How to Assess Cancer Risks

Federal agencies are divided on quantification; OSTP proposes a centralization of authority

Federal decision-making in the control of carcinogens is a hot subject that seems to invite more controversy all the time. Disagreement exists within the government itself over "cancer policy" and especially over whether the science of quantifying cancer risks is far enough advanced for it to be safely used by regulatory agencies in setting standards for human exposure to carcinogens.

The director of the National Cancer Institute (NCI), Arthur C. Upton, has recently circulated a memorandum warning that misuse of risk quantification could lead to public health catastrophes. Although citing no specific instances of misuse, Upton has told *Science* that he is worried lest regulatory officials make the mistake of minimizing cancer risks on the basis of estimates that fail to reflect the underlying uncertainties in the mathematical modeling.

On the other side of the risk assessment issue are the government officials and scientists, including some at the White House Office of Science and Technology Policy (OSTP), who are afraid that risk quantification will either be neglected by some agencies or misused to overestimate risks in support of exposure standards that are too strict and costly.

Back in February, Frank Press, the President's science adviser, sent Donald Kennedy, commissioner of the Food and Drug Administration (FDA), a report* dealing partly with risk quantification which had just been prepared by OSTP. Its principal recommendation was that authority over cancer risk assessment—now widely diffused among the regulatory and scientific agencies—be centralized under the National Toxicology Program (NTP).

The NTP was created last fall by Secretary of Health, Education, and Welfare Joseph Califano, and Kennedy became the first chairman of its executive committee. Through this new entity, four HEW agencies already deeply involved in carcinogenesis and toxicology—namely, FDA, the National Cancer Institute, the National Institute for Environmental Health Sciences (NIEHS), and the National Institute of Occupational Safety and Health (NIOSH)—are to pool resources and join in planning and carrying out bioassays, improving experimental methods, collecting exposure data, and doing other work important to the regulatory agencies concerned with cancer hazards. These agencies are the FDA, the Environmental Protection Agency (EPA), the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (OSHA); all are represented on the NTP executive committee.

In a letter accompanying the OSTP report, Press told Kennedy that he and his staff were confident that the NTP could become a "major mechanism" for carrying through the work already begun by the regulatory agencies in seeking to establish consistent policies through an interagency committee. Although nothing much has been done about it yet, this OSTP proposal or some variation of it may offer the best hope of overcoming interagency confusion and conflict over risk assessment.

Since the OSTP report was issued 4 months ago, the need for a more consistent government philosophy and approach to cancer risk assessment has become increasingly evident. For example, besides the warning memo circulated by Upton, who is no lightweight in matters of this kind, a glaring conflict has had to be resolved between OSHA, which has resisted using risk quantification in setting occupational exposure standards, and a number of other agencies, such as EPA, FDA, and the Council on Wage and Price Stabilization (CWPS).

These agencies, along with OSTP, have viewed with apprehension arguments made by OSHA in appealing to the Supreme Court the decision of a lower court to reject a proposed benzene standard because the health benefits were not quantified. Together with the Department of Justice lawyers who will represent it before the high court, OSHA has now apparently agreed that its case will be presented in such a way as not to indict risk quantification as practiced by other agencies.

Because disagreements over risk quantification seem to arise out of the sheer complexity of the subject, a word about what is involved is in order. Risk assessment begins with a relatively noncontroversial "qualitative" phase in which certain chemicals are identified as potential human carcinogens on the basis of epidemiological studies or, more typically, the finding of a carcinogenic response in tests with laboratory animals.

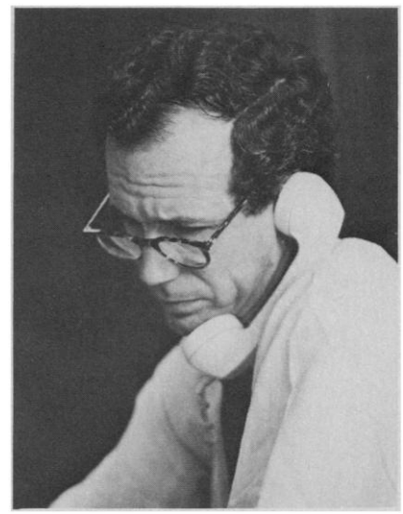

Photo by Eric Poggenpohl

Donald Kennedy

Experts in carcinogenesis still argue over such questions as whether regulatory agencies should regard "promoters" (substances that promote the formation of tumors but do not directly initiate them) as carcinogens. But there is general agreement among the agencies and their scientific advisers that a well-done bioassay or epidemiological investigation represents good science, even though (for obvious reasons) findings from tests with mice or rats cannot be verified by experiments with humans. The reason positive results from a bioassay with laboratory animals are generally accepted as strong evidence of potential human carcinogenicity is that virtually all known human carcinogens cause cancer in test animals.

**Identification, Characterization, and Control of Potential Human Carcinogens: A Framework for Federal Decision-Making.* Available at no charge from the Office of Science and Technology Policy, Executive Office of the President, The White House, Washington, D.C. 20500.

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The qualitative phase of risk assessment is followed by the quantitative phase, and here the science is highly speculative and replete with uncertainty. From the carcinogenic response data obtained at the high dose levels administered in the laboratory it is, of course, necessary to extrapolate downward to arrive at an estimate of the tumor incidence at the very low doses expected in the environment. Then, another leap of faith is necessary if this extrapolation of the carcinogenic response from high dose to low dose is to be accepted as even a crude approximation of human risk. The susceptibility of the highly heterogeneous human population that would be exposed to the carcinogen could differ greatly from the susceptibility found in the small number of relatively homogeneous laboratory animals tested. Also, because humans are exposed to countless pollutants, additive or synergistic effects are always possible.

Yet, despite all the uncertainties associated with it, quantitative risk assessment has rapidly gained a place in the regulation of carcinogens for reasons which its advocates find compelling. As they see it, to have even very crude estimates of human risk, possibly off by several orders of magnitude, is better than to have no estimates at all. Absent some systematic ranking of compounds by risk quantification, an agency trying to decide which of several hundred compounds to regulate first has to choose among them on the basis of numbers of humans exposed, exposure levels, and the economic feasibility of controls—ignoring the carcinogenic potential of the compounds at environmental levels of exposure. All else being equal, ignoring the carcinogenic potential could lead to some compounds of relatively weak potency being regulated ahead of others that are actually more hazardous. In animal tests the dose needed to give a positive response has been shown to vary by as much as a millionfold from one carcinogen to another.

But whatever the advantages of risk quantification, to reach firm conclusions as to the comparative response of laboratory animals and humans to a given carcinogen is still impossible, as Upton emphasized in his recent memorandum. This memo was prepared in early April and sent to Donald Kennedy for him to consider as chairman of the NTP. It warned that current scientific knowledge is too limited for quantitative risk assessment to be used as a "primary basis" for regulatory decisions. Referring to sensitivity differences among species, Upton observed:

> A given exposure to a carcinogen may cause a very low incidence of tumors in one species, whereas the identical exposure may cause a very high incidence in another species. An estimated risk of 4.2 cancers, for example, per 220 million people, as calculated by extrapolation from mouse or rat data, might turn out in reality to be as low as no human cancer, or as high as 420,000 cancers. Although the occurrence of very large errors should be rare, each such error could be a catastrophe. One would not know such errors had occurred until many years after human exposure.

Joseph H. Highland, a scientist with the Environmental Defense Fund (EDF), one of the major public interest law groups, had a major influence on Upton and the preparation of the memorandum. Highland had met with Upton back in the winter to express his concern that quantitative risk assessment was being dangerously pushed beyond the bounds of good science in its use by regulators in deciding which compounds to regulate and how far the regulation should go. He also had discussed this matter with Upton's part-time consultant and former faculty colleague at the University of New York at Stony Brook, Charles Wurster, a professor of biology and one of the founders and current board members of EDF.

Wurster was impressed by Highland's arguments, and he later prepared a draft memorandum which, with some revisions, was to become the memo that Upton sent to Kennedy. As Wurster says, one should not infer from the foregoing that Upton was brought around by Highland or himself to the points of view expressed in the memorandum. Much of Upton's past career as an academic scientist and as a radiation biologist with the Oak Ridge National Laboratory has had to do with carcinogenesis, and he clearly is one of the more experienced and sophisticated people in this field.

Nonetheless, it is evident that Highland via Wurster was, as a lawyer might say, the "proximate cause" of the Upton memo. For his own part, Highland had been aroused by indications at the turn of the year that EPA was planning to make extensive use of risk quantification in identifying those carcinogenic air pollutants most in need of regulation and in arriving at the appropriate "margins of safety" to be observed in controlling them (EPA is still deliberating over what its policies for regulating such substances shall be). In his view, risk quantification in the case of air pollutants is fraught with possibilities for error because of the enormous uncertainty involved in modeling patterns of pollutant dispersal and human exposure.

But now it turns out that Highland has found some of his views challenged by an EDF colleague, Robert H. Harris, who recently returned to the EDF Washington office after a year spent at the University of California at Berkeley working with Bruce Ames, a leading investigator in the field of mutagenesis and carcinogenesis who has under way a project to compare the carcinogenic potency of some 500 different compounds. Although Harris generally agrees with Highland's view that risk quantification has little place in setting exposure standards, he believes that such quantification can be extremely useful in establishing regulatory priorities. Estimates as to the *relative* degree of risk associated with various compounds can be meaningful, he feels, even if absolute numbers for tumor incidence are too much in error to be safely used in establishing exposure standards.

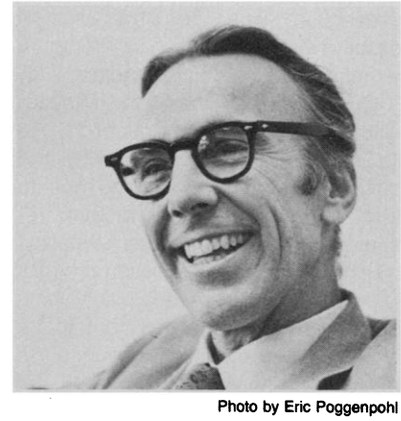
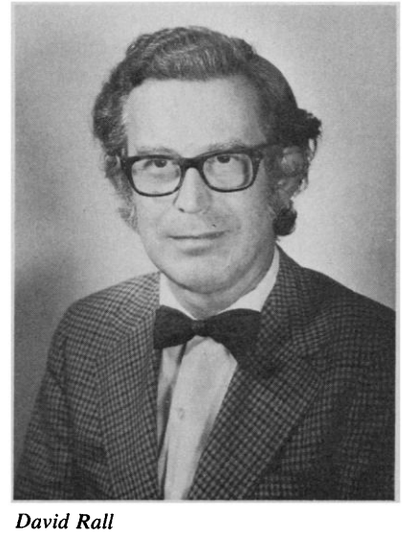


Photo by Eric Poggenpohl

Arthur Upton



David Rall

The OSTP report that calls for centralizing authority over risk assessment activities in the NTP also contains recommendations for extensive use of quantification methodologies. The report calls

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fighting among federal agencies, Gilded Age politicos, and scientists of the National Academy of Sciences. John Wesley Powell, explorer, multidisciplinary scientist, and no mean science politician, became the Survey's second director.

Over the years, USGS became engaged in resource management on a broad front and spun off the Bureau of Reclamation, Bureau of Mines, Federal Power Commission, and Bureau of Land Management. As a provider of information on mineral and water resources the Survey is a major contributor to the making of federal energy policy. Its scientific horizons have broadened steadily with the sophistication of the earth sciences. And a 1962 revision of the Survey's basic law allows it to carry out its examinations outside the "national domain." This it has done in a number of places including the moon.

On the Way to the Forum

As speechmakers, even U.S. presidents like to warm up their audiences with a laugh or two before going on to the serious stuff, and in his remarks to the National Academy of Sciences in late April President Carter got a rise out of the academicians by a reference to their counterparts in the Soviet Union. The transcript has it this way:

"I understand that in the Soviet Union when someone is chosen to their National Academy of Sciences, his or her salary immediately doubles—(laughter)—and a chauffered car is made available for use. I understand there is a slight difference in our own country. (Laughter) You immediately get a bill for membership dues, and you are pledged voluntarily to give advice to your government free of charge. (Laughter) And I thank you for that."

The comparison was not in the original text of his address. Carter interpolated it after the perks of membership in the Soviet Academy were mentioned during the drive over to the Academy by President's Science Adviser Frank Press, himself a member of the NAS. For his own transportation on the job, incidentally, Press takes pot luck from the White House motor pool.

Endangered Review Body Seems to Be in the Clear

A Cabinet-level review committee designed to have the last word on species-endangering federal projects appears to have survived the disenchantment of an influential sponsor, Senator Howard Baker (R-Tenn.).

Baker, the Senate Minority Leader, was cosponsor last year with Senator John Culver (D-Iowa) of an amendment creating a review body with the power to grant exemptions allowing the government to proceed with projects that had been found to threaten flora and fauna protected by the Endangered Species Act (ESA).

Baker had been given a case of home-state pique by the halting of construction on the Tennessee Valley Authority's Tellico Dam, on which some $100 million had already been spent. The action was taken under ESA provisions when the project was judged to threaten extinction to the snail darter, a tiny fish unique to the waters in the area where the dam was being built. The Culver-Baker amendment creating the review body was designed to provide flexibility for ESA when controversy arose over the law's extension last year. The review panel has six federal agency members and one vote is allowed to states involved. Five positive votes are required for an exemption.

In January, the review panel's first formal action was to deny an exemption to the Tellico project (*Science*, 23 February). Baker reacted by framing legislation to have the dam project exempted by direct congressional action and also to have the review council abolished by repeal of the appropriate section of the law.

At a 9 May final markup session of the Senate Environment and Public Works Committee on another extension of ESA, Baker offered an amendment to confer an exemption on the Tellico Dam project. The amendment failed by a final tally of 10 to 3. Baker did not put forward his amendment to abolish the review group. The committee reported out the bill extending ESA for 2½ years. Observers say that the decisiveness of the vote on the exemption in committee makes it unlikely that Baker will carry the fight to the Senate floor.

John Walsh

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for using them to assess carcinogenic potency and to determine the "most likely value" for potential human exposure and the estimate of overall risk.

Such estimates would be made in what the OSTP refers to as the scientific stage, or Stage I, in the control of carcinogens. According to its report, the regulators, or Stage II decision-makers, should be given the most accurate risk estimate possible and "informed clearly about uncertainties in existing scientific data and their impact upon the risk estimate." The regulators would then decide what the margin of safety should be, bearing in mind all other relevant factors, including the feasibility and cost of control.

By implication, at least, the report says that absolutist approaches to the control of carcinogens, as represented by the Delaney clause and the absolute ban it imposes on carcinogenic food additives, should yield to flexible approaches based on risk assessment. In this it appears at one with the National Academy of Sciences Committee on Saccharin and Food Safety Policy and its recommendation for the establishment of a hierarchy of risk categories—high, moderate, and low (while Commissioner Kennedy of the FDA thinks this recommendation by the academy committee goes much too far, he himself favors some relaxation of the Delaney clause). But another Academy body, the Board on Toxicology and Environmental Health Hazards, has observed that the OSTP report "adequately addresses neither the crudeness of these statistical manipulations nor the substantial uncertainties associated with their use" (although this group, too, favors use of risk quantification in regulatory decision-making).

What seems most significant about the OSTP report are not the views expressed on risk quantification but rather the recommendations for improving the decision-making framework. In the interest of ensuring that cancer risk assessment is characterized by "impartial scientific judgment," the OSTP argues that such assessments should not be under the authority of the regulatory agencies themselves, as is now the case, for instance, at EPA, which has its own carcinogen assessment group.

While no specific instances of bias are alleged, authors of the report are understood to feel that, so long as assessments are done on an agency by agency basis, there will be a danger of bias, probably on the side of overregulation of potential carcinogens that may pose little actual risk to humans. Ironically enough, some

of the scientists most worried about possible misuse of risk quantification are fearful of a bias that will result in underregulation.

"Risk quantification is very attractive to regulators," says Highland, "because it can be used to define some problems as nonexistent and to minimize the degree of control necessary for others."

From the standpoint of both those afraid of underregulation and those fearful of overregulation, there seems much to be said for having NTP serve as an arbiter of risk assessment practices. The NTP executive committee is broadly representative of both the scientific and the regulatory agencies and is a step removed from the political pressures and hurly-burly of the regulatory process.

Harris, of EDF, likes the idea of putting NTP in charge of assessing cancer risks. To avoid any appearance of bias, he would prefer that assessments not be done by the regulatory agencies at all, even on a delegated basis.

The OSTP report was not meant as a White House edict that everyone would have to follow. According to David R. Calkins, an OSTP staffer and member of the White House domestic policy group, the report was intended more as a "catalyst" and stimulus to help shape the thinking of the scientific and regulatory agencies and interested congressional committees.

Neither Kennedy nor any of the other officials on the NTP have had time to come to grips yet with the OSTP proposal. How the proposal is ultimately received may depend a lot on the attitude of David P. Rall, who is director of the NTP as well as head of the National Institute of Environmental Health Sciences.

Individuals such as Roy Albert, professor of environmental medicine at New York University and chairman of the EPA carcinogen assessment group, are not likely to look kindly on any suggestion to have the NTP either absorb their programs or assume authority over them. Albert already has indicated as much. But if Rall and most of the other officials on the NTP committee embrace this concept, the chances of its acceptance might be excellent, especially inasmuch as it seems evident that the present interagency confusion and disagreement over risk assessment cannot long be tolerated. At present, it is not even clear how far the disagreement goes. For while Upton has warned of possible catastrophes, he has not flatly rejected use of risk quantification even for establishing exposure standards. He can perhaps be reassured if certain policies are to be universally observed, as for instance with respect to how conservative one should be in the choice of extrapolation models and "confidence limits."

(Kennedy, who feels that risk quantification should have at least a limited role in the setting of exposure limits, says his attitude differs from Upton's only in degree. "I believe Arthur would concede that it allows one to distinguish between compounds that show large differences in potency," he observes.)

In an interview with *Science*, Rall said the OSTP suggestion that authority over risk assessment be centralized in the NTP was intriguing but that before speaking to its merits he would have to think more about it. He expressed a leeriness of "monolithic solutions and structures" and observed that "one of the strengths of science is its diversity."

At a minimum, however, Rall wants NTP to take the lead in research on risk assessment and, over the next year or so, to adopt some principles on both the qualitative and quantitative aspects of making assessments which everybody would be encouraged to follow.

Although it is not one of unconcern, Rall's attitude is clearly more relaxed than Upton's. But the problem of achieving a solid consensus view of risk assessment will no doubt take on greater urgency in everybody's eyes if such assessments become, as has already happened in the case of OSHA's proposed benzene standard, a major point of controversy in regulatory decisions.

—LUTHER J. CARTER

More Help for the Mentally Ill

President Carter has submitted to Congress a Mental Health Systems Act designed to overhaul the Community Mental Health Centers program. Based on recommendations of the mental health commission headed by Rosalynn Carter, the new measure is supposed to make the programs more flexible, promote closer ties with the regular health care system, cause more resources to go to serve the neediest communities, help chronic mental patients, and promote preventive care. The mental health centers program now absorbs about $300 million a year in federal funds; additional activities would add about $100 million to the total tab.

Carter, his wife, and Health, Education, and Welfare secretary Joseph Califano all showed up at a 15 May press conference at the White House to emphasize the need for further expansion of the federal mental health effort. "Fundamentally," said Califano, "the legislation is designed to make mental health part of the whole health system and part of the whole social services system." The new measure would drop the requirement that mental health centers supply an elaborately specified range of services and instead would pressure them to supply the kind of help most needed in their communities.

The measure also attacks the problem of deinstitutionalized mental patients, which has become a scandal in many cities, through various incentives such as supplying money for mental health advocacy services, and encouraging changes in zoning laws and housing standards so that deinstitutionalized people will have a decent place to live.

The bill attempts to put mental health services on an equal footing with medical services by giving them equal status under Medicaid reimbursement schemes. The bill would also "promote cooperative working arrangements" between medical and mental health services—a development long overdue in view of the fact that the majority of mentally ill people are getting such care as they do get from the general health system.

In the prevention category, the new measure would award grants for programs to help teachers, police, and parents to deal with the chronically ill and with mentally ill children.

Califano said it was all a "modest beginning" but he expected a "heavy payoff" from the proposed changes. Rosalynn Carter, who was about to fly off to Chicago to meet with people at the American Psychiatric Association, vowed to put all her energies into getting the measure passed this year. Congress may balk, but the recommendations of the commission at least have had some effect on the Administration, which has already requested a $27 million increase in funds for mental health research.—C.H.

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