Letters

Carcinogen Policy at EPA

I would like to correct some errors in Eliot Marshall's article, "EPA's high risk carcinogen policy" (News and Comment, 3 Dec., p. 975). Marshall was given a lengthy interview during which he was told

1) That I was *not* a proponent of the genotoxic versus nongenotoxic segregation of carcinogens for regulatory purposes. The article alleges that I am. I consider there to be a spectrum of activity between these two extremes, and the same compound might influence both genetic and epigenetic events under appropriate circumstances. Accordingly, I feel it is premature to make hard and fast distinctions between "genotoxic" and "nongenotoxic" carcinogens as a generic practice.

2) That the Environmental Protection Agency (EPA) had no requirement for positive human data on carcinogenicity. The article says we do. The rodent bioassay remains the basis of our program to detect chemicals with carcinogenic potential, and good animal evidence (together with evidence on exposure) is enough to trigger action. We need to think beyond a "black box" interpretation of the rodent bioassay and, for chemicals on which there is good epidemiological data, human experience should be considered as part of the overall database.

The article's treatment of statistical modeling of risk assessment also omits a fundamental point: These models do not provide estimates of absolute risk. The numbers these models generate are most properly treated as rough risk indices that can allow one to compare the risks from different carcinogens or different activities with the same chemical. To treat them as absolute risks is incorrect. Making an issue of whether a risk is 10^{-7}, 10^{-6}, or 10^{-5} is equivalent to asking how many angels can dance on the head of a pin. These numbers take on meaning only when referenced to the model used, the confidence limits, the reliability and nature of the underlying data, and in comparison with other carcinogens to which the modeling is applied. As David Rall pointed out during his 1981 testimony on the National Toxicology Program, it would be inappropriate to use such risk numbers as point estimates of absolute risk and make them the turning point of a regulatory decision. Unfortunately, we have seen a tendency to do this in the past.

In his inset article "The odds on cancer: EPA's recent bets" (p. 976), Marshall makes much of M. Adrian Gross' concern over permethrin, presenting it as a case of EPA versus Gross. This is inaccurate. In March 1981, the science advisory panel for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) concluded that permethrin did not appear to be a potential human oncogen. The subsequent review by EPA's Hazard Evaluation Division (HED) of the oncogenicity data on permethrin was led by Orville Paynter (a Board-certified toxicologist and chief of HED's Toxicology Branch), and scientists from the Canadian government participated. The Canadian scientists concurred with HED's conclusion that permethrin was not likely to be a human carcinogen. When Gross raised his concerns, HED asked two former members of EPA's FIFRA scientific advisory panel—John Doull and Edward Smuckler—to review HED's assessment. Neither of these gentlemen can be considered lightweights in toxicology. Both concurred with HED.

Why toxaphene is listed in Marshall's article is something of a mystery. Certainly EPA had concerns about the carcinogenic potential of toxaphene. However, a more immediate problem was the accumulation of toxaphene (and toxaphene-like materials) in the aquatic environment and the imminent endangerment of fish. Solving the fishes' problems also solved the human health threats, but we emphasized that this should have been dealt with whether or not a human health threat was involved, as EPA's mandate is to protect human health *and* the environment. Contrary to Marshall's assertions, EPA estimates that there is, at most, sufficient toxaphene in distribution stocks for only one growing season.

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Marshall discusses what I believe is a very disturbing trend in government regulatory policies, namely the attempt to establish separate guidelines for evaluating the health effects of "genotoxic" and "epigenetic" carcinogens, with emphasis on softening the restrictions for the latter class of agents. The distinction between these two classes of agents is largely theoretical and has no factual basis in terms of our current knowledge of mechanisms of action of carcinogens, for several reasons.

1) We do not know with certainty that certain carcinogens act through genotoxic mechanisms and others through epigenetic mechanisms. Indeed, recent studies in molecular genetics, developmental biology, and immunology tend to blur the classical distinctions between genetic and epigenetic mechanisms, even in normal biologic processes (*1*).

2) Even if this distinction were true, our current methods for assessing whether or not a given agent is likely to be genotoxic in humans have very serious limitations (*2*); and what is worse, at the present time we do not have well-validated short-term tests for assessing agents that might act through nongenotoxic mechanisms, that is, tumor promoters, hormones, and so forth. Identification of the "epigenetic" agents must, therefore, often be done by exclusion, a risky approach.

3) Most of the known carcinogens produce multiple effects. In fact, when given at sufficient dosage the genotoxic chemicals are usually complete carcinogens and, therefore, probably produce both tumor-initiating and tumor-promoting effects (*3, 4*). Simple tests for genotoxicity may fail to assess the promoting capacity of these compounds. This, and other factors, severely limit attempts to predict the mechanism(s) of action and relative potencies of carcinogens, when findings based simply on genotoxic activity are used. The paradigm of random point mutation as a basis for understanding the carcinogenic action of agents that display genotoxic effects may itself be antiquated, in view of the multistage aspects of the carcinogenic process, probable synergistic (and sometimes inhibitory) multifactor interactions, and the possibility that carcinogenesis in-

volves more complex genomic changes (gene rearrangements, chromosomal translocation, oncogene activation, altered DNA methylation, and so forth) (*1*).

4) Certain tumor promoters (such as the phorbol esters and TCDD) can induce a significant number of tumors in animals, even without prior application of an initiating carcinogen (*3*). In addition, there are a few studies suggesting that, although the primary target of the phorbol ester tumor promoters is cellular membranes rather than DNA (*1*), these compounds may indirectly inflict chromosomal damage, perhaps via the generation of activated forms of oxygen (*5*). If this is the case, then these compounds also have genotoxic activity, albeit through an indirect effect.

5) It is often assumed that tumor promoters and other agents that might act through epigenetic mechanisms will, in contrast to initiating and genotoxic carcinogens, display a threshold in their dose response. The data on dose-response relationships with tumor promoters are skimpy, and I know of no evidence that clearly establishes a threshold for tumor promoters in humans or in experimental systems. Even if this were the case, how would we know how to extrapolate from a specific set of data the actual threshold level in a heterogeneous human population?

6) It is true that the known tumor promoters require repeated application to exert their tumor-promoting effect, whereas the single application of certain initiating carcinogens is sufficient (*3*). This does not necessarily imply a comfortable margin of safety for tumor promoters, because for many substances that are of concern (such as water pollutants, industrial chemicals, and food additives) there is likely to be repeated and prolonged human exposure. Moreover, some of these substances are only slowly degraded and, therefore, will persist or even accumulate in body tissues or the general environment.

7) There is the impression that tumor promoters are much less potent than initiating carcinogens and, therefore, are less hazardous. This is not necessarily the case. On a molar basis TPA is about two orders of magnitude more potent in exerting biologic effects than benzo[*a*]-pyrene, and TCDD is about four orders of magnitude more potent than benzo[*a*]-pyrene (*3*).

8) We know that nature has evolved specific defense mechanisms against some of the genotoxic agents, including conjugation and detoxifying mechanisms and DNA excision repair. We do not know to what extent humans have evolved protective mechanisms against tumor promoters. I do not doubt that such mechanisms exist, but at the present time we do not know their properties or relative efficiencies.

9) A final reason for being concerned about the potential health hazards of tumor promoters and various carcinogenic cofactors that do not appear to act by directly damaging cellular DNA is the evidence that a major fraction of human cancer is due to "lifestyle factors" and that many of these may not act as simple genotoxic agents (*6*). It is essential, therefore, that we not overemphasize our concern with genotoxic agents, downplay the potential health hazards of other types of agents, and thus distort priorities in our efforts at primary cancer prevention.

In summary, although there has been exciting progress in our understanding of the mechanism of action of environmental carcinogens (*1*), the field is in a sufficient state of flux that at the present time it would be premature to alter the existing, well-established guidelines for risk extrapolations of potential hazards to the human population. Specifically, I see no justification for assuming a nonlinear dose response and threshold model for certain carcinogens simply because they do not give a positive response in certain currently used assays for genotoxicity.

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I wish to correct the possible implication from Marshall's article that I am an uncritical supporter of the current Administration's carcinogen regulations. This is not the case. As chairman of the Environmental Protection Agency's (EPA's) Carcinogen Assessment Group, I merely solicited opinions from scientists outside the EPA on possible alternative approaches to carcinogen risk assessment without expressing my own position.

In my view, the real concern ought not to be whether this Administration is more or less conservative than other administrations in its approach to regulation of carcinogens, but rather that there has never been a federal cancer regulatory policy that really works. In looking back over the last dozen years, the one thing that stands out most forcibly is the lack of accomplishment in the area of carcinogen regulation. When one considers the tremendous amount of effort expended by the regulatory agencies, remarkably few carcinogens have been regulated. For example, fewer than a half dozen carcinogens have been regulated by the Air Office of the EPA since 1970. The reason for this poor record is that every attempted regulatory action is fought bitterly. There is no consensus in this country on how and to what extent carcinogens should be controlled. There is a hodgepodge of laws passed over many years by different Congresses which have different philosophies of control and very inadequate guidance as to how to carry them out. These regulatory philosophies include banning carcinogens, regulation by the best available technology, regulation on the basis of weighing risks and benefits, regulation to protect everyone with a margin of safety, regulation to the extent possible by taking economic and technical considerations into account, and so forth. With all of these different approaches, the regulators are given little actual guidance on how to regulate. We have learned a great deal over the years about the problems of regulating carcinogens, and I think that we are now in a much better position to develop a simpler, more comprehensive, and unified approach to carcinogen regulation. What I mean by unified cancer policy can be illustrated by the suggestion I recently made to the Canadian Ministry of Labor, namely, to use economic and technical considerations for all carcinogen regulatory decisions together with annual cancer risk guidance levels (based on the linear nonthreshold extrapolation model) of 10^{-5} for occupational exposure and 10^{-7} for exposure to the general public (these are lifetime cancer risks of 10^{-3} and 10^{-5}, respectively). The ALARA (as low as reasonably achievable) principle should also be part of the regulatory approach. This is an example of a unified approach which applies to ionizing radiation as well as to chemical carcinogens and brings occupational and environmental standards into balance. Parenthetically, the current carcinogen stan-

dards of the Occupational Safety and Health Administration entail lifetime cancer risks as high as 1 percent to 2 percent (10^{-2}), which is completely out of balance with the attempts to control environmental exposure to lifetime risk levels of 10^{-6}. Regardless of the acceptability of this particular approach, the main point is that we need something like it.

I think the federal regulatory agencies under the aegis of the Office of Science and Technology Policy will have great difficulty in effectively formulating an overall cancer regulatory policy because they represent only one of the many groups that are involved with cancer regulation. I suggest that Congress commission the National Academy of Sciences to develop a comprehensive and unified program for the regulation of carcinogens of all types and by all modes of exposure: food, water, air, drugs and cosmetics, consumer goods, and so forth. The Academy is the only body with sufficient stature and detachment to carry out the task; the effort should include the participation of all the concerned parties: academia, labor, industry, the environmental groups, regulatory agencies, and so forth. The program should deal with all aspects of regulation, including risk assessment and the mechanisms required to separate scientific evaluations from the regulatory decision process. This program could be translated by Congress into appropriate legislation that would override all other legislation in the area of carcinogen regulation.

If we cannot achieve a unified and comprehensive system that reflects a reasonable balance among the various views about carcinogen regulation, the whole regulatory enterprise will continue to be bogged down in endless polemics and legal warfare.

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In evaluating government regulatory policies, it is often difficult to separate scientific judgments from policy decisions. Marshall's article addresses several good examples. A congressional staff investigation of the pesticide regulatory program in the Environmental Protection Agency (EPA), under way since last June, analyzed the scientific basis for several recent regulatory actions taken by the EPA in an effort to sort out legitimate scientific refinements in regulatory decision-making from changes in policy. The investigation's findings, conclusions, and recommendations are contained in a staff report presented in December 1982 to the members of the department operations, research, and foreign agriculture subcommittee of the House Committee on Agriculture ("Regulatory procedures and public health issues in the EPA's Office of Pesticide Programs").

Chapter 6 of the report focuses on regulation of pesticides shown to produce cancer in laboratory animals. An in-depth review of several case studies, along with dozens of interviews with staff scientists responsible for analyzing available data on pesticide oncogenicity, led subcommittee staff to conclude that significant changes had indeed been incorporated in the way the EPA balances and juxtaposes experimental evidence under the aegis of "weight-of-evidence" decision-making. The unstated, but observable, changes from past risk assessment policies and procedures described in the report are comparable to those discussed by Marshall—that is, less concern for oncogenic pesticides thought to be nongenotoxic, markedly higher levels of tolerable risks, and greater skepticism in evaluating whether toxic effects observed in animal experiments pose sufficient hazard to man to warrant consideration of restrictive regulatory actions in light of the benefits from use of the pesticide.

Officials of the EPA have disputed the notion that cancer policy has changed in the pesticide program. In a letter dated 22 December 1982 to subcommittee chairman George E. Brown (D–Calif.), Assistant Administrator for Pesticides and Toxic Substances John Todhunter argued that recent decisions are a logical extension of policies established in past pesticide regulatory decisions involving suspect carcinogens. Independent scientists contacted by the subcommittee are currently evaluating these issues and will be called upon to help the subcommittee determine the advisability of alternative risk assessment procedures. Because of his desire to widen the debate on generic cancer policy issues to include the expertise of scientists outside the regulatory community, Chairman Brown plans to hold hearing focusing on the cancer policy issues addressed in the report early in the new session of Congress.

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Fluidized Bed Technologies

Hans Landsberg's article "Relaxed energy outlook masks continuing uncertainties" (3 Dec., p. 973) provides the incidental information that "fluidized bed technologies" are an example of "nonpolluting ways of coal combustion." This is simply not true.

There are some indications that low levels of pollutant emissions with fluidized bed combustion may be achieved at somewhat lower cost than competing technologies. Even this remains to be proved in commercial applications.

Although no method of coal combustion can be considered nonpolluting, emissions of significant pollutants can be reduced to acceptable levels by installing expensive control equipment.

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Shapiro is correct in saying that the description of fluidized bed technologies as "nonpolluting ways of coal combustion" overstates the performance of fluid beds with respect to reduction in air pollutant emissions. His statement that fluidized beds can be operated with lower pollutant emissions than other competing technologies is a more accurate description of the present state of the technology. Fluidized beds do have lower nitrogen oxide emissions and can be operated so that sulfur oxide emissions can be greatly reduced. Particulate control should also be less costly than for conventional pulverized coal boilers.

To date fluidized beds have received only limited application and then only in relatively small installations. The comparative economics of combustion of coal in fluidized beds and in conventional large boilers, both meeting air pollution emission standards, is yet to be demonstrated. I appreciate Shapiro's calling attention to these facts.

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Erratum: In the article "Breast-feeding patterns in low-income countries" by B. M. Popkin *et al.* (10 Dec., p. 1088), Table 2 was printed incorrectly. The data for "Peru, 1978" and "Guyana, 1975" should have been listed under "*Latin America*." The data for "Nepal, 1976" and "Bangladesh, 1976" should have been listed under "*Asia and the Pacific*." The data for "Lesotho, 1977" should have been listed under "*Africa and the Near East*."

Erratum: In the report "Taste flashes: Reaction times, intensity, and quality" by S. T. Kelling and B. P. Halpern (28 Jan., p. 412), an error appeared in Table 2 on page 413. The magnitude estimate for the 1000-millisecond sodium saccharin pulse obtained during the last 100 milliseconds of the pulse duration was 16 ± 1.4, not 1.6 ± 1.4.