion of metabolic, toxicologic, and mechanistic factors as well as structure activity relationships.

The bioassay factors* that were discussed were the relevance/importance of:

1. Tumors with a high versus low background incidence
2. Toxicity in the target organ, i.e. the organ showing chemically related neoplasms
3. Route of administration
4. Consistency between studies
5. Consistency between species/strains/sexes
6. Evidence of progression/regression of tumors
7. Induction of single types of tumors versus multiple types of tumors
8. Induction of benign versus malignant tumors
9. Importance of latency in tumor induction
10. Dose response - tumors only at the Maximum Tolerated Dose (MTD) or at doses below the MTD
11. Tumor site in animals compared to site in humans

The strengths and weaknesses of each factor were discussed.

The consensus of the workgroup was that all of the above factors are important and are relevant in determining human health hazards. Importantly

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*It was assumed that the bioassay was conducted in an adequate manner and that the tumor response was clearly related to the test chemical.

it was agreed that it would not be appropriate to focus too much on a single factor, but that the various factors should be integrated to determine the relevance of the bioassay for hazard identification.

Dr. Popp then lead a discussion on the following toxicologic, mechanistic, metabolic and SAR factors.

1. Genetic Toxicology

- some discussion of the definition of a positive/negative
- application of gene tox data as it applies to weight of evidence and mechanism. Concluded that it was an important risk factor and was important in mechanism decisions.

2. Promotion

- the discussion became bogged down to some degree on a definition of promotion
- consensus that it was important to determine if a chemical would fall into that category
- however, no consensus on how the information would be used for human hazard evaluation. The issue probably needs to be revisited in the future.

3. Cell Proliferation

- discussed the mechanisms involved in cell proliferation, i.e., mitogen versus regeneration
- important to establish if proliferation occurred early, late or throughout the study, magnitude of proliferation, and whether it is in target organ (only or in other organs)
- needs to be looked at on case-by-case basis. No general rule on relevance.

4. Metabolism and tissue binding

- important to know but some skepticism on value for human hazard evaluation.
- interspecies comparisons are important considerations. Important to see if there are similarities, especially in the animal target organ compared to the human target organ.
- the presence and type of binding can be important in understanding a possible mechanism. However, need to be careful not to over interpret the data.
- Understanding of biological half-life (persistence) of chemical is important

5. Physiologic adaptation

- by itself may be of little value for human hazard evaluation, but with information could be useful.
- may be of more use for other toxic endpoints such as reproductive and fetal development studies.

6. SAR

- probably of importance within specific groups/classes of chemicals.
- Important to remember that SAR is not infallible.

There was a consensus that all of the above factors are important in evaluating the potential carcinogenic hazard of a chemical. It was stressed that the information should be pooled with the bioassay data for an in-depth human hazard evaluation.

SUMMARY

It was agreed that this type of information can make a fairly simple discussion more difficult but the results are worth the effort and the current state of the science demands that we do it. However, the totality of the data should be "clear" and "strong" before it is used to enhance or detract the bioassay results.

Moore's original assumption was that "Positive animal studies are presumptive evidence of human hazard identification." It may be appropriate to add the clause "in the absence of other relevant information." In other words, the above factors can add or subtract the weight of evidence of this assumption.

PRE-MEETING ISSUE PAPER

WORKSHOP TOPIC

WEIGHT-OF-EVIDENCE CLASSIFICATION SCHEME

GOALS:

1. To analyze issues relevant for developing weight-of-evidence classification schemes.

2. To propose weight-of-evidence classification(s) that embody discussions from this and the previous workshop.

ISSUE:

How can one integrate all information into an overall weight-of-evidence scheme that reflects the judgment of potential human carcinogenicity of an agent?

Both the OSTP (1985) cancer principles and the EPA (1986) cancer risk assessment guidelines have stressed a weight-of-evidence determination in evaluating potential carcinogenic effects from exposure to chemicals in humans. This entails consideration of all relevant human and long-term animal studies along with metabolic/pharmacokinetic information, various mechanistic considerations, and structure-activity relationships (SAR). Little guidance is given in the EPA guidelines as to how this should be done. The EPA classification is an adaptation of the approach developed by IARC (1982).

DELIBERATIONS AND OUTPUTS:

This workgroup is to perform two tasks. The first is to discuss a number of issues (questions) relevant to making weight-of-evidence determinations. The second task is to review certain existing classifications which can serve as models for identifying attributes for consideration and develop/propose weight-of-evidence classifications.

1. Should a classification scheme emphasize whether an agent has carcinogenic properties in a general sense (i.e., intrinsic carcinogenic activity without regard to species)?

2. Should a classification scheme emphasize the determination of human carcinogenic potential of an agent?

3. Given that the EPA weight-of-evidence determination goes beyond the analysis conducted by IARC in support of human carcinogenicity, should EPA continue to use an IARC-like classification?

4. Should the use of judgmental descriptors like "probable" and "possible" human carcinogens be continued?

5. How can the confidence in the information and level of concern in support of human carcinogenicity be incorporated into a weight-of-evidence determination?

6. Should we expand/condense the number of groups in the EPA classification system?

7. Should the potential for human exposure and carcinogenic "potency" of the chemical be factored into the determination of whether a substance poses a carcinogenic hazard to humans?

8. How should adequacy of testing be added as a component in a classification scheme, since data bases on chemicals vary significantly?

9. Given the deliberations on the relevance of tumors in animals to human carcinogenicity and the current workshop discussions, what might a classification scheme(s) look like?

10. What guidance coming from the hazard identification step might be given as to the means of estimating human carcinogenic risk?

II. Existing Schemes

1. EPA (1986) classification. (attached)

2. IARC (1987) classification. (attached)

3. "Tripartite" scheme. (attached)

III. Possible Future Options

1. Retain the current EPA classification but refine criteria for categorizing the level of evidence.

2. Modify the current EPA classification to harmonize with IARC (1987).

3. Modify the current EPA classification scheme along other lines that incorporate insights obtained from this workshop and elsewhere.

References

*EPA (1986) U.S. Environmental Protection Agency, Guidelines for carcinogen risk assessment. Fed. Reg. 51:33992-34003.

IARC (1982) International Agency for Research on Cancer, IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4, pp 11-14. Lyon.

OSTP (1985) Office of Science and Technology Policy, Chemical carcinogens: a review of the science and its associated principles. Fed. Reg. 50:10371-10442. (*Reprinted, Environ. Health Perspect. 50:201-207, only, 1986.)

* Enclosed for all participants.

Chair's Summary of Weight of Evidence Classification Session

Chair: Gary Flamm

The session began with an introduction from Richard Hill who described what EPA hoped to accomplish from the "weight-of-evidence classification" session. Dr. Hill explained that it has been apparent to the Agency through comments received as a result of the Federal Register Notice of Intent to review its cancer assessment guidelines and through other mechanisms that EPA's current cancer classification system is subject to challenge. A major issue that has arisen in the course of the public comment period is the difference between a "strength-of-the-evidence" approach to classification as opposed to a "weight-of-the-evidence" approach to classification. The argument being that the application of EPA's current classification approach is more like a "strength-of-the-evidence" approach which focuses only on how good the animal cancer data are without adequate regard for the significance of the animal cancer data to humans. The "weight-of-evidence" approach to classification is assumed to focus on the meaning and significance of animal findings to humans. Dr. Hill expressed the view that it is important for the Agency to have the benefit of the discussion and the expression of views flowing from the discussion of this issue by the various experts gathered around the table. He emphasized that it is unnecessary for the group to come to consensus, only to have an indepth and penetrating discussion of the issues.

As a related exercise, a list of 15 chemical carcinogens was circulated to the members of the panel, and the members were asked to evaluate each on a scale of 1 to 10 in which 1 is most relevant to humans and 10 least relevant. The exact charge to the panel was "to the extent you are acquainted with the data on these substances, give your personal evaluation of the likelihood each substance is a human carcinogen under historical exposure. Don't guess or resort to the conclusions reached by IARC, EPA, NTP and others. (Key: 1 [human] to 10 [not human]; N - don't know)." The panel was given approximately 10 minutes to complete the questionnaire.

One important conclusion that can be drawn from this exercise is that for certain carcinogens (i.e., dimethylnitrosamine, 1,2-dibromo-3-chloropropane) there was strong agreement on the significance and relevance of the animal cancer findings to humans. For instance, panelists, with the exception of one, scored dimethylnitrosamine as 2 or less. Similarly, there was good agreement that d-limonene and nitrilotriacetic acid were not likely to be human carcinogens under historical exposure conditions. On the other hand, for many other known animal carcinogens, such as carbon tetrachloride, there was little agreement among panelists with scores at both ends and in the middle of the scale.

Of the 9 chemicals from the list that have been evaluated by EPA (FDA compounds excluded), all but two were designated as B2 (probable human carcinogen) based on sufficient animal tumor findings. Vinyl chloride and formaldehyde were classed higher due to combined human and animal evidence.

This raises the question of whether the B2 (i.e., sufficient animal) category should be subdivided into two or more categories. It was emphasized by some that no single factor could serve to offset the general presumption of relevance of animal data to humans. In all cases a combination of many factors would be required to provide convincing evidence that animal data were not relevant to humans.

It was argued by some panelists that the rationale used by panel members - whether wittingly or unwittingly - to classify certain carcinogens as more or less relevant to humans was predicated on mechanistic considerations and that such considerations were key to any further division of the B2 category. Certain examples were pointed to as supporting this position, for instance, the binding of α_{2u}-globulin and its relationship with renal tumors, certain hormonal disturbances or imbalances, and thyroid cancer and the relationship between urinary stones and bladder tumors.

Some panelists opined that a sliding scale should be used to indicate the degree of relevance of animal data to humans while others were opposed to this approach. One panelist expressed the view that only when the scientific evidence was clear, should any judgment be made about the lack of human relevance; until that time the presumption that the animal data were relevant should hold. Several panelists expressed the view that in virtually all circumstances the judgment that animal data are not directly relevant to humans must involve some consideration of human exposure. One panelist argued that the assurance that BHA is not carcinogenic to humans is strongly dependent on the conditions of human exposure as opposed to the notion that animals are fundamentally and qualitatively different from humans in regard to the induction of cancer by BHA. Similar arguments were made in regard to other agents like those that produce urinary stones.

The panel, after several hours of lively discussion, recognized that there are probably animal carcinogens that would not under specific conditions exert their effects in humans. The panel discussed the level of evidence required to establish that such minimal carcinogens are unlikely to affect humans and discussed various methods of introducing this concept into the EPA risk assessment system.

QUANTITATIVE EVIDENCE ISSUES

- **Dose Scaling Across Species**

  Pre-meeting Issue Paper

  Work Group Summary

- **Incorporation of Mechanistic Data into Quantitative Risk Assessment**

  Pre-meeting Issue Paper

  Work Group Summary

- **Additivity/Independence of Mechanism to Background Processes**

  Pre-meeting Issue Paper

  Work Group Summary

PRE-MEETING ISSUE PAPER

WORKSHOP TOPIC

DOSE SCALING ACROSS SPECIES

GOALS:

1. To discuss the considerations that enter into the choice of a cross-species scaling factor, including identification of the species differences the scaling is intended to adjust.

2. To evaluate arguments in support of various scaling methods that have been proposed.

3. To recommend default dose-scaling methods for use when few chemical specific data are available, along with criteria for use of alternatives when appropriate data are available.

ISSUE:

In view of the developing understanding of comparative pharmacokinetics, how should doses be scaled so as to be expected to be of equivalent carcinogenic effect across species when (a) no chemical-specific data are available, and (b) when metabolic or pharmacokinetic data are available?

Arguments have been made for various dose-scaling factors to be used in the absence of chemical specific data. The OSTP (1985) document recognized there are no clear choices among the factors but stated that using body weight or surface area as conversion factors may be reasonable. The EPA (1986) Guidelines for Carcinogen Risk Assessment choose scaling daily amount by body surface area as a default position. Although the guidelines recommend the use of chemical-specific information on pharmacokinetics and metabolism for scaling, no guidance is given as to how to use them. Progress on this question would be enhanced by a clearly articulated rationale for the choice of any particular scaling method and an enumeration of the specific species differences that scaling is intended to accomodate.

DELIBERATIONS AND OUTPUTS:

The most important focus will be on examining the various elements that contribute to species differences in carcinogenic potency and questioning how and whether a cross-species scaling of dose can serve to correct for them. This will include a discussion of both pharmacokinetic and pharmacodynamic factors, as well as an examination of the various ways in which target-tissue doses can be expressed. Once the demands being placed on a scaling factor are articulated, one can discuss the utility of various data and theoretical formulations (e.g., allometry) in lending support to one or another scaling method. Finally, one can consider how the appropriate scaling method may vary as a function of different amounts and patterns of pharmacokinetics and metabolism, as well as different modes of carcinogenic action.

The deliberations will be guided by focusing on the following set of questions, for which a sense-of-the-meeting position will be sought:

1. Is dose scaling applied in order to correct for pharmacokinetic differences only (i.e., rendering tissue-level exposures equal) or should it also correct for species differences in pharmacodynamics (the effect on elements of the carcinogenic process)?

2. Tissue-level exposures are inherently multidimensional, consisting of changing concentration over time. What considerations enter into choosing an appropriate one-dimensional summary measure (e.g., AUC, peak concentration, mg-eq metabolized)?

3. What relative tissue-level exposures can be expected to produce equal risks across species in view of different numbers of cellular targets, different rates of cell turnover and DNA repair, and different lifespans? How does this expectation on the presumed mechanism of carcinogenicity?

4. What is the utility of allometric predictions of relative tissue exposures in animals and humans following equal administered doses? Is the concept of "physiological time" helpful in equating pharmacokinetic and/or pharmacodynamic processes across species?

5. Can appropriate "default" assumptions about dose scaling be constructed for use in the absence of adequate pharmacokinetic and pharmacodynamic data on a compound? Do such considerations suggest that the current Guidelines recommendation for scaling applied doses by surface area (body weight to the 2/3 power) should be changed?

6. Should the "default" scaling factor depend on whether the putative carcinogenic species is believed to be the parent compound, a stable metabolite, or a reactive intermediate of metabolism?

7. Does the use of target tissue exposures in quantitative risk assessment necessarily entail the prediction of site concordance of induced cancers across species?

Chair Summary of Work Group Session on Dose Scaling Across Species

Chair: Melvin Anderson

1. To discuss the considerations that enter into the choice of a cross species scaling factor, including identification of the species differences the scaling is intended to adjust.

2. To evaluate the arguments in support of various scaling methods that have been proposed.

3. To recommend default dose-scaling methods for use when few chemical specific data are available, along with criteria for use of alternatives when appropriate data are available.

The panel wrestled with the issue of the scientific considerations that enter into development of an appropriate cross species scaling factor. It was recognized that the scaling factor consists of at least two parts. One relates to species differences in pharmacokinetics. This gives rise to differences in tissue dose in various species even though the exposure situations are equivalent. The second relates to tissue sensitivity ,that is, different outcomes in various species even though they receive identical tissue exposures. It was recognized that the current use of a scaling factor is intended in some poorly articulated way to account for both of these factors. Despite the ability to define these two contributing elements in the interspecies scaling factor, in practice it proved virtually impossible for the working group to analyze them independently. This was likely due to their long association in regulatory policy.

Considerable discussion focused on the arguments which support the current default scaling methods. The data of Freireich et al. have been referred to as the basis for selection of the surface area scaling presently used by the US EPA. These data show that the toxicity of various chemotherapeutic agents across species is approximately a function of surface area and not a function of body weight. These particular d ta do not address cancer outcome in various species, but are measures of acute toxicity. In fact they relate different measures of acute toxicity in the two different species - mouse and humans. The rationale expressed by agency (US EPA) representatives for reliance on this data set was that many relationships scale as body surface area, this acute toxicity of chemotherapeutic agents is just one of them, and that it is perhaps to be expected that cancer potency should also follow this kind of relationship. This represents a recapitulation of the historical use of the factor, but not a scientific justification for its use.

In contrast, scientific arguments for interspecies sensitivity of tissues to equivalent exposures might be surmised from analysis of the data on solid tumors caused by radium ingestion in several species. The results of Raabe et al. were discussed and it was suggested that they support a scaling factor related to total absorbed dose per lifetime instead of absorbed dose per day. While these results may be misleading because they represent analysis of radiation carcinogenesis and not chemical carcinogenesis directly, no other compelling information on interspecies tissue sensitivity for cancer causation was provided to analyze the issue with chemicals. There does exist a body of data on chemical carcinogenesis from people subjected to chemotherapy who develop second tumors. These data are somewhat obscured by the very different dosing scenarios in the patients and in the exposed animal populations, but could be reviewed to see if they illuminate the issue of tissue sensitivity to equivalent doses.

There were numerous comments that the position of equal sensitivity of tissues to cancer across species was not appropriate for certain chemicals (the dioxins, for example) and these chemicals that act through receptor mechanisms needed to be looked at carefully. No specific recommendation followed, however, for what would be an appropriate way to express tissue sensitivity (although there was some mention of receptor number as a predictor of response from dioxin type chemials from Dr. Safe).

The default condition, scaling to surface area, as it now stands can be defined as representing either both correction terms - tissue sensitivity and delivered dose - or only one of them. A comment made was made by one participant that pharmacokinetics cannot address the interspecies sensitivity. This really was a restatement of a belief that the scaling factor as historically used and currently defined is for tissue sensitivity alone. This position, as noted below, was not a universally held position in the Federal sector regulatory agencies.

The US EPA uses an adjustment factor related to body surface area and assumes that larger species are at greater risk. The data used by Freiereich et al. to support this factor has been reanalyzed by Travis, who gave an overview of his analysis. By conducting a more complete statistical analysis, a slightly different slope (0.75 vs 0.67) was obtained. The initial published analysis only showed that the slope of 0.67 was consistent with the data and did not determine it exactly. There was discussion about whether the 0.75 power would be a better default position and whether the two agencies (US EPA and FDA) might use the 0.75 power as a common value for their interspecies dose scaling. Not unexpectedly, there was little support of such a move by any agency representatives. Each agency seems comfortable with its own tradition in arriving at the interspecies scaling factor. Various panel members did comment on the fact that conformity in approach to a common problem would

be desirable. A frequently cited study by Crump and colleagues was also discussed. This work correlated the calculated animal and human potencies of various carcinogens and, apparently, found a somewhat better correlation with body weight than surface area. It was felt by the panel and by an observer (Chao Chen, US EPA) that the Crump et al. study does not provide irrefutable support of a body weight correlation.

The topic addressed next was dose scaling. The discussion was still burdened with an inexact definition of what the panel intended when addressing this part of the total cross species scaling problem. Does dose scaling correct for all interspecies differences or only for part of them? Dr. Reitz presented a brief summary of the use of pharmacokinetic modeling to calculate particular measures of tissue dose. He stressed that there were different measures of tissue dose that are expected to be associaited with particular presumed mechanisms of toxicity. These 'mechanisms' are not biological distinction at a fine molecular level, but gross distinctions of the nature of the chemical that causes toxicity. Discussed were cases where the parent chemical is the genotoxic species, where a stable metabolite is the genotoxic species, and where a highly reactive chemical is the form reacting with DNA. Again, it was stressed that some knowledge of the chemistry and biology of the system was required to make these distinctions. The issue of just how much 'mechanistic' information is required before pharmacokinetic data can be used was a lively topic of conversation. There was some limited feeling that the system had to be completely defined in its total complexity before novel data could be used to alter the risk assessment process. The rationale is that there is a process in place now that provides some protection, it should not be lightly changed because an error in the new approach might be to increase risk and should be implemented only after virtually universal acknowledgement that the new approach was a proper method of calculating tissue response.

Despite differences in opinion about when the body of evidence would be sufficient, there seemed to be general agreement that pharmacokinetics could be used to estimate the appropriate measure of tissue dose to aide in dose scaling and to determine relative adjustment factors for interspecies scaling. The issue of the relevant measure of dose to be calculated from pharmacokinetic models was not very thoroughly addressed except noting that the proper choice of tissue dose must be related to the presumed mechanism of carcinogenicity. Similarly, while allometric relationships are valid for many physiological processes, biochemical processes involved in metabolism may not behave nearly so coherently and need to be measured directly to support such dose calculations. At least one comment was directed toward developing a data base to test the expected cross species extrapolation of tissue dose as predicted based by pharmacokinetic arguments for chemicals with various mechanisms of toxicity. It was noted by several participants that dose scaling for reactive metabolites might best be represented as related to an inverse of surface area.

Several comments were taken from the observers. One issue raised was whether it was necessary to build a conservative default position into the decision tree or whether some other process might be applied that considered the entire body of data including the uncertainty with respect to mechanism. The same person (Dr Stevenson, Shell) asked whether there shouldn't be some incentive to encourage work to increase the data base for resolving some of the scientific issues in dose scaling.

The efforts of the panel to successfully address the points in its charge was severely hampered by its inability to attain concensus on what the interspecies scaling factor is really being used to correct for. The question remained heavily mired in policy, in discussions about what the overall scaling factor should be, in recapitulating the rationalization of its present value, and in maintaining a general aversion to creating any new default position. It was extremely difficult to seriously examine the problem in its component parts. The panel, however, is not unique in its inability to define the role played in quantitative risk assessment by factors intended to adjust for 'dose-scaling across species'. There does not seem within the agency any clearly articulated idea of what the factor should address. In fact, among individuals from the three agencies - US EPA, FDA, and CPSC - represented on the panel, there were three very different ideas espoused as to how the correction should be used and as to what was included in the totality of dose-scaling across species.

One said that dose scaling was not appropriate. No correction should be made to the animal dose to account for the species differences and the tissue dose in experimental animals should further be corrected based on a surface area relationship (CPSC). A second espoused the position that the pharmacokinetics could be used to account for dose delivery in humans, and after taking delivered dose in humans into account, a surface area correction should be applied. In this case the surface area correction becomes the interspecies tissue sensitivity scaling factor (US EPA). The third said that the correction was entirely for dose, not tissue sensitivity, and when data on the appropriate delivered dose metric were convincing, they could be used directly. This position suggests that the correction is entirely for delivered dose (FDA). There really is a very remarkable difference of opinion within the federal regulatory agencies on the nature of this interspecies dose scaling factor. It is no wonder that the panel was confused about the problem.

Perhaps this final note should be regarded as simply a personal comment of the chairman, but it seems that the differences among the agencies on interspecies dose scaling are growing further and further apart as more scientific information becomes available. Some common ground needs to be struck to avoid an impression of arbitrary regulation of chemicals by the various regulatory agencies in the federal sector.

PRE-MEETING ISSUE PAPER

WORKSHOP TOPIC

INCORPORATION OF MECHANISTIC DATA INTO QUANTITATIVE RISK ASSESSMENT

GOALS:

1. To identify types of mechanistic and biological data that support or suggest alternative approaches to the current EPA default methods for low-dose extrapolation of dose-response relationships.

2. To evaluate the assumptions and data requirements of proposed mechanistic approaches to quantitative risk assessment.

3. To develop considerations to be applied in choosing approaches to low-dose extrapolation, and in evaluating their reliability.

ISSUE:

How does one apply knowledge of carcinogenic mechanisms to the development and use of low-dose extrapolation techniques?

The current EPA (1986) Guidelines state: "When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenic process exists, a low-dose extrapolation model other than the linearized multistage procedure might be considered on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and weight of evidence which led to the choice." The linearized multistage procedures makes little use of what is known about the process of chemical carcinogenesis, and aims only at setting an upper bound below which the true dose-response relationship is expected to lie.

DELIBERATIONS AND OUTPUTS:

The initial deliberation will examine various proposed approaches to the use of mechanistic data in dose-response analysis. The examination will focus on questions relating to the choice among mathematical extrapolation models, including an analysis of the specific mechanistic interpretations of carcinogenesis invoked by each method. The data required to implement each method, and the ease and reliability with which they may be obtained, will be considered. Finally, the group will be asked to suggest criteria for when particular methods may be used. These criteria should reflect the uncertainty in identifying key mechanisms and the difficulty of reliably measuring key model inputs.

The deliberations will be guided by focusing in the following set of questions, for which a sense-of-the-meeting will be sought:

1. How have data concerning mechanism of carcinogenesis in animals been used to argue that the assumption of linearity of response at low doses may be untenable?

2. What data (other than tumor response) support this conclusion? Are the data useful for quantitative assessment of response?

3. What underlying hypotheses about carcinogenesis support the various approaches to dose-response modeling? Are these hypotheses generally accepted in the scientific community in general terms? for specific chemical responses or modes of action?

4. For key model parameters, what is known of the range of response under normal and chemically-stimulated conditions? Do these ranges limit the conditions under which the models might be applied?

5. With the current state of the science, can criteria be developed which would support the application of alternative dose response modeling procedures as adjucts to current methods? as replacements for current methods?

CHAIR SUMMARY OF WORK GROUP SESSION ON INCORPORATION OF MECHANISTIC DATA INTO QUANTITATIVE RISK ASSESSMENT

Chair: **William Farland**

INTRODUCTION

This session began with an abbreviated discussion of the elements of dose response analysis in risk assessment: the selection of a data set for use, determination of equivalent exposure units between species, and choice of an extrapolation model. In particular, the question of how to extend the information obtained from high dose studies into the range of interest, several orders of magnitude lower, was discussed. The issue was framed as follows: How does one apply knowledge of carcinogenic mechanism(s) to the development and use of low dose extrapolation techniques?

The session can be summarized by focussing on three main questions which were addressed in the discussion, highlighting the points which were made and relating conclusions which were reached by the group. Finally a set of general conclusions is presented in an attempt to further convey the thinking of the workgroup.

QUESTION 1. HOW HAVE DATA CONCERNING TUMOR RESPONSE AND/OR MECHANISM OF ACTION BEEN USED TO EVALUATE THE ASSUMPTION OF LINEARITY OF RESPONSE IN THE RANGE OF "INFERENCE"?

This question was addressed first from the perspective of the analysis of data from exceptionally large cancer studies. Examples which were presented and discussed included the NCTR study, termed the "ED_{01} Study", using 2-AAF, the BIBRA study with nitrosamines and the IRDC study of saccharin. Despite the size of these studies, the point was made that they covered relatively narrow ranges of exposure. In addition, while responses were either linear or superlinear in the observed range, the data do not allow the differentiation of linearity from non-linearity at the low end of the observed range and into the range of inference. These studies also show that for practical reasons, it is not possible to collect data at much lower than a 1% response rate so

that our ability to evaluate the shape of the dose-response curve is limited to this range.

Further discussion led to consideration of theoretical issues related to linearity/non-linearity. These included a brief discussion of such issues as the impact of pharmacokinetics as well as choice of a dose-response model on the shape of the dose-response curve. Saturation of activation or elimination pathways were cited as reasons for some perceived non-linearities of response. In addition, the choice of cross-species factors affecting metabolism and distribution may have profound effects for site-concordance of expected response.

Several points were made about the choice of dose response models. With regard to the linearized multistage approach, the EPA's current "default" model, discussion focussed on the decreasing support for its "biological" underpinnings. Also, its ability to accommodate only tumor response data limits its ability to capture much of the data considered in the weight-of-the-evidence determination. The point was made that it is one among several models which incorporate low dose linearity but that the important issue was a determination of where linearity of response began and what the slope was.

This approach was contrasted with so-called "two-stage models" such as that developed by Moolgavkar and others. These models allow the incorporation of more of the data and, hence, more of an understanding of cancer biology. Use of such models on a routine basis will require an increased understanding of sensitive parameters in the model and how to address them, e.g., data or inference. While the discussion of this general approach was favorable, caution was voiced that more data than is currently collected would be needed to implement their use. In addition the difficulty in collecting needed data, e.g., proliferation rates for initiated cells, reflects limited systems and expensive studies. Such data collection should not be viewed as something which would be routine.

The following conclusions were reached regarding the stated question:

1) High dose tumor data are not very useful in evaluating the low dose shape of the dose-response curve but they are generally all we can expect to have;

2) There are various reasons to expect or at least to hypothesize non-linearity in the high dose region, but there are fewer for the low dose region, i.e., many processes can be expected to become linear at lower doses;

3) Biologically based models can incorporate theories of carcinogenesis but they must be flexible enough to be modified with increases in knowledge. Don't over simplify!

QUESTION 2. WHAT DATA OTHER THAN TUMOR RESPONSE CAN BE USED TO EVALUATE THE ISSUES RAISED IN RESPONSE TO QUESTION 1?

Major topics discussed in response to this question included the role of DNA adducts and cell proliferation in predicting tumor response. With regard to DNA adducts, points were raised about uncertainty in the direct role that certain adducts were playing in the carcinogenic process. Support for their role is based on correlations in the shape of the dose-response curve, efficiency of formation, persistence, site-specificity and other factors. These data allow the dose-response curve to be extended to lower doses if the inference for the role of adducts in causation of tumors is strong enough. Adducts should generally be considered to be linear at low doses although not necessarily at high doses. Examples of these concepts involved discussion of some data sets illustrating linearity such as those for DEN, 2-AAF, and ETO. On the other hand, chemicals such as vinyl chloride, formaldehyde, NNK, and BaP were used to illustrate non-linearity. Data sets from NNK with saturated activation and BaP with saturated detoxication were discussed as examples illustrating the basis for sublinearity and superlinearity of high dose tumor responses.

Cell proliferation data can also be helpful in understanding or predicting tumor response. In addition to allowing for the detection of background

initiation of potential tumors, cell proliferation as an expression of high dose toxicity can lead to enhanced induction of tumor response for relatively weak initiators. This is in contrast to the situation where cytotoxicity actually depresses a tumor response due to either random or selective cell killing. Such enhancement responses can be a response to genotoxicity, e.g., with oncogene activation, but it can also be non-genotoxic in nature, e.g., with α_{2u}-globulin and male rat kidney response. Nevertheless, the cell proliferation response seems most often to represent a high dose phenomenon and needs to be taken into account when extrapolating to lower doses.

Conclusions reached regarding this question were as follows:

1) Data are accumulating to support correlation between certain adducts and tumor response but causation remains an uncertainty;

2) Linearity of adduct formation, although with differing efficiency depending on specific adducts, is expected and seen at low doses, but not necessarily at high doses;

3) Cell proliferation can enhance response of adducts or background processes, but should be regarded as necessary but not sufficient for most tumor responses;

4) Data on adduct formation and cell proliferation can be collected to feed into biological dose-response models but these techniques are limited and may be prohibitively expensive.

QUESTION 3. WHAT ARE THE UNDERLYING BIOLOGICAL PROCESSES WHICH SUPPORT THE USE OF BIOLOGICALLY-BASED APPROACHES TO DOSE RESPONSE?

Discussion of this question stimulated further discussion on several topics described in above sections. It reflected the general belief that cancer is a multistage process which is impacted by such things as pharmacokinetics, mutagenicity, mitogenicity, and cytotoxicity. In addition,

the discussion focussed on hormonal modulation of tumor response. Chemical impacts on hormonal control of cellular processes represent yet another point in the multistage process where chemical impacts can be seen. Examples of this effect are perceived as receptor-based processes, so special consideration must be given to understanding high versus low dose interactions.

The point was made in this part of the discussion that there are techniques available for the incorporation of inexact data into models and for understanding the impact of certain data choices. These techniques must be further explored if we are to be able to use data as have been discussed in the face of uncertainty.

Conclusions reached in this section of the discussion include:

1) All of the data can be built into cancer models if the models are given the necessary flexibility;

2) The question of effects of a chemical on multiple points of the cancer process must be better understood from both the biological and from the modeling perspectives;

3) There is still a long way to go in understanding what the most important biological data are for evaluating tumor responses or predicting tumor response at low doses.

In addition to the general conclusions which summarize each of the discussions on individual questions, the following represent areas of general consensus coming out of the overall discussion:

1) We have to start somewhere to incorporate more data into quantitative risk assessment. The use of pharmacokinetic data to explain the shape of the dose-response curve, i.e., the development of the biologically effective dose concept, appears to be most promising;

2) Bioassay tumor data will continue to be used as the basis for quantitative assessment, but other information is useful and necessary, both qualitatively and quantitatively, to put the tumor data in proper perspective;

3) Novel risk assessment approaches should be encouraged both inside and outside of EPA. Scientific opinion (general consensus) should be used as a criterion for use of these techniques since the process will continue to rely on many inferences;

4) Biological models under development should be flexible and incorporate as much of the biology and data as possible. We should not be satisfied with oversimplifications if we are to improve on existing techniques rather than just replacing them with approaches of equal or greater uncertainty;

5) Research must be encouraged to address areas which have been identified and to develop methods for providing the data necessary to be able to replace assumptions in low dose extrapolation models.

PRE-MEETING ISSUE PAPER

WORKSHOP TOPIC

ADDITIVITY/INDEPENDENCE OF MECHANISM TO BACKGROUND PROCESSES

GOALS:

1. To examine, for several proposed mechanisms of chemical carcinogenesis, whether the biological action of carcinogenic agents is independent from or additive to the processes responsible for the genesis of background tumors.

2. To discuss biological processes that support the theoretical arguments for the additivity or independence assumptions.

3. To recommend procedures for estimating risks at low doses that take proper account of mechanistic aspects of the additivity/independence issue, both in cases where appropriate biological information is available and when it is not.

ISSUE:

How does one combine biological and theoretical arguments into guidance on the existence and magnitude of risk from low-dose exposures to chemical carcinogens?

Questions have arisen as to the means of evaluating cancer risks from chemical exposures when "spontaneous" tumors of the same type occur in unexposed individuals. Some have argued from theoretical grounds that if a chemical acts upon cells in ways similar to the causes of "background" cancer, then even small exposures may marginally accelerate the tumorigenic process, leading to a linear, no-threshold elevation of risk over background at low doses (Crump et al., 1976; Peto, 1978). Alternatively, if a chemical acts in other ways, there would be independence in action between the chemically-induced effects and the background processes, which could possibly lead to excess risks from low doses that are markedly sub-linear. For example, some mechanisms of carcinogenesis may elevate risk over background only when organisms are perturbed out of a "normal physiological range" by high doses. Both the OSTP (1985) document and the EPA (1986) Guidelines for Carcinogen Risk Assessment espouse the use of linear extrapolation as default science-policy decisions but stress the importance of mechanistic, metabolic, and pharmacokinetic information, when it exists, in deriving high-to-low-dose extrapolations.

The theoretical arguments about additivity and independence are couched in very general terms, while the biological investigation of carcinogenic mechanisms addresses the action of specific elements of the process. One now needs to seek the specific biological meaning behind the theoretical concepts of "additivity" and "independence" in order to understand how the theoretical and biological arguments can be brought to bear on the question of estimating risks from low doses of carcinogens. It should be noted that the question here is not one of extrapolating the shape of the dose-response curve between high and low doses, but rather of the behavior that should be expected of any

such extrapolation at doses low enough that the interaction (if any) with the background tumorigenic processes predominates.

DELIBERATIONS AND OUTPUTS:

The initial deliberation will focus on the theoretical arguments about the low-dose consequences of carcinogenic processes that are either additive to or independent from background. The notions of additivity and independence will be examined in the light of various specific proposed mechanisms of carcinogenesis to try to determine what "additivity" and "independence" mean in biological rather than statistical terms. The means of distinguishing between additive and independent effects and of measuring them at low levels will be examined. The final focus is on recommendations about appropriate treatment of possible low-dose risks when some mechanistic knowledge is available.

The deliberations will be guided by focusing on the following set of questions, for which a sense-of-the-meeting position will be sought:

1. Is the additive-to-background position an assumption, or are there data to suggest that it describes the underlying biological truth?

2. How does the statistical argument that low-dose linearity is to be expected when mechanism is additive to background fare in view of knowledge of various mechanisms of carcinogenesis?

3. How can we distinguish cases of independent and additive background in practice? What biological data can help in trying to make this distinction?

4. What is known about the low-dose properties of dose-effect curves for elements of proposed mechanisms of carcinogenesis (e.g., mutation, cytotoxicity, receptor binding)?

5. Practically speaking, are we able to measure very small elevations in these processes over background (so small that they imply trivial cancer consequences) in order to detect a virtual (or practical) threshold?

6. For quantitative purposes, should a putative epigenetic carcinogen be treated as acting independently from or additively to low levels of other such agents in the human environment? of genotoxic agents in the human environment?

7. In view of the above issues, under what circumstances might it be appropriate to assume that carcinogenesis has or does not have a dose threshold? What criteria must be satisfied to treat a carcinogen as acting independently from background, and how should exposures to these substances be viewed vis-à-vis exposures to substances that may be additive to background?

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* Enclosed for all participants.

Chair Summary of Work Group Session on Additivity/Independence of Mechanism to Background Processes

Chair: Daniel Krewski

Introduction

The quantitative estimation of risks associated with low levels of exposure to carcinogens present in the environment is an important part of carcinogen regulation. Presently, there is a strong tendency to employ risk estimation methods which assume that the dose response curve for carcinogenesis is linear in the low dose region. This position is reflected in the principles proposed by the OSTP (1986), who stated that

> "When data and information are limited...and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incorporate low-dose linearity are preferred."

This position is also reflected in EPA's current Carcinogen Risk Assessment Guidelines (EPA, 1986).

While emphasizing risk estimates derived using some form of linear extrapolation, the Agency Guidelines recognize that such estimates may be more appropriately viewed as plausible upper limits on risk, and that the lower limit may well be effectively zero. While the Guidelines also state that procedures for obtaining a best estimate lying somewhere these two extremes generally do not exist at the present time, it may be possible to move away from the upper limit in some circumstances. The Agency has recently taken a concrete step in this direction in its consideration of the possibility of a threshold for the induction of thyroid tumors (Paynter et al. 1988).

Current practice within the Environmental Protection Agency is to use the linearized multi-stage model for low dose cancer risk estimation. The most important aspect of this practice is not the choice of the multi-stage model itself for risk estimation purposes, but rather the linearized form of the model. Because the model is

constrained to be low dose linear, it may be expected to yield risk estimates comparable to those based on other linear extrapolation procedures, including those proposed by Gaylor et al. (19__) and Krewski et al. (1986).

Additivity to Background and Low Dose Linearity

Additivity to background is often cited in support of the assumption of low dose linearity in carcinogenic risk assessment. In the additive background model proposed by Crump et al. (1976) and Peto (1978), spontaneous tumors are associated with an effective background dose, with exposure to carcinogens present in the environment adding to this background dose. In this regard, Crump et al. (1976) stated that

> "if carcinogenesis by an external agent acts additively with an already ongoing process, then under almost any model the response will be linear at low doses".

Hoel (1980) subsequently demonstrated that this result also holds even in the case of partial additivity. This result is reexpressed as follows in the current Guidelines:

> "If a carcinogenic agent acts by accelerating the same carcinogenic process that leads to the background occurrence of cancer, the added effect of the carcinogen at low doses is expected to be virtually linear."

The basic idea behind the additive background model is illustrated in Figure 1. Here, the spontaneous response rate is considered to arise as a consequence of an effective background dose, with the effects of the test chemical acting additively to background in a dose-wise fashion. The fact that the excess risk over background $P(d+\delta) - P(\delta)$ is linear at low doses follows from the fact that the secant between doses of δ and $(\delta+d)$ converges to the tangent to the dose response curve as the dose d of the test compound becomes small.

Within the framework of this model, the only condition required for this result to hold is that the probability of tumor occurrence be a smooth strictly increasing function of dose. No further assumptions are required concerning either the mathematical form of the dose response relationship or the toxicological mechanism by which tumors are induced.

It is worth noting that low dose linearity implied by this model refers to the slope of the dose response curve at an applied dose of zero. Without further assumptions, no further general statements can be made about the magnitude of this slope, nor about the range of low doses over which this linear approximation will hold reasonably well. For the multi-stage model, however, the linear approximation holds very well even at doses which double the background tumor rate, provided that the spontaneous response rate is not exceedingly small (Crump et al., 1976).

Nonlinearity at High Doses

The existence of linearity of low doses does not imply that the dose-response curve will also be linear at high doses. In particular, curvature at high doses can occur due to factors such as saturation of absorption or elimination pathways or pharmacokinetic processes involved in metabolic activation. Nonlinearity at high doses can also occur due to saturation of DNA repair systems or the induction of cellular proliferation. Dose-response curves for chemicals which can both cause DNA damage and induce cellular proliferation can be subject to a high degree of upward curvature, as with the hockey stick shaped dose-response curves for 2-AAF induced tumors of the urinary bladder. Similarly, secondary carcinogens which act as a consequence of high dose toxicity may be effective only at relatively high doses.

It was noted that nonlinearity due to saturation of elimination pathways results in upward curvature (as is the case with methylene chloride), whereas saturation of activation processes leads to downward curvature (as, for example, with vinyl chloride). However, for those processes which saturate in accordance with Michaelis-Menten kinetics, the amount of the proximate carcinogen formed at low doses will be directly proportional to the administered dose since such processes are essentially first order at low doses (Murdoch et al., 1987).

If the pharmacokinetics of metabolic activation are known, dose-response may be assessed in terms of the dose delivered to the target tissue. This may result in a more nearly linear dose response curve, which greatly facilitates statistical extrapolation to low doses (Hoel et al., 1983; Krewski et al., 1986).

Often, the only data available on which to base estimates of low dose risk are the tumor occurrence rates at two or three dose levels used in carcinogen bioassay. It was noted that linear extrapolation procedures such as the linearized multi-stage model applied to bioassay data acquired at high doses may lead to overestimates of risk when the linear component of the dose response curve does not become manifest until much low doses (see Figure 2). It was further noted that linearized estimates of low dose risk are also highly insensitive to the experimental data in the sense that even large perturbations in the data may not have much impact on the estimates of low dose risk. This insensitivity is further demonstrated by the strong association between carcinogenic potency and the maximum tolerated dose shown by Bernstein et al. (1985). For these reasons, estimates of risk based on linear extrapolation of bioassay data provide somewhat crude upper bounds on the risks associated with low levels of exposure.

It was suggested that improved estimates of low dose risk might be attained if additional data on pre-neoplastic effects were exploited. For example, consideration could be given to the use of DNA adducts which may be shown to be related to tumor induction in specific cases. In such cases, it should be possible to monitor adduct formation at doses far below those at which reliable estimates of tumor occurrence rates can be obtained. This information could then be used in conjunction with the bioassay results to obtain more accurate estimates of low dose risks.

Molecular Dosimetry

One area which offers considerable promise for improving our understanding of how neoplastic changes occur at low doses is molecular dosimetry. A forthcoming report by the National Academy of Sciences indicates that different chemicals may induce different kinds of DNA lesions, involving anywhere from two to thirteen sites on molecular DNA. At the same time, there is evidence that spontaneously occurring DNA lesions can be different from those caused by exposure to alkylating agents. This suggests that fingerprinting of DNA damage in exposed and unexposed individuals may provide a means of distinguishing between additive and independent background in practice.

In the case of a genotoxic agent which acts completely independently of background, the dose-response curve for tumor induction can be linear or nonlinear. If neoplastic conversion can occur as the result of a single pro-mutagenic DNA lesion, the linearity of adduct formation at low doses implies linearity with respect to tumor induction. If two or more pro-mutagenic lesions are required to create a malignant cancer cell, however, the dose-response curve will be nonlinear even at low doses. This

essentially represents a multi-hit independent background model in which the dose-response curve is proportional to dose raised to a power equal to the number of DNA lesions required for neoplastic conversion.

Dose-Response Modeling

Dose-response modeling is an integral part of the quantitation of cancer risk. The biological basis for the multi-stage model currently used by the Agency for this purpose is incomplete in that no cognizance is taken of tissue growth or cell kinetics. A moderately large number of stages (up to six or seven) may also be required to describe dose-response curves exhibiting high upward curvature, raising questions of biological interpretation.

For these reasons, more biologically based dose-response models have received considerable attention in recent years. Perhaps the most widely discussed model is the two-stage birth-death-mutation model developed by Moolgavkar, Venzen and Knudson, hereafter referred to as the M-V-K model. This model presumes that initiated cells arise from normal stem cells following the occurrence of a single mutational event. Initiated cells may undergo clonal expansion, and possibly sustain a second mutation to form a cancerous cell. The model also provides for growth of the target tissue over time.

Although this model currently enjoys considerable biological appeal, and can describe a variety of dose-response curves, it may not provide a complete description of the events involved in tumor induction in all cases. For example, more than two mutations may be required for neoplastic conversion in some cases. Similarly,

nongenotoxic factors may be required to foster development of a malignant tissue mass. As additional components are incorporated, the tractability of the model will be reduced.

Despite this potential for further elaboration, the two-stage M-V-K model is viewed as biologically more meaningful than the Armitage-Doll multi-stage model. Application of this model will however require supplementary data on tissue growth and cell kinetics, in addition to bioassay data on tumor occurrence. Attempts to estimate all of the parameters involved in the model without such supplementary data will likely result in unstable estimates (Portier, 1987). Separate estimates of the parameters governing the two mutation rates characterizing the genotoxic processes in the model will also require more elaborate bioassay protocols than those currently in use (EPA, 1987). Nonetheless, applications of this model should be encouraged in order to gain a better appreciation of its practical utility.

General Mechanistic Considerations

A number of mechanistic considerations relevant to low dose risk assessment were identified. First, the examination of non-neoplastic changes involved in carcinogenesis may provide some insight as to the magnitude of low dose risks. For example, data on DNA damage and cellular proliferation may provide a means of obtaining more accurate estimates of low dose risks. This might be done within the context of the M-V-K model or through the use of more sensitive biomarkers such as DNA adducts which can be measured at doses well below those at which tumor occurrence rates can be measured directly.

Whether or not hormonally mediated tumors fall within the additive background framework is somewhat unclear. Such tumors can occur following depression of circulating thyroid produced hormones, with compensatory thyroid hyperplasia induced by thyroid regulating hormones secreted by the pituitary gland (Clayson, D.B., 1989). As noted previously, it has been suggested that this process may demonstrate a threshold dose below which tumors may not occur. On the other hand, if thyroid tumors can occur in nonexposed individuals as the result of natural fluctuation in hormone levels, an additive background model may apply.

The potential risks posed by exposure to low doses of tumor promoting agents are somwhat unclear. If spontaneous promotion can occur, the possibility that an additive background model may apply exists, along with the attendant implication of low dose linearity.

Finally, it was noted that multiple mechanisms may be involved in chemical carcinogenesis, including both genotoxic effects and nongenotoxic effects such as cellular proliferation. In general, existence of multiple pathways of carcinogenesis renders the elimination of partial additivity to background more difficult.

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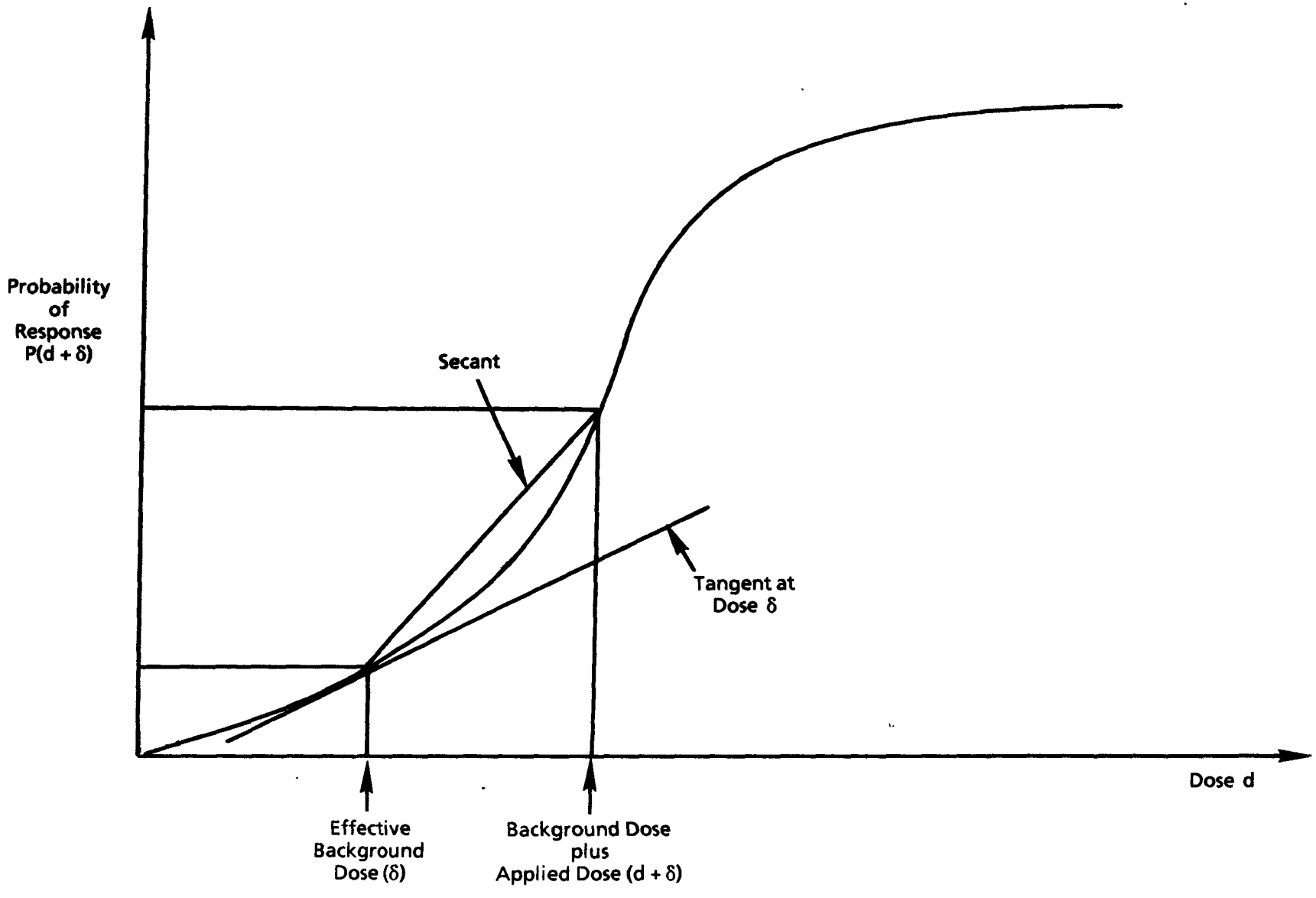


Figure 1. The additive background model.

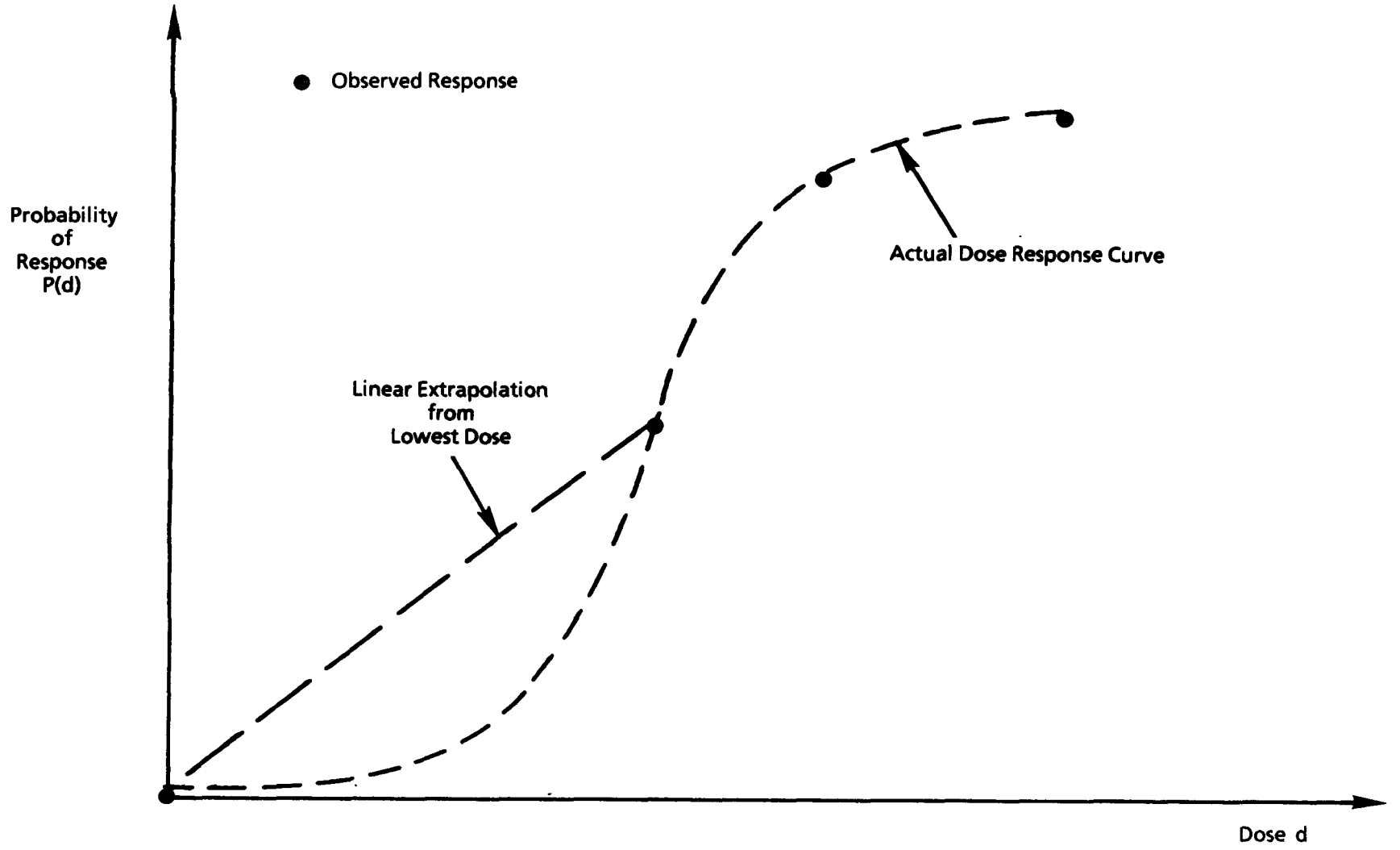


Figure 2. Linear extrapolation of bioassay data.

SUMMARY AND CONCLUDING REMARKS

by John Ashby

Virginia Beach: February 1989

This has been a highly successful meeting. When one reads the work group remits that were prepared prior to the meeting one realizes how much thought and work had preceeded this gathering. In particular, by their design and with the questions they pose, they define the major areas of uncertainty in carcinogen classification and risk assessment modelling. The EPA have therefore essentially called the bluff of those who think there are simple answers to these problems, and in so doing, they provided the right atmosphere for the productive meeting we have just taken part in.

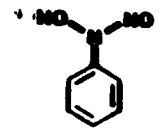
The thing that strikes one most forcibly is that this meeting would have been inconceivable a few years ago. Things are changing rapidly in this area, and the EPA judged the moment correctly to hold this meeting - one no longer has to use the terms non-genotoxic carcinogen or acceptable risk in a lowered voice - they are now subjects for serious study. It is interesting that risk assessment is already a widely discussed topic well beyond scientific arenas - this has been enforced by the sensationalizing of certain putative human hazards. Quite by chance, this topic was aired in a British Newspaper the day I left for this meeting. The topic was the 'toxicity' of potato skins, and it followed closely on the egg/Salmonella debate that is still taking place in Britain. John Akass wrote the following:

'What weight of potato skins does the average man have to eat before he calls an ambulance? We can be trusted with these details because most mature adults are reconciled to the fact that the ordinary run of life contains unpleasant, but acceptable hazards. Institutes that exist to give us the jitters should also tell us how much we should tremble'.

The final sentence of that quotation describes in common words what we have been attempting to achieve for carcinogens over the past days.

It will perhaps help to give an example of the problem we face. I have chosen two rodent carcinogens defined by the US NTP. Both are formally carcinogenic, yet scientific instinct leads us to expect a greater potential hazard for man from the first carcinogen of the two (Slide 1). It is when one attempts to justify that feeling that problems are encountered, because we have not yet collectively agreed the factors that contribute to high or low human hazard ratings for an animal carcinogen. This example could be repeated many times from the large database of the NTP alone (this and related examples are summarized in Mutation Research, 204, 17-115, 1988). Other examples of animal carcinogens with different implicit hazard ratings for humans are shown in Slide 2; it is the scientific formalization of the assumptions made on this slide that is currently required.

An interesting topic has surfaced several times at this meeting - the difference between 'strength of evidence' and 'weight of evidence'. The first is a description of the scientific validity of an observation, the

[Code No.] CAS No. NTP Tech. Report No. (year) Structure or trivial name (alerting substructure in bold)	Structural alert	Salmonella assay resp. (Zeiger)[†]	CARCINOGENICITY DATA Tumor data identified in Summary of NTP Technical Report											
			Tumor site[◆]	Rats (% TBA)[◆]						Mice (% TBA)				
				♂			♀			♂			♀	
				C	L	H	C	L	H	C	L	H	C	L	H
[15] 135-20-6 100 (1978)  Cupferon	+	+	CS HG L S ZG	0 0 0	78 17 40	80 9 46	0 2 0 2	62 56 33 11	79 23 61 8	2 0	7 7	18 10	2 0 4 0	11 4 20 0	13 13 29 4
[103] 63449-39-8 305 (1986) Chlorinated paraffins (C_{23}: 43% Cl)	–	–	HS							12	24	32			

Slide 1. Carcinogenicity data for cupferon (NTP TR 100, 1978) and chlorinated paraffins (NTP TR 305, 1986), as abstracted in Mutation Research, 204, 17, 1987. The symbols used in this Table are described in that paper, but the key ones are TBA = tumour bearing animals, C, L and H are control, low and high dose test groups. The tissue codes are CS = Circulatory system, HG = Harderian gland, L = Liver, S = Stomach, ZG = Zymbal's gland, HS = Haemopoeitic system. The first compound, cupferon, was classified as positive (P) in all four test groups. The second compound was classified using current levels of evidence and gave clear evidence (CE) of carcinogenicity only as a leukaemogen in the male mouse. These two chemicals are therefore representative of putative genotoxic and non-genotoxic carcinogens. The carcinogenicity of the chlorinated paraffin was observed at relatively high dose-levels (top dose of 5g/kg in the mouse) and haemopoeitic tumours appeared in the male mice controls (12% TBA). This slide captures the purpose of the present meeting by highlighting the need to agree a method for ranking carcinogens in terms of possible human hazard.

For Human Risk Assessment :

NaS	≠	DBN	bladder
DEHP	≠	DMN	liver
LIM	≠	DEN	kidney
BHA	≠	MNU	stomach
NaCl	≠	BP	skin
HCHO	≠	S mustard	respiratory
TNM	≠	BCME	lung

Why ? MECHANISM/NATURE OF EFFECT

Slide 2. Examples to illustrate the implicit purpose of this meeting. NaS = sodium saccharin, DBN = dibutylnitrosamine, DEHP = 2-diethylhexylphthalate, DMN = dimethylnitrosamine, LIM = limonene, DEN = diethylnitrosamine, BHA = butylated hydroxyanisole, MNU = N-methyl-N-nitrosurea, NaCl = common salt, BP = benzo[a]pyrene, HCHO = formaldehyde, BCME = bis(chloromethyl)ether, TNM = tetranitromethane S-mustard = bis(2-chloroethyl)sulphide.

assumptions can only yield soft predictions. The fact that it is possible to integrate many different datasets in order to derive a perception of overall risk was most convincingly illustrated by the '10-carcinogen questionnaire' completed by a work group yesterday (elsewhere in this document). The fact that the whole of the scale (1-10) was used (1.7-9.2 infact) confirms that we generally agree that the weight of evidence suggests that sodium saccharin does not present the same human hazard as does vinyl chloride, yet each are clearly carcinogenic in adequate animal studies. Turning now to the main consensus points derived from this meeting.

It seems that there is common agreement that chemicals can elicit a carcinogenic response in rodents by more than one mechanism. The most obvious of these is by direct interaction of the chemical with DNA-genotoxic carcinogens. A range of other possible mechanisms are now being entertained as plausible, but often all we have are empirical markers or hazy hypotheses of how the tumour incidence is increased. Nonetheless, these indications are valuable for they encourage further research, and usually that strengthens belief in an alternative (non-genotoxic) mechanism of carcinogenicity. This leads to probably the major conclusion of the meeting, as follows - <u>If, in the fullness of time, we come to recognize a variety of distinct mechanisms by which chemicals can cause cancer in rodents, then it will follow that each of these mechanisms may require the development of different risk assessment models for extrapolation to human carcinogenic hazard</u>. <u>Further, some of these mechanisms may be shown to be of low or zero relevance to man</u>. The meeting accepted this as a working hypothesis and then discussed its implication if established experimentally as true.

The electrophilic or genotoxic carcinogens are perhaps the easiest to recognize, and they probably present the greatest individual potential human hazard. The key points when approaching their definition and assessing their likely human hazard were discussed as follows:

a) Useful SAR data exist already.

b) Genotoxicity assessment is possible using *in vitro* and *in vivo* assays.

c) DNA adducts *in vivo* can provide useful indications of exposure, but such data should not be over-interpretated in terms of degree of carcinogenic initiation.

d) Non-genotoxic effects (toxicities) such as hormonal changes, hyperplasia, necrotic effects, etc, induced by the same chemical may play a critical role in the eventual carcinogenic outcome of a bioassay. These may also influence the observed dose-response relationships, itself affecting risk assessment.

e) Conservative low-dose extrapolation of data may be in order, albeit such extrapolation may be modified by data indicating metabolic/species/DNA-repair (etc) differences, or the critical involvement of non-genotoxic toxicities of the chemical.

The current problem faced is that this profile fails to fit an increasing number of animal carcinogens - these seem to be demanding of separate treatment. The meeting declined to label these agents simply as

non-genotoxic carcinogens, rather, it was considered necessary to synthesize a variety of data leading to a confident prediction of a mechanism independent of induced primary DNA damage. Both positive and negative sources of data are theoretically available for integration, as follows:

Negative:

a) Non-alerting chemical structure.

b) Conclusion of non-genotoxicity, particularly in vivo.

c) Absence of DNA lesions in vivo.

d) Evidence indicating the potential for bioaccumulation, ie, a failure to metabolize and excrete the agent rapidly.

Positive:

e) Evidence for an alternative mechanism of carcinogenic action.

f) Weak or highly specific carcinogenic effect in rodents, especially if in a tissue with a significant spontaneous tumour incidence. Factors such as long latency period and the induction of benign as opposed to malignant tumours also figure here.

Other Factors:

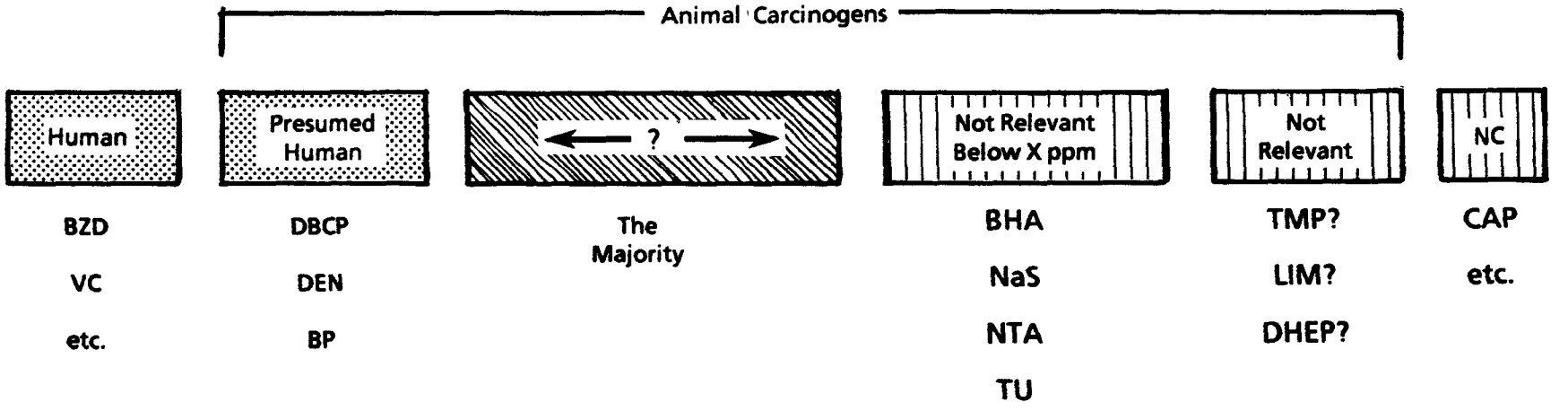
g) Knowledge of metabolic factors that cannot operate in man, of carcinogenic dose-levels that could not be achieved in man, or of pharmacokinetic factors unique to rodent species.

h) Specific knowledge that the mechanism of carcinogenic action could not apply to man.

When all of these factors are considered it may be possible to classify animal carcinogens according to the scheme shown in Slide 3. Examples of chemicals that could possibly fill these separate boxes (Slide 3) are shown beneath each box and are discussed briefly in the legend to the slide. Of course, the majority of animal carcinogens are currently in the centre box, and only experimental data (in addition to the bioassay data) can lead to a chemical being upgraded or downgraded in terms of potential human hazard. Much discussion took place regarding how such studies could be encouraged by the 'rewarding' of new data by a movement in classification, but the matter was not resolved. Use of either a sliding scale or sub-sections within the central box were discussed (ie, near to a presumed human hazard, or nearer to an assumed rodent specific/high dose carcinogen).

Substantial data were presented during the meeting indicating that butylated hydroxyanisole (BHA) is probably the best candidate to date for placing in the category 'not relevant to humans at expected exposure level'. This was because the rodent forestomach tumour data indicate the absence of carcinogenicity below ~2% in diet. Likewise, the several male rat kidney-specific carcinogens that lead to retention of $\alpha 2\mu$-globulin in the kidney are the nearest to being established as of no relevance to man [chemicals such as limonene (lim) and trimethylpentane (TMP)].

At the other extreme, all present at the meeting were agreed that agents such as dibromochloropropane (DBCP), the fire-retardant TRIS, the several nitrosamines such as DEN and benzo[a]pyrene can probably be regarded as likely human carcinogens, given appropriate exposure - even in the absence of positive human epidemiological data [all examples in this text were used



Slide 3. A classification scheme that allows for animal carcinogens to be segregated into different levels of potential human hazard. This scheme represents a synthesis of the several such schemes proposed at the meeting. The assignment of chemicals to particular categories is speculative at this stage. Note how this classification scheme is based as weight of evidence, not just strength of evidence for individual datasets. Chemical abbreviations not identified in the legend to Slide 2 are as follows: BZD = benzidine, VC = vinyl chloride monomer, DBCP = dibromochlorpropane, NTA = nitrilotriacetic acid, TU = thiourea, TMP = trimethylpentane and CAP = caprolactam.

as illustrations of principles during the meeting; they should not be regarded as precedents for the principles being discussed in the absence of a more detailed review of the literature].

A critical aspect of assigning a tentative mechanism of action to a carcinogen is that it can influence the type of model used for the extrapolation of the animal cancer data to man. Thus, evidence is building up to indicate that liver-specific carcinogens that induce peroxisome proliferation in the liver (agents such as DEHP) will be non-carcinogenic as dose-levels that do not lead to perturbations in lipid metabolism in the liver. Further, the magnitude and type of the hyperplastic wave that usually follows peroxisome proliferation can influence the eventual tumour incidence, as is thought to apply also to the longevity of the test species and its spontaneous liver tumour incidence. Such complex and linked requirements for carcinogenicity are most efficiently handled by multi-stage models, perhaps based on that described by Moolgavkar and his colleagues. Further, there are some indications that this particular mechanism of carcinogenicity (peroxisome proliferation) may not be relevant to humans, in which case the risk assessment is essentially achieved with that knowledge (but fact ≠ assumption, see earlier).

Risk assessment models were discussed in great detail, and the following general conclusions were drawn:

a) There is an urgent need to stop talking about modelling in the abstract, and to start to use them. Data should be published and methods compared in an open manner.

b) Particular attention should be paid to developing multi-stage models.

c) Attention should be afforded to deriving empirical 'markers' of carcinogenicity for use in low-dose studies on agents reported to be carcinogenic at higher dose-levels (eg, Swenberg's use of kidney foci as markers of TMP-induced kidney cancer in male rats).

d) Attempts should be made to isolate those stages in a multi-stage model that are directly chemically dependent. This will open the door to consideration of additive effects (enhancement of spontaneous tumour incidence) and inductive effects (the initiation of novel tumours by the test agent).

In order that any of the above hopes can be realized, the meeting recognized that certain disciplines must be exercised by all involved; three being discussed in detail:

1) That terminology should be tightened up. Thus, it is of little value to use a loose word such as 'hyperplasia'. If this word is considered relevant to a particular carcinogen or putative carcinogenic mechanism, the following facts (and probably more) should be clearly identified.

    a) Was the hyperplasia acute or chronic, focal or general?
    b) Was its observation acute or extended?
    c) Was a single measurement or an integrated measurement made?
    d) How was hyperplasia monitored -
        i) S-phase cells
        ii) mitotic figures
        iii) tissue weight

e) When used for risk assessment, will hyperplasia in the whole tissue or for a sub-population of cells be used?

2) What is the specificity for carcinogenicity of the marker event being used. For example, is $\alpha 2\mu$-globulin also accumulated in tissues other than the male rat kidney during exposure to limonene, and if so, why are tumours not induced in those tissues?

3) The issue of 'scaling dose' requires urgent classification. At present it is used in two ways. First, via surface area of a species, to derive trans-species dose extrapolation. Second, via pharmacokinetic results, to rationalize differences in carcinogenic outcome between species or routes of administration.

In summary, in order to make progress in this highly complex area we need to agree a common language based on sound scientific observations.

Two final considerations seem to be important. First, it is clear that molecular studies of proto-oncogene activation should soon resolve many of the fundamental aspects of chemical carcinogenicity. These should impinge directly on mechanisms of action, and as such they should influence risk-assessment models in a fundamental manner. Second, the issues at stake here are fundamental to a sound policy for the categorization and risk assessment of chemical carcinogens. As such, progress should be attempted at a fundamental level and on a broad front. In particular, these principles should not be evaluated and developed in an adversarial

atmosphere with a major chemical of commerce. If that happens, this critical issue will become clouded by political factors of no true relevance to chemical carcinogenicity.

In closing, I would congratulate Dr. Hill and his colleagues for organizing such a stimulating and open-minded meeting. Progress in this area is urgently required, but it can only be based upon sound science.

APPENDIX A

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APPENDIX C

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APPENDIX D

INTRODUCTORY PLENARY SESSION[1]

[1]This section includes the text and/or summary of four presentations given during the Introductory Plenary Session on Wednesday, January 11. Because EPA had not asked the speakers to prepare formal papers, the following texts are based on tape-recordings of each speaker's presentation, edited for clarity. Each speaker has reviewed and approved the material presented here.

INTRODUCTORY PLENARY SESSION

John A. Moore, An EPA View

In 1986, some 3-odd years ago, EPA published in final form its guidelines for carcinogen risk assessment. However, as I think almost everybody in this room knows, the Agency began using them in 1984 while it was drawing comment on its draft guidelines. I think we made it clear then, and if we didn't, we'll make it clear today, that we see those guidelines as needing to have a use in all seasons, both at the time they were published, as well as into the future. In order for them to maintain some degree of utility, it's incumbent upon us to make sure that they reflect advances or current beliefs as they relate to scientific knowledge, as well as to take stock of the experience that we've gained from their use these last several years. I think on net the Agency feels that the guidelines have served them reasonably well. They are in the main, we believe, reasonable principles for the consistent review of carcinogenic data.

At the same time, I think there is within the Agency a consensus that they can and probably should be improved. Improvement can occur in two broad ways. One can make basic changes in the guidelines themselves, and/or one can make changes in the implementation practices within the framework of the guidelines as they currently exist. A number of months ago, a technical group within the Agency reviewed the guidelines with an eye towards identifying areas that may be ripe for more intensive investigation. They recommended that

wholesale revision of the guidelines probably was not appropriate. They also identified, however, two broad topics that merited further scrutiny. First, the weight-of-the-evidence process that's used for evaluating whether or not a chemical process may pose a carcinogenic risk to man and, secondly, the issues associated with quantitative dose response assessment.

There were four activities that were planned and have been pursued. First, we solicited Agency-wide the various offices at headquarters, as well as regions, for comments on what they thought of the guidelines. Next, we conducted a limited number of interviews of certain people within the Agency and also outside of the Agency; for example, people who had served in our science advisory groups and who had reviewed products of the use of the cancer guidelines, as well as State government people. These guidelines, although they're developed to assist the Agency in getting on with its business, certainly end up having implications far beyond the borders of EPA. We're keenly aware of that and would like to make sure that we understand how they're being used outside of the Agency, with the idea of their either being used properly from our perspective or possibly being misused. Not that there's necessarily much we can do about it, but we certainly should be aware of it. Thirdly, we identified through the Federal Register the fact that we were considering guideline review, and fourthly, we began planning for the workshop that begins today.

The first three of those activities have been completed. Upon completion of this workshop, we will synthesize what we think we've heard and plan some course of action. A preliminary evaluation of the first three things identified three themes.

(1) Some people felt that the guidelines in their current application were just fine; we don't need to change a thing. If you have to change something, tinker with it on the margin at best; for instance,

maybe change some language to reflect the changes in language that IARC guidelines had undergone since the Agency's guidelines had come out.

(2) A number of people said the guidelines are fine. The problems are with how you people use the guidelines. In this case, the claim is that we don't always use the breadth or totality of the information that's available on a given chemical, even though the guidelines clearly allow that and maybe even suggest that that's what should be done on a case-by-case basis. They assert that we too often are rote, if you will, in our application of default positions and, indeed, maybe need to analyze a little bit more in some areas. An example that somebody might give is that we always seem to pick the most sensitive indicator, as opposed to the most appropriate indicator in that data set. They make a distinction between the two. Why do you always do this? Why don't you show a little bit more selectivity?

(3) Finally, there are those that are on the opposite end of the spectrum, in that no matter how you try to tinker with the guidelines, they really require a reanalysis. Two main areas were commonly cited that need to be looked at in order to make an improvement on the current product. One is this identification of human carcinogenic hazards, while the other pertains to quantitative questions associated with a risk extrapolation. Obviously the workshop that we're headed into here tries to draw upon these two aspects. What is the process that you need to go through to make that initial qualitative determination? How do you express it? Secondly, how do you get into some quantitative expression of the risk?

We identified under those two broad areas five topics that we think are of priority interest, based on our own beliefs and experiences, as well as comments that were received. They are reflected in the

five breakout activities for the meeting. Let's go through the two qualitative topics.

There are obviously a number of issues surrounding the question of whether or not a chemical poses a carcinogenic hazard to humans. Questions have arisen about the current classification scheme built into the guidelines. For example, our Science Advisory Board more than once has pointed out the difficulty in interpreting experimental data and placing it along that continuum between B2 and C. I don't get many comments and letters talking about the A or the E part of the guidelines. They all focus around B2, C; B2-C. This range is broad, and everyone's focusing right there. Are the guidelines truly doing everything that they should be doing? Is the problem inherent in the classification scheme or is it a flaw in how we use the classification scheme? I think we need to take a look at that.

What is the relevance in the finding of tumors in animals and of other experimental data to human carcinogenicity? We're asking this group to hopefully consider the bases for judging the relevance of the experimental data. What can you do and what can't you do? How far can you go and still be basically following a logical application of science, as opposed to doing something else that represents a decision, but not necessarily the logical step or a comfortable step based on where we are with existing knowledge.

The guidelines state, and the Agency believes, that positive animal studies are presumptive evidence of potential human carcinogenic hazard. But at the same time, I don't believe the presumption is infallible. I think the challenge is to better capture the fervor of our belief associated with any particular chemical. Can we, or as some people say, must we admit that in certain cases animal tumors or experimental findings may be of less relevance to humans? How do, or should, we distinguish between a one species' response and a multiple species' response? How do we do a better job if we've got two

responses, rat and mouse, and the nature of the second tumor response is different from a histogenic standpoint? We don't express that very well. Can we do better?

Certainly, concordance across species is used to strengthen one's belief a chemical is a human carcinogen. If it's positive in elephants, giraffes, rats, and mice and they all produce the same type of tumors, similar dose-response, etc., we're sure it is one. We all use it that way, I think, fairly effectively. But how about trying the case when the data don't quite fit together. We don't do it very well or don't agree on how to do it, and when we're done, I don't think we communicate these cases very well.

Let me get out a pet peeve. The fact that dimethylnitrosamine is a flaming genotoxic agent and a carcinogen in dozens of species probably doesn't have a lot of relevance to what we do in our day-to-day practice as a regulatory agency. I don't see too many DEN's. I think the things that we struggle with are the paradichlorobenzenes or the diethylhexophthalates or the ethylene thioureas. Paradichlorobenzene: mouse liver tumors by gavage; male rat kidney tumors; two species. What do you do with it? DEHP is nongenotoxic but produces clearly reproducible effects in bioassays. What does that mean? Ethylene thiourea produces thyroid tumors. What does one do with it, in that these tumors might be secondary to a disruption in physiologic responses that are hormonally derived. These are the types of things that the Agency struggles with, not the boring negatives or the flaming positives.

You've got to assemble all experimental and other information into a weight-of-evidence expression. I think we've got to realize by weight-of-evidence statement, we're not simply trying to amass the evidence in support of carcinogenicity, but to assess thoroughly in that expression whatever may be the overall implications of the data

for humans. And whatever is done, how do you get that across in something less than a 32-chapter book?

Let's now go to quantitative issues. Agency experience and reviewed comments suggest that we need to evaluate carefully several topics relative to quantification of risk. For example, the guidelines give guidance on interspecies scaling in the absence of any relevant information. They implied at the time they were written, that if one had some pharmacokinetic data, it probably would help to bridge the gap. Let's take methylene chloride, in that we have that information. Everybody said, okay, now, let's do it! Then came the discussions, and we found we don't have agreement on how or what to do. Do you apply it only across human doses? Do you scale doses across species. How does one account for possible differences in pharmacodynamics? Hopefully, we can get some sense out of that session at the workshop.

Another question is when to quantitate cancer risk, and some claim we often seem to be oblivious to the qualitative data. Should we always proceed on the same path? In one case, you might have a strong, robust data set that makes everybody comfortable. Both sexes, both species, dose-response, etc. In another case, you have little evidence of carcinogenicity; you believe it's reproducible, but the response is fairly modest; one sex, one site. Yet we treat the two cases the same because the paradigm we use does not consider the qualitative evidence that goes into it. Should we always take the same route or should we be doing something different? If you forget what the Agency says in response to that question, look at what the Agency does and it probably gives a clearer insight as to what it's all about. I think the Agency struggles with the fact of having to do the same thing all the time or feeling compelled that it's got little choice but to do the same thing at all times.

You've got two parts of the Agency, the Office of Water, as well as the Pesticide Program, that often say, given a C categorization, we're not going to do a quantitative cancer risk estimate. Why are they doing that? I think part of the reason is they don't believe the outcome if quantitative procedures are rotely applied. There's a glimmer there of something maybe one should look at. It's fine to say you're not going to extrapolate risk, but the next question is, okay, what are you going to do? After all, there certainly was some type of positive response; it wasn't negative.

Maybe this will be the last meeting that we'll have to discuss scaling doses across species. What do we do and how do we do it? Can we finally come to an agreement on what needs to be done rather than continue to say, well, there are two ways we do it and both make sense. Frequently, we argue both sides and then go different ways. The public sits there and wonders what's going on. Can we do better? I think there's been a more serious insight on that issue in the last year that might allow us to move off the dime a little bit one way or another. Hopefully, you'll look at that.

In what way can biological data, bearing on potential carcinogenic mechanisms, be used in selecting the means for extrapolating from high doses to low doses. We don't mean something different necessarily. We can accept some alternative if it's clearly better, but difference for difference sake isn't going to necessarily get us anywhere. I'm uncomfortable about always using the upper 95% confidence limit on the linear component as a means of expressing what it is that might happen. Isn't there something else that could be included as part of the equation, like central tendency, or MLE? I don't know what it is, but expressing the worst all the time, which is what we do, doesn't give the true picture. How can we do it better?

Lastly, what are the consequences of whether a chemical induces tumors by actions that are similar to or different from those accounting for background tumors. Do you treat a mouse liver tumor or a mouse lung tumor response differently than some other type which is rare? If the answer is yes, what's the decision logic that goes along with doing that rather than having it be a black box that comes out with any particular chemical?

Believe it or not, we assembled the participants of this workshop in the belief that they'd be able to work on the five topics that we identified. They have something special to lend to those five topics. With that in mind, we urge you to stay on those five topics.

I think there's certainly a fair amount of grist for the mill in those five topics. It isn't as if you won't have something to do. Identify those issues that you think might be right for some intensive evaluation or re-evaluation now, as contrasted to those that need further work and might be ripe for consideration 3 or 5 years from now or 10 years from now. For those that are amenable to possible change, identify the range of options. I'm not sure a consensus will jump out on all of these issues, so what we really want is a very good casting of the pros and the cons associated with those. Let's be candid as to what speaks for it and what speaks against it. On the other hand, if consensus doesn't emerge, don't run away from the issue.

The other thing, let's not discuss some pending regulatory decision in the guise of this meeting, whatever it may be. Let's check our baggage at the door. We all carry it, we all have our biases. I gave you a couple hints of mine in this talk. Let's try to make it as open as possible. Remember, the Agency is at the beginning of a fairly long path deciding what should be revised and how to do it. If there is revision, there will be ample opportunity to comment on

and further massage whatever those changes may be. This meeting is not going to be the basis for coming up with something.

My last comment would be that, as you'll hear this morning and I hope continue to hear throughout the conference, there is more than one way of doing something. The way the Agency's cancer risk assessments are being done in some instances with certain types of chemicals is different from the way others are doing it. Cognizant of the fact that these differences exist, I'm not at all happy that the differences do exist. I think this world gets smaller and smaller and I think we always need to see if one can reconcile differences rather than continue to watch differences grow one way or another. To the degree that there are differences, the key thing is at least to try to understand why the differences exist. Then maybe from that point you might try to reconcile some of these differences. For instance, certainly the B2-C approach is addressed differently internationally than is currently done by EPA, or possibly elsewhere in this country.

Thank you.

Frederica Perera, A Public Health View

I'd like to start by giving a broadbrush context to this whole discussion. The context of this workshop is that we have a very major problem in this country today. That is to say, there are 460,000 deaths each year in the U.S. from cancer and the great majority of these are preventable. Preventable because they're attributable to environmental factors; not only lifestyle factors, (such as smoking and diet) which involve voluntary behavioral choices, but involuntary exposures to industrial and manmade carcinogens in the workplace, in the ambient air, the drinking water, and the food supply. While it's really not possible to estimate the exact contribution of any one of these to the total burden of human cancer, I think we all recognize that exposure to these industrial or manmade carcinogens is pervasive and significant. This is the special province and responsibility of EPA, and, we need to deal more effectively with these problems.

Therefore, I would suggest that the standard for review for these guidelines is whether they provide a workable, scientifically supportable system for the timely assessment of carcinogens and for their regulation in order to prevent cancer. That's my jumping-off spot.

Turning to the 1986 guidelines, as I discussed in my written comments to EPA, I think that the basic principles are justified. These principles are the reliance on experimetnal data in the absence of epidemiology and the general assumption that carcinogenesis is a non-threshold phenomenon. In part, this latter assumption is derived from the inability to define population thresholds.

I had specific comments and criticisms about certain aspects of the '86 guidelines, including the classification scheme. I'm concerned about the fact that this scheme could easily become a kind of pigeon-holing system with automatic regulatory implications that are not biologically founded. For example, category C, or "possible carcinogens" includes certain chemicals with at least one clear positive test result, such as vinylidene dichloride, styrene, lindane, para-dichlorobenzene, all significant human exposure. Certain offices in EPA have proposed to regulate those chemicals because they fell into the C rather than the B ("probable") category. I think there is no biological basis for this approach. I would recommend that the revised guidelines state clearly that a chemical with a clear positive bioassay result and significant human exposure will be a candidate for regulation as a carcinogen.

Moving on now to the second area that I think needs strengthening; that is the area of the criteria for reviewing pharmacokinetic-based risk assessments and mechanistic models. Of course, the guidelines now state that EPA will consider such data, but as Jack Moore said, they're not sure how to do it. I think there's a need for consistent minimum criteria to be met by each model and assessment that is presented to the Agency for its consideration.

On my next slide, I've listed the type of information one would ideally want to have. This is not a trivial research agenda here, as many of you know. The list includes: identity of the active species' or critical metabolite for carcinogenesis; an understanding of whether pharmacokinetic processes are linear or saturable; and whether the carcinogen itself can affect or modulate any of these processes. (We know, for example, that formaldehyde can induce cell proliferation, bind to DNA, cause mutation, and inhibit DNA repair.) Also, one would want to identify chemical interactions that are likely in the human exposure situation, as well as differences between chronic and acute exposure; whether there are interspecies

differences; and, very importantly, the range of interindividual variation in the human population. I will be discussing this last point in a moment. To summarize, proposed models should be accompanied by a clear discussion of uncertainties and assumptions in the model and by results of sensitivity analysis.

Similarly, with mechanistic models or theories, there should be a requirement for adverse supporting evidence. For example, in the last 5 or 10 years, we have repeacedly seen proposals to split up the world of chemical carcinogens into those which directly damage DNA, the genotoxic carcinogens, and those which appear to act by other mechanisms. However, it just isn't that simple: there is no bright line between these two groups. Indeed, data from the EPA GeneTox program, from Dr. Mike Waters and his colleagues, show that many so-called classical nongenotoxic carcinogens, are indeed positive in several, not just one, but several short-term tests for genetic toxicity. These include DDT, asbestos, diethylstilbestrol, chloroform, trichlorethylene, perchlorethylene, phenobarbital, ethyl alcohol, and sodium saccharin. In addition, recently, researchers at NIHS, Drs. Reynolds and Marshall, have shown that two so-called non-genotoxic liver carcinogens, furan and furfural, in fact, induce a novel mutation in rat oncogene and liver tumors.

Let us turn to the central question here: "Is low-dose linearity a valid assumption?" Low-dose linearity follows from either the notion that individuals are not homogeneous in their responses or that the effect of any single carcinogen of concern has the ability to add on to the effect of ongoing processes and background exposures.

Let's examine whether there are new data that shed light on this question. Results of human studies on metabolism, DNA binding, and DNA repair show that indeed in humans there is considerable variability between individuals in terms of the metabolism of aromatic amines, polycyclic aromatic hydrocarbons, and other

environmental chemicals. For example, there is a range of 3 to 160 for specific aspects of human metabolism. In vitro studies with the carcinogens benzo(a)pyrene, aflatoxin B1, and dimethylnitrosamine show a 150- to 200-fold variation in DNA binding. With respect to enzymes involved in DNA repair, human studies show a 2- to 65-fold range.

Indeed, human studies also suggest very wide variation. We have recently studied a group of foundry workers with exposure to polycyclic aromatic hydrocarbons and have seen in the exposed group a range in adduct levels 0 to 2.8 femtomoles of adduct per microgram of DNA. Similarly, in smokers of about a pack and a half a day, DNA adduct levels differed widely. The same variability was seen by other researchers in a study of O_6-methylguanosine adducts in patients from China, presumably exposed to dietary nitrosamines. Cis-platinum is a chemotherapy agent that is given to patients in treatment for epithelial cancers. The doses are standardized to body surface area. Here, too, researchers have seen wide variation, as was true for ethylene oxide-hemoglobin and 4-aminobiphenyl-hemoglobin adducts.

On the question of background levels, in each of the studies just discussed, with the exception of cis-platinum, the so-called unexposed or control group also had a mean adduct level significantly greater than 0 and again there was a range in results. While these phenomena certainly need to be investigated further, this information is supportive of the assumption of low-dose linearity.

Finally, I want to turn to an issue which is not adequately addressed in the guidelines. One often hears that the linearized multistage model is a very conservative model and is always going to give an upper bound estimate of the risk. But neither this model nor other models that are available are fully addressing the problem that there are certain segments of the population that are likely to be more

susceptible to the effects of carcinogenic exposures. These include the young, people with pre-existing disease, and the elderly, for example. Of great concern are young children, of whom in this country today we have 18 million between the ages of 1 and 5 years, and 22 million, 0 to 5 years. At this age, children can be assumed to be more vulnerable to the effects of environmental carcinogens than adults. First of all, they have a greater intake on a kilogram-of-body-weight basis of drinking water (>3.5 times); and a two- to six-fold greater consumption of food. Thus, their intake of carcinogens in these media is correspondingly greater than for adults.

Secondly, certain physiological factors can increase their susceptibility to exposure: greater retention of dose, decreased detoxification, less effective DNA repair systems, higher rate of proliferation, and immature immune systems. Finally, this young population has a longer future lifetime over which cancer can develop as a result of their early exposures. In other words, their future lifetimes will exceed the latency of cancer. For these three reasons, EPA should routinely do risk assessments for children as a separate population.

James Wilson, An Industry View

The job change is still in the future by a month...I've been afflicted with Potomac fever, I guess. My assignment is the industry perspective, and I'm a little hesitant to advertise what I have to say as representative of the views of industry, whatever industry may mean. Even among my colleagues at Monsanto, there's a healthy difference of opinion on a number of the issues that we will talk about. Among my colleagues active at the American Industrial Health Council, there are perhaps even larger, or at least equal differences of opinion, and outside of these groups, there exists an even greater diversity of views. So what you'll get this morning is a personal perspective strongly colored by my 20-odd years of experience as a research chemist in the chemical industry. The question is, is it appropriate now to consider some changes in the way the carcinogen risk assessment guidelines are drawn?

Let me first talk about the purpose of these and other such guidelines. Recall that they're intended primarily for use by professionals, frequently fairly inexperienced professionals. Professionals, whether they're toxicologists, physicians, architects, engineers, or whatever, share a few key traits, and for us this morning, the most important of these is their orientation towards solving particular problems. Each sick person to a doctor, each bridge to a structural engineer, presents a unique case, with unique problems. The problem facing the professional is usually fairly well defined: to make the sick person well, to design a bridge to cross a particular river at a particular point. In developing a solution to each of these particular problems, the professional relies on both general and specific knowledge, and upon judgment built up over time as different problems are addressed and solved. Professionals necessarily have to rely on an incomplete base of information for solving the problems. Whenever possible, they rely on scientific

information because they, like the rest of us, find such information reliable. But when that's not available, they have to make do with what's at hand. Each profession develops its own rules of thumb, lessons that are learned over years by practitioners and passed on from one to another, that help them in this process of solving particular problems. Much of what can be found in the carcinogen risk assessment guidelines turns out to be this kind of preset, codified rule. Most of these come from toxicology, and have evolved in response to the profession's need to set adequately safe limits for exposure to toxic substances.

Toxicology is a relatively young profession, one whose underlying science base is not so well developed, perhaps, as those of engineering and medicine. Some of its rules of thumb have a basis in science, but they're purely practical. One example is the use of the most sensitive species or test as a basis for setting standards. This can be understood in terms of the demands on the profession, but is patently inconsistent with the way scientists analyze data. Most people believe that science-based procedures give better results than those based solely on practice. They do this, at least in part, because we now recognize science as a process for developing reliable knowledge. To borrow a phrase from the English physicist John Zyman, who published a little book on the subject about 10 years ago, "science provides the best basis for making decisions in a material world, when relevant scientific information is available." This being the case, it's obviously in the interest of the Agency to adopt and use the most scientific methods that it can, and in the interest of all of us for the Agency to do so. In my opinion, in the roughly 5 years that have elapsed since serious work was done on these guidelines, there have been significant changes in the science underlying some parts of the guidelines. I suggest that these parts should be revisited.

One thing that has become abundantly clear in the last few years is the importance of mitotic rate to cancer risk. Scientists in the field of biochemical genetics recognized more than 2 decades ago that mutations essentially don't occur unless a cell with damaged DNA undergoes division. The implications of this for carcinogenicists were not recognized by scientists in that field until about a decade ago, when, independently, two groups of scientists, Moolgavkar and Knudson, and Greenfield, Ellwein, and Cohen, found they had to take the age distribution and mitotic count to explain the quantitative incidence of cancer. Todd Thorslund, then at the Agency, was one of the first people in risk assessment to recognize the potential importance of this finding of the Moolgavkar-Knudson theory to cancer risk assessment, and he started working on his ideas sometime about 1985. We are still working on the implications this theory poses for cancer risk assessment, and how to take them into account. One of the critical implications is that any treatment that increases mitotic rate over background also increases risk. This means, among other things, that those people who are larger are more highly at risk than those who are smaller, as a recent paper by Albanes pointed out. More cells means more mitoses over a lifetime, and thus a greater chance that a cell suffering a mutation in a critical locus will occur. Both overfed people and overfed rats have higher cancer rates.

Now, more importantly for our purposes here today, is that data on dose response of mitotic rate assumed a much larger importance than any of us had recognized in the past. Results coming from Cohen and Ellwein's work suggest that acutely elevated mitotic rate and treatment in which a burst of increased cell division occurs, chang risk only to a very small degree. They found further that the risk from chronic elevation is very nonlinear. The guidelines need to recognize the fact that this data is important and that it will be becoming available over the next few years.

Another implication of the theory, which Moolgavkar has forcefully pointed out recently, is that the approximation used by Crump and his coworkers in devising the linearized multistage extrapolation procedure fails at high incidence. That is, it fails under precisely the conditions where it is most likely to be employed by the Agency and others, where the tumor incidence is something over .3, or over 30 percent. Under these conditions, the separate contributions of mitogenic cell division stimulation and mutagenic direct attack on DNA begin to interact in a synergistic fasnion. A hockey stick-shaped dose response curve is then the result.

Under these conditions, even with a strongly genotoxic agent such as benzopyrene or 2-acetylaminofluorene, the dose response is not necessarily linear, as the work of Gaylor and his colleagues on the ED-01 study have pointed out. Another indication of that is in a paper by Zeise and Crouch on benzopyrene in the rat forestomach. Thus, the linearized multistage procedure can be claimed to be a plausible upper bound of the risk only if the mitogenic contribution to the incidence can be distinguished. The guidelines need to take that into account.

The discussion of interspecies extrapolation has generated much more heat than light over the past few years. It's time now for this to be addressed. Within the last few years, some real scientific understanding of this process has begun to emerge. Personally, I am convinced by the work of Travis and his associates that the default scaling procedure should be that of the three-quarters power of body weight, but not everyone agrees. More important is that our understanding of the factors that control dose scaling have been expanding much more rapidly. For instance, the difference of opinion between the Dow Chemical Company and the EPA over low-exposure extrapolation on the effects of dichloromethane may turn on whether a detoxification product, such as a formaldehyde derivative from the glutathione pathway, is formed spontaneously, by a direct chemical

reaction, or by an enzymatic reaction of some kind. That kind of point becomes the determining factor in how an extrapolation is to be performed. We've gone beyond what is consistent with the default procedures that are called for in the guidelines. The guidelines need to recognize that more sophisticated information can be, and is being obtained.

Another new development is the accumulation of data that allow us to draw conclusions about the ability of animal models to predict human cancer hazard. Some consensus now exists on predictability in a number of cases. For example, the rat bladder is known not to be a good model for human cancer hazard, concerning exposure to aminobiphenyl or other polynuclear aromatic amines, most likely due to a pharmocokinetic difference between man and the rat. On the other hand, recent human evidence confirms that inert implants that cause chronic inflammatory response increase the chance that a tumor will form at the site of inflammation. Further, it's very likely that a repeated injection of any substance into the same spot in a human will cause a tumor at that spot, from the same mechanism as that of a solid-state carcinogen. However, such tumors by themselves in animals are not predictive of a human cancer hazard for the material that's injected. The physiology of the rat urinary tract, especially in the young male rat, is different enough from that of humans that substances that induce bladder calculi only under conditions found in rat urine are not predictive of human cancer hazard. The same thing can be said of the nephrotoxins that complex with α_{2u}globin and retard its decomposition leading to the sequence of events described by Swenberg and his coworkers. Even though the evidence of carcinogenic response to inhaled polynuclear aromatic hydrocarbons is surprisingly sparse, nearly everyone believes that they pose a serious threat. Most of us assume that the hazard comes from the genotoxic properties of the metabolites of benzopyrene and so on, yet there's good evidence of action through a mitogenic mechanism as well. The angiosarcomas introduced in rats by inhaled

vinyl chloride do predict human response; we don't know if chemically similar compounds do the same. Finally, we come to the interesting case of rodent goitrogens. Clearly, there are significant quantitative differences between humans and rats in the way they respond to ethylene thiourea or sulfamethazine. McLuin believes there are also qualitative differences, and that the rodent tumors are not predictive of human response. There is some evidence to support this view, but there is not a consensus on that conclusion. In summary, the first question to be asked of any animal experiment is, does the model allow us to predict a human response? The guidelines need to recognize this fact.

The fields of DNA adducts and oncogenes have exploded, or the two fields have exploded and now they're growing together. We can say a few things for certain about the information that's derived from those kinds of experiments. The one thing that is clear, however, at least in theory, is that DNA adduct information can be used as an indicator of integrated chronic exposure. Information much beyond that has still to be deciphered.

Let me close with a reminder that people outside the Agency will use the results of the classification scheme, if not the scheme itself, for purposes outside of the Agency's control. Many will use the classification as an indication of the danger posed by the substance. Chemicals that are "known carcinogens" will be regarded, probably correctly, as more dangerous than those that are probable carcinogens, and so on. I suspect that, conscious or not, within the Agency the classification scheme serves a purpose similar to that used by people outside of the Agency. I would suggests two possible alternatives: either make the classification "possible carcinogen" a very large one, by including virtually all compounds for which there are inadequate data; or discard from the classification scheme altogether all substances except those regarded by the Agency as serious threats to human health. For instance, Monsanto commented on

one example of a competitive situation where the classification of one compound as a category C and another compound as not classified was used to effect the sale of a particular product to customers. If that were the only example of this kind of distortion of commerce that ever occurred, the subject would not be worth further discussion. However, that's very unlikely. What happened once is probably happening at other times, and should be kept in mind as the Agency considers revisions to that part of the guidelines. Thank you very much.

Kees Van Der Heiden, A European View[1]

Dr. Van Der Heiden described the European approach to carcinogen evaluation, noting that while the operational definitions are similar, strict guidelines do not exist and most compounds are evaluated on a case-by-case basis. Use of mechanistic data is important in classifying, and it is likely that carcinogens act by various important mechanisms. Some distinctions can be made; for example, one can have clearcut genetic mechanisms and clearcut nongenetic mechanisms. Indirect genetic mechanisms are more difficult to deal with, however, and attempting to separate genetic from nongenetic mechanisms is not simple in practice.

The general approach in both Europe and the United States is similar in that it starts with an evaluation of weight of evidence. However, in Europe, weight of evidence is based on whether a compound is a carcinogen in experimental animals rather than a human carcinogen. The basic weight-of-evidence evaluation in regard to experimental animal evidence is about the same internationally.

Beyond the initial animal bioassay evaluation, additional information is usually requested. However, if good positive results are found in a bioassay, then other information, e.g., biokinetics, pharmacokinetics, scaling factors, is not necessary. A number of mechanistic considerations are usually pursued with the results of short-term tests of DNA interaction; mechanistic studies are preferred over multiple bioassays. Information on nutritional imbalance or physical/chemical properties of the compound are then utilized in evaluating the results.

In emphasizing a mechanistic approach to classification, most chemicals are found to fall somewhere in between genotoxic and nongenotoxic. For these substances, a choice must be made. For the genotoxic compounds, a clear, nonthreshold approach is used to calculate risk: a simple, linear

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[1]This is a summary of remarks based on the taped presentation. It has been reviewed and approved by the speaker.

nonthreshold model which draws a straight line from the lowest positive point to zero. For nongenotoxic compounds, risk assessments utilize a threshold approach based on mechanistic considerations and the assumption of the reversibility of the effect.

Carcinogens fall into basically three groups: genotoxins, nongenotoxins, and uncertain mechanisms. While compounds can be placed in the latter group if there is limited evidence from animal bioassays, e.g., tumors only at high dose levels, these are compounds which are in some way questionable.

The regulatory approach for clear, genotoxic carcinogens has been to avoid exposure to the extent possible. When there is an alternative, a genotoxic carcinogen is not allowed. When there is a profound technological need, a limit value is derived employing a simple calculation to adjust body weight differences between the test species and humans. The limit value is thus different from an acceptable daily limit. Scaling factors are not used. Since there has been no agreement despite extensive discussion, this method was considered the best choice.

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