Recommendation 82-5

Federal Regulation of Cancer-Causing Chemicals

(Adopted June 18, 1982)

The following recommendations broadly address the procedures by which federal agencies identify, evaluate, and regulate substances that pose a potential risk of human cancer. For many years these regulatory activities have been among the most controversial engaged in by federal agencies. They implicate important health and economic values and attract the interest of groups throughout society. Some of the issues dealt with in these recommendations are not peculiar to the context of carcinogen regulation. The statutory procedures agencies follow in regulating human exposure to cancer hazards, for example, are applicable to many other environmental and health hazards. While these recommendations may thus have broader application or impact, they are based on an evaluation of agency performance in this context alone.

I. Priority Setting

Estimates of the number of chemicals that may pose a risk of human cancer describe a universe larger than government agencies can evaluate or regulate. Agency resources for scientific review and regulatory proceedings are shrinking, and the capacity of manufacturers and users of chemicals to implement costly controls is likewise limited. In these circumstances, attention should be concentrated on those chemicals that pose the greatest risks and can be controlled most economically. As agencies have increasingly recognized, accomplishing this objective requires establishment of priorities.

Priority setting should be part of any program directed at determining the health effects of chemicals, as well as of programs designed to establish exposure limits. Each regulatory agency should set its own priorities, but there is also value in interagency selection of candidates for regulation and, particularly, for further testing.

Although candidates for evaluation and regulation should be carefully selected, any ranking based on abstract criteria, however rational, will be vulnerable to new information about human exposure or health effects and to public concerns. Agencies should explain departures from established priorities, but should retain flexibility to respond to new problems.

Criteria for selecting candidates for regulation should include the extent of the hazard posed by a chemical—a function of its potency, the conditions of exposure, and the number of people exposed. The extent of the hazard can often be expressed in quantitative terms. Agencies should also consider the effectiveness and cost of alternative control measures as well as other effects of regulation. Estimates of the cost-effectiveness of regulating specific chemicals can be helpful in selecting priorities. Because of the complexity of these criteria and the continuing need to obtain additional information, selection of candidates for regulation will often be an iterative process.

Priority setting should be a public process which affords interested persons an opportunity to communicate their own views to the agency. Varied techniques exist short of rulemaking under the Administrative Procedure Act for providing such opportunities, including public meetings, use of expert advisory panels, and publication in the Federal Register of invitations to submit data and views. Under whatever system, preliminary rankings risk being misinterpreted as definitive judgments about the hazards of chemicals before manufacturers and users have had an opportunity to present evidence or arguments. Accordingly, agency announcements of priorities should make clear the tentative character of underlying scientific assessments and describe the opportunities for interested persons to supply contrary or confirmatory information.

Recommendation

1. To the extent compatible with other demands on their resources, agencies should establish and follow systems for ranking chemicals as candidates for scientific evaluation or regulation. Agencies should generally adhere to the priorities thus established, but must retain the flexibility to respond to new hazards or to public concerns about other chemicals.

2. Priority setting should be part of selecting chemicals (a) for further testing, (b) for intensive scientific and regulatory evaluation, and (c) for administrative action to limit or eliminate exposure.

3. To the extent allowed by law, priorities should be set by agencies with the objective of maximizing the net benefits to society of agency action. Thus, in setting priorities, the agency should consider the expected benefits and costs of various alternatives. Although the criteria for selecting chemicals for further testing may be different, the criteria for selecting chemicals for regulation should take account of the health hazards posed by chemicals, including the

potency of the chemicals, levels of exposure, the number of people likely to be exposed, and the costs and cost-effectiveness of methods for controlling exposure, to the extent that these may be known.

4. Because agencies differ in their functions and their selection of candidates for evaluation and regulation must be coordinated with other agency programs, each agency should establish its own priorities. The several agencies responsible for regulating carcinogens should, however, periodically compare their rankings and, where feasible, coordinate their testing, evaluation, and regulatory efforts. Consultation with scientific, industrial, and public interest organizations should be encouraged.

5. Agency procedures for setting priorities should permit interested members of the public to submit information and views concerning specific candidates. Agencies should consider adopting priority-setting systems through rulemaking, but more informal methods are appropriate for ranking individual chemicals for evaluation and regulation. Any agency announcement that a product or chemical is a candidate for further evaluation or for regulation should explain both the bases of that assessment and its preliminary nature and should describe available procedures for confirming or negating its preliminary conclusions.

II. Interagency Coordination

Responsibility for regulating chemicals that pose a risk of human cancer is shared by several agencies, including most notably the Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA), Food and Drug Administration (FDA), and Consumer Product Safety Commission (CPSC). Only in recent years have these agencies attempted to coordinate their activities to assure consistency and enhance the benefits of regulation. While the agencies' criteria for identifying and evaluating potential carcinogens have in fact not been conflicting, their decisions have sometimes appeared difficult to reconcile, usually because of differences in legislation.

The creation of the Interagency Regulatory Liaison Group in 1977 rested on the premises that federal regulation of chemical carcinogens should proceed from common principles of scientific evaluation and should be coordinated administratively. While these premises remain valid, other mechanisms may be equally effective in assuring coordination. Opportunities for productive coordination exist in several areas: establishment of government-wide principles of scientific evaluation; agreement on test guidelines for toxicological experiments and other

studies of health effects; ranking of chemicals for testing; and monitoring and enforcement of exposure controls.

The four agencies have on several recent occasions cooperated in the regulation of specific chemicals. They once assembled a central scientific working group to evaluate formaldehyde, a chemical of common interest, and they agreed on a common list of chemicals that were high priorities for coordinated regulation. Though diverse statutory procedures have sometimes discouraged joint administrative proceedings, opportunities at the preproposal stage for cooperation in evaluating health effects and performing economic analysis have not yet been fully exploited.

Recommendation

1. Interagency coordination in identifying, evaluating, and regulating potential human carcinogens should be encouraged. Effective coordination can reduce governmental costs, minimize inconsistency among the agencies, and better illuminate the economic costs of alternative control options.

2. Agencies should continue to cooperate in identifying chemicals for which further testing is needed to permit regulatory assessments. The National Toxicology Program should continue to elicit joint agency rankings of candidates for testing.

3. Regulatory agencies should collaborate with government scientific bodies, including the National Toxicology Program, National Institute of Environmental Health Sciences, and National Center for Toxicological Research, to obtain agreement on guidelines for the conduct and evaluation of toxicological tests. This effort need not result in public rulemaking to adopt test protocols, but scientists outside government should have an opportunity to contribute to the development of test guidelines. Cooperative guidelines should also be considered for short-term tests and epidemiological studies, but current guidelines should not discourage development of improved test methods.

4. To the extent permitted by statute, agencies responsible for regulating carcinogens should adhere to common criteria for evaluating and interpreting health effects data. Agencies should avoid inconsistency in their approaches to mixed scientific-policy issues, such as whether to assume a no-threshold model of carcinogenesis, whether to perform quantitative estimates of

human risk, or whether to allow evidence that a chemical produces an increase in cancer in laboratory animals through mechanisms that do not suggest human risk.

5. Agencies responsible for regulating carcinogens should continue to explore joint evaluation of the potential health hazards of chemicals that are candidates for regulation by more than one agency, for instance, by use of a multi-agency advisory panel for any particular substance.

6. Agencies should explore other opportunities to collaborate before the initiation of formal administrative proceedings to regulate a chemical. These may include joint development of exposure estimates and joint preparation of economic analyses of alternative regulatory approaches.

7. Agencies should, after eliciting the views of interested persons, consider conducting joint administrative proceedings when they contemplate regulating the same chemical. Statutory diversity may, however, complicate or even preclude such proceedings.

III. Chemical Selection and Guidelines for Testing and Evaluation

The selection of chemicals for study, the design of protocols for laboratory experiments, and the establishment of criteria for interpreting study results are important parts of the process for regulating substances that pose a risk of human cancer. These are essentially scientific functions which should not be dictated by narrow policy considerations. The important desiderata are scientific integrity and consistency.

At the same time, it remains true that much toxicological testing performed in the United States—by government laboratories and by or on behalf of private industry—is performed to aid regulatory decisionmaking. Numerous toxicological studies are performed to support marketing approval for food additives, pesticides, and pharmaceuticals. FDA and EPA have both conducted similar studies on substances within their regulatory jurisdiction. The agencies have also relied on studies commissioned by the National Cancer Institute. The NCI bioassay program has more recently fallen under the supervision of the National Toxicology Program, whose supervisory board includes representatives of the regulatory agencies. NTP currently accepts nominations of chemicals for testing from the agencies.

Under the auspices of the former Interagency Regulatory Liaison Group, the four agencies studied here (EPA, OSHA, FDA, and CPSC) actively sought agreement on joint protocols for toxicological testing and on criteria for evaluation of study results.

Recommendation

1. In conjunction with the National Toxicology Program and in consultation with scientific organizations outside government, regulatory agencies should continue efforts to develop consistent guidelines for toxicological testing. These test guidelines should reflect current scientific consensus but also awareness of the resource limitations that constrain both government and industry. The guidelines developed or espoused by the agencies should not be issued as formal regulations. Rulemaking would needlessly prolong the process of reaching agreement, and formal regulations would limit the ability of agencies, producers, and testing laboratories to design protocols or adapt existing guidelines to new circumstances.

2. Agencies should adhere to similar test guidelines and similar criteria for interpreting test results. Any departure from common standards should be specifically and convincingly justified.

3. The National Toxicology Program should continue to encourage the participation of EPA, OSHA, FDA, and CPSC in its selection of chemicals for testing. It should be willing, on request, to assist agencies in their evaluation of study findings. The NTP special working group to evaluate the carcinogenicity of formaldehyde for all of the four regulatory agencies represents one promising experiment in the effort to assure consistency among the agencies.

IV. Advisory Panels

Assessment of the health risks posed by chemicals requires substantial information about their toxicity and about the conditions under which humans are exposed to them, as well as understanding of the techniques for obtaining such information. Techniques for toxicological evaluation, exposure estimation, and quantitative assessment of human risk increasingly demand state-of-the-art expertise. Evaluation of potential human carcinogens also requires impartiality in assessing the quality and interpreting the results of toxicological and epidemiological studies. In the scientific world, new research findings are customarily exposed to peer review before they become accepted as reliable. Increasingly, regulatory agencies have concluded that the data on which they rely, and the interpretations they give these data, should be subjected to peer review before becoming the bases for regulatory decisions.

Several proposals have recently been advanced to mandate and institutionalize this peer review function. Some of these proposals call for strict separation of risk assessment from the process of evaluating and selecting regulatory options. These proposals raise difficult issues respecting the design of procedures for administrative decisionmaking about chemical

carcinogens. The function of assessing risk can be distinguished analytically from the choice of regulatory responses, but separating them in practice is more difficult. The close relationships among issues of toxicity, exposure, and the cost of controls make the process of agency evaluation an interactive one. Accordingly, mechanisms for exposing agency judgments to peer review should be flexible enough to permit frequent interchange with agency policy makers.

One method that agencies have successfully used for institutionalizing peer review is consultation with expert advisory panels. These panels have taken several forms, ranging from informal working groups of agency scientists assigned to review a single chemical to standing committees of independent experts who advise on numerous candidates for regulation. Advisory panels can contribute objectivity as well as expertise to agency decisions. Their advice has sometimes prevented erroneous regulatory actions; more frequently, their role has been to illuminate complex issues and enhance the quality, and thus the credibility, of agency scientific analysis.

Advisory panels comprised in whole or in part of non-federal employees are governed by the Federal Advisory Committee Act (FACA), unless exempted by specific legislation. The FACA requires individual chartering and biennial re-approval and mandates practices that are designed to assure the balance, openness, and integrity of advisory committees. Most of these requirements are salutary, and the following recommendations endorse their observance by panels even where not formally subject to the FACA. Certain of the Act's provisions, however, have discouraged agencies from seeking outside peer review. The recommendations advanced here are intended to encourage agency resort to expert advisory panels without necessarily endorsing every requirement of the FACA. None of these recommendations should be construed as superseding either that Act, where applicable, or federal conflict of interest laws.

Recommendation

1. Peer review of experimental findings and scientific judgments is an important means of validating the technical bases of regulatory decisions concerning carcinogens. To the extent compatible with existing law, agencies should structure their decisional processes to incorporate mechanisms for scientific peer review.

2. Expert advisory panels represent one valuable means for obtaining scientific peer review of agency decisions. Advisory panels can provide information that will aid agencies in setting

priorities, in evaluating scientific data prior to initiation of administrative proceedings, and in evaluating evidence submitted by interested persons during public proceedings.

3. The design, composition, and operation of an advisory panel should fit the function it is to perform; no uniform approach is optimal. A standing advisory panel, with responsibility for reviewing the scientific bases of major actions by a particular program, can contribute consistency in addition to expertise, and it provides a ready forum for agency consultation. To assure that the panel has access to relevant expertise, sub-units can be appointed to evaluate specific chemicals or issues. An agency that lacks a standing advisory panel, however, should not forgo opportunities to create ad hoc panels to review the scientific bases of contemplated regulatory actions.

4. The role of an expert advisory panel may embrace evaluating data concerning the health effects of chemicals, interpreting those data and characterizing the chemicals' effects, and estimating the likely frequency of those effects under different exposure conditions. When an agency rejects an advisory panel's scientific judgment, it should explain the bases for that rejection. When an agency selects a regulatory approach whose bases appear inconsistent with a panel's advice, it should explain the legal, social, or other reasons that dictate or justify that choice.

5. Members of an expert advisory panel should be selected primarily for their expertise in relevant scientific fields. Qualified scientists, even if employed by the agency they are to advise, by other government agencies, or by commercial organizations, may appropriately be selected to serve on advisory panels. In the selection of panel members, attention should be given to assuring balance in scientific orientation and viewpoint. The organizational affiliations of all panel members should be a matter of public record. The financial holdings and relationships of potential panel members should be carefully screened by the appointing officials and periodically reviewed thereafter to prevent conflicts of interest. If a panel includes members who are not disinterested with respect to a particular substance, those members should not participate in the panel's discussions of that substance.

6. Advisory panels should be accessible for consultation by the appointing agency at frequent intervals and on short notice. Consultation should usually occur before any announcement of a plan to regulate a chemical. Even when the Federal Advisory Committee Act does not apply, many of its requirements represent appropriate guides for the operation of advisory panels. Referrals of issues to advisory panels and meetings of agency officials with panel members should be matters of public record. Advance public notice of panel meetings

should be provided where practicable. Panels should meet in open session except when reviewing data that are entitled to confidential treatment or, unless restricted by statute, when the panel members vote to close their deliberations. All panel conclusions and recommendations should be reduced to writing and become a part of the material to be considered in any ensuing administrative proceeding.

7. Advisory panels established to evaluate scientific data for, and provide advice to, more than one agency may often be useful. Such panels can be particularly valuable in recommending chemicals for further study or testing. Where a chemical is of interest to more than one regulatory agency, a single advisory panel may be an efficient way of obtaining an independent assessment of its potential health effects. Interagency panels should be subject to the same restrictions as to composition, operation, and scope of responsibility as panels appointed to serve a single agency.

V. Generic Rulemaking

Agencies responsible for regulating potential carcinogens have attempted to develop and publish criteria for evaluating scientific data that underlie their decisions. These efforts have included informal statements of policy, proposed interpretative regulations, binding substantive standards, and interagency policy statements. The motives underlying these efforts to establish a framework for evaluating evidence concerning individual chemicals have been as diverse as the forms they have taken. One objective has been to obtain agreement among the agencies on the scientific criteria and policies that inform regulation of carcinogens. Another objective has been to improve understanding, among the public and within agency staffs, of the principles that guide agency decisions. Some agencies have also attempted to frame these principles as rules of decision in order to forestall repetitive disputes in proceedings to regulate individual chemicals.

The desirability of assuring agency adherence to common principles of scientific interpretation seems clear. Equally important is conformity of these principles with the best current understanding of the mechanisms of carcinogenesis, of toxicological and epidemiological research, and of quantitative risk assessment. Attempts to treat decisional guides as though they were binding substantive rules may conflict with the need to remain sensitive to developments in rapidly changing fields.

The efforts of individual agencies to establish criteria for identifying and evaluating potential human carcinogens have been criticized on several counts. In addition to disputing the content

of agency judgments, industry critics have questioned the appropriateness of analytic frameworks that discourage individualized assessment of the capacity of chemicals to cause cancer. The duration of agency rulemaking proceedings suggests difficulty in obtaining scientific agreement in this area, but the controversy more often betrays disagreement over agency policy judgments rather than over their distillation of scientific consensus.

Recommendation

1. In appropriate cases generic rules legitimately may be the basis for summary administrative resolution of recurrent issues, provided they do not foreclose reexamination of scientific conclusions respecting carcinogenicity of particular substances. Agencies should proceed cautiously in using this technique because the complexity and uncertainty of the issues involved and continuing advances in scientific understanding of the mechanisms of human cancer impede development of binding general principles.

2. Agencies should be encouraged to develop systematic statements of the principles that they will apply in identifying, ranking, and evaluating chemicals that may pose a risk of human cancer. The systematizing process should ordinarily involve opportunity for submission of data and views by interested persons outside the agency. Whenever an agency expects to limit argument over principles that will guide decisions in proceedings to regulate individual chemicals, compliance with statutory requirements for rulemaking is essential before the principles are formulated.

3. Agency statements may appropriately address the design and interpretation of scientific studies, the measurement or estimation of human exposure, the performance of quantitative risk assessment, and the selection of regulatory responses. These statements should attempt to distinguish between elements that are intended to summarize current scientific consensus and others that represent policy judgments reached in the absence of consensus. Policy judgments are an inevitable component of regulatory decisions and, where similar issues arise recurrently, are appropriately resolved on a generic basis. But where scientific developments in the near term are likely to require modification, or where individual studies or chemicals are often likely to deviate from the "norm," they should not be framed as binding rules.

4. Many issues involved in identifying, evaluating, and regulating potential carcinogens are common to all agencies and should be resolved consistently. These issues range from the criteria for interpreting scientific studies to the selection of mathematical models for estimating

human risk. Though scientific uncertainty surrounding many of these issues requires considerations of value and policy, disparate agency responses should be avoided or convincingly justified.

VI. Quantitative Assessment of Risk

Various pressures and incentives have encouraged regulatory agencies to explore methods for quantifying the risk of potential carcinogens. At the same time the use of quantitative risk assessment in making regulatory decisions has provoked fierce controversy. Industrial interests have generally urged agencies to regard quantification as an essential step in evaluating measures for controlling carcinogens. Consumer groups and labor unions, on the other hand, have cautioned against excessive reliance on techniques whose reliability remains uncertain. The agencies themselves have for some time had difficulty reaching consensus on the issue.

Criticism of quantitative risk assessment stems in part from doubts about its reliability. Reliance on animal models as qualitative predictors of human risk often may be unavoidable, and the further extrapolation from effects observed at high doses to the unmeasurable effects predicted at low doses compounds uncertainty. Critics also point to the wide range of risks at low doses predicted by different extrapolation models. A further criticism is that quantitative risk assessment can too easily be exploited to compute the dollar value implicitly assigned by regulators to human life.

Despite these criticisms, quantitative risk estimation has an appeal for both analysts and decisionmakers. Without some means of describing the magnitude of the health effects associated with exposure to a carcinogen an agency must find some other basis for deciding what controls to require. Legislation sometimes provides an answer. The Delaney Clause, for example, makes quantification of the risk of a carcinogenic food additive superfluous. Under any statute that permits or instructs the agency to weigh the costs against the health consequences of alternative means of controlling exposure, however, a method to quantify risks has proved essential.

Quantitative risk assessment can help illuminate many of the choices that agencies confront in regulating carcinogens. Even with its uncertainties, the technique facilitates comparison of the risks posed by different substances, which can aid in establishing priorities for regulation. Similarly, quantitative risk assessment can illuminate the choice among diverse regulatory options. A common unit of measurement for evaluating the health benefits of different options

can materially advance analysis of a multidimensional decision even if the measurements are unverifiable and the benefits are not converted into dollars.

Recommendation

1. Quantitative risk estimates can be valuable in setting priorities for regulation of carcinogens, comparing the human health consequences of alternative control measures, and in analyzing the costs and benefits of regulatory options. To the extent regulatory statutes allow and available data permit, agencies should attempt to estimate and describe the magnitude of the risk posed by prevailing levels of exposure to substances considered for regulation. Within the same constraints, agencies should also attempt to describe the size of the health benefits provided by measures required to reduce or eliminate human exposure.

2. Given the limitations of techniques for quantitative risk assessment and different statutory criteria for limiting or eliminating exposure, risk estimates ordinarily will be only one consideration. The weight accorded such estimates should reflect:

(a) The statutory criteria governing agency decisions;

(b) The adequacy of available data on carcinogenic potency and on the type, levels, and duration of human exposure; and

(c) The acceptance of the methods used to estimate future health effects.

3. Any description of the magnitude of the risk associated with prevailing exposures or of the estimated health benefits of exposure controls should explicitly identify:

(a) The toxicological, epidemiological, and exposure data on which it rests;

(b) The assumptions underlying any extrapolations from animals to man or from high to low exposure levels;

(c) Other assumptions about the behavior of the substance or about the characteristics of human exposure to it; and

(d) The range of uncertainty associated with the estimates.

4. Quantitative estimates of risk associated with exposure to a substance—particularly when expressed in terms of lives likely to be lost or cases of cancer likely to occur—have a power to

captivate public and press attention. Such estimates should be accompanied by statements stressing their imprecision and uncertainty. When the available health effects data are seriously deficient or little is known about human exposures to a substance, the risk of misinterpretation may justify an agency decision not to attempt quantitative estimates of risk or health benefits.

VII. Public Participation

Several values are served by public participation in the regulatory process. Perhaps preeminent is the value of fairness to those who may be directly affected by government action. The "right to be heard" before government acts adversely to important private interests is well established in American administrative law. This is reflected in the Administrative Procedure Act and by most regulatory statutes.

A second purpose served by broad public participation in agency decisionmaking is avoidance of mistaken even though well intentioned judgments that rest on incomplete information. In the context of carcinogen regulation this value enjoys a high rank. Decisions concerning human exposure to potential carcinogens should rest on sound scientific and economic judgments. Estimates of risk and cost require information that agencies often lack, as well as analytical skills that are found in industry and many public interest organizations. Accordingly, agency procedures should facilitate participation by those in the private sector with relevant scientific and economic expertise.

A third important value served by public participation is balance. Agency decisions concerning environmental health hazards require government to take large chances with both human life and private business. Data are invariably inadequate and estimates of future consequences are problematical; these uncertainties simply complicate an already difficult task. Determining the appropriate level of human exposure to a substance reasonably found to cause cancer is fundamentally a normative exercise in which there are no experts. Because decisions are left to regulators with sometimes scant Congressional guidance, agency procedures should facilitate broad participation and vigorous debate to assure agency understanding of diverse viewpoints.

Finally, the opportunity to influence agency thinking, coupled with an awareness that agency procedures permit broad participation, contributes to the acceptability of agency decisions.

Public health or scientific interests may not have participated in the regulatory process on equal footing with commercial interests. The extent to which this disparity, if it exists, is a

function of lack of resources and whether it should be addressed through public funding of citizen participation are questions that transcend carcinogen regulation. The arguments for and against funding should be considered in the broader context.

Recommendation

1. In setting exposure limits for carcinogens, agencies ordinarily should follow procedures that assure opportunities for all affected interests, commercial and non-commercial alike, to submit information and views before final decisions are reached. Procedures may appropriately vary with the requirements of agency organic statutes, with the characteristics of the activity or products whose regulation is contemplated, and with the need for prompt action to limit exposure.

2. Agencies should encourage and facilitate the participation of independent experts in toxicology, epidemiology, risk and exposure estimation, and other relevant technical disciplines. A useful way of eliciting participation in the regulatory process by independent scientists is through the use of standing or ad hoc advisory panels.

3. Congress should refrain from imposing procedural requirements, such as section 701(e) of the Federal Food, Drug, and Cosmetic Act, which are so burdensome that agencies search for regulatory approaches that have the effect of precluding effective participation in their decisionmaking processes by affected interests.[1]

Citations:

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[1] See also Administrative Conference Recommendation 71-7 (Rulemaking on a Record by the Food and Drug Administration), 2 ACUS Recommendations and Reports 42 (1973); and Recommendation 72-5 (Procedures for the Adoption of Rules of General Applicability), 2 ACUS Recommendations and Reports 66 (1973), 1 CFR 305.72-5.