

a summary of
America's War on "Carcinogens":
*Reassessing the Use of Animal Tests to
Predict Human Cancer Risk*
(based on an ACSH book of the same name)

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THIS SUMMARY IS BASED ON ACSH'S PUBLICATION,

America's War on "Carcinogens":
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Predict Human Cancer Risk*

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PREFACE

Prevention of disease is critical to advancing public health. Yet this book, *America's War on "Carcinogens": Reassessing the Use of Animal Tests to Predict Human Cancer Risk* — the most recent publication of the American Council on Science and Health (ACSH) — makes clear that efforts to use high-dose animal studies to characterize risks posed to humans by potential chemical carcinogens are badly flawed. The flaw lies not with the studies, for animal studies play an important role in identifying potential hazards to human health. Rather, the flaw is in how the study results are interpreted and used to inform decision makers and the public about potential cancer risks. Problems with the use of these studies cast doubt on the scientific credibility of risk assessments and help to distort perceptions among the public as to which risks matter most.

America's War on "Carcinogens" identifies many concerns about the inference that substances found to increase tumor rates in test animals in a high-dose laboratory study are also likely to cause problems in humans. In some cases, the route of exposure used in the study differs from typical human exposure routes (e.g., the use of stomach tubes to deliver the substance into the animal). In most studies, the dose administered to the test animals far exceeds typical human exposures. For example, it is not uncommon for the daily dose administered to the animal to exceed the typical lifetime dose experienced by people, and for that amount to be given to the animal every day of its life. The vast difference between "real-world" human exposures and the conditions in these studies has given rise to "the increasing suspicion that the findings in these rodent bioassays are not relevant to human risk."¹ In fact, in a random survey of members

of the Society of Toxicology, nearly three in five (58%) respondents disagreed with the statement that “If a scientific study produces evidence that a chemical causes cancer in animals, then we can be reasonably sure that the chemical will cause cancer in humans”² — and these are the experts who should know!

Not all high-dose animal studies have been misinterpreted. A rethinking of the results from studies of chloroform shows how their findings can be viewed more carefully and wisely. Chloroform forms as a byproduct of treating drinking water with chlorine to kill disease-causing microbes. Studies of mice and rats exposed to chloroform by a stomach tube indicated that chloroform exposure causes a clear increase in tumor incidence. Based on these findings, the U.S. EPA classified chloroform as a “probable human carcinogen” for many years. However, other studies indicate that in animals administered the same level of chloroform in their drinking water, a route clearly more relevant to human exposure, there is no significant increase in tumor incidence. Now, based on these studies and significant mechanistic data, EPA classifies chloroform as “likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions” but “not likely to be carcinogenic to humans by any route of exposure” at lower levels.

Does careful qualification of the applicability of these study findings matter? The case of chloroform shows how it can. A reduction in water chlorination, perhaps due to concern about the risks posed by chloroform and other disinfection byproducts, helped spread a cholera epidemic in Peru that killed thousands and sickened many more.³ Clearly, getting the science right — rather than “playing it safe” by broadly interpreting the results of these animal studies and unnecessarily restricting exposure to a compound — can have important public health implications.

The results of rodent cancer studies are also, of course, of interest to journalists and the public. Perhaps because these tests have been used for so many years to make prominent claims about various health hazards, most people believe these tests are accurate indicators of human risk. The same study reporting that

nearly 3 in 5 toxicologists doubt these tests predict human health risks also found that 3 in 4 members of the general public believe these are predictive. Can the public be blamed for being irrational, or do these beliefs reflect the messages they have received from government agencies and the media? The problem may be that the substantial uncertainty surrounding the extrapolation of the findings from these studies to typical human exposures is not being communicated. Perhaps the public is being given the impression that the findings from high-dose animal studies provide relatively direct answers to questions about human risk, rather than being one piece of a puzzle that must be worked out as scientists wrestle with the extrapolation of results from high dose to low dose, across routes of exposure, and, of course, from animals to humans.

The inflated importance that the results of these animal studies appear to have in the minds of the general public can have substantial public health consequences. It may be in part because of the weight placed on such results that the general public is more concerned about speculative causes of cancer identified in animal studies than they are about relatively well established causes of cancer that have been characterized extensively and rigorously in epidemiology studies that are described in this book. Public misperception of the magnitude of risks can have two important repercussions. First, people may make bad decisions for themselves and their families. If the costs of organic food, purchased to avoid the hypothetical cancer risks from pesticides, reduces total consumption of fruits and vegetables, a family will clearly be worse off than if they ate recommended amounts of conventionally grown produce. Second, people may exert pressure on the government, leading government agencies to focus excessively on addressing negligible risks while placing too little effort on reducing larger risks.

America's War on "Carcinogens" makes an eloquent plea for improving the use of animal study findings to predict human cancer risks. It is important for public health that the plea be heeded. Better use of scientific information will improve the scientific credibility of the exercise and give confidence that when a threat is identified, it is real. Efforts to better communicate

about carcinogenic hazards should help the public to make better decisions by keeping the risks in perspective. Enjoy the book.

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- ¹ Cohen, S.M. (2004) *Human Carcinogenic Risk Evaluation: An Alternative Approach to the Two-Year Rodent Bioassay*. *Toxicological Sciences* 80:225-229
- ² Kraus, N., Malmfors, T., and Slovic, P. (1992) *Intuitive Toxicology: Expert and Lay Judgments of Chemical Risks*. *Risk Analysis* 12:215-232
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- ⁴ Anderson, C. (1991) *Cholera Epidemic Traced to Risk Miscalculation*. *Nature* 354:255

FOREWORD

As we went to press with *America's War on "Carcinogens,"* we had just passed a dubious national anniversary: November 2004 marked the forty-fifth anniversary of America's first major "carcinogen" scare. Just prior to Thanksgiving, a federal official announced that there was a "cancer-causing" chemical in the cranberry crop — and the safety of one of the staples of holiday dinner was immediately in doubt. Americans panicked and threw out their cranberry sauce.

The great "cranberry scare" of 1959 was the first of many "cancer scares." What do these scares have in common? They were based on the observation that the chemicals in question caused cancer when fed to laboratory animals in high doses.

But do the results of high-dose animal cancer tests in themselves allow us to accurately predict human cancer risk? In ACSH's bold new book, scientists come together to consider that question, and respond with a resounding — and paradigm-shifting — "no."

Animal testing is a critical part of modern biomedical research. But so is common sense. As you will read in the pages that follow, laws, regulations, and even the popular wisdom have come to accept the “mouse is a little man” concept, the argument that since we cannot test chemicals on people, we need to rely on animals as our surrogate. In some ways this is true, and what ACSH asserts is not that we should discount animal testing — but that we should interpret the results of such tests in a more sophisticated (and less knee-jerk) manner.

At this time, there are laws and regulations in effect that are premised on the assumption that if a high dose of a chemical causes cancer in a laboratory animal, we must, out of caution, assume that it will also increase human cancer risk, even if the human exposure is extremely low in comparison.

For example, the Delaney Clause, part of the 1958 Food, Drug, and Cosmetic Act, requires that the FDA ban from the food supply any synthetic chemical that causes cancer in animals. No ifs, ands, or buts about it. The law (and ones similar to it, including California’s “Proposition 65”) focuses considerable amounts of our cancer-fighting resources on the purely hypothetical risks of trace environmental chemicals — solely because those chemicals have been designated “carcinogens” in animals. The ongoing attempt to purge our air, water, and food supply of traces of any synthetic chemical that causes cancer in animals is suspect in itself, but it becomes even more absurd when one considers that nature abounds with chemicals (including those in the natural food supply) that cause cancer in animals. The more we test both natural and synthetic chemicals on animals, the more of them we must classify as “carcinogens.”

Cancer is the second leading cause of death in the United States. Effective cancer prevention measures should be among our top priorities in public health. But we will never succeed in reducing our nation’s cancer toll if we continue to focus on trace levels of chemicals that cause cancer in animals but have never been shown to cause human cancer at the levels of typical human exposure.

The time is long overdue to call for a national reassessment of the use of animal cancer testing to predict human cancer risk.

American consumers should not be subject any longer to the “carcinogen *du jour*” scares that have dominated the headlines for the past five decades. Corporations should not be forced to withdraw perfectly useful and safe products from the market (or take unnecessary efforts to purge chemicals from the environment) just because a substance is labeled an animal carcinogen. In our pursuit of methods to reduce the risk of cancer in America, science and common sense, not rhetoric, scare tactics, and hyperbole, should prevail.

In this book, scientists associated with the American Council on Science and Health call upon Congress, the National Cancer Institute, the National Toxicology Program, our nation’s regulators, scientists from many disciplines, as well as members of the media to step back from the familiar but scientifically baseless mantra that “if it causes cancer in animals, it must be assumed to be a human cancer risk.” Such a simplistic, unscientific, inconsistent approach to ferreting out risks for human cancer is a losing strategy in the war on cancer.

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December 2004
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INTRODUCTION

Since the 1950s, Congress and regulatory agencies have been engaged in a “war on carcinogens,” attempting to reduce the toll of cancer by reducing human exposure to trace levels of synthetic chemicals that might pose a cancer risk. This “war” is based on the following premises:

- Cancer is causally linked to modern technology.
- Cancer rates increased dramatically during the twentieth century as a result of increased exposures to cancer-causing chemicals.

- Low-level exposures to synthetic chemicals in food, water, and the general environment pose a human cancer risk.
- We can identify chemicals that increase human cancer risk through experiments in which high doses of a chemical in question are administered to laboratory strains of rodents for the greater part of their lifetimes.
- Only a small number of chemicals are carcinogenic.
- Only synthetic chemicals are known to cause cancer in animals; natural chemicals are never “carcinogens.”
- Chemicals that cause cancer at high doses in animals pose a human cancer risk no matter how low the human exposure is.
- All traces of synthetic chemicals that test positive in animal cancer tests should be eliminated from food, water, and the general environment in an effort to reduce human cancer risk.

As research on the causes of cancer progressed during the second half of the twentieth century, *everyone of these concepts was proven to be false*. Yet many members of the general public and some environmentalists still believe them. Even more important, these ideas — and particularly the concept that the results of high-dose animal cancer tests can be readily generalized to low-dose human exposures — are the basis of laws and regulations that still affect the economy and misdirect valuable resources.

This report, a summary of the American Council on Science and Health (ACSH) book *America’s War on “Carcinogens”*: *Reassessing the Use of Animal Tests to Predict Human Cancer Risk*, takes a critical look at the U.S. war on carcinogens, with a particular emphasis on the role of animal carcinogen testing as a method of determining whether a substance poses a cancer risk to humans.

1. IS CANCER A “MODERN DISEASE”?

One of the basic assumptions of the “war on carcinogens” is that the group of diseases collectively known as cancer is an exclusively modern problem, attributable in large part to increased exposure to synthetic chemicals in the environment.

During the second half of the twentieth century, it was often claimed that the United States and other technologically advanced countries were facing an epidemic of cancer deaths caused by man-made agents. Actually, however, there is no general epidemic of cancer deaths, nor was there in the past fifty years. It is true that the proportion of all deaths due to cancer has increased greatly during the past century; however, these increases are primarily attributable to the greater longevity (aging) of the population and the substantial impact cigarette smoking has had in increasing a spectrum of cancer risks, rather than to exposure to synthetic chemicals.

Although reliable data are lacking, it is generally thought that cancer was relatively uncommon in ancient times; this is to be expected, since cancer is primarily a disease of older people, and most people died young from other causes throughout most of human history. Today, cancer accounts for a smaller proportion of total deaths in developing countries than in technologically advanced nations; again, this is to be expected, since a larger number of people in developing countries die early in life, from infectious diseases or other causes, and do not live long enough to die from cancer.

2. THE USE OF ANIMALS IN MEDICAL RESEARCH AND CARCINOGEN TESTING

Experiments involving animals play crucial roles in many fields of scientific research, including product safety testing. The use of living animals is necessary because

they can reflect the complex, dynamic interactions that occur in the human body. ACSH accepts and endorses the use of animal testing in biomedical research, when used and interpreted appropriately.

Toxicologists usually evaluate substances for carcinogenicity using a test (bioassay) in which high (near-toxic) doses of the substance are administered to laboratory animals for the greater part of their lifetimes. Multiple doses are usually used, and both sexes of two species of animals (usually, rats and mice) are included. At the end of the study or when individual animals die, all parts of the animals' bodies are examined microscopically for evidence of cancer and other toxic effects. An increased incidence of tumors in the test animals (over and above that occurring in control animals) is considered evidence for carcinogenicity. Carcinogenicity testing is designed to answer a yes/no question: does the substance cause cancer? The testing was planned in this way because the U.S. laws that require such testing, such as the Delaney clause of the Federal Food, Drug, and Cosmetic Act, only recognize two possibilities — i.e., a substance is either a carcinogen or not a carcinogen.

3. LIMITATIONS AND RESULTS OF ANIMAL CARCINOGEN TESTING

The two-year rodent bioassay is considered the “gold standard” for carcinogenicity evaluation. However, as scientific understanding of the causation of cancer has increased, doubts have arisen about the confidence placed in these tests and about how the results of animal carcinogen testing should be interpreted.

One of the basic assumptions inherent in the use of animal carcinogenicity tests is that a finding of carcinogenicity obtained in one species applies to other species, including humans. However, not all substances that induce tumors in one species do so in others. In some instances, findings may even differ between rats and mice, two rodent species that are far more

closely related to one another than either is to humans. In other words, a substance that causes cancer in mice may not cause cancer in rats — much less in humans.

A surprisingly high percentage of chemicals — as high as 50% in some series — test positive in animal carcinogenicity tests conducted at the maximum tolerated dose (MTD). As suggested by Drs Bruce Ames, Lois Gold, and their colleagues, a likely explanation for many of these positive results is that toxicity at high doses leads to increased cell turnover, which in turn increases the risk of cancer. In instances in which this is the only phenomenon contributing to the carcinogenicity of the substance and in which similar cell proliferation does not occur at lower doses, the applicability of results obtained at the MTD to lower, more realistic doses of the same substance is highly questionable.

Because of difficulties in extrapolating from one species to another and from high to low doses, as well as other methodological limitations, animal carcinogenicity testing, by itself, cannot yield a straightforward answer to the key question “Does this animal carcinogen, as currently used and at the levels to which people are usually exposed, increase the risk of human cancer?” Instead, carcinogenicity testing, like other types of toxicity testing using animals, should only be a source of information on *potential* effects and should be carefully interpreted, in combination with other types of scientific evidence, in order for meaningful conclusions to be reached. Unfortunately, it is often not used in such a way.

4. THE KNOWN CAUSES OF HUMAN CANCER

The known causes of human cancer, as established by epidemiological studies, include older age; hereditary factors; tobacco use (especially in the form of cigarette smoking); various aspects of diet, as well as related lifestyle factors such as obesity and physical inactivity; certain chronic infections; excess alcohol consumption (particularly in combina-

tion with cigarette smoking); the use of certain pharmaceuticals; various aspects of sexual and reproductive patterns; excess exposure to ionizing radiation; exposure to sunlight (a risk factor for skin cancer); certain high-dose occupational exposures; and possibly exposure to certain pollutants, such as radon and environmental tobacco smoke. Of the modifiable cancer risk factors (i.e., those other than age and heredity), tobacco and diet are by far the most important, each accounting for roughly 30% of all cancer deaths.

5. HOW EPIDEMIOLOGY COMPARES WITH TOXICOLOGY

The currently available epidemiologic evidence indicates that the major avoidable causes of cancer are lifestyle-related. Epidemiologic studies have not linked increased cancer rates with low-level exposures to “carcinogenic” substances in food, water, and the general environment. Epidemiology suggests that individual chemicals play important roles in cancer causation only in situations of high-dose exposure, e.g., tobacco smoking, prolonged high occupational exposure, or exposure to high doses in the form of a limited number of specific pharmaceuticals.

Toxicologic studies of carcinogenicity provide a very different picture. Toxicology research has not focused on lifestyle factors, many of which are complex and difficult or impossible to investigate in animal experiments. Instead, most toxicologic studies have investigated the effects of high-dose exposure to individual chemicals — primarily synthetic ones.

Most known human carcinogens are also carcinogenic in experimental animals. However, the converse is not true. Most of the substances that have tested positive in animal carcinogenicity tests are of no known relevance to the causation of human cancers.

6. ANIMAL CARCINOGENS IN NATURE

Two basic premises of those who point to the value of animal cancer tests in predicting human cancer risk are that “carcinogens” are synthetic, not natural, and that they are relatively few in number. However, research has shown that carcinogenicity is common among naturally occurring chemicals as well as synthetic ones, and the proportion of chemicals that test positive for carcinogenicity in at least one animal species is actually quite high. Of the relatively small number of naturally occurring food components that have been evaluated for carcinogenicity, about half have been found to be carcinogenic in animal tests; this is about the same as the proportion of synthetic chemicals that test positive. Many commonly consumed foods, including lettuce, mushrooms, apples, coffee, broccoli, bread, yogurt, mustard, and soy sauce, contain naturally occurring rodent carcinogens. Except for high-dose exposure to mycotoxins — substances such as aflatoxin, produced by fungi that are sometimes found in improperly stored peanuts and grain products — few if any of these substances are believed to contribute to human cancer.

Scientists do not know the reasons for the presence of all of the carcinogenic, mutagenic, and toxic substances in foods. However, one theory is that some of these substances help plants defend themselves against their enemies, such as fungi, as well as insects and other animal predators.

Although it is impossible to calculate the exact amounts — since dietary habits vary greatly among individuals and since the proportion of natural food chemicals that have been tested for carcinogenicity is small — it seems evident that people consume a much larger quantity and variety of naturally occurring rodent carcinogens than synthetic ones. The current double standard, by which synthetic substances are very tightly regulated while naturally occurring substances are virtually ignored, does not make scientific sense. The very fact that many ordinary foods and naturally occurring food components would not pass the regulatory criteria applied to synthetic chemicals indicates that something is amiss with the current system of evaluating carcinogenic hazards.

7. USE OF ANIMAL DATA AND HUMAN EPIDEMIOLOGY BY REGULATORY AND RESEARCH AGENCIES TO PREDICT HUMAN CANCER RISK

The International Agency for Research on Cancer (IARC), U.S. National Toxicology Program (NTP), and U.S. Environmental Protection Agency (EPA) evaluate and classify the carcinogenicity of various substances and exposures. Although these evaluations do take into account mechanistic data, species differences, and epidemiological evidence, they unfortunately do not include quantitative assessments of carcinogenic risk, and they do not balance risks against benefits. They may inadvertently mislead the public into thinking that all listed substances are of equal importance in the causation of cancer, thus overwhelming people with “background noise” about cancer causation and diverting attention from the major preventable causes of cancer. They may also deter people from using certain valuable pharmaceuticals, which, appropriately used, may have benefits that greatly outweigh the small risk of cancer that they may present.

These agencies sometimes classify substances as “probable” or “likely” human carcinogens solely on the basis of animal test data, even if no evidence exists that the substance poses a cancer risk to humans. Such designations may prompt restrictions on the use of a substance and efforts to minimize the public’s exposure to it, despite a lack of evidence that such measures will improve human health. For example, extensive and expensive remediation and cleanup projects have been undertaken to rid the environment of traces of PCBs, which were designated “probable” human carcinogens by the EPA on the basis of animal test data alone, even though there is no data indicating that such efforts will have public health benefits.

The mission of the U.S. National Cancer Institute (NCI) includes collecting and disseminating information on cancer to the public. Unfortunately, however, the NCI has not taken a lead

role in informing the public about whether exposure to trace levels of synthetic chemicals in the environment contributes to the human cancer toll. A recently published NCI booklet on cancer and the environment fails to clearly inform the public that other causes of cancer are far more important than any hypothetical risks posed by exposures to trace levels of synthetic chemicals in the environment.

8. ANIMAL CANCER TESTING IN LAWS AND REGULATIONS

Two important laws that that rely heavily on animal carcinogen testing as a basis for decisionmaking are the Delaney clause and California's Proposition 65.

The Delaney Clause

The Delaney clause is part of an amendment added in 1958 to the Federal Food, Drug, and Cosmetic Act. It established zero tolerance for animal carcinogens in certain categories of food ingredients — food additives, color additives, new animal drugs, and (until a 1996 change in the law) pesticide residues in processed foods if those residues become concentrated during processing. The clause does not apply to naturally occurring substances in foods, to substances Generally Recognized as Safe (GRAS), or to food additives approved before 1958.

The Delaney clause was controversial when it was passed and it became more so in subsequent decades. Because of our increased ability to detect ever-smaller amounts of substances in foods, the standard became more stringent as time went on. When the Delaney clause was first enacted, the technology of the time did not allow the detection of minuscule amounts of substances that had been found to cause tumors in laboratory animals given very large doses. It was then possible to measure the levels of most substances in concentrations of parts per million. It is now possible, however, to detect extremely minute traces of some residues — as low as parts per quintillion (parts per 1,000,000,000,000,000,000).

One probably unintended result of the Delaney clause has been to preclude the replacement of GRAS substances or those approved before 1958 with newer, possibly safer or more effective alternatives, because the law forbids any risk whatsoever for substances given new regulatory approvals but holds the older substances to a looser standard. Thus, the clause discourages innovation.

The fact that the Delaney clause applies to some categories of food ingredients but not others has peculiar consequences. The clause can be and has been used to ensure that even trace amounts of substances that have never been shown to be harmful to human health are excluded from the food supply, provided that these substances fall into the categories covered by the various versions of the Delaney clause. On the other hand, substances known to be hazardous when consumed in large amounts can be permitted in the food supply in smaller amounts if they fall into categories to which the Delaney clause does not apply. For example, tolerance levels have been set for aflatoxins — a group of mycotoxins — in foods, even though substantial epidemiologic evidence indicates that they, albeit at levels much higher than the permitted amounts, contribute to the causation of human liver cancer. Aflatoxins, unlike almost all substances covered by the various Delaney clauses, can pose real risks under some circumstances, yet they are not subject to a zero-tolerance standard simply because they are naturally occurring substances, rather than intentional food additives.

The most unworkable application of the Delaney clause — that pertaining to pesticide residues in processed foods — was repealed in 1996. However, this outdated clause still applies to several other categories of food ingredients.

Proposition 65

In 1986, California voters approved an initiative that became the Safe Drinking Water and Toxic Enforcement Act of 1986, better known by its original name of Proposition 65. Proposition 65 requires the state to publish a list of chemicals known to cause cancer or birth defects or other reproductive harm. With reference to carcinogens, inclusion in the list is often based exclusively on the results of animal carcinogenicity tests. The

law prohibits California businesses from knowingly discharging amounts of the listed chemicals that exceed specified thresholds into sources of drinking water. Also (and this second aspect of the law is far more prominent and visible), Proposition 65 requires businesses to notify Californians about the presence of listed chemicals in consumer products. This notification can be given by a variety of means, such as by putting a label statement on a consumer product, posting signs at a workplace, distributing notices at a rental housing complex, or publishing notices in a newspaper.

Proposition 65 is essentially a “right-to-know” law. As with other “right-to-know” laws and regulations that have been promulgated in recent decades, it focuses on providing information rather than increasing public understanding of environmental health issues or placing information in an appropriate context. “Right-to-know” laws and programs are not based on an evaluation of health risk; rather, they frequently assume, erroneously, that any exposure to a substance may result in adverse health effects and are based on providing information about ostensibly hazardous substances even where there is no risk.

No scientific studies have investigated the impact of Proposition 65 on human health and therefore no evidence exists to indicate whether it has had any effect. Since no such studies seem to be planned, it is likely that the health impact of Proposition 65, if any, will never be known. Given that the law notifies citizens primarily about hypothetical risks, it is unlikely to protect human health in any meaningful way. What is known, however, is that Proposition 65 has increased the costs for companies doing business in California and increased the prices paid by California consumers.

9. HEALTH SCARES BASED ON ANIMAL CARCINOGEN TESTING

During the past half-century, positive results from animal carcinogen testing have prompted numerous health scares, some of the most memorable of which are

briefly reviewed here. The accounts presented here focus primarily on situations that occurred in the U.S.; in some of these instances, government authorities in other countries reached decisions that differed from those of U.S. authorities; substances taken off the market in the U.S. may not have had the same fate in other parts of the world.

Aminotriazole (Amitrole) in Cranberries – 1959

The very first cancer scare based on animal carcinogen testing occurred in early November 1959. The timing was extremely unfortunate because the scare focused on cranberries, a key component of the traditional American Thanksgiving dinner. Residues of the herbicide aminotriazole (amitrole), which had previously been shown to be carcinogenic in an animal experiment, were found in some shipments of cranberries. Although the dose of the herbicide that had been used in the animal carcinogen test was the equivalent of a person ingesting 15,000 pounds of cranberries every day for years, the presence of any amount of aminotriazole on the berries was considered unacceptable because of the Delaney clause. The announcement of the problem set off a nationwide crisis in which cranberry products were pulled off store shelves and restaurants stopped serving cranberry products. Although a testing program was quickly set up, and cranberries reappeared in the marketplace before Thanksgiving, a precedent was set for large-scale food scares based on the presence of trace amounts of “carcinogens” in foods.

DDT – 1962 to Present

The insecticide DDT (dichlorodiphenyltrichloroethane) was introduced into widespread use during World War II and became the single most important pesticide responsible for maintaining human health during the next two decades. DDT has been credited with saving at least 100 million lives that would otherwise have been lost to malaria or other insect-borne diseases during the 20 years when it was extensively used. In the 1960s, DDT came under suspicion both because of positive results in animal carcinogenicity tests and because it was suspected of harming wildlife, especially birds of prey. Although both the wildlife-related evidence and carcinogenicity data were contradictory and

inconclusive, and although epidemiologic evidence has not linked DDT to increased cancer rates in humans, DDT was banned in the U.S. in 1972.

Cyclamate — 1969

Cyclamate was used as a sweetener in low-calorie foods and beverages in the U.S. in the 1950s and 1960s. In 1969, the manufacturer of cyclamate reported that a high-dose study in rats had shown an excess number of bladder tumors. In response to this study, cyclamate was taken off the market in the U.S. Ironically, later research failed to confirm the supposed carcinogenic effect of this sweetener. Nevertheless, cyclamate has never returned to the U.S. market, although it is approved for use in about 50 other countries.

Nitrites — 1972

Sodium nitrite is a key ingredient in the meat curing process; it helps to give cured meats their characteristic color and flavor and inhibits the germination of the bacterial spores that cause botulism. Closely related substances called nitrates are naturally present in many vegetables. Nitrates and nitrites can react with other food substances to form nitrosamines, which are known carcinogens. In the 1970s, the results of an animal experiment seemed to indicate that nitrite itself was carcinogenic, and headlines suggested that foods like bacon or hot-dogs might pose a cancer risk to humans. This did not trigger a ban on nitrites because nitrites were “grandfathered” at the time of the Delaney clause, and thus regulators were not automatically required to ban them on the basis of an animal carcinogenicity finding but were allowed to place their risks into perspective. Further investigation uncovered major flaws in the animal experiment, and no further evidence has appeared indicating that nitrite is a carcinogen. Steps have been taken to modify the processing of cured meats in ways that greatly decrease nitrosamine formation.

Red Dye #2 — 1976

Red dye #2, also called amaranth, was one of the most widely used food-coloring agents during most of the twentieth

century. In 1970, a Soviet study indicated that it caused cancer in rats, but the study's results were considered questionable. Nevertheless, media coverage reported that foods like maraschino cherries could pose a human cancer risk. A study that FDA completed in 1975 was supposed to determine definitively whether red dye #2 had carcinogenic effects. Unfortunately, the study was very poorly conducted and had numerous flaws. The FDA attempted to draw conclusions from the data anyway and in 1976 revoked its approval of the dye, preventing any further use in foods.

Saccharin – 1977

Several years before saccharin came under suspicion, another sweetener used in low-calorie foods and beverages, cyclamate, had been taken off the market with little fuss or attention. But when saccharin came under scrutiny in 1977, all of America noticed, because banning it would have meant that no low-calorie sweetener would be available. Several long-term, high-dose studies in rats indicated that saccharin could cause bladder cancer. When the FDA announced its intention to ban saccharin based on those studies, public reaction was overwhelmingly negative. Acting in response to the massive public outcry, Congress passed a law that imposed a moratorium on the proposed ban and required warning labels on packages of saccharin-containing foods and beverages as well as warning notices in stores that sold them. Congress repeatedly extended the moratorium, and the FDA never banned saccharin. Subsequent research showed that the rat bladder tumors resulted from a high-dose phenomenon unique to that species. Epidemiological studies have not found a link between saccharin use and bladder cancer in individuals who consumed high doses of saccharin for most of their lives.

Ethylene Dibromide (EDB) – 1983

EDB was used as an agricultural fumigant to control nematode worms in citrus fruit. It was also used to prevent insect and mold infestation of grain stored over long periods of time, to eliminate insects from the milling machinery used to grind grain

into flour, and to control tropical fruit flies in fruit. EDB is an animal carcinogen, but its use was tolerated because experts believed that no residues remained on food. This assumption was eventually found to be incorrect. Minute residues of EDB were found in treated foods and in 1983, residues of EDB were found in groundwater as well. In 1984, after several months of frightening statements and miscommunication, EPA banned EDB.

Alar — 1989

Alar was the trade name for a compound containing the active ingredient daminozide, a hormonelike substance that can slow the growth of plants. Alar was used in the production of some varieties of apples. Several studies of both Alar and a byproduct of Alar showed increases in certain types of tumors in mice fed very high doses of either substance. The results of these studies were not appropriate for safety evaluation because the maximum tolerated doses (MTDs) of the test substances had been exceeded, and there was clear evidence that the test animals were experiencing toxic effects. Nevertheless, EPA chose to phase out the use of Alar. Shortly thereafter, an alarming segment on a TV news program, which described Alar as “the most potent cancer-causing agent in the food supply,” started a public panic over the safety of apples. Consumers’ concern became so great that the manufacturer of Alar withdrew the product from the market before the phase-out would have taken place. The company took this action in response to the concerns of apple growers, who were losing sales regardless of whether they used Alar on their crops.

Acrylamide — 2002

In 2002, Swedish researchers discovered that acrylamide, a substance that had previously been shown to be a carcinogen in high-dose animal tests, was present in baked or fried starchy foods, where it had been produced during cooking. This finding prompted news stories suggesting that French fried potatoes could cause cancer.

This discovery has prompted much research, but it has not led to any official recommendations for changes in eating habits or cooking practices. This response seems appropriate.

Acrylamide is only one of a large number of naturally occurring or cooking-induced animal carcinogens in food, and there is no reason to think that it poses any unique risk. Epidemiologic studies do not show any evidence of a cancer hazard to humans from ingesting traces of acrylamide. Nonetheless, acrylamide caused another “cancer scare.”

PCBs in Farmed Salmon — 2003

In the summer of 2003, an environmental group published a report that said that “cancer-causing polychlorinated biphenyl (PCB) levels” in farmed salmon were so high that they raised health concerns. News stories carried the message that eating farm-raised salmon could increase cancer risk.

In actuality, the levels of these substances were no higher than those in other foods such as meat and poultry, and well within the limits established by the FDA (although they were indeed higher than the levels found in wild salmon). PCBs are animal carcinogens, but decades of research, including studies of workers occupationally exposed to very high levels of PCBs, have not linked them to human cancer. Since there was no evidence of real harm from PCBs in farmed salmon and all samples examined met FDA and WHO standards, one might well ask why much was made of this issue in the first place. One answer may lie in the fact that some people are opposed to the idea of fish farming for other reasons, either philosophical or environmental. The presence of such parallel objectives may further confuse consumers who are trying to evaluate the true degree of risk involved in a health “scare.”

10. COSTS OF USING ANIMAL TESTING ALONE TO PREDICT HUMAN CANCER RISK

Overreliance on animal carcinogenicity testing as a predictor of human health has diverted both public attention and money from important and proven causes of cancer. In addition, it has sometimes led to the unnecessary

replacement of useful and safe products with inferior and/or more costly alternatives.

The failure to distinguish between true and trivial risks misinforms the public. As the adage states, “when everything is dangerous, nothing is.” When the word “carcinogen” is repeatedly used to designate anything and everything that causes cancer at high doses in laboratory animals, then the same word used in relation to observations in human populations loses its meaning. People cannot — and should not be expected to — distinguish the few real hazards that are hidden in lengthy lists of hypothetical ones.

11. RECOMMENDATIONS

In the absence of good epidemiologic data pertaining to the health effects of a particular substance, well-designed animal testing will continue to play an essential role in the prediction of human cancer risk — but so should common sense. Under no circumstances should a high-dose animal test on one or two species alone be used to classify a chemical as a potential human carcinogen or serve as the basis for a legal or regulatory action to ban a substance. Animal testing should not be viewed as sufficient to predict risk to humans — in the absence of additional supporting data, such as epidemiologic evidence or data pertaining to the mechanisms by which a substance exerts its effects in different species. Instead, positive results of animal testing, combined with knowledge of human exposure levels, should serve as an impetus for further research to determine whether the finding is applicable to humans.

Animal tests are an important and necessary part of the safety evaluation of a substance. However, a positive result in one or two high-dose animal tests does not necessarily indicate a risk to human health. On the other hand, if a chemical shows positive results in multiple tests in a variety of animal species, and if the dose-response pattern is confirmed, then the test results should

warrant serious attention and may justify efforts to limit human exposure to the substance in question. The system currently used to minimize the potential risk posed by aflatoxin in foods, through testing of foods and the establishment of action levels (maximum allowable levels of the substance in foods), provides a model for how such circumstances might be appropriately addressed.

Nothing in this monograph should be construed as implying that cancer is an unimportant public health problem or that efforts to decrease the cancer death toll are not worthwhile. Rather, the intent is to demonstrate that an all-out assault on “carcinogens” is not the most effective way to fight the war against cancer. Much more can be gained from other types of anti-cancer efforts — including tobacco education and dietary modification programs — than from attempts to purge from our environment trace amounts of substances that have caused cancer in laboratory animals at high doses. Such attempts are worse than useless because they can threaten our standard of living, our economic growth, and our prosperity as a society through misdirection of resources and unnecessary restrictions, while providing no material improvement in public health.

ACSH makes the following specific recommendations:

- The National Cancer Institute, under the leadership of the National Institutes of Health, should address the broad topic of using animal tests to predict human cancer risks and issue formal recommendations on the benefits and limitations of animal testing, preferably in the form of a document that would provide a basis for the National Toxicology Program and the Environmental Protection Agency to modernize their definitions and classifications of carcinogens to reflect the best current scientific evidence.
- The United States Congress should convene special hearings to develop new guidelines that would require these agencies to give priority in cancer prevention and cancer education efforts to data derived from human epidemiologic studies, incorporate into any discussion or proposed regulation the concepts of extent of exposure and dose response, insist on

the use of modern methods for systematically reviewing the totality of evidence from animal studies, acknowledge the multiple and far-reaching negative ramifications of relying on animal testing as the principal basis for extrapolation to predict human cancer risk, and reconstruct the risk assessment paradigm to bring it in line with up-to-date scientific knowledge.

- Even in the absence of a comprehensive reevaluation of the use of animal testing, the National Toxicology Program should reassess its criteria for the listing of substances as carcinogens to clearly separate human from animal carcinogens. After this separation, further discussion of known human carcinogens should include a reference to the conditions under which the substance raises human cancer risk and the relevance in terms of preventive action for the general consumer.
- The Environmental Protection Agency's guidelines for classifying substances into different categories by carcinogenic potential should be revised to take into account the reality that high-dose animal test results, considered alone, are poor predictors of human cancer risk.
- All remaining applications of the Delaney clause and California's Proposition 65 should be repealed.
- The news media should be discouraged from indiscriminately using the word "carcinogen," which implies the existence of a human cancer risk, when referring to substances that have merely been shown to cause cancer in high-dose laboratory tests in animals.

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see the full-length version of this monograph)

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Q. *What is the main purpose of ACSH's monograph and what are its conclusions?*

A. ACSH's main purpose is to explain that the current approach of fighting an all-out war against chemical or physical agents that cause cancer in animals at high doses—often erroneously termed “carcinogens,” as opposed to actual human carcinogens—is not an effective way to prevent human cancer. ACSH's main conclusion is that the animal tests used to determine whether a substance is a “carcinogen” in humans have inherent limitations and should not be viewed as sufficient, without substantial supporting data, to predict human cancer risk.

Q. *So, ACSH is opposed to animal testing? Hasn't animal testing been important in medical science?*

A. ACSH most definitely does *not* oppose the use of laboratory animals in product safety testing or in medical research. Experimentation in laboratory animals is an essential component of biomedical science. Without animal experimentation, most of the medical advances of the past century would not have been possible. In this monograph, ACSH is exclusively addressing the question of whether high-dose animal carcinogenicity tests accurately predict cancer risk in humans; ACSH is not criticizing animal experimentation in general.

Q. *If a substance causes cancer in experimental animals, doesn't that mean that it causes cancer in humans?*

A. Not necessarily. There are important differences between one species and another. Carcinogenicity tests are usually conducted in rats and mice, but rodents are not little humans. Their bodies often handle a substance in ways that differ from what happens in the human body. Also, it's important to realize

that in animal experiments, the chemicals being tested are given to the animals in extremely high doses. These high doses can cause responses in the animal's body that are quite different from what happens when animals or people are exposed to much smaller, more realistic amounts of the same substance. For example, when you give saccharin to rats in extremely high doses, it forms crystals in the urine that damage the bladder and increase the likelihood that bladder cancer will develop. But crystals don't form in the bladders of other types of animals given large doses of saccharin, and they don't form in rats when smaller, more realistic doses of saccharin are administered. Thus, the results of the high-dose test in rats don't apply to people's normal use of saccharin as a low-calorie sweetener.

Q. *Cancer is a lot more common nowadays than it was in the past. Is this due to chemicals in our environment?*

A. Cancer is indeed more common than it used to be, but it's not because people are being exposed to more cancer-causing chemicals in the environment. Instead, cancer has become more common because our life expectancy has increased. It's important to realize that cancer is largely a disease of older people; more people develop cancer today than a century ago because more people live long enough to get it. A second major reason why cancer has become more common is the increase in cigarette smoking during the twentieth century. Cigarette smoking is the number one cause of preventable cancer in the world. Cigarettes first became popular during and after World War I, and they increased in popularity for several decades after that, leading to a major epidemic of smoking-related cancers in the middle and late twentieth century. An additional reason why some types of cancer may seem more common is that modern diagnostic methods are finding some cancers that would never have been detected decades ago. Aside from the effects of aging, cigarettes, and more accurate and sensitive diagnostic techniques, there has been no epidemic of cancer in the United States.

Q. *Do chemicals play any role in human cancer?*

A. Yes, primarily in situations in which people are exposed to very high levels of cancer-causing substances. Cigarette smoking is an obvious example. Smokers expose their bodies to large amounts of tobacco smoke carcinogens, many times a day, usually for decades. Other examples of chemicals increasing cancer risk involve high-level, long-term exposures to various occupational and pharmaceutical substances. There have been instances in the past in which repeated, high-dose exposure to certain chemicals on the job without adequate protection led to increased risks of particular types of cancer. And it is well known that the use of certain medications, such as cancer chemotherapy drugs or estrogen replacement therapy, is associated with increased cancer risks; careful consideration must be given to the risks and benefits of such drugs before decisions are made about their use.

Q. *ACSH's monograph seems to imply that it may sometimes be acceptable to allow a substance to remain in foods even if that substance has been shown to cause cancer in an animal experiment. That may be an uncomfortable idea for some people. Do you think that people can really accept the idea of allowing "carcinogens" in the food supply?*

A. Many people find this idea uncomfortable until they learn that many animal carcinogens are *naturally* present in the food supply. A surprisingly large number of naturally occurring substances in foods turn out to be carcinogens when they're tested in the same kinds of animal experiments that are used to test pesticides and other synthetic chemicals. Lettuce contains naturally occurring animal carcinogens. So do mushrooms, apples, broccoli, bread, yogurt, mustard, soy sauce, and many other foods. We don't worry about eating these foods, and we don't need to. The amounts of carcinogenic chemicals that they contain are minute; they're many orders of magnitude lower than

the amounts that have caused cancer in animal experiments. These foods are safe to eat. Similarly, foods can be safe to eat despite containing synthetic substances that cause cancer in animals when given in extremely large doses.

Q. *Granted, there isn't much we can do about natural carcinogens, but wouldn't we be better off if we avoided all exposure to synthetic carcinogens?*

A. No, not really. Resources are limited, and money that is spent on one project cannot be spent on something else. Environmental regulation and control of so-called toxic substances are expensive. It is important to consider whether money spent in these ways is yielding improvements in public health that justify the cost. Also, we must realize that when a product is taken off the market, it may have to be replaced by substitutes that are less effective or more expensive. For example, the insecticides that have replaced DDT—banned primarily because it caused cancer in lab animals at high doses—are far more costly than DDT was, a crucial consideration in developing countries, where the need for protection against mosquitoes that carry malaria is greatest.

Q. *Are there any recent examples of situations in which the results of animal carcinogenicity tests may have led to unwarranted concerns about human health?*

A. Yes. One recent situation involves acrylamide. In 2002, Swedish researchers discovered that this substance, which is known to cause cancer when fed to rats in extremely high doses, is produced during the cooking of fried or baked starchy foods, such as French fries, potato chips, breakfast cereals, and bread. Although this discovery is new, acrylamide is not; people have been consuming it for hundreds if not thousands of years. There is no evidence linking acrylamide in foods to human cancer.

Another recent example involves trace amounts of PCBs in fish.

In 2003, an environmental group published a report saying that farmed salmon contained alarmingly high levels of PCBs, chemicals that at high doses are known to cause cancer in laboratory animals. Actually, the levels of PCB residues in the salmon were quite low and well within the limits established by the Food and Drug Administration for PCB residues in food. In fact, they were comparable to levels of PCBs found in other foods, such as meat and poultry. Much is known about the effects of PCBs in humans, and there is no evidence they have caused human cancer, not even in people who were exposed to very high levels of PCBs on the job for many years. But the charges were made anyway, on the basis of high-dose animal test results. There is no reason for people to be concerned about eating farmed salmon.

Q. *Are U.S. government agencies doing a good job of using animal carcinogenicity test results to predict human cancer risks?*

A. In ACSH's view, no. In all fairness, however, we must acknowledge that this is at least partly due to the existence of outdated laws that don't allow regulatory agencies to exercise good scientific and policy judgment. ACSH believes that regulatory efforts should be guided by the answer to the question, "Does this substance, as currently used and at the levels to which people are usually exposed, increase the likelihood of human cancer?" Unfortunately, under our current system, the question that's usually under consideration is, "Does this substance, when administered in extremely high doses, increase the likelihood of cancer in rats and mice?" That's the wrong question. If you address the wrong question, you're likely to come up with wrong answers.

Q. *If we can't win the war on cancer by eliminating carcinogens, what should we be doing instead?*

A. Focus on the proven risk factors. Don't smoke cigarettes. Eat a sensible diet. Stay active and keep your weight under

control. Drink alcoholic beverages only in moderation. Use sunscreen. Practice safe sex (some sexually transmitted diseases have been shown to increase cancer risk). Follow your doctor's guidance about screening tests. If you work with toxic substances on the job, follow safety guidelines scrupulously.

You've heard this type of guidance before, of course, but it's still the best advice. Many cases of cancer are caused by lifestyle factors that are well understood—such as cigarette smoking. Much more can be accomplished by addressing these factors. Chasing after trace levels of supposed “carcinogens” in the environment does nothing to reduce our nation's cancer toll. In fact, by diverting attention and resources from the proven risk factors, such misguided efforts actually decrease our ability to lower the cancer toll in humans.

Q. *Is there any circumstance under which ACSH would interpret the results of animal cancer tests as being predictive of possible human cancer risk?*

A. Yes. If a chemical when tested on several different species of animals increases the risk of cancer—and there is a “dose response” noted (that is, the risk of cancer increases as the dose of exposure is increased)—then ACSH believes it would be prudent to limit human exposure to that chemical. For example, a naturally occurring chemical called aflatoxin is sometimes found on peanuts. Aflatoxin causes cancer in a number of animal species and there is a dose response, with higher doses showing increased cancer rates in animal studies. It is U.S. federal policy to set limits on the amount of natural aflatoxin permitted in our food supply. This type of prudence—limiting human exposure to chemicals that cause cancer in many species—is starkly different from the current policies applied to synthetic chemicals that are labeled “carcinogens” and purged from the environment as a result of experiments only on rodents.

Q. *Isn't it better to be safe than sorry, to err on the side of safety by assuming that any chemical that causes cancer in*

lab animals may also pose imminent danger to humans?

A. This assumption—known as the “precautionary principle”—seems reasonable at face value but is actually both false and dangerous. While it is appropriate to consider potential dangers posed by chemicals, there are several compelling arguments against the use of the precautionary principle. First, the outright rejection of chemicals shown to cause harm in high-dose animal tests does not necessarily make us safer, and in many cases can do more harm than good. A perfect example is the insecticide DDT, which was banned primarily due to high-dose animal test results. As a direct result of the ban—and the subsequent implementation of inferior but “safer” alternatives—death rates from malaria have dramatically increased worldwide.

Second, the precautionary principle demands an all-or-nothing approach to risk analysis that neglects the complexity of public health issues and necessitates labeling chemicals “safe” or “unsafe.” Such categorizing fails to acknowledge that “completely safe under all circumstances” is an unattainable ideal and that there are ranges of possible risk levels; certain chemicals may pose high risk in some circumstances but considerably fewer, or none, in others. For example, saccharin’s ability to cause cancer in high-dose rat tests prompted the FDA to propose a ban on the sweetener. However, it was later determined that saccharin showed a carcinogenic effect due to a chemical mechanism *specific to male rats, and only at high doses*. In the same vein, subscribers to the precautionary principle fail to realize that it is impossible to prove a negative. If scientific progress were dependent on a guarantee of safety under all circumstances, we would never progress.

Finally, the precautionary principle neglects the concepts of “comparative risk-analysis” and net beneficial gain. In evaluating a chemical’s safety we must not only consider the risks it may pose to human health; those risks must be weighed against the risks associated with banning it. The precautionary principle

notoriously assumes that erring on the side of safety will result in net gain. Failure to perform a comparative risk analysis has, in many cases, led to the banning of chemicals whose net beneficial effects far outweigh either minor or hypothetical risks they pose. Certain pharmaceuticals serve as examples. While some chemotherapy drugs can increase risk of developing a second cancer after decades of aggressive treatment, the benefits of chemotherapy in these circumstances far exceed the risk of developing complications. Therefore, while the precautionary principle seems prudent at first glance, under more complete analysis it is both unwise and unscientific.

Q. *ACSH says that animal tests—particularly isolated ones—do not predict human cancer risk. But what else do we have? We can't test high doses of chemicals on humans to see if they cause cancer. Since we have no other option, why don't we just stick with the high-dose animal tests—even though we know they are not effective in predicting human cancer risk?*

A. It is without scientific merit to argue that a tool or method (in this case high-dose animal testing) should continue to guide cancer risk assessment despite the evidence that it is ineffective in predicting risks simply on the grounds “there is nothing else” but the status quo. Rodent cancer tests not only fail to predict human cancer risk accurately but divert our attention and limited resources from confronting and preventing the known causes of human cancer.

Second, ACSH does not reject animal cancer tests in their entirety—only the use of isolated animal cancer test findings to declare chemicals “likely” or “probable” human carcinogens, with all the regulation such a classification entails. We have stated that one or two high-dose animal cancer tests on rodents should NEVER be used to support the conclusion that a chemical should be classified and regulated as a human carcinogen “just in case.” On the other hand, ACSH concludes that if a chemical has been shown to increase cancer frequency in a variety of studies, using different species of animals—and if there is

a finding of a “dose-response” relationship (where lesser exposures to the chemical causes some cancer, but higher doses causes more)—it would be prudent to consider limiting exposure to that chemical.

Further, ACSH recommends, in cancer prevention interventions by regulatory, research, and educational agencies, that far more attention be given to reducing the toll of human cancer by focusing on risks that have been identified not through animal tests but through epidemiological studies of risks in human populations.

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