EPA's High-Risk Carcinogen Policy

The government is changing the way it identifies dangerous chemicals, with potentially tragic consequences, critics say

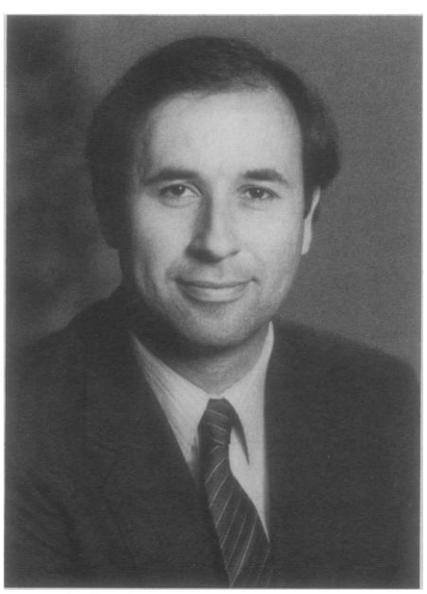
The Administration is rewriting the government's policy on cancer-causing substances this winter and is already drawing fire for its proposals. Congressional critics believe the Administration is being less than frank about the revision, which, they say, will tolerate a higher cancer incidence and create a framework that will allow much greater risks in the future. A major complaint is that this is happening with little public discussion.

Representative George Brown, Jr. (D–Calif.), a senior member of the House agriculture and science committees, says the Administration has already allowed a 100-fold increase in the cancer risk without advertising the change. "At some point they've got to confront the fact that they are actually changing policies, and we have been urging them, if they have a responsible policy, to make it clear and let it be subjected to some scrutiny by the Congress." But Brown says, "The present effort is to fuzz it up."

Representative Albert Gore, Jr. (D–Tenn.), began looking into the subject in a hearing on formaldehyde on 20 May in the science subcommittee on investigations, which he chairs. What he learned was "disturbing." He says, "The upper echelon science policy-makers have made a crass, calculated, cynical change in the traditional policy of seeking to prevent cancer." Recent decisions to relax regulatory standards, Gore believes, "will probably result in hundreds of thousands of additional deaths attributable to cancer." In order to reduce the regulatory burden on industry, Gore says, the Administration has "reached way down into the processes of government to control the science. They think that if you control the science you can control the conclusions about whether to control this or that substance. What they're doing is not supportable."

Gore and Brown see evidence of the government's willingness to take bigger chances in recent decisions on pesticides and toxic substances. Unlike food additives, which must be completely free of suspected carcinogens under the Delaney clause of the Food and Drug Act, these compounds are covered by legislation requiring only that "significant" hazards be reduced by "reasonable" means. In this flexible area, Brown says, the government has shifted quietly from tolerating a statistical risk of one extra cancer in a million people to a new standard of allowing 1 per 10,000 people. His point seems confirmed by recent pesticide rulings and by a 10 February Environmental Protection Agency (EPA) memo on formaldehyde.

Environmental scientists like Frederica Perera at the Natural Resources Defense Council and Ellen Silbergeld at the Environmental Defense Fund are also troubled by EPA's schemes for ranking potential carcinogens into strong and weak categories. They distrust the judgment of a key figure in this campaign, John Todhunter, the 33-year-old assistant administrator of EPA for pesticides and toxic substances. Until 1981, Todhunter was chairman of the biochemistry program at the Catholic University in Washington, D.C., and before that, a fellow of the Roche Institute of Molecular Biology in Nutley, N.J. He has expressed doubts about the validity of some animal tests that suggest carcinogenicity, traditionally accepted as an indication of hazard for humans, and he has asked for hard-to-get proof based on human cancer statistics. The critics are worried specifically by his interest in dividing suspected carcinogens into "genotoxic" and "epigenetic" categories (those that directly affect the cell's genetic mechanism and those that do not). The reason for making the distinction is to allow for differential regulation, permitting greater human exposure to the "epigenetic" substances.



John A. Todhunter

Defender of EPA's "flexible" policy

This approach has already been proposed by a key EPA advisory group led by Roy E. Albert of New York University's Medical Center as the basis for dealing with hazardous compounds in drinking water. Albert's proposal is being considered as EPA's new carcinogen policy. Several well-known scientists, including Arthur Upton, director of New York University's department of Environmental Medicine, have said our understanding of cancer is too weak to justify such a distinction in policy. A similar scheme has been used to justify permitting widespread exposure to a new insecticide, permethrin, which has caused excess liver and lung tumors in mice in at least one, arguably two, laboratory studies.

To the critics, these policies amount to a shift from a preventive stance to one of limiting damage after it has appeared. They refer to the emphasis on human data as "counting dead bodies." This is a poor way to deal with carcinogens, they say, for 20 years may elapse between exposure to a carcinogen and the appearance of the disease. Once cancer does appear, it is extremely difficult to determine which of many factors may have caused it. Animal data are the best available. If the Administration does not like them, it should finance the human epidemiology that might produce better insight, Brown says.

The debate is likely to heat up this winter, in part because the White House Office of Science and Technology Policy (OSTP) has just released a new paper on the subject titled "Potential Human Carcinogens: Methods for Identification and Characterization." Although bland, it does discuss the genotoxic-nongenotoxic distinction and says that the present method of estimating health effects exaggerates risks. Denis Prager, the OSTP official who chaired the drafting group,

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explains that the paper gives a scientific justification for some new government-wide policies yet to be announced. He says they cannot be deduced by reading the scientific document. The paper was sent out for comment in November, having been bottled up until after the election. The guidelines themselves will be written later, perhaps in February, and reviewed separately.

Federal officials agree that changes are being made in policy, but say they will not affect public health. They believe the critics are exaggerating the risks to gain support for their own approach to regulation, a mechanistic one that would make life more convenient for environmental lawyers.

Todhunter, the point man for the Administration in this debate, says he would resist any new proposal that might harden into a rigid legal framework. Risk assessment is a "scientific and not a legal matter," he says. "Our friends in the environmental movement lose sight of that. There is a push to get a categoric statement that all things that do x, y, or z are carcinogens, and we should take regulatory action of type c. Certainly it may be legally simple," Todhunter says, "but scientifically I don't think it's very defensible."

Todhunter says the agency should be allowed to use its discretion more often. This "weight-of-the-evidence posture," as he calls it, is based on a general procedure spelled out in 1976 by the then head of EPA, Russell Train. Todhunter describes it as "rational" and "flexible." It does not say explicitly when to act or when to tolerate hazards, which is frustrating for outsiders trying to keep track of policy. But Todhunter says, "I get very concerned about the adoption of any particular scientific paradigm, because you might wake up tomorrow and find that it was wrong. If you adopt it as policy, it is very difficult to change."

Todhunter says there is no explicit policy other than Train's 1976 guidelines. But there are well-established practices. In recent times, EPA has tried to control any potential carcinogen whose use would present a statistical

The Odds on Cancer: EPA's Recent Bets

The most easily spotted change in EPA cancer policy is a tendency to tolerate higher risks. Several recent decisions give a sense of what is tolerated now, as compared with the past goal of controlling substances thought to pose a risk of causing one excess cancer per million people.

• *Ethylene bisdithiocarbamates* (EDBC's), fungicides used widely on fruits, vegetables, grains, nuts, and other commodities, offer the most recent case. Since 1977, EPA has been gathering data on six compounds in this family in a proceeding known as Rebuttable Presumption Against Registration (RPAR), in which manufacturers are asked to defend the safety record of compounds already on the market. On 5 November, EPA announced a favorable decision for EDBC's: it will allow the manufacturers to apply for "reregistration" (new production licenses) despite the apparent carcinogenicity of EDBC's, largely because "some of the scientific findings are inconclusive," that is, because EDBC manufacturers challenged the validity of studies in which EDBC's produced tumors in mice. Meanwhile, the companies will be allowed to continue selling 27 million pounds annually for the next 2 years, while financing new studies on the possible harmful effects and preparing reregistration documents. As a precaution, professional sprayers and mixers of EDBC's will be required to wear protective clothing.

By EPA's estimate of 14 October, the residues of EDBC's in food alone, through conversion to the metabolite ethylene thiourea, will pose a statistical threat of creating between 5 in 10,000 and 5 in 100,000 excess cancers in the general population. For the professionals exposed to EDBC's continuously through a 40-year career, the threat is said to be between 1 in 100 and 9 in 100,000 excess cancers.

• *Ferriamicide*, a new version of the ant poison mirex, was granted an emergency waiver from EPA pesticide controls on 29 September (*Science*, 5 November, p. 548). EPA banned the use of this compound in 1977, partly because of its carcinogenic potential and partly because of its formidable staying power in the environment. In the case of mirex, the persistence is measured as a half-life of 12 years. EPA agreed to allow three states to use the compound on an emergency basis between September and the end of June 1983, but a federal court has temporarily blocked the decision.

An EPA staff memo dated 29 September calculates that the carcinogenic threat of this decision, based on residues expected in meat and milk, will be 4.99 to 6.65 excess cancers per 100,000 people. This is based on a 1-year exposure, although some EPA staffers argued that in view of mirex's longevity, the risk estimates should have been based on a longer period. In the memo obtained by *Science*, a draft of the final document, a sentence has been crossed out. It says, "Normally a potential oncogenic risk of 1×10^{-6} is considered acceptable."

• *Permethrin*, a new insecticide used on cotton since 1977, was given an expanded registration in October for use on food crops. On 13 October, EPA published a decision on the amount of permethrin residue it will allow in agricultural commodities, a standard that allows for a generous 500 percent expansion of the permethrin market. Among the commodities that will contain permethrin are beef, pork, chicken, lamb, milk, eggs, broccoli, brussels' sprouts, cabbage, celery, cauliflower, lettuce, pears, and potatoes.

Setting the tolerance levels was controversial because an EPA staff pathologist, M. Adrian Gross, argued that the compound presents an intolerable statistical risk of causing new cancers. EPA rejected Gross's argument on the grounds that, regardless of what the statistics say, the biological evidence of carcinogenicity is weak, because laboratory mice are known to develop spontaneous tumors of the kind seen in the permethrin studies.

While arguing that permethrin is probably not carcinogenic, EPA calculated the carcinogenic risks based on the rate at which permethrin produced tumors in mice. The staff came up with the following statistical estimate, cited in a memo dated 24 September and signed by John Melone, chief of the Hazard Evaluation Division: "The upper limits on risk computed by the six extrapolation procedures . . . are all in the 10^{-6} to 10^{-4} range. The highest

risk of causing cancer in more than one in a million people, described as a risk of more than 1×10^{-6}. A potential carcinogen has been defined as anything that produces tumors in laboratory animals. Statistical models with broad error margins are used to extrapolate from measurable effects in animals to unmeasurable effects at low doses, and these numbers are adjusted to reflect humans' greater weight and body surface area. Allowing an extra 200 to 300 cancer cases in a population of 220 million has been seen as reasonably close (within the margin of error) to allowing no excess cancers. In exceptional instances, risks of 1 in 100,000 and, rarely, 1 in 10,000 have been tolerated.

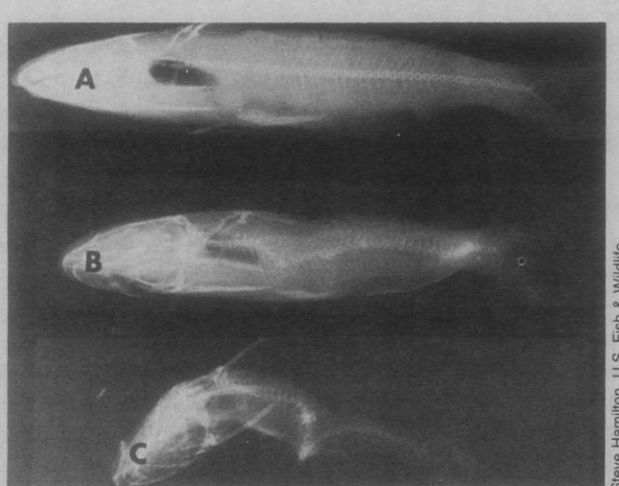
Todhunter regards criticism based on reading the statistical risks as a "straw man." These numbers are valuable only as a bureaucratic aid, he says, in that they allow officials to rank options by relative weight. They do not mean much in biological terms, for they treat all suspect carcinogens as equally carcinogenic, which may be wrong. Todhunter does favor a close reading of the biological data, and, in fact, he is trying to change the way animal data are interpreted to allow for distinctions between strong and weak compounds. Needless to say, this is controversial. Many scientists who agree that statistical analyses may overstate the risks do not agree that EPA's biological expertise is strong enough to support policy distinctions of this kind.

The clearest discussion of this can be found in correspondence last summer between peer reviewers and Roy Albert, who has served since 1976 as chairman of EPA's carcinogen assessment group. In June, Albert's group drafted an addendum making significant changes in Train's 1976 carcinogen guidelines. Albert's rules are to be used specifically for regulating pollutants in water, but they are also intended for general application in other EPA proceedings. They are likely to be pivotal in determining future EPA actions on suspect carcinogens. Albert sought comments from a score of distinguished researchers. His peers

result (about 1×10^{-4}) is obtained from the multistage model. . . ." Thus, the cancer risk is about 1 in 100,000, according to EPA.

Gross says that EPA's risk figure understates the real hazard. He points out that the published figure is based on an estimate of the amount of permethrin EPA believes actually will be consumed in foods. But if one calculates the risk using the legal maximum exposure set by EPA in October, the "allowable daily intake" of 0.05 milligram per kilogram per day, Gross says that the maximum risk increases to about one cancer per 1000, a very large risk.

• *Toxaphene*, a pesticide which has been applied to a variety of crops since 1947, is thought to pose a serious carcinogenic threat to humans, and is a known toxin to wildlife. EPA began proceedings to cancel its registration in 1977, and in mid-October of this year Todhunter announced that he would go forward immediately with cancellation. However, EPA decided to allow existing stocks (over 16 million pounds were sold last year) to be sold over the next 4 years and used "under very limited terms and conditions because such use is judged to be the most desirable means of achieving disposal of these stocks." EPA has funds for buying out dangerous products, but decided not to use them. Among the "minor uses" allowed are aerial spraying on cotton, corn, and small grains during times of severe infestation by armyworms, cutworms, and grasshoppers.



Steve Hamilton, U.S. Fish & Wildlife

The broken back syndrome in catfish

The effects of toxaphene, a suspect carcinogen. Fish A, the control, received no toxaphene and 670 milligrams per kilogram of vitamin C. Fish B received the same amount of vitamin and a large dose of toxaphene. Fish C received a small dose of toxaphene and 63 milligrams per kilogram of vitamin C. EPA has ordered toxaphene off the market, but will allow over 10 million pounds to be used between now and 1986.

Toxaphene-like residues have been found, among other places, in the fish of the Great Lakes. EPA calculated that the cancer risk from exposure to toxaphene through eating fish in the Mississippi Delta is greater than 1 in 100.

• *Formaldehyde*, not a pesticide but an industrial compound used widely in foam insulation, was the focus of an intense scientific debate over its potential carcinogenicity earlier this year (*Science*, 18 June, p. 1285). In 1981 a staff scientist at the Occupational Safety and Health Administration, Peter Infante, was threatened with dismissal because he was too energetic in making known a finding of carcinogenicity (*Science*, 7 August 1981, p. 630). EPA may decide to regulate formaldehyde as a toxic substance, but has declined thus far to classify it under the Toxic Substances Control Act as an item requiring priority attention.

EPA's demurral was articulated in a memo signed by Todhunter on 10 February 1982, a document that gives some of his views on risk assessment. He points out that the normal risk of getting cancer in the United States is about one in three, and claims that it would be impossible to detect a jump in cancer incidence on the order of 1 per 10,000. The increment would be lost in the background noise. Todhunter wrote that "federal agencies do not tend to regulate risks of 1×10^{-5} or lower and tend to be ambivalent about risks between 1×10^{-4} and 1×10^{-5}. Certainly (as absolute risks) these risk levels could never be detected any normal way. . . ." His office, he explained, regards as a "low concern range" risks of 1 in 10,000 or less, presumably because in this range no one can measure the effect on the human population. Todhunter concluded that formaldehyde seems to fall into this category, adding that human exposure data are still too sketchy to warrant a final judgment.—**E.M.**

gave a mixed and quite critical review.

Most commenters agreed with his scheme for ranking biological evidence for carcinogenicity according to definitions used by the International Agency for Research on Cancer (IARC). Evidence would be called sufficient, limited, or inadequate. Compounds in the last category would not be controlled as carcinogens; those in the first, would be. Those in the middle might or might not be controlled, and, if they were, with less urgency than those in the first category. This middle group would include chemicals that have been judged carcinogenic based on (i) a single study, single strain, or single species of laboratory animal, (ii) weakly structured experiments, such as those with few individuals, or (iii) an increase in tumors that often occur spontaneously, such as lung and liver tumors in mice. Permethrin, for example, would probably fall in the middle category.

Most commenters disagreed with Albert's second proposal, which was to rank carcinogens according to their apparent genotoxicity. Chemicals thought not to affect the cell's genetic mechanism directly, in this proposal, would be regulated by a "conventional toxicological" approach, rather than the usual method for dealing with carcinogens. Instead of extrapolating in linear fashion from measurable effects to unmeasurable low-dose effects in fixing standards, Albert proposed to determine the highest dose in animals at which no carcinogenic effect is seen, and then divide by 1000 to create a safety margin.

Umberto Saffioti, chief of experimental pathology at the National Cancer Institute, wrote that this approach was "developed in the Stone Age of toxicology, best described by the statement I once heard: 'Find a no-effect level in animals, divide by 100, and pray.' " He added that the old toxicological method should not be applied to carcinogens because in the case of normal poisoning, the target cell dies, whereas with cancer, the target cell proliferates "and the health effect keeps progressing when the toxic agent is no longer there."

Like others, Saffioti said there is little scientific basis for regulating genotoxic agents differently from other carcinogens. Steven Lewis, a toxicologist for Exxon, agreed: "There are substantial empirical data to refute the assertion that carcinogenic potential (and associated risk) can be quantitatively estimated from mutagenic potency of a particular material." But he came up with a different conclusion. Since it is wrong to make distinctions, Lewis said, why not regulate both genotoxic and nongenotoxic compounds by the old toxicological approach?

Arthur Upton was skeptical: ". . . I doubt that we know enough today about the mechanisms of carcinogenicity or about testing for genotoxicity to utilize such a distinction as the basis for regulatory decision-making." John Weisburger, director of the Naylor Dana Institute of the American Health Foundation, who himself devised a scheme for ranking carcinogens, wrote: "While we appreciate the fact that the draft of EPA's document recognizes the need to distinguish between genotoxic carcinogens and nongenotoxic compounds, the methods to delineate risk as described do not appear to be useful." I. Bernard Weinstein of Columbia University's Cancer Center wrote: ". . . this is part of a misconception that is being perpetrated that carcinogenic agents that do not have demonstrable mutagenic activity are somehow safer than those that can be shown to be mutagenic." By Albert's count, the comments were divided about equally between favorable and unfavorable.

If applied to water pollutants, Albert's proposal would allow considerably higher exposure to suspect compounds than would the "multistage" model now in use. By Albert's calculation, his scheme would increase the tolerable waterborne exposures roughly as follows: for the pesticide aldrin, the number of micrograms per liter would rise by a factor of 18 to 285; for hexachloroethane, by a factor of 19 to 369; for TCDD, by a factor of 13 to 181; for benzene, by no change to a factor of 10; for DDT, by a factor of 158; and for heptachlor, by a factor of 13 to 179.

EPA officials have not decided what technique they will use in setting criteria for water quality, and Albert has not yet prepared a final draft of his proposal. However, the administrative staff at EPA is eager to have Albert follow through on his plan. It could mark the beginning of a new era of carcinogen regulation, one in which compounds are ranked by risk according to their behavior in bioassays, a far more complex process than the statistical approach now used.—**ELIOT MARSHALL**

Computer Expert Signs Off from World Center

MIT professor resigns as chief scientist of French-backed center, says international ideal undermined, blames founder

An MIT computer science expert who took a leading role in a French-sponsored information science research center to benefit Third World countries has withdrawn from the project on grounds that the center had diverged from its original goals and been politicized by the actions of its originator, Jean-Jacques Servan-Schreiber.

Seymour Papert, professor of mathematics and education at MIT and an authority on artificial intelligence and education, had taken a leave of absence from MIT to act as chief scientist at the Paris-based *centre mondial pour la micro-informatique*. He resigned in mid-November and has returned to this country. Four other prominent non-French computer scientists who had been involved in the establishment of the center earlier disengaged from the project.

The French government late last year made public its plans to put substantial resources into a center for work on the social applications of computers to assist development in the Third World and in modernization in France and other industrial countries. The initiative, championed by Servan-Schreiber appeared to jibe closely with the Mitterrand government's policies (*Science*, 19 February, p. 948).

The original emphasis on international activities had attracted pledges of participation from about a dozen leading computer scientists from outside France. Their association and, particularly, the enlistment as center director of Nicholas Negroponte, head of a highly regarded research group at MIT, and of Papert as chief scientist, was regarded as a major coup conferring immediate international standing on the center. This participation served to counter suggestions by skeptics that the French might intend to use

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