PESTICIDE FOOD SAFETY ACT OF 1988

HEARINGS

BEFORE THE

SUBCOMMITTEE ON DEPARTMENT OPERATIONS, RESEARCH, AND FOREIGN AGRICULTURE

OF THE

COMMITTEE ON AGRICULTURE HOUSE OF REPRESENTATIVES

ONE HUNDREDTH CONGRESS

SECOND SESSION

ON

H.R. 4937

JULY 28 AND SEPTEMBER 7, 1988

Serial No. 100-99

Printed for the use of the Committee on Agriculture

U.S. GOVERNMENT PRINTING OFFICE

90-175 WASHINGTON : 1988

For sale by the Superintendent of Documents, Congressional Sales Office
U.S. Government Printing Office, Washington, DC 20402

regret very much we had to cut short our hearing; however, hopefully that did afford people the opportunity to review the testimony by Dr. Moore, of the EPA.

I have a feeling that everybody here today will tell the subcommittee that the current system of regulating food use pesticides really doesn't work very well. Likewise, we all have very different notions on how to fix the problem. This is a very, very crucial issue for agriculture and obviously for the rest of the country.

You referred to the Delaney Clause as a paradox, Mr. Chairman. I guess in all candor, I don't think it is a very reasonable standard for pesticides and the demands of the statute really don't marry up very well with the FIFRA Act. These conflicts between these two statutes really result in what I call regulatory gridlock and it weighs very heavily on the EPA and the proper administration of that policy.

This does equate, I think, to lost consumer confidence and the American farmer suffers as a direct result. So I see the subcommittee is very uniquely positioned to really try to address these issues and I look forward to the testimony of the witnesses who are here today.

Mr. BROWN. Any other committee members have any statements to make?

[No response.]

Mr. BROWN. In that case, we then will welcome Dr. Charles Benbrook, the executive director of the board of agriculture, National Academy of Sciences, and the former distinguished staff director of this subcommittee.

You may proceed with your testimony, Dr. Benbrook.

STATEMENT OF CHARLES M. BENBROOK, EXECUTIVE DIRECTOR, BOARD OF AGRICULTURE, NATIONAL ACADEMY OF SCIENCES

Mr. BENBROOK. Thank you, Mr. Chairman, Mr. Roberts, members of the subcommittee, it is a pleasure to be here. It has been a long time since I sat up there and watched what goes on down here. I will try to act on some of the lessons I learned in my earlier role on the subcommittee's staff.

I have a written statement that I would ask to be included in the record, and I will merely summarize a few points.

Mr. BROWN. Without objection, it will be fully entered.

Mr. BENBROOK. Mr. Roberts, you are right, the regulatory program addressing pesticides is subject to a sort of chronic gridlock and one of the most difficult issues that gives rise to this gridlock deals with what regulatory action should be taken on a set of older pesticides that have been shown to cause cancer in laboratory animals.

This problem that EPA faces dealing with several dozen older pesticides really was what led the agency 4 years ago to seek the help of the National Academy of Sciences. We were asked to study this problem and come up with some recommendations on ways to perhaps resolve or unravel the basic fundamentals that give rise to this gridlock.

Four years later, and a lot of hard work and a lot of additional data having flowed under the bridge, I can't say that there is any

real reason for hope. The system is no simpler; the scientific issues are no more clear-cut; the political decisions are no easier. I would urge this subcommittee, as just a general notion, to be very wary of legislative changes now that add substantial complexity to the program. The regulatory program is very complex already. It is outstripping the resources of the agency to implement it; it is outstripping the economic capacity of registrants to pay for the science and the legal work that has to be done to deal with the regulatory requirements and it is outstripping the ability of the farmer to pay for the crop-protection chemicals.

You really have to start asking yourself, is this system worth it and do we really want to continue in the direction we are going? Is there enough public interest at stake?

Another general point I want to make—it is a matter of great confusion amongst people—involves the circumstances that give rise to the concentration of a pesticide in processed foods.

As you remember, the Delaney Clause problem in pesticide regulation arises when a pesticide residue concentrates in a processed food to a level above that which appears in the raw food, or the fresh food product. This fact of concentration triggers the need for a tolerance to be established under section 409 of the Food, Drug and Cosmetic Act, a part of which is the so-called Delaney Clause.

So the issue of concentration as a legal matter is key to the problem that gave rise to the National Academy study, and the problem addressed in the Roberts–Brown bill.

Now, a lot of people will come up here and say that pesticides rarely concentrate. They will cite thousands of tests that have been run which never or rarely find instances were pesticides concentrate. It is very important for you to understand basically when pesticides do concentrate.

If you have a pesticide that appears on food, on the external surface where it is washed off, either by the consumer or in processing, then it will rarely concentrate. If it is a pesticide that biologically degrades in the presence of air in the environment soon after it is sprayed, it will rarely concentrate. But there are a number of pesticides that are systemic or which become embedded in the fruit, or meat of a vegetable or other foodstuff, and whenever you take some of that food and process it into other products that involve breaking it into component parts, that is where you have a high likelihood of concentration in at least one of those component parts.

When you take corn and turn it into corn oil; or other crops and turn them into oil, oftentimes whatever pesticides are in the residues or on the soybean or in the corn kernel, they will either concentrate in the oil or in the mash that is left after the crushing of grain into oil. Whenever you dry fruit or vegetables—which simply involves taking water and hence weight out—you will have a higher concentration of any pesticide residues by weight in the dried product.

So there are certain circumstances where you are going to get concentration fairly regularly, and other circumstances when you almost never will. It is important to recognize the difference.

As a regulatory matter, as long as for a few processed products made from corn or citrus or soybean or wheat, as long as a few

products are subject to this phenomenon of concentration, from EPA's point of view, that triggers the whole set of regulatory considerations that are dealt with in the Roberts-Brown bill.

So it is true that concentration above published tolerance levels rarely occur, but it is also true that as a regulatory matter, it occurs enough that it is a major problem.

Speaking to the Roberts-Brown bill that is before the subcommittee, I believe that this bill reflects as simple and literal a translation of the recommendations of the National Academy into legislation as is possible. I believe in crafting the bill, Congressman Roberts, you sought to develop a bill that simply and cleanly deals with the fundamental recommendations in the Academy report and I think that it does that pretty well.

It eliminates the inconsistency in the standard between raw and processed food by applying basically the same negligible-risk standard to residues in both raw and processed foods. It calls for a consistent negligible-risk standard to be applied to both, and it deals with the fundamental issue of inconsistent standards being applied to old and new pesticides by proposing an important change in the reregistration process.

I would like to speak to that issue because, fundamentally, the problem with reregistration, the problem that EPA has in regulating older pesticides, stems from two or three dozen older pesticides that are still very valuable tools to farmers but happen to also pose potentially substantial risks to either man or the environment. So it is this pool of older products that keeps coming up over and over again that really is the problem. Until EPA can work through them in the reregistration process and come up with ways that those products can be used in accordance with contemporary standards, this issue will not go away.

In the context of reregistration and in the context of having the same negligible-risk standard apply to new or old pesticides, the Roberts-Brown bill proposes that the act of reregistering a pesticide become essentially the same, or in the words of the bill, the "functional equivalent of an initial registration."

Now, some people believe that this marks no change from the current statute, but let me assure you it certainly does in practice. Today, for EPA to suspend or cancel a pesticide, it has to have sufficient data and scientific information to prove that a substantial risk is faced, either by man, by a farmer or applicator of the pesticide, or to wildlife. This proves to be often a very difficult scientific task, so a pesticide basically remains on the market and in use until there is a substantial body of evidence that there is considerable harm being done.

This is really a very serious problem because it places a scientific burden on the agency that it can only handle in one or two or three regulatory cases each year. So the idea behind turning reregistration into basically the same process as registration, following a longer period of time, is to give the agency an opportunity for a clean review of a pesticide, based on current standards and currently registered products. The question the agency would face is whether an older pesticide basically cuts the butter in terms of the balance of risks and benefits that it poses.

Analytically and technically, this is an important difference because in this case, EPA evaluates the risk of a pesticide in contrast to other registered alternatives. It is often much easier for EPA to say that pesticide X is safer than pesticide Y. It may have a much more difficult time, however, predicting with any degree of certainty the absolute risk associated with either, but at least it can make a judgment that one is safer than the other. If the risks from one pesticide are substantially greater than another which offers about equal benefits, under the Roberts-Brown reregistration process the agency would be expected to leave on the market the safer pesticide and not reregister the one that is proven to pose greater risk but not significantly greater benefits.

Now, given that there are many products registered for most major uses of pesticides, and sometimes several products from a similar chemical class, it is very likely that EPA is going to find itself forced to evaluate the relative risks and benefits for 6, 8, 10, even more products that are, say, herbicides for corn or soybeans. It is going to prove, I think, a lot easier for the agency to determine, say, the 4 safest out of a set of 6 pesticides, or the 2 most risky out of a set of 10, and take appropriate regulatory action on those than it will be to come up with an absolute certainty of what the risks are for each one of those compared to some absolute standard.

So this is the concept behind this new approach to reregistration and I believe it would greatly facilitate the task that EPA faces when it comes up to major groups of products about which they really are not sure which is the most risky or the least risky or how to proceed.

The legislation also has, I think, an important title which would move along the process of developing some integrated pest-management systems. I think that it is likely that the subcommittee will return to those issues as it begins to craft the research title of the next farm bill, but I would be glad to answer any questions on that title.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Benbrook appears at the conclusion of the hearing.]

Mr. BROWN. Thank you very much, Dr. Benbrook.

Mr. Roberts.

Mr. ROBERTS. Yes, thank you, Mr. Chairman.

I would just like to state from a few paragraphs of a previous statement when we had the hearing before when I stated, in the eyes of our farm organizations, and more especially, the farmers and ranchers of this country, nothing is more important than the confidence of the consumer in the safety of our food supply. I know I speak for many of my colleagues that, as a farm State Member of this Congress, no prospect worries me more than the notion or a real fear of pesticide residues would or could cause a real choice and a real frustration and a real fear on the part of the consumer as they try to purchase the kinds of foods that we purchase in this country at the grocery store.

We are very proud of what we think is the best quality food in the history of the world at the lowest possible price and in that respect, I think agriculture has been, what, maybe hunkering down

in the weeds too much in a defensive posture. We have to accept this challenge. We have to become much more, I think, aggressive in embracing what you referred to as an end to the complexity of the problem and the regulatory gridlock.

I want the subcommittee to know, and I want all present to know, that the NAS report, which you are largely responsible for, is indeed a watershed study. It is a blueprint for change, if you will, in the processes and the policies that do govern the pesticide residue.

We in the Ag Committee should embrace the report; we should encourage the elevation of safety standards to the rational and consistent regulation of pesticide residues. Now, that is a tall order and I notice that you had on your dark hat this morning in terms of doom and gloom. I still remain, I guess, an eternal optimist, but I want to pay a large amount of personal credit to Dr. Benbrook, Mr. Chairman, for his efforts in this regard and if we are to achieve success, and we must, it will be in large part to the efforts of very dedicated folks like yourself.

So in behalf of the farmers and ranchers in my district and in Kansas, I want to thank you for your efforts.

Now, since apparently that caused the TV lights to go off with all of that milk of human kindness, let me ask just a couple of questions.

You know that we received some criticism in regard to the Roberts-Brown bill, H.R. 4937, that this bill is too loose; that we need greater elaboration similar to the bill that has been introduced by our friend and colleague, Mr. Waxman, H.R. 4739. On page 5, that you did not read, in the first paragraph, you have indicated: "There is now widespread agreement that both exposure and potential risk is heavily concentrated in relatively few foods following the use of perhaps a dozen pesticides."

If this is so, do you believe that the approach used by the bill introduced by the chairman and myself or the Waxman bill would achieve the greatest risk reduction, because that is what we want, and in terms of cost, and most important, I want real progress. I don't want an issue; I don't want to debate it anymore, and so in terms of minimal disruption to agriculture in the shortest period of time to get some progress, which approach do you think would be best?

Mr. BENBROOK. First of all, Mr. Roberts, under FIFRA and any subsequent legislation affecting FIFRA, for it to bring about any real risk reduction, it is going to require leadership from EPA and some determination to bring that about. Laws alone can't do it.

But to answer your question directly, risk could be reduced much more quickly under the Roberts-Brown bill. It is less prescriptive; it is more flexible and, as a result, it can be enacted, or acted upon much more quickly.

The Waxman bill, on the other hand, is fairly complicated both technically and procedurally. It requires many things to happen, and establishes a precise set of rules and process, which will themselves require much effort to fully specify and implement, until this is done, probably no regulatory action or real risk reduction would be brought about until the various procedures had been car-

ried out fully in accordance with the new provisions in that statute.

So I think that if somebody wanted to go in and identify the highest risk uses of pesticides, and take actions to reduce risk, they could do so most quickly and expeditiously under the Roberts-Brown bill.

Mr. ROBERTS. Want to and can do are two different things. We are going to hear from some witnesses on down the road here that simply do not trust the EPA to do that job and I would say that mistrust would be regardless of who has that responsibility. On one hand, if you really dot the I and you cross the T and you come with some very rigid guidelines and definitions, I think you can make the argument that, by golly, this is what you are going to do, now do it. On the other side of it, if you do it that way, you may cause a tremendous cost and disruption to agriculture that may or may not have a bearing on the safety issue and I would like to see some progress.

I would like to see at least some degree of flexibility so that the EPA Administrator will not step into a hornet's nest every time he makes a decision. We have had enough of that. We have had enough of this adversity. That is the point I am trying to make.

My time is expired, Mr. Chairman. I think I will yield back at this point, but I do have two other questions for Dr. Benbrook at a later point.

Mr. BROWN. We will get back to you.

Mr. Stenholm.

Mr. STENHOLM. Dr. Benbrook, some suggest that we don't have leadership within EPA. I have, for a long time, wondered how we get leadership from any of the administrative offices of our government when we continue to have such diversity of opinion among those who are asking for the leadership. It is almost impossible, I believe, for anyone to give leadership when there is not an agreement on what action needs to be taken.

For example, I am told that there are studies that show that if we eliminate all pesticides from the face of the earth that there would still be 99 percent of the known carcinogens still present in the world. Is that a reasonable statement?

Mr. BENBROOK. I think it is sufficiently hypothetical to not be very relevant to the current debate. There are a lot of things that cause cancer. Some of them are natural and some of them are man-made. There is the beginning of some very interesting work to try to understand the relative degree of risks that are imposed by man-made and natural carcinogens, but I don't think that we know quite enough yet to say with certainty that 99 percent of the carcinogens are natural or man-made or whatever, but it is an important area to try to get a better handle on because we just might be missing the boat fairly substantially with our current set of policies.

It has raised an important question, but I don't think that the science is so clear that it would support a major change in regulatory policy. That is my opinion.

Mr. STENHOLM. You, in your testimony, lean toward supporting the bill that we are considering today. It appears that you support the establishing of tolerance levels for various pesticides rather

than having an absolute ban based on an ability to measure the presence of various carcinogens? Is that correct?

Mr. BENBROOK. That is right, and the idea being that it is now possible, at least regulatory agencies are doing it fairly regularly, to define a level of exposure for toxic chemicals below which there really is no prudent basis for great concern about there being a health hazard. I think that that can be done now in the case of most pesticide residues in food and the point of the NAS Delaney report is that the vast majority of pesticide uses under current farming practices are going to result in a residue well below that level. The vast majority.

There is already sufficient information in the files of EPA to identify most of those uses that are clearly above that level. But instead of contemplating 600 active ingredients and some 15,000 food uses of pesticides that aren't going to be fully reregistered until the year 2050, assuming Congress appropriates sufficient funds and doesn't change the law six times in between, instead of this enormous task, the problem becomes manageable by focusing on just these uses that may pose greater than negligible risk.

If you take the current uses of pesticides and say, "Which ones pose a risk that is possibly above a negligible level," you go from tens of thousands of uses of individual pesticides down to just a few hundred. Then you can begin to deal with those.

When you find a use of a pesticide that appears that it may pose risks above the negligible level, you ask yourself, "Is the data that suggests such risk valid, is that data scientifically sound? Are the residues really there?" That is the first thing you ask. We can do a better job of doing exposure assessments from pesticides in the diet so we look at the data and say, "Are the real residues there?" Oftentimes, they are not. There are many orders of magnitude less than what the published tolerance level is.

Just by a simple analysis of the exposure, one soon loses that concern. But in some instances, there will still be a concern. Then you have to say, "Is there a way we can use the pesticide to reduce the level in the foods," and oftentimes there are. You can use it in a different way, a different formulation, but after you go through all the steps, there is still going to be some uses that pose greater than negligible risk, and it is those uses that should be acted upon in an expeditious way.

If the regulatory agency can get to the point where it can convince the public and the Congress that it is routinely identifying these potentially risky uses, and as a result reducing risk without a lot of hand-waving, then there is going to be some confidence restored in this whole process. But right now, because nothing is happening on any front, the public gets the impression that all pesticides must be equally bad. It is just as bad to eat Mr. Roberts' wheat as your constituents' cattle and Mr. Brown's citrus.

But it is just not that way. That is the point of the Academy report, that there is a way to proceed where we can identify the worse risks and take whatever steps are necessary to do something about it. It is a relatively small proportion of all uses of pesticides, a very small proportion of the total pesticides used in American agriculture.

That is my speech.

Mr. STENHOLM. I appreciate your answer.

Mr. BROWN. Dr. Benbrook, the point that is raised here about the relative burden of carcinogenic elements represented by pesticides, even though there is probably not an adequate scientific basis for it, is an interesting question, as you have indicated, and it would be, I think, helpful for our record if there were any published material that indicates what this relative burden from pesticides might be.

Of course, this opens up the whole question of other routes of exposure to humans of carcinogens and these come through the air, through any number of different things, both natural and man-made sources. If there is available anything that would throw any light on this subject that you know of, I would appreciate your making that available to the subcommittee.

Mr. BENBROOK. Mr. Chairman, Dr. Bruce Ames, who is a distinguished microbiologist and member of the National Academy, has really pioneered this whole concept of trying to develop a ranking system for man-made versus natural carcinogens. In the wake of all the press attention our report engendered when we released it, Dr. Ames and I engaged in a quite interesting dialogue through the mail. I have all of his pertinent articles. I would be glad to submit a package of materials for the record.

[The information follows:]

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October 5, 1988

Honorable George E. Brown, Jr.
Chairman
House Subcommittee on Department
Operations, Research, & Foreign Agriculture
2256 Rayburn House Office Building
Washington, D.C. 20515-0536

Dear Mr. Chairman:

I appreciated the opportunity to testify before the subcommittee September 7 on the Roberts-Brown food safety bill.

Please find enclosed material in response to your questions regarding cancer risks from exposure to natural and manmade substances: the most recent article in Science by Dr. Bruce Ames describing his relative risk ranking scheme, and correspondence with Dr. Ames exploring some of the interesting analytical challenges that must be overcome to develop a more refined analysis. I agree fully with you that Dr. Ames research raises significant questions, both in evaluating pesticide regulatory policy, and in considering how certain applications of biotechnology in plant variety development should be evaluated, or even possibly regulated.

As you know, a very different body of law, regulations, legal precedents, and public attitudes address natural constituents of food, in contrast to manmade chemicals (pesticide, animal drug, or food additive residues). Since the goal of all such laws is public health promotion, a re-evaluation of these policies seems warranted to assure that a proper balance is being struck in our regulatory programs. A part of such an analysis should be a more sophisticated and complete empirical assessment of the nature and level of risks from manmade and natural chemicals in food. I would urge DORFA to pursue how such a study could be undertaken.

I also enclose information in response to Mr. Stenholm's questions regarding cancer trends. Please find the Executive Summary of the most recent NCI Atlas of Cancer, a review article of epidemiological studies on cancer risks faced by farmers, and a just published report on a new epidemiological study done in Italy.

There is a growing body of evidence regarding the presence of nitrates and triazine herbicide residues in drinking water in major farming regions. These chemicals can react in the stomach to form nitrosamine compounds, many of which are known to be potent carcinogens. Until recently, the principal route of exposure, and concern among farmers relative to pesticide risks stemmed from occupational exposures. It is now extremely

important, I believe, to evaluate the potential risks to farm families and rural communities from water-based exposures. Again, I would urge DORFA to consider holding a hearing, or undertaking other information generating activities to explore the adequacy of ongoing research designed to determine the magnitude of farm-related toxic hazards.

I would like to offer congratulations to you and the subcommittee upon the final passage of the FIFRA. After so many years of effort, it must be a considerable relief. Without doubt, the bill will help a great deal in resolving some of the major problems in the registration process.

Again, thanks for the opportunity to appear before the subcommittee.

Sincerely,

Charles M. Benbrook
Executive Director

Enclosures
c: Skip Stiles w/enclosures

Ranking Possible Carcinogenic Hazards

BRUCE N. AMES,* RENAE MAGAW, LOIS SWIRSKY GOLD

This review discusses reasons why animal cancer tests cannot be used to predict absolute human risks. Such tests, however, may be used to indicate that some chemicals might be of greater concern than others. Possible hazards to humans from a variety of rodent carcinogens are ranked by an index that relates the potency of each carcinogen in rodents to the exposure in humans. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance.

EPIDEMIOLOGISTS ESTIMATE THAT AT LEAST 70% OF HUMAN cancer would, in principle, be preventable if the main risk and antirisk factors could be identified (*1*). This is because the incidence of specific types of cancer differs markedly in different parts of the world where people have different life-styles. For example, colon and breast cancer, which are among the major types of cancer in the United States, are quite rare among Japanese in Japan, but not among Japanese-Americans. Epidemiologists are providing important clues about the specific causes of human cancer, despite inherent methodological difficulties. They have identified tobacco as an avoidable cause of about 30% of all U.S. cancer deaths and of an even larger number of deaths from other causes (*1, 2*). Less specifically, dietary factors, or their absence, have been suggested in many studies to contribute to a substantial proportion of cancer deaths, though the intertwined risk and antirisk factors are being identified only slowly (*1, 3, 4*). High fat intake may be a major contributor to colon cancer, though the evidence is not as definitive as that for the role of saturated fat in heart disease or of tobacco in lung cancer. Alcoholic beverage consumption, particularly by smokers, has been estimated to contribute to about 3% of U.S. cancer deaths (*1*) and to an even larger number of deaths from other causes. Progress in prevention has been made for some occupational factors, such as asbestos, to which workers used to be heavily exposed, with delayed effects that still contribute to about 2% of U.S. cancer deaths (*1, 5*). Prevention may also become possible for hormone-related cancers such as breast cancer (*1, 6*), or virus-related cancers such as liver cancer (hepatitis B) and cancer of the cervix (papilloma virus HPV16) (*1, 7*).

Animal bioassays and in vitro studies are also providing clues as to which carcinogens and mutagens might be contributing to human cancer. However, the evaluation of carcinogenicity in rodents is expensive and the extrapolation to humans is difficult (*8–11*). We will use the term "possible hazard" for estimates based on rodent cancer tests and "risk" for those based on human cancer data (*10*).

Extrapolation from the results of rodent cancer tests done at high doses to effects on humans exposed to low doses is routinely attempted by regulatory agencies when formulating policies attempting to prevent future cancer. There is little sound scientific basis for this type of extrapolation, in part due to our lack of knowledge about mechanisms of cancer induction, and it is viewed with great unease by many epidemiologists and toxicologists (*5, 9–11*). Nevertheless, to be prudent in regulatory policy, and in the absence of good human data (almost always the case), some reliance on animal cancer tests is unavoidable. The best use of them should be made even though few, if any, of the main avoidable causes of human cancer have typically been the types of man-made chemicals that are being tested in animals (*10*). Human cancer may, in part, involve agents such as hepatitis B virus, which causes chronic inflammation; changes in hormonal status; deficiencies in normal protective factors (such as selenium or β-carotene) against endogenous carcinogens (*12*); lack of other anticarcinogens (such as dietary fiber or calcium) (*4*); or dietary imbalances such as excess consumption of fat (*3, 4, 12*) or salt (*13*).

There is a need for more balance in animal cancer testing to emphasize the foregoing factors and natural chemicals as well as synthetic chemicals (*12*). There is increasing evidence that our normal diet contains many rodent carcinogens, all perfectly natural or traditional (for example, from the cooking of food) (*12*), and that no human diet can be entirely free of mutagens or agents that can be carcinogenic in rodent systems. We need to identify the important causes of human cancer among the vast number of minimal risks. This requires knowledge of both the amounts of a substance to which humans are exposed and its carcinogenic potency.

Animal cancer tests can be analyzed quantitatively to give an estimate of the relative carcinogenic potencies of the chemicals tested. We have previously published our Carcinogenic Potency Database, which showed that rodent carcinogens vary in potency by more than 10 millionfold (*14*).

This article attempts to achieve some perspective on the plethora of possible hazards to humans from exposure to known rodent carcinogens by establishing a scale of the possible hazards for the amounts of various common carcinogens to which humans might be chronically exposed. We view the value of our calculations not as providing a basis for absolute human risk assessment, but as a guide to priority setting. One problem with this type of analysis is that few of the many natural chemicals we are exposed to in very large amounts (relative to synthetic chemicals) have been tested in animals for carcinogenicity. Thus, our knowledge of the background levels of human exposure to animal carcinogens is fragmentary, biased in favor of synthetic chemicals, and limited by our lack of knowledge of human exposures.

B. N. Ames is associated with the Department of Biochemistry, University of California, Berkeley, CA 94720. R. Magaw and L. Swirsky Gold are associated with the Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720.

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virus (*19, 20*). Considering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they may represent the most significant carcinogenic pollution of the food supply in developing countries. Such pollution is much less severe in industrialized countries, due to refrigeration and modern techniques of agriculture and storage, including use of synthetic pesticides and fumigants.

Preparation of foods and beverages can also produce carcinogens. Alcohol has been shown to be a human carcinogen in numerous epidemiologic studies (*1, 21*). Both alcohol and acetaldehyde, its

Table 1. Ranking possible carcinogenic hazards. *Potency of carcinogens*: A number in parentheses indicates a TD_{50} value not used in HERP calculation because it is the less sensitive species; (−) = negative in cancer test. (+) = positive for carcinogenicity in test(s) not suitable for calculating a TD_{50}; (?) = is not adequately tested for carcinogenicity. TD_{50} values shown are averages calculated by taking the harmonic mean of the TD_{50}'s of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD_{50} value (most potent) is used instead. For each test the target site with the lowest TD_{50} value has been used. The average TD_{50} has been calculated separately for rats and mice, and the more sensitive species is used for calculating the possible hazard. The database, with references to the source of the cancer tests, is complete for tests published through 1984 and for the National Toxicology Program bioassays through June 1986 (*14*). We have not indicated the route of exposure or target sites or other particulars of each test, although these are reported in the database. *Daily human exposure*: We have tried to use average or reasonable daily intakes to facilitate comparisons. In several cases, such as contaminated well water or factory exposure to EDB, this is difficult to determine, and we give the value for the worst found and indicate pertinent information in the References and Notes. The calculations assume a daily dose for a lifetime; where drugs are normally taken for only a short period we have bracketed the HERP value. For inhalation exposures we assume an inhalation of 9,600 liters per 8 hours for the workplace and 10,800 liters per 14 hours for indoor air at home. *Possible hazard*: The amount of rodent carcinogen indicated under carcinogen dose is divided by 70 kg to give a milligram per kilogram of human exposure, and this human dose is given as the percentage of the TD_{50} dose in the rodent (in milligrams per kilogram) to calculate the *H*uman *E*xposure *R*odent *P*otency index (HERP).

Possible hazard HERP (%)	Daily human exposure	Carcinogen dose per 70-kg person	Potency of carcinogen: TD_{50} (mg/kg)		References
			Rats	Mice	
		Environmental pollution			
0.001*	Tap water, 1 liter	Chloroform, 83 μg (U.S. average)	(119)	90	*96*
0.004*	Well water, 1 liter contaminated (worst well in Silicon Valley)	Trichloroethylene, 2800 μg	(−)	941	*97*
0.0004*	Well water, 1 liter contaminated, Woburn	Trichloroethylene, 267 μg	(−)	941	*98*
0.0002*		Chloroform, 12 μg	(119)	90	
0.0003*		Tetrachloroethylene, 21 μg	101	(126)	
0.008*	Swimming pool, 1 hour (for child)	Chlorotorm, 250 μg (average pool)	(119)	90	*99*
0.6	Conventional home air (14 hour/day)	Formaldehyde, 598 μg	1.5	(44)	*100*
0.004		Benzene, 155 μg	(157)	53	
2.1	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg	1.5	(44)	*28*
		Pesticide and other residues			
0.0002*	PCBs: daily dietary intake	PCBs, 0.2 μg (U.S. average)	1.7	(9.6)	*101*
0.0003*	DDE/DDT: daily dietary intake	DDE, 2.2 μg (U.S. average)	(−)	13	*16*
0.0004	EDB: daily dietary intake (from grains and grain products)	Ethylene dibromide, 0.42 μg (U.S. average)	1.5	(5.1)	*102*
		Natural pesticides and dietary toxins			
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 0.3 μg	(0.2)	0.2	*40*
0.006		Diethylnitrosamine, 0.1 μg	0.02	(+)	
0.003	Sake (250 ml)	Urethane, 43 μg	(41)	22	*24*
0.03	Comfrey herb tea, 1 cup	Symphytine, 38 μg (750 μg of pyrrolizidine alkaloids)	1.9	(?)	*103*
0.03	Peanut butter (32 g; one sandwich)	Aflatoxin, 64 ng (U.S. average, 2 ppb)	0.003	(+)	*18*
0.06	Dried squid, broiled in gas oven (54 g)	Dimethylnitrosamine, 7.9 μg	(0.2)	0.2	*37*
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg	96	(−)	*47*
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg	(?)	52	*48*
0.1	Mushroom, one raw (15 g) (*Agaricus bisporus*)	Mixture of hydrazines, and so forth	(?)	20,300	*104*
0.2	Natural root beer (12 ounces; 354 ml) (now banned)	Safrole, 6.6 mg	(436)	56	*105*
0.008	Beer, before 1979 (12 ounces; 354 ml)	Dimethylnitrosamine, 1 μg	(0.2)	0.2	*38*
2.8*	Beer (12 ounces; 354 ml)	Ethyl alcohol, 18 ml	9110	(?)	*23*
4.7*	Wine (250 ml)	Ethyl alcohol, 30 ml	9110	(?)	*23*
0.2	Comfrey-pepsin tablets (nine daily)	Comfrey root, 2700 mg	626	(?)	*103*
1.3	Comfrey-pepsin tablets (nine daily)	Symphytine, 1.8 mg	1.9	(?)	
		Food additives			
0.0002	AF-2: daily dietary intake before banning	AF-2 (furylfuramide), 4.8 μg	29	(131)	*44*
0.06*	Diet Cola (12 ounces; 354 ml)	Saccharin, 95 mg	2143	(−)	*106*
		Drugs			
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg	1246	(2137)	*51*
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2000 mg	(542)	506	*107*
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg	(150)	30	*108*
16*	Phenobarbital, one sleeping pill	Phenobarbital, 60 mg	(+)	5.5	*50*
17*	Clofibrate (average daily dose)	Clofibrate, 2000 mg	169	(?)	*52*
		Occupational exposure			
5.8	Formaldehyde: Workers' average daily intake	Formaldehyde, 6.1 mg	1.5	(44)	*109*
140	EDB: Workers' daily intake (high exposure)	Ethylene dibromide, 150 mg	1.5	(5.1)	*55*

*Asterisks indicate HERP from carcinogens thought to be nongenotoxic.

received by today's uranium miners. Two particularly contaminated houses were found that had a risk estimated to be equivalent to receiving about 1200 chest x-rays a day (*49*). Approximately 10% of the lung cancer in the United States has been tentatively attributed to radon pollution in houses (*49*). Many of these cancers might be preventable since the most hazardous houses can be identified and modified to minimize radon contamination.

General outdoor air pollution appears to be a small risk relative to the pollution inhaled by a smoker: one must breathe Los Angeles smog for a year to inhale the same amount of burnt material that a smoker (two packs) inhales in a day (*12*), though air pollution is inhaled starting from birth. It is difficult to determine cancer risk from outdoor air pollution since epidemiologists must accurately control for smoking and radon.

Some common drugs shown in Table 1 give fairly high HERP percentages, primarily because the dose ingested is high. However, since most medicinal drugs are used for only short periods while the HERP index is a daily dose rate for a lifetime, the possible hazard would usually be markedly less. We emphasize this in Table 1 by bracketing the numbers for these shorter exposures. Phenobarbital (HERP = 16%) was investigated thoroughly in humans who had taken it for decades, and there was no convincing evidence that it caused cancer (*50*). There is evidence of increased renal cancer in long-term human ingestion of phenacetin, an analgesic (*51*). Acetaminophen, a metabolite of phenacetin, is one of the most widely used over-the-counter pain killers. Clofibrate (HERP = 17%) is used as a hypolipidemic agent and is thought to be carcinogenic in rodents because it induces hydrogen peroxide production through peroxisome proliferation (*52*).

Occupational exposures can be remarkably high, particularly for volatile carcinogens, because about 10,000 liters of air are inhaled in a working day. For formaldehyde, the exposure to an average worker (HERP = 5.8%) is higher than most dietary intakes. For a number of volatile industrial carcinogens, the ratio of the permitted exposure limit [U.S. Occupational Safety and Health Administration (OSHA)] in milligrams per kilogram to the TD_{50} has been calculated; several are close to the TD_{50} in rodents and about two-thirds have permitted HERP values >1% (*53*). The possible hazard estimated for the actual exposure levels of the most heavily exposed EDB workers is remarkably high, HERP = 140% (Table 1). Though the dose may have been somewhat overestimated (*54*), it was still comparable to the dose causing cancer in half the rodents. An epidemiologic study of these heavily exposed EDB workers who inhaled EDB for over a decade did not show any increase in cancer, though because of the limited duration of exposure and the relatively small numbers of people monitored the study would not have detected a small effect (*54, 55*). OSHA still permits exposures above the TD_{50} level. California, however, lowered the permitted level over 100-fold in 1981. In contrast with these heavy workplace exposures, the Environmental Protection Agency (EPA) has banned the use of EDB for fumigation because of the residue levels found in grain (HERP = 0.0004%).

Uncertainties in Relying on Animal Cancer Tests for Human Prediction

Species variation. Though we list a possible hazard if a chemical is a carcinogen in a rat but not in a mouse (or vice versa), this lack of agreement raises the possibility that the risk to humans is nonexistent. Of 392 chemicals in our database tested in both rats and mice, 226 were carcinogens in at least one test, but 96 of these were positive in the mouse and negative in the rat or vice versa (*56*). This discordance occurs despite the fact that rats and mice are very closely related and have short life-spans. Qualitative extrapolation of cancer risks from rats or mice to humans, a very dissimilar long-lived species, is unlikely to be as reliable. Conversely, important human carcinogens may not be detected in standard tests in rodents; this was true for a long time for both tobacco smoke and alcohol, the two largest identified causes of neoplastic death in the United States.

For many of the chemicals considered rodent carcinogens, there may be negative as well as positive tests. It is difficult to deal with negative results satisfactorily for several reasons, including the fact that some chemicals are tested only once or twice, while others are tested many times. The HERP index ignores negative tests. Where there is species variation in potency, use of the more sensitive species, as is generally done and as is done here, could introduce a tendency to overestimate possible hazards; however, for most chemicals that are positive in both species, the potency is similar in rats and mice (*57*). The HERP may provide a rough correlate of human hazard from chemical exposure; however, for a given chemical, to the extent that the potency in humans differs from the potency in rodents, the relative hazard would be different.

Quantitative uncertainties. Quantitative extrapolation from rodents to humans, particularly at low doses, is guesswork that we have no way of validating (*1, 5, 10, 11, 58*). It is guesswork because of lack of knowledge in at least six major areas: (i) the basic mechanisms of carcinogenicity; (ii) the relation of cancer, aging, and life-span (*1, 10, 42, 59*); (iii) the timing and order of the steps in the carcinogenic process that are being accelerated; (iv) species differences in metabolism and pharmacokinetics; (v) species differences in anticarcinogens and other defenses (*1, 60*); and (vi) human heterogeneity—for example, pigmentation affects susceptibility to skin cancer from ultraviolet light. These sources of uncertainty are so numerous, and so substantial, that only empirical data will resolve them, and little of this is available.

Uncertainties due to mechanism in multistage carcinogenesis. Several steps (stages) are involved in chemical carcinogenesis, and the dose-response curve for a carcinogen might depend on the particular stage(s) it accelerates (*58*), with multiplicative effects if several stages are affected. This multiplicative effect is consistent with the observation in human cancer that synergistic effects are common. The three steps of carcinogenesis that have been analyzed in most detail are initiation (mutation), promotion, and progression, and we discuss these as an aid to understanding aspects of the dose-response relation.

Mutation (or DNA damage) as one stage of the carcinogenic process is supported by various lines of evidence: association of active forms of carcinogens with mutagens (*61*), the changes in DNA sequence of oncogenes (*62*), genetic predisposition to cancer in human diseases such as retinoblastoma (*63*) or DNA-repair deficiency diseases such as xeroderma pigmentosum (*64*). The idea that genotoxic carcinogens might show a linear dose-response might be plausible if only the mutation step of carcinogenesis was accelerated and if the induction of repair and defense enzymes were not significant factors (*65*).

Promotion, another step in carcinogenesis, appears to involve cell proliferation, or perhaps particular types of cell proliferation (*66*), and dose-response relations with apparent thresholds, as indicated by various lines of evidence: (i) The work of Trosko *et al.* (*67*) on promotion of carcinogenesis due to interference with cell-cell communication, causing cell proliferation. (ii) Rajewsky's and other work indicating initiation by some carcinogenic agents appears to require proliferating target cells (*68*). (iii) The work of Farber *et al.* (*69*) on liver carcinogenesis supports the idea that cell proliferation (caused by partial hepatectomy or cell killing) can be an important aspect of hepatocarcinogenesis. They have also shown for several chemicals that hepatic cell killing shows a toxic threshold with dose. (iv) Work on carcinogenesis in the pancreas, bladder and stomach

lack the knowledge to do low-dose "risk assessment." We also are almost completely ignorant of the carcinogenic potential of the enormous background of natural chemicals in the world. For example, cholinesterase inhibitors are a common class of pesticides, both man-made and natural. Solanine and chaconine (the main alkaloids in potatoes) are cholinesterase inhibitors and were introduced generally into the human diet about 400 years ago with the dissemination of the potato from the Andes. They can be detected in the blood of almost all people (*12, 90*). Total alkaloids are present at a level of 15,000 μg per 200-g potato with not a large safety factor (about sixfold) from the toxic level for humans (*91*). Neither alkaloid has been tested for carcinogenicity. By contrast, malathion, the main synthetic organophosphate cholinesterase inhibitor in our diet (17 μg/day) (*16*), is not a carcinogen in rodents.

The idea that nature is benign and that evolution has allowed us to cope perfectly with the toxic chemicals in the natural world is not compelling for several reasons: (i) there is no reason to think that natural selection should eliminate the hazard of carcinogenicity of a plant toxin that causes cancer in old age past the reproductive age, though there could be selection for resistance to the acute effects of particular carcinogens. For example, aflatoxin, a mold toxin that presumably arose early in evolution, causes cancer in trout, rats, mice, and monkeys, and probably people, though the species are not equally sensitive. Many of the common metal salts are carcinogens (such as lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) despite their presence during all of evolution. (ii) Given the enormous variety of plant toxins, most of our defenses may be general defenses against acute effects, such as shedding the surface lining of cells of our digestive and respiratory systems every day; protecting these surfaces with a mucin layer; having detoxifying enzymes that are often inducible, such as cytochrome P-450, conjugating enzymes, and glutathione transferases; and having DNA repair enzymes, which would be useful against a wide variety of ingested toxic chemicals, both natural and synthetic. Some human cancer may be caused by interfering with these normal protective systems. (iii) The human diet has changed drastically in the last few thousand years, and most of us are eating plants (such as coffee, potatoes, tomatoes, and kiwi fruit) that our ancestors did not. (iv) Normal metabolism produces radiomimetic mutagens and carcinogens, such as hydrogen peroxide and other reactive forms of oxygen. Though we have defenses against these agents, they still may be major contributors to aging and cancer. A wide variety of external agents may disturb this balance between damage and defense (*12, 42*).

Implications for Decision-Making

For all of these considerations, our scale is not a scale of risks to humans but is only a way of setting priorities for concern, which should also take into account the numbers of people exposed. It should be emphasized that it is a linear scale and thus may overestimate low potential hazards if, as we argue above, linearity is not the normal case, or if nongenotoxic carcinogens are not of very much concern at doses much below the toxic dose.

Thus, it is not scientifically credible to use the results from rodent tests done at the MTD to directly estimate human risks at low doses. For example, an EPA "risk assessment" (*92*) based on a succession of worst case assumptions (several of which are unique to EDB) concluded that EDB residues in grain (HERP = 0.0004%) could cause 3 cases of cancer in 1000 people (about 1% of all U.S. cancer). A consequence was the banning of the main fumigant in the country. It would be more reasonable to compare the possible hazard of EDB residues to that of other common possible hazards. For example, the aflatoxin in the average peanut butter sandwich, or a raw mushroom, are 75 and 200 times, respectively, the possible hazard of EDB. Before banning EDB, a useful substance with rather low residue levels, it might be reasonable to consider whether the hazards of the alternatives, such as food irradiation, or the consequences of banning, such as increased mold contamination of grain, pose less risk to society. Also, there is a disparity between OSHA not regulating worker exposures at a HERP of 140%, while the EPA bans the substance at a HERP of 0.0004%. In addition, the FDA allows a possible hazard up to a HERP of 0.3% for peanut butter (20 ppb), and there is no warning about buying comfrey pills.

Because of the large background of low-level carcinogenic and other (*93*) hazards, and the high costs of regulation, priority setting is a critical first step. It is important not to divert society's attention away from the few really serious hazards, such as tobacco or saturated fat (for heart disease), by the pursuit of hundreds of minor or nonexistent hazards. Our knowledge is also more certain about the enormous toll of tobacco—about 350,000 deaths per year (*1, 2*).

There are many trade-offs to be made in all technologies. Trichloroethylene and tetrachloroethylene (perchloroethylene) replaced hazardous flammable solvents. Modern synthetic pesticides displaced lead arsenate, which was a major pesticide before the modern chemical era. Lead and arsenic are both natural carcinogens. There is also a choice to be made between using synthetic pesticides and raising the level of plants' natural toxins by breeding. It is not clear that the latter approach, even where feasible, is preferable. For example, plant breeders produced an insect-resistant potato, which has to be withdrawn from the market because of its acute toxicity to humans due to a high level of the natural plant toxins solanine and chaconine (*12*).

This analysis on the levels of synthetic pollutants in drinking water and of synthetic pesticide residues in foods suggests that this pollution is likely to be a minimal carcinogenic hazard relative to the background of natural carcinogens. This result is consistent with the epidemiologic evidence (*1*). Obviously prudence is desirable with regard to pollution, but we do need to work out some balance between chemophobia with its high costs to the national wealth, and sensible management of industrial chemicals (*94*).

Human life expectancy continues to lengthen in industrial countries, and the longest life expectancy in the world is in Japan, an extremely crowded and industrialized country. U.S. cancer death rates, except for lung cancer due to tobacco and melanoma due to ultraviolet light, are not on the whole increasing and have mostly been steady for 50 years. New progress in cancer research, molecular biology, epidemiology, and biochemical epidemiology (*95*) will probably continue to increase the understanding necessary for lengthening life-span and decreasing cancer death rates.

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96. A national survey of U.S. drinking water supplies identified the concentrations of about 20 organic compounds. The mean total trihalomethane concentration was 117 μg/liter, with the major component, chloroform, present at a mean concentration of 83 μg/liter (83 ppb). Raw water that is relatively free of organic matter results in drinking water relatively free of trihalomethanes after chlorination. These studies are reviewed in S. J. Williamson, *The Science of the Total Environment* **18**, 187 (1981).
97. Public and private drinking water wells in Santa Clara Valley, California, have been found to be contaminated with a variety of halogenated hydrocarbons in small amounts. Among 19 public water system wells, the most commonly found contaminants were 1,1,1-trichloroethane (TCA), and 1,1,2-trichloro-1,2,2-trifluoroethane (Freon-113). TCA was found in 15 wells generally at concentrations of less than 50 ppb, though one well contained up to 8800 ppb, and Freon-113 was found in six wells at concentrations up to 12 ppb. Neither chemical has been adequately tested for carcinogenicity in long-term bioassays. In addition to these compounds, three wells also contained carcinogenic compounds at low concentrations. Water from public supply wells may be mixed with treated surface water before delivery, thus the concentrations of these compounds that people actually receive may be somewhat reduced. Thirty-five private drinking water supply wells were examined; the major contaminant was the carcinogen trichloroethylene (TCE), at levels up to 2800 ppb. TCA and Freon-113 were also found in some wells, at maximum levels of 24 ppb and 40 ppb, respectively. Though fewer people drink from private water wells, the contaminant concentrations may be higher because the water is not mixed with water from other sources [California Department of Health Services, California Regional Water Quality Control Board 2, Santa Clara County Public Health Department, Santa Clara Valley Water District, Environmental Protection Agency, *Ground Water and Drinking Water in the Santa Clara Valley: A White Paper* (1984), table 8]. Trichloroethylene may not be a carcinogen in humans at low doses [R. D. Kimbrough, F. L. Mitchell, V. N. Houk, *J. Toxicol. Environ. Health* **18**, 369 (1985)].
98. Contaminated drinking water in the area of Woburn, Massachusetts, was found to contain 267 ppb trichloroethylene, 21 ppb tetrachloroethylene, 12 ppb chloroform, 22 ppb trichlorofluoromethane, and 28 ppb 1,2-*trans*-dichloroethylene [S. W. Lagakos, B. J. Wessen, M. Zelen, *J. Am. Stat. Assoc.* **81**, 583 (1986)].
99. The amount of chloroform absorbed by a 6-year-old child in a chlorinated freshwater swimming pool has been estimated [J. A. Beech, *Med. Hypotheses* **6**, 303 (1980)]. Table 1 refers to the chloroform in an average pool (134 μg liter) and for a 37-kg child. Three other trihalomethanes were identified in these freshwater pools: bromoform, bromodichloromethane and chlorodibromomethane. C. Lahl, T. Vondracek, B. Gabel, B. Seidel, W. Thermann [*Water Res.* **15**, 803 (1981)] have estimated absorption in covered swimming pools.
100. J. McCann, L. Horn, J. Girman, A. V. Nero, in *Short-Term Bioassays in the Analysis of Complex Environmental Mixtures*, V. S. Sandhu, D. M. De Marini, M. J. Mass, M. M. Moore, J. L. Mumford, Eds. (Plenum, New York, in press). This estimate (Table 1) for formaldehyde in conventional homes, excludes foam-insulated houses and mobile homes. The figure is a mean of the median or mean of the reported samples in each paper. For benzene, the figure is a mean of all reported median or mean samples. The level of benzene in Los Angeles outdoor air is similar [U.S. EPA Office of Air Quality Planning and Standards, EPA 450/4-86-012, 1986].
101. The average adult daily PCB intake from fried estimated by the FDA in fiscal years 1981/1982 was 0.2 μg day^{-1}. Many sightly different PCB mixtures have been studied in long-term animal cancer bioassays; the calculation of TD$_{05}$ was from a test of Aroclor 1260 which was more potent than other PCBs [*14*].
102. The average consumption of EDB's residues in grains has been estimated by the EPA for adults as 0.006 μg kg^{-1} day^{-1} and for children as 0.013 μg kg^{-1} day^{-1} [U.S. EPA Office of Pesticide Programs, *Ethylene Dibromide (EDB) Scientific Support and Decision Document for Grain and Grain Milling Fumigation Uses* (8 February 1984)].
103. The leaves and roots of Russian comfrey are widely sold in health food stores and are consumed as a medicinal herb or salad plant or are brewed as a tea. Comfrey leaf has been shown to contain 0.01 to 0.15%, by weight, total pyrrolizidine alkaloids, with an average level of 0.05% for intermediate size leaves [C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, L. W. Smith, *Aust. J. Chem.* **33**, 1105 (1980)]. The main pyrrolizidine alkaloids present in comfrey leaves are echimidine and 7-acetylviposuamine, neither of which has been tested for carcinogenicity. Almost all tested 1,2-unsaturated pyrrolizidine alkaloids have been shown to be genotoxic and carcinogenic [H. Mori *et al.*, *Cancer Res.* **45**, 3125 (1985)]. Symphytine accounts for 5% of the total alkaloid in the leaves and has been shown to be carcinogenic [C. C. J. Culvenor *et al.*, *Experientia* **36**, 377 (1980)]. We assume that 1.5 g of intermediate size leaves are used per cup of comfrey tea (Table 1). The primary alkaloids in comfrey root are symphytine (0.6 g per kilogram of root) and echimidine (0.5 g per kilogram of root) [T. Furuya and M. Hikicha, *Phytochemistry* **10**, 2217 (1971)]. Comfrey-pepsin tablets (300 mg of root per tablet) have a recommended dose of one to three tablets three times per day. Comfrey roots and leaves both induce liver tumors in rats [I. Hirono, H. Mori, M. Haga, *J. Natl. Cancer Inst.* **61**, 865 (1978)], and the TD$_{05}$ value is based on these results. These pyrrolizidine alkaloids tested have been found to be at least

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DEPARTMENT OF BIOCHEMISTRY BERKELEY, CALIFORNIA 94720

June 26, 1987

Dr. Charles M. Benbrook
Executive Director
Board on Agriculture
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Dear Dr. Benbrook:

You have been criticizing our work erroneously, and this letter is a request to read our recent paper in Science more carefully, and to think more deeply about the implications for the NAS-NRC report on pesticides.

In the June issue of Insight magazine, you are quoted as saying, "I don't think there are any natural products that would come anywhere near the magnitude of the risk of EDB in oranges and grain at the levels it was found prior to its cancellation." One of the main points of our Science paper was to show that this is not true. The residue levels we used for EDB in grain were taken from the EPA document justifying the ban of EDB. These were actual levels on what the American public was consuming at the time of the ban. Our HERP index value for this intake, 0.0004%, is trivial compared to many commonly consumed natural substances reported in the table in Science. The residue of EDB on oranges is primarily on the skin, and the intake was even less than from grain. The HERP index is a ratio of the human exposure dose (in mg/kg/day) to the carcinogenic potency in rodents (in mg/kg/day) reported as a percentage.

In our paper we emphasized that the potential hazards from pesticide residues should be viewed in the context of many larger natural exposures and that it is not scientifically credible to use the results from rodent tests done at the MTD to directly estimate human risks at low doses. We said,

> "For example, an EPA "risk assessment" (92) based on a succession of worst case assumptions (several of which are unique to EDB) concluded that EDB residues in grain (HERP = 0.0004%) could cause 3 cases of cancer in 1000 people (about 1% of all U.S. cancer). A consequence was the banning of the main fumigant in the country. It would be more reasonable to compare the possible hazard of EDB residues to that of other common possible hazards. For example, the aflatoxin in the average peanut butter sandwich, or a raw mushroom, are 75 and 200 times, respectively,

the possible hazard of EDB. Before banning EDB, a useful substance with rather low residue levels, it might be reasonable to consider whether the hazards of the alternatives, such as food irradiation, or the consequences of banning, such as increased mold contamination of grain, pose less risk to society...."

The paper, and my previous paper in Science, also point out that we are eating 10,000 times more of nature's pesticides daily than man-made pesticides and that only a handful of these have been tested in animal cancer tests. The frequency of positive results in animal bioassays is high for both nature's pesticides and man-made pesticides (40-60%), so there is every reason to think we will find a whole new world of carcinogens among the natural chemicals when more are tested. We are slowly compiling a long list of the natural chemicals we think should be tested, and we are impressed with how large are the amounts ingested and how close most are to the toxic level. Our paper points out the case of solanine and chaconine:

"...Solanine and chaconine (the main alkaloids in potatoes) are cholinesterase inhibitors and were introduced generally into the human diet about 400 years ago with the dissemination of the potato from the Andes. They can be detected in the blood of almost all people (12,90). Total alkaloids are present at a level of 15,000 µg per 200-g potato with not a large safety factor (about sixfold) from the toxic level for humans (91). Neither alkaloid has been tested for carcinogenicity. By contrast, malathion, the main synthetic organophosphate cholinesterase inhibitor in our diet (17 µg/day)(16), is not a carcinogen in rodents."

"...There is also a choice to be made between using synthetic pesticides and raising the level of plants' natural toxins by breeding. It is not clear that the latter approach, even where feasible, is preferable. For example, plant breeders produced an insect-resistant potato, which had to be withdrawn from the market because of its acute toxicity to humans due to a high level of the natural plant toxins solanine and chaconine (12)."

Thus, in your report you point out that tomatoes are allowed to have the most residues, and you also say, "Advances in classical plant breeding...offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations if more profitable chemical controls are not available...." I don't think you would have made such a statement if you had read and absorbed my 1983 Science paper (Vol. 221, pp. 1256-1264). Of course, tomatine, one of the alkaloids in tomatoes, is a chemical, too. It is untested in rodent cancer bioassays and is present at 36,000 µg/100 g tomato and is orders of magnitude closer to the toxic level (as are solanine and chaconine) than are man-made pesticide residues.

In the New York Times you were quoted as dismissing our work because we didn't have the latest data. We are not certain whether you were referring to residue data or the results of animal bioassays. With respect to the residue levels we did use the latest published FDA data on actual pesticide residues found in food. Residue data was available for only a few of the chemicals that you evaluated in the NAS report. For our purposes, it would be useful to have more published data on actual residues. The methodology in your report did a different thing: hypothetical worst-case analyses assuming that every farmer used every possible allowable pesticide at the maximum allowable

residue levels. I do think, by the way, that it was quite useful and reasonable for you people to have analyzed permissible residue levels and thought there was much useful material in your report. We have used permissible levels for worker exposures in a recently submitted paper on PERP values [Permissible Exposure/Rodent Potency as contrasted with our HERP values (actual exposure)] for occupational exposures to carcinogens, which often come out extremely high, incidentally.

We, of course, realize that the latest actual exposure figures from the FDA which we quoted don't include every possible pesticide, but they are a reasonable attempt, and we haven't seen any results (including your own) that our estimate of 45 µg of possibly carcinogenic pesticide residues consumed in a day (assuming everything not tested will be a carcinogen) is going to be very far off. For comparison, we also mention in our paper that there are about 500 µg of carcinogens in a cup of coffee (hydrogen peroxide and methylglyoxal), 185 µg of carcinogenic formaldehyde in a slice of bread, 10 times more formaldehyde in a cola, 760 µg of carcinogenic estragole in a basil leaf, a gram of burnt material from cooking our food, nitrosamines formed in our gas ovens, etc.

With respect to animal bioassay data, the NAS report does calculate Q* with animal bioassay data that are not in the published literature and that we would like very much to have for our Carcinogenic Potency Database. Do you know how we might obtain these data? We have converted your Q* and TMRC values to approximate our PERP index, and we calculate that all of the permissible risks in the NAS report lumped together produce a PERP value about the equivalent of consuming (HERP) the alcohol in one glass of wine per week. This sort of comparative analysis, and not using the word "risk" for mathematical juggling in the dark, will help to prevent people from converting your numbers to absurdities. Lawrie Mott of the Natural Resources Defense Council, for example, was quoted by the New York Times as saying, "Using the worst-case risk estimates, the number of cancer cases caused by the 28 pesticides in this country is 1.46 million over the 70-year lifetime exposure. But...the risk numbers 'significantly understate' the perils of cancer to consumers...."

I am not terribly concerned, as pointed out in the paper, about the carcinogenic risks from basil leaves and peanut butter sandwiches, as I don't believe any of these hypothetical worst-case risks far from the toxic dose will have much relation to reality. Our paper discusses the work of Farber and others, which suggests that a mutated oncogene in the liver isn't enough for carcinogenesis and that you need clonal selection (promotion), which you can get through toxicity. I think one is commonly supplying toxicity in animal tests by using the maximum tolerated dose and therefore that the true dose response will fall off sharply with dose. I think we should be looking more for toxicity reactions (hepatitis B, alcoholic cirrhosis, sunburn, etc.) in human cancer.

I am becoming convinced, though I won't go into detail here, that attempting to regulate carcinogens at 10^{-6} (lifetime) hypothetical worst-case risks, though better than a Delaney approach, is counterproductive for several reasons. The world is full of risks much above that, so paying attention to minor risks diverts scientists and regulators from more serious and productive work, thus decreasing public health. Public health is also decreased when one confuses the public so that they lose sight of what is important in the

plethora of risks. Since epidemiological evidence on disease indicates that we should be eating more fruit and vegetables, not less, raising their prices may be costly in terms of public health. If the levels of natural pesticides are raised closer to the toxic level by plant breeding, an inevitable consequence of eliminating man-made pesticides, this will probably decrease public health as well.

I enclose a recent article on one of the most eminent epidemiologists' reservations about "risk assessment" and some of my writings that you should find of interest. I would appreciate a copy of the clarification letter you send to Insight about the quote I started this letter with. Do come visit if you are here in the Bay Area. We have some mutual interests to discuss. As an inducement, I'll tell you about the natural compound we are all eating in large amounts that has many of the properties of dioxin.

Yours truly,

Bruce N. Ames
Professor and Chairman

BNA/ssk
Enclosures
Peto
Water II
Science Review
Ranking

cc: National Research Council Committee
(w/enclosures)

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DEPARTMENT OF BIOCHEMISTRY BERKELEY, CALIFORNIA 94720

July 24, 1987

Dr. Charles M. Benbrook
Executive Director
Board on Agriculture
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Dear Dr. Benbrook:

In my letter to you of June 26, I would like to correct one sentence. We calculated the equivalent of all of your permissible hazards lumped together as the equivalent of the alcohol in 2 beers a year. This number was based on using the numbers from your Tables 3-17, 3-18, and 3-19. These Tables indicate the dose as mg pesticide. This is an error in your Tables, and our calculation is therefore incorrect. It should be mg/kg, which is indicated in your Appendix B. When we noticed the discrepancy, we made some phone calls to check which part of your report was correct and have determined that it is Appendix B. My sentence should therefore read:

> "We have converted your Q* and TMRC values to approximate our PERP index, and we calculate that all of the permissible risks in the NAS report lumped together produce a PERP value about the equivalent of consuming (HERP) the alcohol in one glass of wine per week."

I enclose a revised page 3 of my letter as a substitute for your files. I await your reply to my letter.

Yours truly,

Bruce Ames

Bruce N. Ames
Professor and Chairman

BNA/ssk
Enclosure

cc: National Research Council Committee
(w/enclosure)

NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue Washington D C 20418

BOARD ON AGRICULTURE

TELEPHONE
(202) 334-3062

August 3, 1987

Dr. Bruce Ames
Chairman
Department of Biochemistry
University of California - Berkeley
Berkeley, CA 94720

Dear Dr. Ames:

Thank you for your provocative letter of June 26. My apologies for not responding sooner--we have spent the last two weeks settling into a new building.

Your letter raises so many interesting issues and challenges, I hardly know where to begin. I am certain that your Science article stimulated thinking and research in the appropriate disciplines and that it will no doubt continue to be a topic for discussion and debate both in scientific and regulatory circles. The Board on Agriculture's recent report on pesticide residues in food will also be the topic of future analysis and debate. The end result of your article and our report should be a more informed judgment and rational regulation of possible carcinogenic substances in food.

Let me briefly clarify the objectives of the NRC report. The committee's charge was to analyze the impact of the Delaney Clause on the pesticide tolerance setting system and to provide EPA with a means to analyze these effects. It was not our objective to rank the relative risks of pesticides or foods based on actual residues. Data gaps prevent such a comparative risk assessment using actual or even anticipated residue data.

The worst-case rankings contained in the report are only meaningful when viewed in the larger context of the committee's charge. The worst-case risk methodologies underlying the committee's analysis were the only way the committee could empirically answer questions basic to its charge regarding the nature and distribution of potential oncogenic risk in different kinds of foods. The committee had no choice but to use EPA's TMRC exposure estimates in conducting its analysis. Actual residue data is available on relatively few pesticides, and often for only some of the crops on which these pesticides are registered. Selective incorporation of actual residue data for some of the 28 pesticides studied in depth would have biased the results.

Moreover, the committee lacked confidence in the consistency and representativeness of the "actual residue data." Depending upon who

requests or develops the data, the analytical methods and procedures underlying the measurement of "actual residue data" may differ markedly. You will soon discover this as you compile an actual residue database for pesticide risk assessment.

In view of these limitations, the committee decided after a year and a half of discussion that it had two options: It could report its analytical findings based on the TMRC methodology, or, it could include essentially no findings in the report, presenting only its sense of the distribution and potential risk from herbicides, insecticides, fungicides, old and new pesticides, and residues in raw versus processed foods. After considerable internal discussion, the committee was convinced of the validity of the report's basic findings despite the fact that the committee knew the data might be used to misrepresent the committee's findings. Moreover, the findings led directly to important recommendations which would have no basis without the justification inherent in the tables and analysis in Chapters 3, 4, and 5.

In your recent Science article, the analysis of pesticide exposure focuses on relatively few pesticides--those detected by FDA in one of its market basket surveys. You are aware, I am sure, of the many deficiencies in FDA's testing methods both in terms of sample size and residues detected. As a result, your conclusions are limited to the quality of this data. Likewise, the NRC report's "worst-case"/"permissible level" risk assessments have come under similar criticisms. We are all limited by the quality and completeness of data on pesticide toxicity and dietary exposure. The tables and lists presented in our report are all based on risks associated with permissible levels of residues. They are primarily intended to demonstrate the distribution of risk and the merit of distinguishing between possible "big" risks in contrast to certain "de minimus" risks, and to demonstrate to EPA the types of analyses that may be useful in devising a more rational regulatory program for pesticide residues in food.

The committee agrees that cancer risk from other sources is greater than risks posed by pesticides, but would argue that this conclusion is not particularly relevant to its charge, which was to offer EPA suggestions on how to assess options for regulating cancer causing pesticide residues in food. Whether cigarettes or comfrey tea present greater risks than pesticides is not germane to the analysis. It is, however, an issue readily addressed in the context of the NRC report's analytical framework, and the regulatory implications of which may be evaluated using the principles inherent in the report's recommendations. If a concensus emerges and cancer risk from natural contaminants or constituents in foods pose greater risk than pesticides, this recognition will challenge Congress, federal agencies, and the public to confront many basic assumptions about how public health can and should be improved.

The basic point of your letter, as I understand it, is that some natural carcinogens are much worse than most, if not all, tested synthetic chemicals. Such a judgment must ultimately rest upon knowledge of both dose and toxicological potency, and many other factors that may intervene in determining how humans respond to exposure to various agents. Some scientists also theorize that humans have developed a degree of "genetic resistance" to some natural carcinogens. I've read persuasive arguments on several sides of these issues, including the important points you and your colleagues made in response to letters following the 1983 Science article. I am not aware of recent evidence that has shifted markedly the center of these debates. I would greatly appreciate your views on significant new developments in the sciences underlying risk assessment and pertinent to these issues.

You state that regulatory actions against most pesticides are hard to justify in terms of relative risk reduction achieved. I am a strong believer in the concept of relative risk and attach a recent paper articulating in more detail how I envision relative risk decision-making within the context of FIFRA. I am most anxious, however, to gain a firmer sense of how fast a concensus within the scientific community might emerge in support of your basic hypothesis. If and when it does, the implications for EPA/FDA and FIFRA/FDCA will be profound, indeed almost unimagineable. I'm sure you and others will encounter a whole new set of challenges in forging a political concensus for fundamental change in regulatory priorities.

I'd like to raise a few questions regarding the substance of your letter. I am unsure of the exposure estimates used to derive HERP rankings. In your letter you say that if every pesticide not tested is assumed carcinogenic, then a reasonable estimate of carcinogenic pesticide residue in the diet will be 45 ug. Is this per day for an "average" diet? How did you calculate this number? In your most recent Science article, you note that exposure to three noncarcinogenic compounds is 105 ug; more than twice the exposure you estimate for all carcinogenic and all untested pesticides (based on the assumption that they will all be positive). Your method of estimating dietary exposure to pesticides from FDA market basket results is one way to develop a rough estimate of exposure. The completeness and accuracy of this method is constrained by the extent of coverage and accuracy of the FDA surveys.

Another perspective on total exposure can be gained by working back from "worst-case" estimates. For the 28 pesticides we studied in depth, total "worst-case" TMRC exposure for a 70 kg adult is 53.7 mg per day. If actual residues are 10% of tolerance levels, and if 10% of the possible acres are treated on average, "anticipated" total exposure would be 0.537 mg/day. Different assumptions will, of course, yield different estimates. Your 45 ug estimate, if I interpret it correctly, would arise from an assumption that about 1% of acres are treated, with residues at 10% of the

tolerance level. One must also consider wide variation in exposure based on regional- or age-based differences in diet. The TMRC calculation assumes an average adult diet with no regional or other variation.

You may note that EPA's special review and/or re-registration documents, another important source of more accurate exposure data on pesticides, indicate that in general "most likely" or "anticipated residue" levels are between 1/100 and 1/10 of TMRC exposure estimates. Some major products of concern--the EBDC's, benomyl, alachlor, for example--have anticipated residues at about 10% of TMRC. Residues of certain compounds, such as the EBDC metabolite and conversion product ETU, will increase during cooking and after ingestion, making assessment of actual exposure and risk more complex.

As you note in your letter, it is incorrect to assume that absence of detection by FDA is proof of absence from the food supply. Of the 28 oncogenic pesticides we studied in depth (for which EPA could supply Q^*'s), about one-third are not detected by either of the two methods routinely used by FDA. At least 14 of the 53 pesticides on the so-called Waxman list are not detected by FDA's routine multiresidue screens. A recent GAO report documents the range of sensitivity of FDA's residue tests (Pesticides: Need to Enhance FDA's ability to Protect the Public from Illegal Residues. GAO/RCED 8707. October 1986.). Most importantly, FDA's multiresidue tests do not cover some of the most worrisome and widely used oncogenic pesticides, particularly fungicides used on fruits and vegetables. Furthermore, in no case does FDA look for oncogenic metabolites or conversion products that are known or suspected oncogens.

I am intrigued by your method for calculating the TD_{50} index. Would you please provide, as an example, your calculations for EDB, and formaldehyde, and for the pesticides atrazine and alachlor (summary data from these two pesticides is enclosed). In particular, I am not certain how the TD_{50} is extrapolated from the animal data and how several studies are combined. Is the least squares method always used? Although I do not thoroughly understand the TD_{50}, I agree that a measurement of its type will be useful for ranking the potency of carcinogenic compounds and also in the formulation of sound public policy.

I maintain that worst-case estimates are not entirely irrelevant scientifically or in a regulatory context. They serve as an estimate of potential risk among more highly sensitive or highly exposed population groups, i.e. sensitive individuals who eat a lot of local fresh fruits and vegetables, all of which may have been treated with a specific set of pesticides, sometimes at rates and in ways that increase anticipated residue levels above "normal" levels. In future work, the Board hopes to push ahead with the incorporation of "actual" or "anticipated" residue data in our database. We'd like to add water-based exposure to our dataset and undertake a study on exposure and hazard for children (proposal enclosed as approved by the NRC).

I'd like to discuss a joint effort to expand and refine the assessment and comparison of natural versus synthetic risks. Upon reviewing your HERP calculation, I suggest developing a modified HERP index based on a Q^* potency indicator and our collective data sets for additional pesticides and natural contaminants. The goal of this exercise would be to compare natural and chemical risks using analytically comparable methods and consistent assumptions in exposure estimates. The Board on Agriculture is meeting in November in conjunction with the opening ceremonies for the Plant Gene Expression Center in Berkeley. Perhaps we can get together that week to discuss this venture further.

We would be glad to share with you and your colleagues other data in our files on pesticides. I might note that a member of the Board's staff, Richard Wiles, has spoken with Lois Swirsky Gold concerning EPA's Q^*'s and their derivation from animal data. Please give me a call at 202/334-3062 so we can discuss these intriguing questions in greater depth and the possibility of getting together in Berkeley.

Sincerely,

Charles Benbrook

Charles M. Benbrook
Executive Director

Attachments

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 128, No. 4
Printed in U.S.A.

A CASE-CONTROL STUDY OF BRAIN GLIOMAS AND OCCUPATIONAL EXPOSURE TO CHEMICAL CARCINOGENS: THE RISK TO FARMERS

MASSIMO MUSICCO,[1] MILENA SANT,[2] SILVIA MOLINARI,[1]
GRAZIELLA FILIPPINI,[1] GEMMA GATTA,[2] AND FRANCO BERRINO[2]

Musicco, M. (National Research Council, 20133 Milano, Italy), M. Sant, S. Molinari, G. Filippini, G. Gatta, and F. Berrino. A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. *Am J Epidemiol* 1988;128:778–85.

During 1983 and 1984, 240 newly diagnosed cases of brain glioma and 742 controls (465 non-glioma nervous system tumors and 277 patients with other neurologic diseases) were recruited and interviewed in the neurologic and neurosurgical departments of two hospitals in Milan, Italy. The occupational histories of cases and controls were compared, and relative risk estimates, adjusted for sex, age, residence, and socioeconomic status, were computed using the Mantel-Haenszel method. A statistically significant risk increase was found for farmers (relative risk (RR) = 1.6, $p = 0.0025$). This risk increase was attributable to those farmers who reported the use of chemicals (insecticides or fungicides, herbicides, and fertilizers). Among the three groups of investigated agrochemicals, only the use of insecticides or fungicides was associated with a significant increase in relative risk (RR = 2.0, $p = 0.006$). Many farmers exposed to fungicides reported the use of commercial compounds of copper sulfate. Some of these compounds contain methyl urea, which has a specific carcinogenic effect on the nervous system in animals. These data suggest that the occupational exposure of farmers to agrochemicals might be responsible for the observed excess risk of brain glioma in farmers.

agriculture; glioma; insecticides; occupational diseases

The evidence of the existence of chemical carcinogens for the nervous system is supported by a large amount of data. In the experimental setting, some *N*-nitroso compounds (mainly *N*-nitroso alkyl ureas) are capable of inducing tumors of the nervous system in animals (1). In humans, a number of observational studies and case reports have reported associations between brain tumors and occupational and nonoccupational exposure to vinyl chloride (2–4), *N*-nitroso compounds (5–7), pesticides (8–10) and formaldehyde (11, 12). A recent hospital-based case-control study (13) showed an increased relative risk for occupation in the rubber industry and for some indicators of dietary and nondietary exposure to *N*-nitroso compounds, together with a protective effect of fruit.

Received for publication March 3, 1987, and in final form November 25, 1987.

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(The complete article is held in the committee files.)

Herbicides and Cancer:
A Review and Discussion of Methodologic Issues

Aaron Blair and Shelia Hoar Zahm

Occupational Studies Section

National Cancer Institute

June, 1988

Presented at the International Symposium

on

Occupational Cancer Epidemiology

Vancouver, British Columbia

In the late 1970s and early 1980s, investigators in Sweden reported over 5-fold risks for soft-tissue sarcoma and lymphoma among persons exposed to phenoxyacetic acid herbicides and chlorophenols (10-12). The possibility that these widely used and important commercial chemicals might be human carcinogens prompted a number of epidemiologic investigations. Reports from over 20 additional studies are now available. Results from these investigations, which employed cohort and case-control designs, have not been consistent, but as of yet the discrepancies cannot be explained. The purpose of this paper is to provide a brief overview of available findings, to note consistencies and inconsistencies, to consider methodologic issues, particularly for case-control studies that might account for these inconsistencies, and to identify areas of research needing development.

(The complete report is held in the committee files.)

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DEPARTMENT OF BIOCHEMISTRY BERKELEY, CALIFORNIA 94720

July 24, 1987

Dr. Charles M. Benbrook
Executive Director
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2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Dear Dr. Benbrook:

In my letter to you of June 26, I would like to correct one sentence. We calculated the equivalent of all of your permissible hazards lumped together as the equivalent of the alcohol in 2 beers a year. This number was based on using the numbers from your Tables 3-17, 3-18, and 3-19. These Tables indicate the dose as mg pesticide. This is an error in your Tables, and our calculation is therefore incorrect. It should be mg/kg, which is indicated in your Appendix B. When we noticed the discrepancy, we made some phone calls to check which part of your report was correct and have determined that it is Appendix B. My sentence should therefore read:

> "We have converted your Q* and TMRC values to approximate our PERP index, and we calculate that all of the permissible risks in the NAS report lumped together produce a PERP value about the equivalent of consuming (HERP) the alcohol in one glass of wine per week."

I enclose a revised page 3 of my letter as a substitute for your files. I await your reply to my letter.

Yours truly,

Bruce Ames

Bruce N. Ames
Professor and Chairman

BNA/ssk
Enclosure

cc: National Research Council Committee
(w/enclosure)

UNIVERSITY OF CALIFORNIA, BERKELEY

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DEPARTMENT OF BIOCHEMISTRY

BERKELEY, CALIFORNIA 94720

June 26, 1987

Dr. Charles M. Benbrook
Executive Director
Board on Agriculture
National Research Council
2101 Constitution Avenue, N.W.
Washington, D.C. 20418

Dear Dr. Benbrook:

You have been criticizing our work erroneously, and this letter is a request to read our recent paper in Science more carefully, and to think more deeply about the implications for the NAS-NRC report on pesticides.

In the June issue of Insight magazine, you are quoted as saying, "I don't think there are any natural products that would come anywhere near the magnitude of the risk of EDB in oranges and grain at the levels it was found prior to its cancellation." One of the main points of our Science paper was to show that this is not true. The residue levels we used for EDB in grain were taken rrom the EPA document justifying the ban of EDB. These were actual levels on what the American public was consuming at the time of the ban. Our HERP index value for this intake, 0.0004%, is trivial compared to many commonly consumed natural substances reported in the table in Science. The residue of EDB on oranges is primarily on the skin, and the intake was even less than from grain. The HERP index is a ratio of the human exposure dose (in mg/kg/day) to the carcinogenic potency in rodents (in mg/kg/day) reported as a percentage.

In our paper we emphasized that the potential hazards from pesticide residues should be viewed in the context of many larger natural exposures and that it is not scientifically credible to use the results from rodent tests done at the MTD to directly estimate human risks at low doses. We said,

> "For example, an EPA "risk assessment" (92) based on a succession of worst case assumptions (several of which are unique to EDB) concluded that EDB residues in grain (HERP = 0.0004%) could cause 3 cases of cancer in 1000 people (about 1% of all U.S. cancer). A consequence was the banning of the main fumigant in the country. It would be more reasonable to compare the possible hazard of EDB residues to that of other common possible hazards. For example, the aflatoxin in the average peanut butter sandwich, or a raw mushroom, are 75 and 200 times, respectively,

the possible hazard of EDB. Before banning EDB, a useful substance with rather low residue levels, it might be reasonable to consider whether the hazards of the alternatives, such as food irradiation, or the consequences of banning, such as increased mold contamination of grain, pose less risk to society...."

The paper, and my previous paper in Science, also point out that we are eating 10,000 times more of nature's pesticides daily than man-made pesticides and that only a handful of these have been tested in animal cancer tests. The frequency of positive results in animal bioassays is high for both nature's pesticides and man-made pesticides (40-60%), so there is every reason to think we will find a whole new world of carcinogens among the natural chemicals when more are tested. We are slowly compiling a long list of the natural chemicals we think should be tested, and we are impressed with how large are the amounts ingested and how close most are to the toxic level. Our paper points out the case of solanine and chaconine:

"...Solanine and chaconine (the main alkaloids in potatoes) are cholinesterase inhibitors and were introduced generally into the human diet about 400 years ago with the dissemination of the potato from the Andes. They can be detected in the blood of almost all people (12,90). Total alkaloids are present at a level of 15,000 μg per 200-g potato with not a large safety factor (about sixfold) from the toxic level for humans (91). Neither alkaloid has been tested for carcinogenicity. By contrast, malathion, the main synthetic organophosphate cholinesterase inhibitor in our diet (17 μg/day)(16), is not a carcinogen in rodents."

"...There is also a choice to be made between using synthetic pesticides and raising the level of plants' natural toxins by breeding. It is not clear that the latter approach, even where feasible, is preferable. For example, plant breeders produced an insect-resistant potato, which had to be withdrawn from the market because of its acute toxicity to humans due to a high level of the natural plant toxins solanine and chaconine (12)."

Thus, in your report you point out that tomatoes are allowed to have the most residues, and you also say, "Advances in classical plant breeding...offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations if more profitable chemical controls are not available...." I don't think you would have made such a statement if you had read and absorbed my 1983 Science paper (Vol. 221, pp. 1256-1264). Of course, tomatine, one of the alkaloids in tomatoes, is a chemical, too. It is untested in rodent cancer bioassays and is present at 36,000 μg/100 g tomato and is orders of magnitude closer to the toxic level (as are solanine and chaconine) than are man-made pesticide residues.

In the New York Times you were quoted as dismissing our work because we didn't have the latest data. We are not certain whether you were referring to residue data or the results of animal bioassays. With respect to the residue levels we did use the latest published FDA data on actual pesticide residues found in food. Residue data was available for only a few of the chemicals that you evaluated in the NAS report. For our purposes, it would be useful to have more published data on actual residues. The methodology in your report did a different thing: hypothetical worst-case analyses assuming that every farmer used every possible allowable pesticide at the maximum allowable

residue levels. I do think, by the way, that it was quite useful and reasonable for you people to have analyzed permissible residue levels and thought there was much useful material in your report. We have used permissible levels for worker exposures in a recently submitted paper on PERP values [Permissible Exposure/Rodent Potency as contrasted with our HERP values (actual exposure)] for occupational exposures to carcinogens, which often come out extremely high, incidentally.

We, of course, realize that the latest actual exposure figures from the FDA which we quoted don't include every possible pesticide, but they are a reasonable attempt, and we haven't seen any results (including your own) that our estimate of 45 µg of possibly carcinogenic pesticide residues consumed in a day (assuming everything not tested will be a carcinogen) is going to be very far off. For comparison, we also mention in our paper that there are about 500 µg of carcinogens in a cup of coffee (hydrogen peroxide and methylglyoxal), 185 µg of carcinogenic formaldehyde in a slice of bread, 10 times more formaldehyde in a cola, 760 µg of carcinogenic estragole in a basil leaf, a gram of burnt material from cooking our food, nitrosamines formed in our gas ovens, etc.

With respect to animal bioassay data, the NAS report does calculate Q* with animal bioassay data that are not in the published literature and that we would like very much to have for our Carcinogenic Potency Database. Do you know how we might obtain these data? We have converted your Q* and TMRC values to approximate our PERP index, and we calculate that all of the permissible risks in the NAS report lumped together produce a PERP value about the equivalent of consuming (HERP) the alcohol in one glass of wine per week. This sort of comparative analysis, and not using the word "risk" for mathematical juggling in the dark, will help to prevent people from converting your numbers to absurdities. Lawrie Mott of the Natural Resources Defense Council, for example, was quoted by the New York Times as saying, "Using the worst-case risk estimates, the number of cancer cases caused by the 28 pesticides in this country is 1.46 million over the 70-year lifetime exposure. But...the risk numbers 'significantly understate' the perils of cancer to consumers...."

I am not terribly concerned, as pointed out in the paper, about the carcinogenic risks from basil leaves and peanut butter sandwiches, as I don't believe any of these hypothetical worst-case risks far from the toxic dose will have much relation to reality. Our paper discusses the work of Farber and others, which suggests that a mutated oncogene in the liver isn't enough for carcinogenesis and that you need clonal selection (promotion), which you can get through toxicity. I think one is commonly supplying toxicity in animal tests by using the maximum tolerated dose and therefore that the true dose response will fall off sharply with dose. I think we should be looking more for toxicity reactions (hepatitis B, alcoholic cirrhosis, sunburn, etc.) in human cancer.

I am becoming convinced, though I won't go into detail here, that attempting to regulate carcinogens at 10^{-6} (lifetime) hypothetical worst-case risks, though better than a Delaney approach, is counterproductive for several reasons. The world is full of risks much above that, so paying attention to minor risks diverts scientists and regulators from more serious and productive work, thus decreasing public health. Public health is also decreased when one confuses the public so that they lose sight of what is important in the

plethora of risks. Since epidemiological evidence on disease indicates that we should be eating more fruit and vegetables, not less, raising their prices may be costly in terms of public health. If the levels of natural pesticides are raised closer to the toxic level by plant breeding, an inevitable consequence of eliminating man-made pesticides, this will probably decrease public health as well.

I enclose a recent article on one of the most eminent epidemiologists' reservations about "risk assessment" and some of my writings that you should find of interest. I would appreciate a copy of the clarification letter you send to Insight about the quote I started this letter with. Do come visit if you are here in the Bay Area. We have some mutual interests to discuss. As an inducement, I'll tell you about the natural compound we are all eating in large amounts that has many of the properties of dioxin.

Yours truly,

Bruce N. Ames
Professor and Chairman

BNA/ssk
Enclosures
Peto
Water II
Science Review
Ranking

cc: National Research Council Committee
(w/enclosures)

Mr. BENBROOK. Just to help put things in perspective somewhat, the best job we can do, given the state of epidemiology, is estimate that for different cancers, we are aware of different causative agents, but as sort of a general matter, about 30—and perhaps as high as 50 percent of cancers are caused by something in the diet, dietary factors, whether it is fat, saturated fat, total calories, cholesterol or something in the fat, or pesticides, no one really knows how to break down what it is about the diet, whether it is calories, et cetera, that is the causative agent and I think it is going to be quite a long time before that science is fully clarified.

Mr. BROWN. The information that you can submit will be helpful. It goes beyond just natural or man-made. It goes to the point that there are man-made carcinogens that impact upon human beings other than through the route of diet, or from the results of the application of pesticides. There are a lot of other ways in which man-made carcinogens can impact upon human beings.

Mr. Grandy, do you have any questions?

Mr. GRANDY. Yes, I do, Mr. Chairman. Thank you.

Dr. Benbrook, I wanted to pursue one aspect of the Delaney Clause which I find confusing and perhaps you could give us your views on this.

It is my understanding that under the Delaney Clause, it would be possible to reregister and authorize as supposedly safe a pesticide that contained a mild carcinogen, and at the same time—in other words, you would eliminate a mild carcinogen, consider it maybe more safe, and at the same time, as you are eliminating that mild carcinogen, you are avoiding or accepting into the food supply a pesticide which may not be a carcinogen, but may be more dangerous. Is that correct?

Mr. BENBROOK. That is correct, Mr. Grandy. In fact, you could be allowing continued use of a carcinogen that is clearly more potent than the one that you are not allowing on the market——

Mr. GRANDY. Could you give the committee an example.

Mr. BENBROOK. Let me give you a specific example. There is a particular fungicide, a new fungicide, that was developed because the agrichemical industry has known for years that most of our current fungicides are quite toxic. Eight of 11 are carcinogens. One was developed by a particular company that, when fully tested, caused very mild—some would say equivocal carcinogenic effect. The data was such that scientists could argue back and forth whether it poses any carcinogenic risk, but if you did a risk assessment upon it and came up with a risk number for this fungicide's use on hops, the carcinogenic risk that this new fungicide would have posed was on the order of—if my memory serves me correctly—of a 10 to the minus 8 or 9, so this would be 1/100th of a 1 in a million negligible risk standard.

At the same time, the major older fungicide that remains in use on hops today poses a risk of approximately 10 to the minus 4, or 1 in 10,000. The reason that the new product was not allowed on the market is that it was fully tested before EPA made a regulatory decision to register its use on hops, and it was determined that the level of the residue of the fungicide in the hops concentrates as you manufacture beer, thereby triggering the Delaney Clause which says there shall be zero, or no risk added to the food supply. But

the older product, which wasn't tested until the early 1970's and was in use 20 years before it ever was tested for cancer, it remains on the market basically untouched by the Delaney Clause because the Delaney Clause has never once been applied retroactively to any product on the market.

This is what gave rise to the Academy recommendation that whatever standard you have, it should be applied consistently to both new and old pesticides, because what you have now is a serious bias against anything new.

Mr. GRANDY. So do I understand Roberts-Brown to address that through the reregistration and registration equivalent?

Mr. BENBROOK. It does it there and it also does it by establishing a consistent negligible-risk standard to be applied whenever evaluating dietary cancer risk.

Mr. GRANDY. Can you contrast that with the Waxman approach to the same problem?

Mr. BENBROOK. The Waxman approach shares many features, but it is much more complex an approach. The Waxman bill establishes a discrete quantitative standard of 10 to the minus 6, and it also has rather precise language on how that has to be calculated. It also makes reference to the most sensitive population group which will cause the agency to have to determine what part of the population might consume most of the food, or might be most susceptible. In most cases, that is going to be infants and children.

So, because the Waxman bill has many other features, both technical and procedural, it is difficult for me to contrast that. However, it is certainly possible that if all existing pesticides were brought simultaneously into compliance with the Waxman bill, you would also eliminate this old-versus-new bias.

My concern is, and the concern of many people who have studied both bills, is that while the two bills may allow EPA to go in much the same direction, the procedural difficulty of the Waxman bill may make it harder to get there.

There is a considerable history behind this concern. Mr. Brown has been through many oversight hearings about problems with the special review process, problems with market data from IBT. When serious problems arise, Congress has tended to pass a more complicated, procedurally encumbered process to try to force EPA to go in a given direction, but what happens is that EPA just gets bogged down because it is very difficult to do precisely what the legislation says.

I think that is the principal concern the Congress ought to have in evaluating a simple approach like the Roberts-Brown bill, versus a procedurally quite inflexible and complicated approach as reflected in the Waxman bill.

Mr. GRANDY. But, if I can just conclude, based on what you said earlier about the incongruities of the Delaney Clause in terms of zeroing in on what is dangerous and perhaps what is not, would you conclude that the Roberts-Brown is perhaps a safer vehicle when it is all tallied because you are moving to those areas of risk, perhaps, with more flexibility?

Mr. BENBROOK. I think that the Roberts-Brown bill is going to get the agency much quicker to a point where it can take action.

Now, whether it does so at that point is going to be a matter of the political will.

What is essential is that there has to be a consensus reached within the Congress on what the rules are, and the process for trying to unravel this problem. My biggest concern about the Waxman bill is that even if the Congress reached a judgment, consensus that that is the way to go, it might prove a very circuitous route to get to the ultimate objective.

Mr. GRANDY. Thank you, Mr. Chairman.

Mr. BROWN. Thank you, Mr. Grandy.

Dr. Benbrook, I have no further questions for you. We appreciate your being here this morning.

Mr. Roberts has an additional question.

Mr. ROBERTS. Dr. Moore did testify at our last hearing that the science of risk assessment is very fluid, and if we were to embrace—

A rigid definition and descriptive approach I think we might be unwittingly substituting a new set of problems for the old sent of problems that we find in regards to the rigid definition found in the Delaney Cause.

I know that there are those who will say that our approach is not sufficient for a regulator to fulfill the policy directives, i.e., public safety, at the EPA. And to answer that question, I suppose—and, as I pointed out, I feel the other approach simply is too complex, will lead to more problems than answers. So, to answer that question, I suppose I would like to ask you to describe whether the prevailing thought that you have stated here today on what is a risk that is very negligible, is it sufficiently thought out or, to be more accurate, will it be accepted by a majority of scientists and, more importantly, by the public?

And in this regard, perceived risk by the public in regards to what is in the national media, and I am not trying to perjure that one way or the other, and what is a real risk both short term and long term may be, you know, very different. I have an article here from a March publication, by a Mr. Mike Cummings, saying "Daring To Live," and he points out research respondents rank risks. He has a civic organization, college students, members of a business club, and then experts. You are in that latter category.

And they rank the top 30 risks to society. No. 1 by the college students and by the civic organization is nuclear power; No. 1 by the experts is motor vehicles, in terms of an immediate problem. Now I could go through the whole list here, everything from swimming and skiing and X-rays and even contraceptives, and we are going to leave that one alone this morning, and all of that, even power mowers. But you can see the perceived risk and then the actual risk. And Lord knows, we have tried to define the actual risk here with these many hearings as long as I can remember.

Are we ready to go to a negligible risk standard to get the kind of public acceptance necessary to back that kind of confidence? Is it possible?

Mr. BENBROOK. Mr. Roberts, you are very perceptive in noting that this is not going to be an easy road to travel regardless of what piece of legislation this Congress or the next one might craft in this area, or regardless of the guidance provided to the EPA and

regardless of whatever actions EPA might take. There is going to remain in our society considerable difference of opinion in terms of the willingness of people to accept involuntary risks, of which pesticide residues in food is clearly a principal example. So, the controversy is not going to evaporate under any circumstances.

However, to answer your question directly, yes, I think that it is possible for EPA to make and take regulatory actions based on a negligible risk standard that will command the confidence and respect of both the scientific community and the public. And, Mr. Roberts, they have done it. The current EPA in the last 6 or 8 years have taken a few such actions which appear to be inconsistent with the Delaney Clause, but they took them anyway and they published the basis of their judgment in the Federal Register, and people basically accepted it.

I think it is clear where the problem will arise. There are lots of instances where people will readily agree that the risks are clearly so small that one should not be worried about them. But in a few other instances, people will agree that risks are clearly great enough that something should be done; hence, EPA will take action to reduce risks or a company will voluntarily withdraw a registration of a pesticide. There have been examples of both. But in the middle—between clearly negigible and unarguably serious risks—there are going to remain certain instances where it becomes a matter of considerable scientific uncertainty about what the risks really are and hence, ultimately, a political judgment on how risk adverse regulatory agencies ought to be.

But I do think that there is a reasonably well defined notion of what negligible risk is amongst Federal regulatory agencies—not just pesticides, but OSHA and FDA and across the board—and the ability of EPA to defend such actions both in the court of public opinion and in courts of law. However, the debate is going to go on.

Mr. ROBERTS. One follow-up question, Mr. Chairman, and I will make it short.

Do we need a number in order to quantify and build that kind of confidence? And then I guess that depends on your point of view if, in fact, you are going to say that Diminicide should not be used on a crop like peanuts and point out the risk involved in extensive tests with laboratory animals, and that the risk is, as you say, 10 to the minus whatever it is. Some people might say yes, and some people might say no, I don't want to take that chance, and that we shouldn't take that chance.

A colleague of mine on the Tobacco and Peanuts Subcommittee did a little research and pointed out that the average human consumption to the degree that was fed to the laboratory animal, i.e., the lab rat, that an individual would have to eat 600 pounds of peanut butter a day in order to receive that kind—or that kind of level.

Now, if you pose it in that context why people are going to say, "Well, that's ridiculous and I'll keep on eating, you know, Peter Pan," and the schoolchildren of America will continue to eat their peanut butter sandwiches. And that is what worries me.

Do we need a number? I think numbers pose a greater problem than what we are trying to accomplish in the bill.

Mr. BENBROOK. Well, I think that as a practical matter there is such a degree of confluence, if you will, in the regulatory actions of different Federal agencies around a one in a million, or 10 to the minus 6 standard that that is sort of a generally accepted notion of a negligible risk level.

But I don't think that you have to specify in legislation what that number is. I think the regulatory agency is going to be bound by generally accepted public policy actions and legal precedents, and the views of the scientific community. It may tend to wiggle around between 10 to the minus 6 and 10 to the minus 4. It is in that range where it is going to be very difficult. But you picking 10 to the minus 5 isn't going to make it any easier.

Mr. ROBERTS. No. If you pick that, why somebody is going—you know, if you pick a number, somebody is going to say change the number.

Mr. BENBROOK. Yes.

Mr. ROBERTS. On both sides.

Mr. BENBROOK. Let me add one other thing. I know that it is reassuring to some to think of ridiculous examples of how much a person would have to eat to consume a dangerous amount of a pesticide. But I can tell you that as more and more actual residue data comes in, and as we look at dietary exposure to pesticides more realistically, the data will likely still lead to some instances where risks are well above a negligible level. This is why as more research is done, as EPA develops groundwater data and better tools, it is not going to make the problem go away. It will allow the agency to pinpoint where the problem is much more accurately, but still it will be there in some instances. And either the regulatory agencies are going to have to convince the public that that level of risk is acceptable, or steps will have to be taken to do something about it.

Mr. ROBERTS. But the bottom line is you get the bad actors out of there.

Mr. BENBROOK. That is right. And they are not going to go away by making comparisons to how much peanut butter you would have to eat to become ill, or receive the same dose fed to a rat in an animal experiment.

Mr. ROBERTS. I appreciate that. Thank you for your contribution, Chuck.

Mr. BENBROOK. Thank you.

Mr. BROWN. Chuck, before you leave, Mr. Stenholm has another question.

Mr. STENHOLM. Dr. Benbrook, can you recite or furnish for the record the occurrence rate of cancer over the last several years?

Mr. BENBROOK. The National Cancer Institute does an excellent report about every 5 years; it is kind of a statistical update of cancer trends, and they came out with one, I believe, earlier this summer or within the last year. Perhaps I could get the "Executive Summary" of that report and provide it for the record with the other material.

Mr. STENHOLM. I would like to include that information as an attachment to your testimony.

Mr. Roberts, you read the study that ranked nuclear power as the No. 1 threat.

It certainly would be my hope as a member of this committee that we could approach the subject of agricultural chemical utilization in a national manner. From a farmer's perspective, I do not know of a single producer that wants to continue to use any chemical that in fact is going to be injurious to himself, his family, his neighbors and those that will live on that farm after they leave.

We need to have a meeting of the minds between all parties that would like to lessen the dangers of pesticide contamination. However, we need to do so within the confines of common sense.

Mr. BROWN. Thank you very much, Mr. Stenholm. Thank you, Dr. Benbrook.

Our next witness is Dr. John McCarthy, director of scientific and regulatory affairs of the National Agricultural Chemicals Association.

STATEMENT OF JOHN F. McCARTHY, DIRECTOR, SCIENTIFIC AFFAIRS, NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION, ACCOMPANIED BY GEORGE L. ROLOFSON, MANAGER, GOVERNMENT RELATIONS, CIBA-GEIGY CORP.

Mr. MCCARTHY. Thank you, Mr. Chairman. Accompanying me here today is Dr. George Rolofson, from the Ciba-Geigy Corporation.

Mr. Chairman and members of the subcommittee, I am grateful for the opportunity to testify today on behalf of the National Agricultural Chemicals Association on H.R. 4937, the "Pesticide Food Safety Act of 1988."

I have a written statement which was submitted on July 28, which I request be entered into the record, and I will just summarize a few points here.

Mr. BROWN. Without objection, it will be in the record.

Mr. MCCARTHY. All members have a vital interest in this legislation and look forward to working with you and your subcommittee as it examines proposals to address the inconsistencies in EPA's legal authority in this area. Mr. Chairman, we must solve the inconsistency in our food safety laws. As the National Academy of Sciences reported in their report a year ago, it makes no sense to have a dual standard for raw and processed foods and for old and new pesticides which have been found to have an oncogenic response in laboratory animals.

From day one, we have consistently supported the basic recommendation contained in the NAS report: specifically, the concept of negligible risk applied across the board for raw and processed foods for both old and new pesticides where there is evidence of an oncogenic response in animal tests.

We have stressed, at the same time, the need for flexibility in the methodology for determining what constitutes a negligible risk. The process of risk assessment is complex. It is continuously evolving. New and improved methodology is appearing such that it would be a mistake to freeze the science through legislative action.

Mr. Chairman, the proposed legislation presented in title II provides not only a solution to the inconsistencies noted earlier, but provides the necessary flexibility to allow recent and future advances in the science of risk assessment to be applied to the regis-

PESTICIDE FOOD SAFETY ACT OF 1988

Invited Testimony
by
Charles M. Benbrook, Ph.D.*

Mr. Chairman, Congressman Roberts, and other members of the subcommittee, it is indeed a privilege and great honor to appear before you today to address the "Pesticide Food Safety Act of 1988."

This bill, and this hearing will hopefully mark an important step forward in the pesticide oversight and legislative activities of the DORFA subcommittee. During the subcommittee's extensive oversight of EPA regulatory actions and policy changes in 1982-1983, your efforts brought to light the Agency's ambivalence regarding how to treat residues of potentially cancer-causing pesticides in food. In 1983 Chairman Brown wrote the Agency, raising a variety of questions about EPA's interpretation of the Delaney Clause, its applicability to pesticide residues in food, and its plans for dealing with the dual standards for regulation inherent in the Food, Drug, and Cosmetic Act (FDCA) and FIFRA statues.

Chairman Brown's letter provoked EPA to assess its own policies in this area, and no doubt contributed to the Agency's decision to commission the National Research Council's Board on Agriculture to assist the Agency in developing a scientifically sound basis for the regulation of oncogenic residues. The findings, conclusions, and recommendations of the NAS study are contained in the report Regulating Pesticides in Food: The Delaney Paradox (National Academy Press, 1987). A copy of this report was provided to members of the subcommittee and staff upon its release in May 1987.

Discussions since the report's release, and a variety of other events (i.e. Court of Appeals decision on de minimus, Proposition 65) have served to sharpen public understanding of the regulatory dilemma faced by EPA in carrying out its statutory responsibilities. And now with the introduction of the "Pesticide Food Safety Act of 1988," the subcommittee has progressed from oversight and problem definition to the drafting of legislative remedies. The subcommittee deserves great praise for the courage and commitment needed to exercise both its oversight and legislative responsibilities in this highly controversial and extremely complex area of regulatory and public health policy.

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*Testimony presented September 7, 1988 before the Subcommittee on Department Operations, Research, and Foreign Agriculture (DORFA), Committee on Agriculture, U.S. House of Representatives. Dr. Benbrook is the Executive Director of the Board on Agriculture, National Research Council, National Academy of Sciences.

Principal Recommendations of the NAS Report

Regulating Pesticide Residues in Food: The Delaney Paradox (hereafter referred to as the Delaney Report) made four principal recommendations. Herein I describe the relationship between provisions in the "Pesticide Food Safety Act of 1988" (hereafter referred to as the Roberts-Brown bill) and the NAS Delaney report.

First, two important points deserve note. The NAS committee which carried out the study and produced the report was not asked, and did not dwell at length on the need for, or substance of legislation to implement its recommendations. The committee felt that its recommendations could, in large part, be acted upon administratively, or through legislation, or through a combination of legislative and administrative reforms.

Since completion of the project, the adverse Court of Appeals decision regarding the legal basis of the Food and Drug Administration's de minimus policy has weakened the likelihood that EPA could implement the report's recommendations administratively and withstand legal challenge, which would likely follow. Legal experts differ both in their views regarding the ultimate scope of the recent Court of Appeals decision, and whether and how litigation might evolve if EPA moves ahead to administratively adopt a negligible risk standard.

A second key point--the NAS committee viewed its four principal recommendations as interrelated and interdependent. It felt that a strong case could be made for each of its recommendations, both on scientific and policy grounds, but only when adopted as a package. The reason for this important caveat will soon become evident.

Recommendation 1: Consistency

> "Pesticide residues in food, whether marketed in raw or processed form or governed by old or new tolerances, should be regulated on the basis of consistent standards. Current law and regulations governing residues in raw and processed food are inconsistent with this goal." (Delaney report, page 11)

To a large extent, this consistency recommendation both drives and shapes the other recommendations. It also poses the principal statutory challenge this subcommittee must resolve in crafting legislation.

The Roberts-Brown bill addresses head-on the major statutory provisions that give rise to inconsistent treatment of oncogenic pesticide residues in food:

* The inconsistency between how residues in raw commodities and fresh produce are treated, in contrast to processed foods is eliminated in a straightforward fashion in Title II. Pesticide residues that concentrate on processed foods are removed from

Section 409 of the FDCA, and hence outside the reach of the Delaney Clause.

* The inconsistency between new and old pesticides is addressed in Title I, which proposes a simple, yet far-reaching change in the re-registration provisions of FIFRA. By making re-registration the functional equivalent of registration, the Roberts-Brown bill would provide EPA a much more realistic statutory mandate and process with which the Agency could assess and regulate new and old pesticides with a consistent set of rules and scientific criteria.

While an elegant analytical case can be made for consistent treatment of pesticide residues, plain old common sense provides perhaps the most compelling basis for striving toward consistency. But how can EPA work toward consistency, short of either canceling all food uses of oncogenic pesticides, or leaving all such uses essentially unregulated?

Recommendation 2: Adoption of a Negligible Risk Standard

> "A negligible risk standard for carcinogens in food, applied consistently to all pesticides and to all forms of food, could dramatically reduce total dietary exposure to oncogenic pesticides with modest reduction of benefits." (Delaney report, page 12)

The need for and nature of this recommendation is best described in the committee's own words:

> "The committee believes that the elimination of oncogenic pesticide residues from human food is an appropriate aspiration of regulation. The committee recognizes, however, that residues of several dozen oncogenic pesticides may be found in hundreds of different foods. Many such residues pose little risk to humans, whereas some clearly warrant attention and, quite probably, regulatory action. The problem of implementing action against many pesticides with limited personnel and resources should be minimized. Moreover, the challenge for regulators grows increasingly complex as science and technology advance. Improvements in analytical chemistry and residue detection capabilities, new toxicological data, changing pesticide use practices, and the development of new pesticides and foods establish an urgency and the feasibility to devise a strategy for attaining a safer food supply." (Delaney report, page 12)

The Roberts-Brown bill calls for the application of such a standard in establishing, reviewing, adjusting, and when necessary revoking tolerances for oncogenic pesticide residues in fresh and/or processed foods.

Moreover, the language in Section 204 of the Roberts-Brown bill provides the Administrator clear and appropriate guidance regarding how to apply the standard. As recommended in the Delaney Report, the bill would:

* Apply a negligible risk standard to the estimated dietary risk from exposure to a given pesticide used on a given crop, taking into account residues in or on both fresh and processed foods derived from the crop.

* Require EPA to use realistic assumptions and the best available data in developing risk estimates, and when comparing risks associated with one pesticide in contrast to risks from other pesticides registered for the same crop use or uses.

Another key point deserves mention. The NAS committee discussed at virtually every meeting whether to recommend a quantitative benchmark for negligible risk as part of its definition of this important concept. The committee was both sensitive to and well aware of valid arguments both for and against specifying a quantitative benchmark in the definition of negligible risk. In the end, the committee was persuaded that quantitative risk assessment methods, and the science underlying estimates of oncogenic risks, were too fragile and changeable to either assert that risks below a certain level are truly "negligible," or that risks above the "negligible" level indeed pose a significant risk of cancer in man. Such judgments, in the committee's view, can only be made on a case-by-case basis following a thorough review of the complete toxicological database available on a particular chemical. Even then, such judgments may be very hard to make.

In the absence of a defensible scientific basis to establish a quantitative benchmark for negligible risk, the committee felt constrained to merely define what it meant by such a risk level, while utilizing 10^{-6} as one commonly accepted benchmark in its analytical exercises. For many years regulatory officials in EPA, FDA, and other agencies will continue to face a difficult set of scientific and policy issues in reaching judgments regarding negligible risk. The language and approach taken in the Roberts-Brown bill regarding the definition of negligible risk is sensitive to, and consistent with the NAS committee's findings and recommendations regarding the need for consistent application of a negligible risk standard.

Recommendation 3: Target High-Risk Pesticides and Crop Uses

> "The committee's analysis (described on pages 50-66) suggests that about 80 percent of oncogenic risk from the 28 pesticides that constitute the committee's risk estimates is associated with the residues of 10 compounds in 15 foods. Logic argues that the EPA should focus its energies on reducing risk from the most worrisome pesticides on the most-consumed crops, and compelling reasons support such a strategy." (Delaney report, page 14)

A great deal of additional research on the magnitude and distribution of oncogenic pesticide residues (and risk) in food have been undertaken, and is ongoing within EPA, state regulatory agencies, private organizations, and academic institutions since the May 1987 release of the NAS Delaney report. While individuals differ markedly in their view of the magnitude and true significance of pesticide-related cancer risk, there is now widespread agreement that both exposure and potential risk is heavily concentrated in relatively few foods following the use of perhaps a dozen oncogenic pesticides.

In contemplating the challenge EPA faces in re-registering some 200 plus food use pesticides, this point takes on great significance. If and as EPA determines that some pesticide risks indeed exceed a negligible level, and further finds that risks exceed benefits, the Agency can substantially reduce risks by targeting regulatory action toward the relatively few pesticide uses associated with the greatest risks. For the farm community, the other side of the coin is reassuring--most current uses of potentially oncognic pesticides contribute very modestly, if at all to dietary cancer risk, and hence are not likely to warrant severe regulatory restrictions, at least not on the basis of dietary cancer risks.

The three preceding recommendations constitute both an approach, and a new set of rules for establishing tolerances and regulating oncogenic pesticides. The last recommendation addresses the need for EPA to augment its current approach to risk assessment and risk-benefit balancing through adoption of an analytical framework designed to facilitate two key goals--highlighting the relative risks and benefits associated with the use of all the pesticides registered for control of a given pest on a given crop; and second, assisting the Agency in assuring that its regulatory actions actually reduce total risk after crop producers have switched to other products following a regulatory action.

Recommendation 4: Adoption of an Analytical Framework

> "The EPA should develop improved tools and methods to more systematically estimate the overall impact of prospective regulatory actions on health, the environment, and food production. Rapid advances in computer technology, as well as the EPA's successful efforts to computerize major data sets like the Tolerance Assessment System (TAS) make such progress readily attainable." (Delaney report, page 15)

The committee explained the need for such a framework by pointing out that:

> "Use of new analytical tools and data bases could help the EPA get ahead of its growing work load. The refinement of such a system would allow the EPA to project with increased confidence a wide range of impacts associated with its regulatory actions. For example, the committee's rudimentary analysis demonstrates that certain strategies for implementing

> the Delaney Clause could increase dietary risk, and vigorous application of the Delaney Clause to tolerances for residues in processed foods may not be the most effective strategy for minimizing dietary exposure to oncogenic pesticides." (Delaney report, pages 15-16)

As stated earlier, the committee felt that its four recommendations were justified when considered as a package. It would remain extremely difficult for EPA to target high-risk uses of pesticides without a new analytical framework, nor strive toward consistency in applying a negligible risk standard to new and old pesticides, and residues in fresh and processed foods.

The committee felt compelled to point out one particularly key linkage among its recommendations:

> "The adoption of a negligible-risk standard would provide added justification for the agency to reduce relatively high risks while deferring actions on relatively low or perhaps even zero risks. The committee would not endorse the adoption of such a standard if it were not consistently applied to all pesticides and all forms of human food." (Delaney report, page 13)

Legislative Proposals Impacting Re-registration

For the last several years the subcommittee has passed legislation containing an extensive set of amendments involving the re-registration process. Indeed, many people consider the amendments developed to accelerate the re-registration process as the most important feature of the legislation the full Committee on Agriculture is scheduled to markup in the near future.

The relationship between the Roberts-Brown bill re-registration provisions and those in the FIFRA bill passed earlier this month by the subcommittee warrants some discussion. Put simply, the amendments address different issues, and are very different in content. They are not mutually exclusive. Prior to full committee markup, I would urge the subcommittee to consider how the two provisions could be integrated.

The key change proposed in the Roberts-Brown bill is simple: it would make re-registration the functional equivalent of registration. Many people erroneously assume that this is indeed now the case with the current FIFRA. While the language of FIFRA could arguably be read in support of the notion that registration and re-registration are the same, in practice the two actions are very different.

In the case of reviewing an application for a new registration, the Agency requires the applicant to meet all applicable data requirements before reaching a decision regarding potential risks, and moreover the

burden rests on the applicant to prove that risks are slight, and that benefits exceed risks. The product is not allowed on the market until proven safe.

In the re-registration process, the shoe is on the other food. EPA is compelled to leave a pesticide product on the market despite datagaps, and even when there are rather clear indications of significant risk. For most active ingredients, the first several years of the re-registration process entails little more than identifying and filling datagaps. Once the data is in, EPA then proceeds to conduct a new risk assessment. If it determines that the risks from some uses are potentially excessive, the Agency then has to initiate either the special review or cancellation processes, which generally take a few more years, at a minimum, to complete. Only then are benefits seriously evaluated.

Under current law, the decision to not re-register a pesticide only triggers the beginning of another protracted, costly administrative process. This is why Dr. Moore of EPA repeatedly highlights the statute itself as a principal constraint in working through the backlog of chemicals that are winding their way through re-registration.

The Roberts-Brown bill goes to the heart of this problem by changing the standard EPA is required to apply when considering an application for re-registration, and by furthermore conferring regulatory significance to a decision not to re-register a pesticide. It also deals with the very real issue of Agency resources by placing the burden on registrants to apply for re-registration, and submit with such an application a complete dataset (which will no doubt include references to data already submitted to the Agency). Last, it would extend the routine re-registration period from 5 to 12 years, in recognition of the fact that a pesticide which can meet the current standards for safety and efficacy, based on a complete and up-to-date dataset, is likely to remain a valuable and safe product for many years to come. As a practical matter, a thorough review of all old pesticides once every 12 years would do far more to protect the public health than the type of piece-meal, step-wise assessment that occurs today.

The extensive re-registration amendments in the subcommittee passed bill would establish a five phase re-registration process taking an estimated 9 years to complete. Several provisions are both needed and clearly compatible with the Roberts-Brown bill. Specifically, it would be desirable to retain the fee structure and related amendments from the subcommittee passed bill in any future package of re-registration amendments; the penalty provisions in the subcommittee bill for non-compliance with the procedural requirements of the re-registration process also belong in any future set of amendments, as well as provisions addressing inadequate or fraudulent data.

The major differences in the two bills are the change in the standard, and the extension of the re-registration time period from 5 to 12 years. The timetable called for in the two bills is very similar, and could easily be reconciled.

One important point deserves emphasis relative to timetables. The NAS Delaney report, and other reports and studies have documented that the risks associated with current pesticide use patterns are highly variable. Relatively few pesticides account for the lions share of risk; just a few uses for the riskiest pesticides account for the bulk of exposure; water quality and other environmental problems generally arise from certain combinations of soil type, climate, and application methods; worker safety problems reflect particular combinations of practices, in the absence of recommended safety precautions, and so.

As a result, the public health and environmental goals of FIFRA would be advanced most cost-effectively by providing EPA authority and flexibility to target its re-registration, special review, and cancellation efforts at those pesticides which appear most worrisome. EPA has a pretty clear idea of which products belong in this category. It would be preferred for EPA to select 15 of the most hazardous products, and act to reduce risks to acceptable levels from them over the next 24 months, rather than to work its way through the first two or three of five phases of re-registration on some 600 active ingredients. In striving to provide a statutory mandate to implement the NAS report's recommendations, the Roberts-Brown bill would go a long way toward focusing Agency resources and effort on potentially significant risks.

In summary, I believe it is fair to say that the provisions of the Roberts-Brown bill would substantially reconcile within the FDCA and FIFRA statutes the principal statutory constraints EPA faces in implementing the four major recommendations in the NAS Delaney report. Please note my choice of words--it was deliberate.

The Roberts-Brown bill would provide EPA critical new authority, tools, and direction. It would not, nor can any legislation, dictate that such new authority be exercised with a sense of urgency and commitment to reducing public health risks. Moreover, as this subcommittee is well aware, there are many other factors which must realistically be taken into account, including--

* Funding levels to support the re-registration process.

* New developments in the scientific arena, including a rapidly growing database on pesticide risks stemming from surface-water and ground-water contamination.

* State regulatory efforts and initiatives, like Proposition 65; ongoing litigation, and the prospect of new cases involving regulatory actions based upon a de minimus theory.

* Political changes in the executive and legislative branches of government.

For better or worse, the DORFA subcommittee opened this can of worms. The issues were bound to arise, and pose tough choices both for Congress and regulatory officials. By crafting this bill and holding this hearing, the subcommittee has taken a commendable step forward in resolving a complicated, at times seemingly impenetrable regulatory problem. Thanks for the opportunity to appear before you this morning. I would be pleased to answer any questions.

/

(Attachment follows:)

Atlas of U.S. Cancer Mortality Among Whites: 1950-1980

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Public Health Service,
National Institutes of Health

DHHS Publication No. (NIH) 87-2900

Results

U.S. Rates

Mortality rates between 1950 and 1980 rose most dramatically for lung cancer, with female rates rising 36% each five years compared to 20% for males (figure 2). Other striking increases (over 10% per five years) were seen in both sexes for malignant melanoma, multiple myeloma, and connective tissue tumors, and for laryngeal cancer among women. Rates for cancers of the lip and stomach in both sexes, and for non-melanoma skin and liver cancers among women, dropped over the same period by 19% or more per five years. Decreases of more than 10% per five years were also seen for cancers of the bone and rectum in both sexes, for cancers of the cervix, corpus uteri, nasal cavity, and thyroid gland among women, and for non-melanoma skin cancer and Hodgkin's disease among men. During the 1970s, the highest mortality rates were seen for lung, colon, and prostate cancers among men and for breast, lung, and colon cancers among women (figure 3). These sites, along with the corpus uteri, also had the highest incidence rates during this period.[13,40]

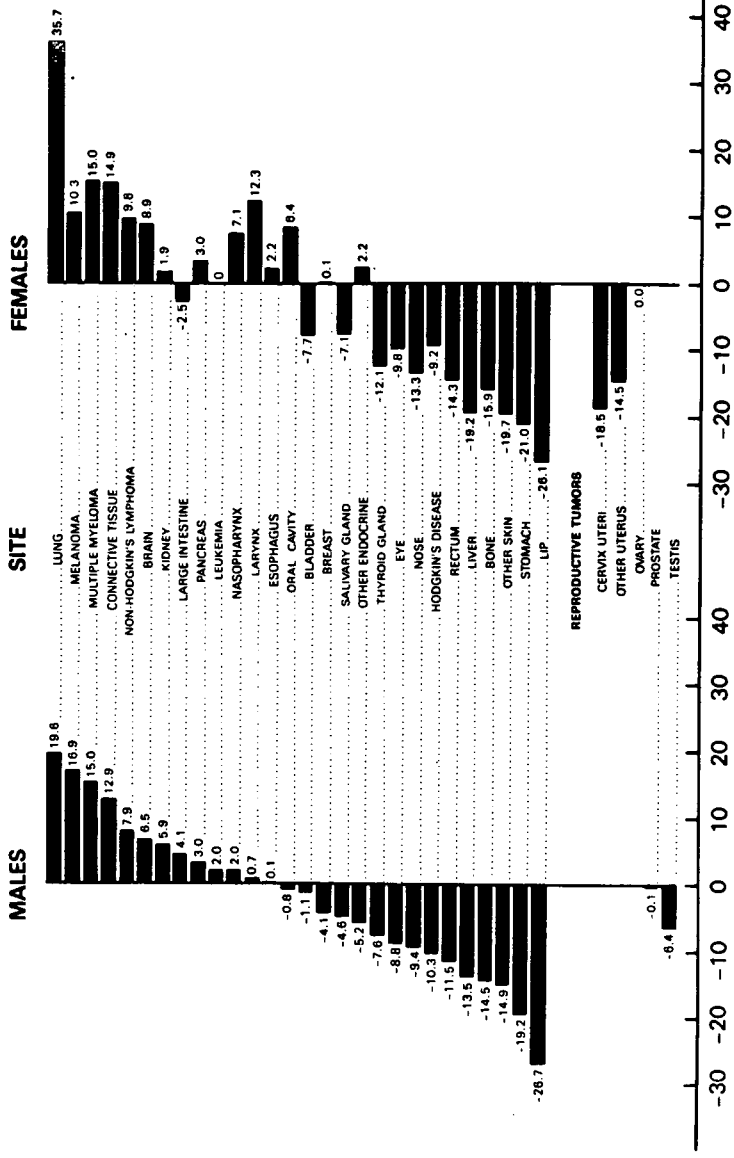
Although the model used to examine time trends fits the U.S. data very well, examination of those sites with a poorer fit pointed to noteworthy changes in the patterns of the rates over time. Sharp downturns in mortality rates for Hodgkin's disease and testicular cancer and a sharp increase for female lung cancer were seen during the 1970s for all age groups.

An examination of the interaction of age and time effects on the U.S. mortality rates identified certain cancer sites where patterns differed by broad age group (20-44, 45-69, 70+). The most common pattern revealed declining rates over time for the youngest age group but not for the others; this was the case for cancers of the colon, rectum, bladder, lymphomas, multiple myeloma, and leukemia for both males and females; breast cancer for males; and corpus uteri, thyroid, and other endocrine tumors for females. For malignant melanoma and connective tissue cancer, the rates for the youngest group increased slightly, compared to a greater increase over time for the older ages among males and females. For females, cancers of the oral cavity, esophagus, and larynx showed a decreasing trend for the youngest ages, an increasing trend for the middle ages, and a stable pattern for the oldest group. For brain cancer, rates for the oldest group of males and females increased dramatically over time, to surpass those of the middle age group which previously had the highest reported rates.

The mortality rate variability, as measured by the interquartile range, was similar for men and women for most sites during the 1970s, except for cancers of the bladder, rectum, colon, and oral cavity which showed at least a 20% greater variation among men. The degree of variability was largest in the 1970s for cancers of the lung, rectum, colon, lip, oral cavity, nasopharynx, and eye among both men and women (figures 4 and 5), bladder among men, and cervix uteri and breast among women. Leukemia showed the least variation for both men and women during this time period. The interquartile ranges for cancers of the eye, other endocrine glands, nasopharynx, and lip appear unusually large among women for the 1950s because over 25% of the SEAs had no deaths due to these causes. While an apparent homogeneity of rates (e.g., leukemia, cancers of the pancreas or prostate) does not preclude the existence of geographic clusters of high rates, it does indicate that on the whole rates are not as variable for these cancers as for others. For nearly all sites, the variability of rates has decreased over time (figures 4 and 5). However, a dramatic increase in rate variation has occurred for female lung cancer, indicating the emergence of wide geographic differences since the 1950s.

The general trend toward increasing homogeneity of cancer rates over time is further supported by a comparison of the overall U.S. rates with the corresponding medians of the distribution of the SEA-specific rates. The overall U.S. rate for a tumor which occurs predominantly in densely populated areas is higher than the median rate of the SEA distribution because the total number of deaths in the U.S. rate will be heavily weighted by these populous areas. In the 1950s, U.S. rates for several sites were more than 20% higher than their corresponding median rates (cancers of the nasopharynx, larynx, rectum, and endocrine system in both sexes; eye cancer in women; cancers of the bladder, colon, esophagus, and oral cavity in men). However, in the 1970s only a single cancer site (rectal cancer among men) revealed such a large difference. This measure of "urban effect" dropped for male lung cancer from an 18% excess in the 1950s to a 1% deficit (i.e., the U.S. rate 1% lower than the median) in the 1970s, indicating that increases in male lung cancer rates have been taking place mainly in less populous areas. Similarly, U.S. cervical cancer rates were below the median rates for every decade, indicating that deaths due to this cancer have been occurring more in less populous areas for at least 30 years.

Figure 2. — U.S. Cancer Mortality Time Trends, 1950-1980, by Site for Males and Females



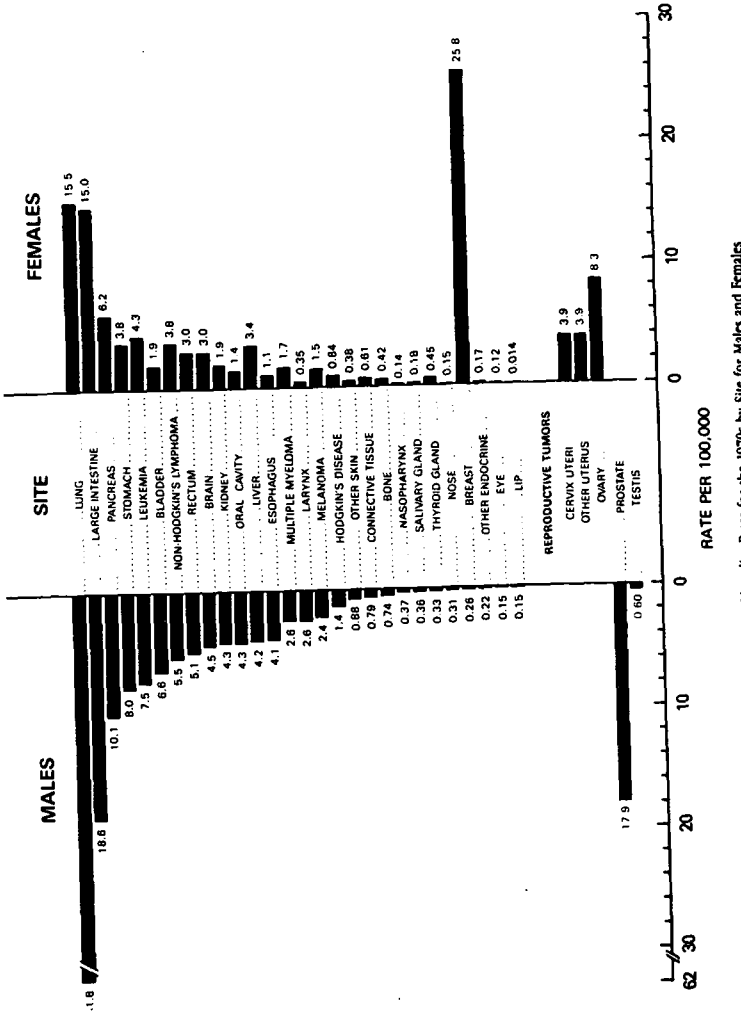


Figure 3. — U.S. Cancer Mortality Rates for the 1970s by Site for Males and Females

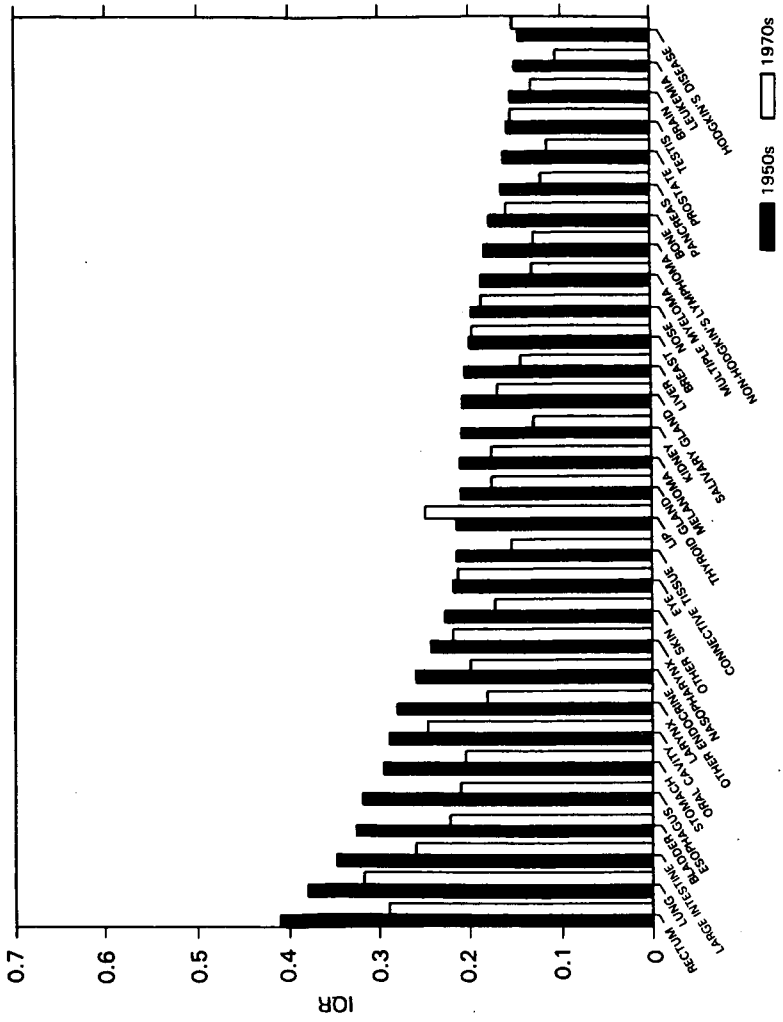


Figure 4 — Interquartile Range of Cancer Mortality Rates among Males for the 1950s and the 1970s, by Site

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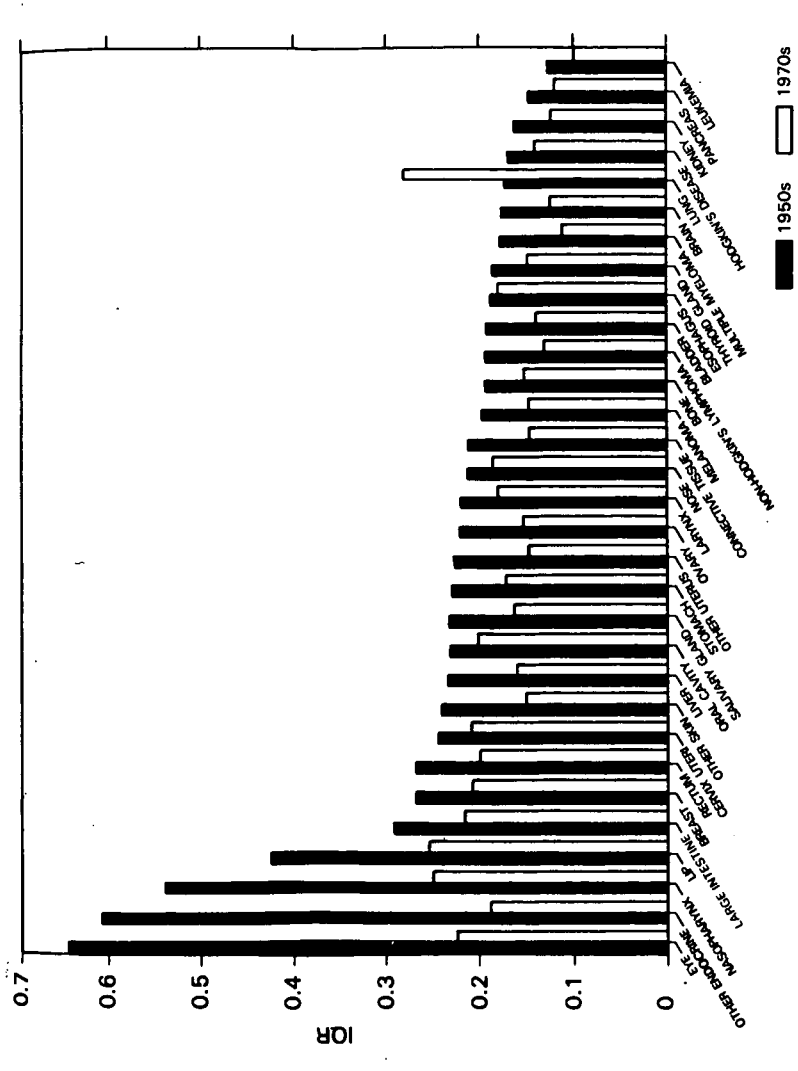

Figure 5 — Interquartile Range of Cancer Mortality Rates among Females for the 1950s and the 1970s, by Site

Geographic Patterns

Described below are the patterns for the most commonly occurring cancers, along with possible explanations based mainly on correlation and analytic studies conducted by the National Cancer Institute, usually in collaboration with other research groups, in response to earlier cancer atlases.

Oral cavity: Rates for men were high in all time periods in the urban Northeast, and in several metropolitan areas and port cities elsewhere. However, in the 1970s high-rate areas predominated along much of the east coast. The urban association among males appeared to correspond with levels of alcohol consumption and tobacco smoking, the major risk factors for oral cancer.[41] Among females, however, the rates were highest in rural counties of the South, especially in the earlier time periods. A case-control interview study of North Carolina women implicated the long-standing habit of dipping snuff, i.e., placing finely ground smokeless tobacco between the gum and cheek.[42] This cluster of oral cancer was less pronounced in the 1970s as rates among women declined in the rural South and high-rate areas appeared along the Pacific and Florida coasts. This newly-emerging pattern resembles that for female lung cancer, suggesting the influence of cigarette smoking.

Esophagus: Rates for men were elevated in urban centers, especially in the Northeast, although clustering in this area diminished in the 1970s. Among females, rates remained high in the urban Northeast and showed some increases in the Far West and Florida, while the high rates initially observed in scattered parts of the rural South became less conspicuous in the 1970s. The geographic patterns resemble those for oral cancer and suggest the effects of alcohol consumption, smoking, and possibly smokeless tobacco on both cancer sites.[43] Poor nutrition may also contribute to the patterns of occurrence, since dietary deficiencies seem responsible, along with alcohol intake, for the much higher rates of this cancer among blacks.[44,45]

Stomach: The patterns for both males and females have featured a cluster of excessive mortality in primarily rural counties in the North Central region, which appeared correlated with the concentration of high-risk ethnic groups from northern Europe.[46] This cluster has become less apparent in the 1970s. A similar aggregation in certain southwestern states seemed related to the excess risk among the Hispanic groups in this area. Higher rates have also persisted in northern urban areas. In the face of substantial nationwide reductions in mortality over the 30-year period, rates in both sexes declined less rapidly in areas of New England, Appalachia (parts of OH, WV, VA, KY, TN), Florida, Texas and southern California.

Large intestine, excluding rectum: In both sexes there has been a consistent North-South gradient, with rates being higher in the northern parts of the country, partly due to the elevated risks of urban populations with higher socioeconomic levels.[47] Clustering has been most evident in the Northeast and Midwest. Also, the North-South differential has diminished with time, as more areas in the South have displayed rising mortality rates than in the North. Despite the lack of a sex differential in the geographic patterns, there has been a rising national trend in colon cancer mortality among males accompanied by a decline in females, most evident in the urban Northeast. It is interesting that the lower rates in the South have prevailed even in areas attracting large numbers of retirees from the North, thus prompting a case-control study in Florida retirement communities.[48] Preliminary data suggest there is no rapid reduction in risk of colorectal cancer, but the younger the age at migration, the lower the risk. It remains to be seen what aspect of the southern environment or lifestyle may be protective. Another study opportunity was provided by a cluster of high rates in a rural agricultural area of eastern Nebraska. In a case-control interview study, the elevated risk of colon cancer was primarily among persons of Czechoslovakian background, who predominate in the study area.[49]

Rectum: The geographic patterns for rectal cancer resemble those for colon cancer, suggesting risk factors in common. However, the rates are generally higher in males than females and have declined over time in both sexes, at least partly due to improvements in survival.

Liver, gallbladder, and biliary passages: These diseases were not separable by ICD code prior to 1958, so they are presented in combination for the entire time period. Mortality rates for liver cancer may be markedly influenced by the potential misclassification of metastatic disease as primary neoplasms. However, among females the geographic pattern for this category is consistent with previously identified high-rate areas of biliary tract cancer in the North Central region, the Southwest, and Appalachia.[50,51] Mexican Americans, who reside primarily in the Southwest, and residents of Appalachian communities[52] have a high incidence of gallstones, the major risk factor for biliary tract cancer.

Pancreas: In all time periods the amount of geographic variation was less evident than for most other tumors. Nevertheless, clusters of high-rate areas were seen in the urban Northeast and in Louisiana and the Mississippi delta area. In general, the rates for pancreatic cancer have been greater in urban areas and highly correlated with the patterns of lung cancer, especially in males, suggesting the influence of smoking habits on both tumors.[53]

In a case-control study in southern Louisiana, preliminary results suggest that smoking patterns and dietary habits may contribute in part to the high rates in this area.[54]

Nose, nasal cavities, and sinuses: There is little evidence of geographic clustering of these rare tumors, but a correlation study suggested a possible link between employment in the furniture manufacturing industry and risk of nasal cancer.[55] A case-control study based on death certificates revealed an excess risk associated with woodworking occupations.[56] Subsequently, a case-control interview study in Virginia and North Carolina indicated increased risks of nasal adenocarcinoma among furniture workers and textile workers, while increases in squamous cell cancers were related to cigarette smoking.[57,58]

Larynx: Among males, excess mortality has persisted in the Northeast corridor and in urban areas elsewhere in the country. While rates have declined in the urban Northeast, a cluster of high rates has emerged in New England. Rates have also tended to increase in the Midwest and North Central states, and more generally in rural areas throughout the country.[59] The distribution of laryngeal cancer has been correlated with lung, esophageal, and oral cancers in a manner consistent with the action of tobacco and/or alcohol consumption on the risk of these tumors. Elevated mortality from laryngeal cancer has been reported in coastal areas where shipyards operated during World War II,[60] consistent with some reports implicating an effect of asbestos exposure, but a case-control study of laryngeal cancer in coastal Virginia revealed no excess risk associated with shipbuilding.[61] Among females, there has been a rapid increase in mortality throughout the country, with high rates emerging in the 1970s in the Northeast and in California.

Trachea, bronchus, lung, and pleura: Among males the mortality rates in the 1950s were high in urban areas of the North and in certain seaboard areas of the South, especially along the southeast Atlantic and Gulf coasts.[62] The geographic pattern appeared consistent with variations in smoking habits and with occupational exposures, including shipbuilding and ship repair.[60] Case-control interview studies in coastal areas of Georgia,[63] Virginia,[61] and Florida[64] revealed an elevated risk of lung cancer associated with shipbuilding, especially during World War II. In coastal Virginia a cluster of mesothelioma was identified and also linked to shipyard exposures to asbestos.[65] Case-control studies are under way to clarify reasons for the high rates along the Gulf Coast, and preliminary analyses of Louisiana data suggest an excess risk among the Cajun population, due at least partly to smoking practices, including the heavy use of hand-rolled cigarettes.[66] During the 1970s the elevated mortality declined in the Northeast and became more pronounced in the South, both in rural and urban counties.[67] A high-rate cluster in Louisiana extended inland along the Mississippi River. Among females the rate of increase rose sharply throughout the country in the 1970s, with aggregations of high rates in Florida and along the mid-Atlantic and west coasts.

Breast: The geographic patterns have remained relatively stable over time, with most low rates in the South and high rates concentrated in the Northeast, especially in urban areas. However, the North-South differences have diminished, in association with rising rates in many areas of the South, notably in Appalachia. When the geographic patterns were analyzed by age group, only postmenopausal women (55+ years) showed a northern predominance, along with ethnic correlations and positive socioeconomic gradients.[68] In contrast, the rates for premenopausal women (20-44 years) were distributed almost uniformly across the country and correlated most closely with county birth rate (fertility) characteristics.

Cervix uteri: High rates were scattered throughout the South, with the heaviest concentration in Appalachia, which correlates with the tendency of this tumor to affect rural women in the lower socioeconomic classes.[69] Rates in the North remained low except for parts of northern New England. Although mortality has declined substantially throughout the country, the rates in several midwestern states decreased less rapidly, so that in the 1970s a cluster of relatively high rates appeared in these states as well as in Appalachia.

Corpus and other uterus: Some clustering of relatively high mortality rates has persisted in the mid-Atlantic and midwestern states. Mortality has declined nationwide, but less rapidly in the North Central and Far Western states. Because of favorable survival rates and the potential misclassification of cervical cancer deaths, the mortality pattern for this cancer is much less informative than incidence data. The latter have revealed regional and temporal variations that correlate with the use of estrogens prescribed at menopause.[70]

Ovary: Mortality patterns have shown little change, with scattered high rates in both urban and rural areas across the northern part of the country and in some urban areas along the West Coast. A correlation with the distribution of breast cancer has been described.[68,69]

Prostate: Although geographic variation is rather limited, some clustering of high-rate areas persisted in the northeastern and North Central states, particularly in rural areas. Rates over time remained generally stable, except for some clustering of areas with rising rates in Florida and California. Correlation analyses have suggested that ethnic factors may influence the distribution of this cancer.[71]

Testis: There is little indication of geographic aggregation for this disease. Despite an upward trend in incidence rates, mortality from testicular cancer has dropped precipitously with improvements in therapy and resultant survival rates.[72,73]

Kidney: In both sexes the rates for renal cancer have remained elevated in the North Central region, with some high-rate areas also in the Northeast. The North-South differential declined over time as rates in the South rose more rapidly than in the North, especially in males. In Minnesota a case-control study of renal adenocarcinoma (which comprises about 85% of renal cancer) revealed elevated risks associated with German and Scandinavian ancestry, which partially explain the geographic variation.[74]

Bladder: Among males, bladder cancer rates were consistently high in urban and rural areas of the Northeast, in urban areas around the Great Lakes, and in southern Louisiana. Over time the high-rate areas became more pronounced in the midwestern states, including Ohio and Michigan, and time-trend analysis showed that rising rates were most evident throughout the central portion of the country. Among females, high-rate areas were seen mainly in upstate New York and New England. Occupational factors appeared to contribute to the geographic distribution among males, with rates particularly high in counties where the chemical industry is heavily concentrated.[75] A series of case-control studies in high-rate areas revealed excess risks among workers exposed to various chemicals,[76] and among truck drivers and others occupationally exposed to motor exhausts.[77,78] In northern New England, preliminary analysis of a case-control study suggests that work in the leather and textile industries may contribute to the high rates for both sexes in that area.

Melanoma of the skin: A striking southern predominance has persisted over time, with both sexes showing high rates mainly in the Southeast and South Central regions. This pattern is consistent with the effects of sunlight exposure on the distribution of melanoma.[79] The mortality rates have risen in all parts of the country, although recently a high-rate area has emerged among males in California.

Other skin: Elevated mortality in the southern part of the country was seen also for nonmelanoma skin cancers, despite the low case-fatality rates for these common neoplasms. In incidence surveys across the country, the distribution of basal-cell and squamous-cell carcinomas of the skin was found to be strongly affected by the amount of exposure to sunlight.[79,80] In contrast to melanoma, the death rates for other skin cancers have declined over time, especially in the South.

Brain and other parts of the nervous system: No clear pattern was seen except for scattered high rates for both sexes in the Southeast. It is often difficult to distinguish between primary and metastatic neoplasms of the brain based on death certificate data, so that the geographic distribution may be influenced by variations in the quality of medical care and reporting systems.

Thyroid gland: In both sexes some high-rate areas were seen in the Rocky Mountain and North Central states. Overall there has been a steady decline in mortality rates.

Bone: High rates were seen in the Southeast among females, but geographic and temporal variations in mortality are confounded by fluctuations in diagnosis and reporting, especially the inclusion of metastatic tumors to bone.[81]

Connective tissue: Rates for both sexes have risen over time, with scattered high rates appearing in various parts of the country. In the 1970s a high-rate area emerged among women residing in West Virginia and Maryland. A rising incidence of this cancer has also been reported, but diagnostic and reporting practices probably contribute to the temporal and spatial variations of this tumor.[82]

Hodgkin's disease: Mortality rates have declined over time for both sexes, associated with improvements in survival, but relatively high rates have persisted in the urban Northeast and in several North Central states. The North-South gradient in Hodgkin's disease applies mainly to young adults and has been invoked along with other risk factors to suggest a possible viral etiology.[83]

Non-Hodgkin's lymphoma: In both sexes the rates were generally low in the South and elevated in the metropolitan centers and in coastal areas of California. This pattern seems related in part to socioeconomic status, which has shown a positive correlation with this neoplasm.[84] Over time there has been an upward trend in mortality rates, most notably in central and eastern areas of the U.S. Some clustering has appeared in North Central and midwestern states, especially in females. In a survey of death certificates from Wisconsin, an excess risk was detected among farmers.[85] In Kansas, where high rates emerged in the 1970s, a case-control interview study suggested a risk associated with the farm use of herbicides, especially phenoxyacetic acids.[86]

Multiple myeloma: High rates were scattered throughout the North Central region, especially among males. An upward trend in mortality has been seen in all parts of the country, especially in people over 55 years of age, and elevated rates have been associated with urbanization and high socioeconomic level.[87] In a survey of death certificates in Wisconsin, an excess risk was associated with various agricultural occupations that deserve further study.[88]

Leukemia: In both sexes, scattered high rates for adult leukemia were seen throughout the central part of

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the country from Texas to Minnesota. The slight upward trend in mortality among males is also most pronounced in the central portion of the country. Many high-rate counties have been located in agricultural communities, notably cotton-producing areas where heavy pesticide use is a common practice.[89] Case-control surveys of death certificates in Nebraska and Wisconsin have revealed associations with various agricultural activities, thus providing leads for further investigation.[90-92]

Discussion

This publication has updated the earlier cancer atlas for the white population with 10 additional years of data and has evaluated the trends in cancer mortality by SEA over a 30-year period. Death registration has been required in all U.S. states for over 50 years. Although several earlier NCI monographs have examined the geographic distribution and time trends of cancer mortality,[4,5,93] only recently have sufficient data become available to examine these patterns simultaneously in finer detail than at the state level. It is important to recognize that some geographic and temporal variations provide signals to environmental hazards, but for many tumors fluctuations in diagnosis, reporting, survival time, and migration may complicate the picture.

The mortality patterns for most cancers showed a tendency toward geographic uniformity over time, as reported previously using data by state or broadly-grouped counties.[94,95] However, in our study the variation in rates was quantified in a way that allows for comparison of cancer sites. In particular, the decreasing rate variability for most cancers suggests a lessening of regional differences in the prevalence of risk factors. Increasing standardization of diagnostic measures and death certification practices may contribute to the reduction in geographic differences, as may the wider distribution of improved medical care and more favorable survival rates.

The maps presented here can be used to identify not only areas where cancer mortality rates are elevated, but also areas where rates are changing more rapidly than the average U.S. experience. The maps are reproduced in half-page size on facing pages to facilitate a comparison of geographic patterns over time. The 1970s map may be viewed as a supplement to the previous atlas, as the statistical methods are unchanged except for the use of SEAs for all cancer sites and the exclusion of cancer deaths of persons under 20 years of age. With the addition of the time trend maps, it is now possible to identify areas which deserve further study by virtue of recent elevations and/or upward trends in cancer mortality.

The reader must be mindful of the limitations of this mortality survey as an epidemiologic pointer to studies of cancer etiology. In some instances the assumption of consistency of diagnosis, treatment, and death certification practices across place and time may not be justified. For example, a comparison of cause of death as coded on the death certificate with the diagnosis on hospital records[96] showed a high rate of discrepancies for colon and rectal cancer. As noted earlier, changes in ICD coding practices over time for several cancer sites also may have affected the patterns noted. Finally, certain cancers may be over-reported on death certificates, as suggested by the finding in some cancer registry areas that liver cancer mortality rates were higher than the corresponding incidence rates.[97] Patterns of mortality for cancers that are rapidly progressive and almost certainly fatal should most accurately reflect patterns of incidence, while the maps are less informative for cancers with favorable survival rates or problems in classification.

Despite the limitations of these data, it is clear from previous experience that the maps for certain malignancies have prompted analytic investigations that clarified associations with environmental and lifestyle hazards. The updated static and dynamic maps presented in this volume should enhance the utility of cancer mapping as an epidemiologic resource that facilitates research into the origins and eventual control of cancer.

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