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Project Summary

Report of the EPA Workshop on the Development of Risk Assessment Methodologies for Tumor Promoters

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At a workshop sponsored by the EPA Office of Research and Development in February 1987, thirteen expert panelists discussed research needed to support the development of risk assessment methodologies for tumor promoters. The panelists exchanged current data on promotion, identified data gaps, and formulated general and specific research recommendations. Available data suggest that there are probably at least three stages of carcinogenesis – initiation, promotion and progression – and that there are agents that are associated predominantly with these three stages.

The panelists agreed that the mechanism of promotion is not currently understood, and they suggest that there may be several different mechanisms of promotion. Available data suggest that promotion is substantially different from initiation and that traditional risk assessment models for carcinogens are not appropriate for promoters. The panelists agreed that not enough data are currently available to assess the risks of promoters and that substantial research is needed in several areas, including: mechanisms of initiation, promotion and progression; the behavior of promoters in humans, especially epidemiological studies; development and validation of statistical models for initiation/promotion systems; the behavior of promoters in organs other than the skin and the liver; interspecies differences in promotion; expansion of the chemical data base for known and potential promoters; synergism among promoters; and development validation of *in vitro* screening models for known experiment promoters.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, DC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

In recent years, there has been a growing recognition that risk assessment of tumor promoters is important but is precluded by a lack of data. In 1982, the U.S. Environmental Protection Agency (EPA) Office of Toxic Substances held a workshop to examine how information on promoter activity could be incorporated into risk assessment. Participants agreed that such information should be incorporated into risk assessment but could not offer the Agency guidance on how to do this. Recently, both the Science Advisory Board in its review of perchloroethylene and the EPA Office of Pesticides and Toxic Substances' panel

on dioxin recommended that the EPA consider integrating promotional activity into the traditional risk assessment.

With regard to promoters, the current EPA *Guidelines for Carcinogen Risk Assessment* state:

> Agents that are positive in long-term animal experiments and also show evidence of promoting or cocarcinogenic activity in specialized tests should be considered as complete carcinogens unless there is evidence to the contrary because it is, at present, difficult to determine whether an agent is only a promoting or cocarcinogenic agent. Agents that show positive results in special tests for irritation, promotion or cocarcinogenicity and no indication or tumor response in well conducted and well designed long-term animals studies should be dealt with on an individual basis.

While this approach was not felt to be wholly satisfactory, there was not enough consensus to develop an alternative approach in terms of either a qualitative judgment of how likely an agent is to be a promoter, or, quantitatively, of how great a cancer risk a promoter might pose for given levels of exposure.

As a first step towards risk assessment for tumor promoters, the EPA Office of Research and Development convened a workshop on "Development of Risk Assessment Methodologies for Tumor Promoters" on February 3-5, 1987, in Bethesda, Maryland. The workshop provided an opportunity for expert scientists to pool their knowledge and set research goals to improve the scientific bases for risk assessment of promoters. The group was asked not to address specific chemicals, but rather to identify research concerning promoters as a class of substances, and to prioritize this research according to its impact and utility for risk assessment. The workshop was chaired by Dr. Roy Albert (University of Cincinnati Medical Center), Dr. Robert Langenbach (National Institute of Environmental Health Science), and Dr. William Farland (EPA Carcinogen Assessment Group).

The full report is based solely on the workshop discussion and panelist comments. As such, it reflects the opinions and data of a limited number of participants exchanged over a brief period of time and therefore does not provide a comprehensive treatment of the various subject areas. The amount of information provided on a particular topic in the report does not indicate its relative importance, and there may be important aspects of tumor promotion that are not touched on in the report.

Discussion

At the workshop the panelists agreed that available data suggest that there are probably at least three stages of carcinogenesis – initiation, promotion and progression – and that there are agents that are associated predominantly with these three stages. Initiation was described as a sudden change probably involving DNA that is irreversible over a long period of time. There is a growing body of data suggesting that the initiation stage is relatively common and involves nonspecific damage to DNA. There is also evidence that there may be a spectrum of initiated cells that vary in their degrees of initiation and thus in their susceptibility to promotion. Promotion was defined as "the reversible selective clonal expansion of initiated cells and the reversible alteration of gene expression." A list of criteria for chemicals that can only promote was developed. Progression was defined by a majority of panelists as "an irreversible change in DNA towards malignancy."

The panelists agreed that the mechanism of promotion is not currently understood, and they suggested that there may be several different mechanisms of promotion. Available data suggest that promotion is substantially different from initiation and that traditional risk assessment models for carcinogens are not appropriate for promoters.

Promoters appear to show more extreme differences in species and strain responses than carcinogens. The panelists agreed that much more work needs to be done to understand these differences from a mechanistic standpoint. Epidemiological studies should be conducted to obtain human data, and existing epidemiological data on promotion should be examined as a potential source of information on human promoters. Although no agents have been unequivocally classified as human promoters, data indicate that several chemicals may be working as human promoters.

Available data suggest that promotion is reversible in the liver and skin, but currently there are not enough data to ascertain whether reversibility is characteristic of all promoters in all systems. There was concern that there may be synergism among promoters. Research is needed to study this phenomenon and to identify the kinds of promoters that are likely to interact.

There is a need to develop and validate statistical models for promotion and to develop data to test the models. The two-stage birth-death-mutation model, developed by Moolgavkar, Venzon and Knudson, was discussed at the workshop. The panelists agreed that it appears to provide a good theoretical framework from which to propose and interpret studies on promotion. Various approaches to validating the model were discussed, including an initiation/promotion/initiation protocol using multiple doses of both the initiating and promoting agents.

The panelists agreed that not enough data are currently available to assess the risks of promoters and that substantial research is needed in several areas, including:

- Mechanisms of initiation, promotion and progression, particularly data on dose-response and frequency of response.
- The behavior of promoters in humans. Epidemiological studies of promoters in humans are a high priority The panelists suggested several populations for epidemiological studies.
- Development and validation of statistical models for initiation/ promotion systems.
- The behavior of promoters in organs other than the skin and the liver.
- Interspecies differences in promotion.
- Expansion of the chemical data base for known and potential promoters The panelists offered several suggestions of chemicals to study.
- Synergism among promoters.
- Development and validation of *in vitro* screening models for known experimental promoters. If successful, the *in vitro* approach should expedite the selection of chemicals for *in vivo* study.

The full report summarizes the discussion at the workshop. The first day of discussion focused on current knowledge of promotion. Panelists exchanged data and identified data gaps. On the second and third days, general and specific research needs were identified.

The full report is organized into 13 sections that reflect the major themes of discussion at the workshop. Each section has been synthesized from many different parts of the discussion that pertain to the topic. A list of the panelists and observers can be found in Appendix A. The agenda is provided in Appendix B, and premeeting comments prepared by the panelists can be found in Appendix C.

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The complete report, entitled "Report of the EPA Workshop on the Development of Risk Assessment Methodologies for Tumor Promoters," (Order No. PB 88-230 743/AS; Cost: $25.95, subject to change) will be available only from:

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