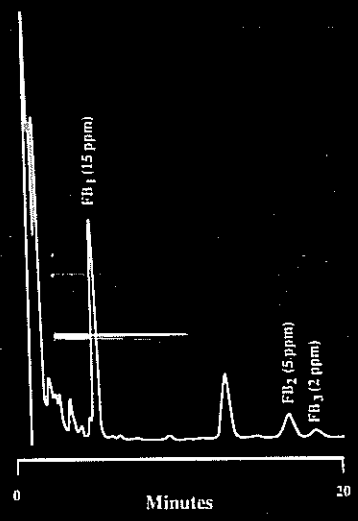
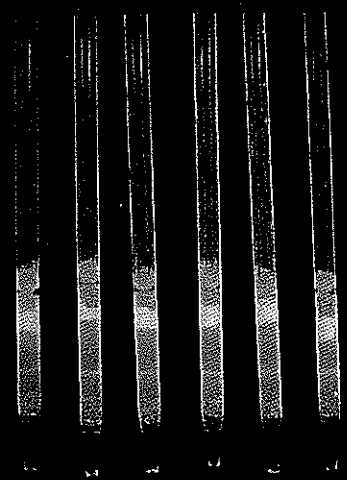
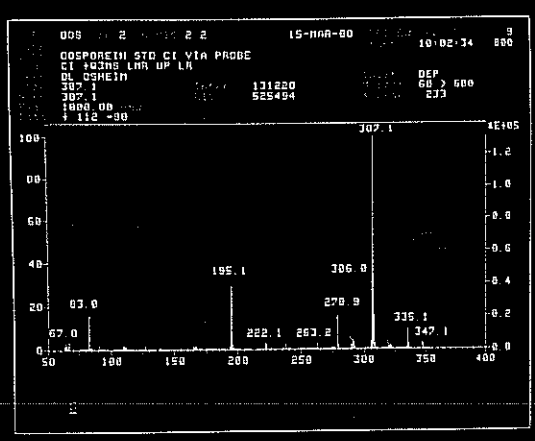
CAST
Council for Agricultural Science and Technology

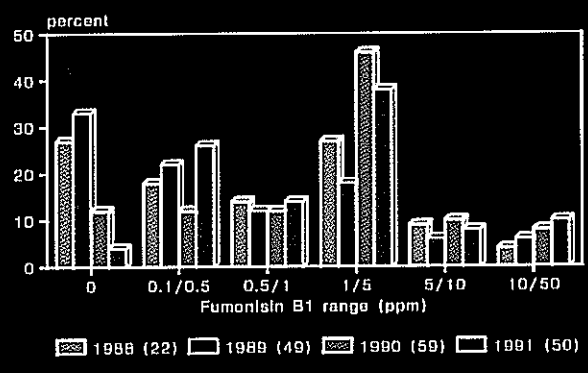


Food Safety

The Interpretation of Risk







Comments from CAST 1992-1 April 1992

Council for Agricultural Science and Technology

137 Lynn Avenue, Ames, Iowa 50010-7197 • (515) 292-2125

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The Council for Agricultural Science and Technology (CAST) is a nonprofit organization comprised of 29 member scientific societies and many individual, company, nonprofit, and associate society members. CAST's Board of Directors is composed of 48 representatives of the scientific societies and individual members, and an executive committee. CAST provides scientific information on key national issues in food and agriculture to policymakers, the news media, and the public. As an educational organization CAST takes no advocacy positions on issues.

The primary mission of CAST is the publication of task force reports written by scientists from many disciplines. The National Concerns Committee screens proposals from all sources and recommends to the Board certain topics for approval as task force projects.

Through representatives on the CAST Board of Directors, the member societies are responsible for the policies and procedures followed in developing, processing, and disseminating the documents produced. Depending on the nature of the publication, the society representatives nominate qualified persons from their respective disciplines for participation in the preparation. Aside from these involvements, the member societies have no responsibility for the content of any CAST publication.

Careful selection of topics, diverse writing groups, and active participation by all task force members assures readers that a balanced statement on agriculturally related social, economic, environmental, energy, and health issues will result.

The authors named in each publication are responsible for the contents. Task force members serve as independent scientists and not as representatives of their employers. They receive no honoraria, but are reimbursed for expenses. CAST publishes and distributes the documents.

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No. CC1992-1 April 1992

Council for Agricultural Science and Technology

Author

F. J. Francis, Department of Food Science, University of Massachusetts, Amherst, Massachusetts

Cover Photographs

Upper left — High Performance Liquid Chromatography/fluorescence tracing of o-phthalaldehyde derivative of fumonisin mycotoxins showing typical result in a corn sample containing fumonisins B_1, B_2, and B_3 at 15, 5, and 2 parts per million (ppm) or micrograms/gram. Slide courtesy of Frank Ross, USDA, APHIS, National Veterinary Services Laboratories, Ames, Iowa.

Middle left — Aflatoxin minicolumn (AOAC Official Methods of Analysis, Method 975.36), shown here under long-wave ultraviolet light with a series of corn extracts containing aflatoxin concentrations ranging from 0 to 20 parts per billion (ppb) or nanograms/gram. Blue band in the lower portion of each column is the aflatoxin. Slide courtesy of Frank Ross, USDA, APHIS, National Veterinary Services Laboratories, Ames, Iowa.

Lower left — Positive ion chemical ionization mass spectrum of oosporein, a mycotoxin produced by *Penicillium, Acremonium, Oospora,* and *Chaetomium* spp. Mass spectral methods typically detect and confirm the presence of chemical substances at extremely low concentrations, such as picograms/gram or parts per trillion. Slide courtesy of Frank Ross, USDA, APHIS, National Veterinary Services Laboratories, Ames, Iowa.

Lower right — The usefulness of accurate analytical methods is shown here in the results from a four year survey of Iowa corn for the presence of fumonisin mycotoxins. Because fumonisins have only been known for a short time, their significance is now being established. The distribution shows the presence of fumonisin B_1 in ppm every year for 1988, 1989, 1990, and 1991. The samples for this survey (number in parentheses after each year) were obtained from Dr. Charles R. Hurburgh, Iowa State University, Ames. The fumonisin was detected in the corn samples using High Performance Liquid Chromatography. Slide courtesy of Frank Ross, USDA, APHIS, National Veterinary Services Laboratories, Ames, Iowa.

Foreword

The CAST National Concerns Committee recommended to the Board of Directors that CAST prepare a report in the Comments from CAST series addressing issues related to the interpretation of risk in foods. The topic was approved by the CAST Board of Directors at the August 1991 board meeting.

Dr. F. J. Francis, Professor Emeritus of Food Science at the University of Massachusetts, was selected to author the report. Distinguished scientists with expertise in food chemistry, the CAST Editorial Review Committee, and the CAST Executive Committee reviewed the final draft. The CAST staff provided only editorial and structural suggestions and published the report.

On behalf of CAST, we thank Dr. Francis and the reviewers who gave of their time and expertise to prepare and review this report as a contribution of the scientific community to public understanding. Also, we thank the employers of the author and reviewers who made the time of these individuals available at no cost to CAST. The members of CAST deserve special recognition because the unrestricted contributions they have made in support of the work of CAST have financed the preparation and publication of this report.

This report is being distributed to members of Congress, the U.S. Department of Agriculture, the Environmental Protection Agency, the Food and Drug Administration, the Agency for International Development, Office of Technology Assessment, Office of Management and Budget, media personnel, and to institutional members of CAST. Individual members of CAST may receive a copy upon request.

Gale A. Buchanan
President

Stanley P. Wilson
Executive Vice President

Kayleen A. Niyo
Scientific Editor

Contents

Summary

Food safety involves a number of concerns, and probably the most important is food microbiology. However, this report is confined to chemicals. Four areas are involved: the accumulation of data, the interpretation of risk, the communication of risk, and the management of risk. This report concentrates on the accumulation of data and the interpretation of risk, primarily from chemicals. The accumulation of data depends primarily on animal and epidemiological models. The interpretation of risk depends on who is doing the interpreting, since "scientists" and "consumers" interpret risks in different ways.

The kinds of testing done to estimate risk to human health differ between substances that may cause cancer (carcinogens) and those that do not. Conventional testing of noncarcinogens uses an animal model (usually rodents) to establish the relationship between dosage level and adverse responses. The No-Observed-Effect-Level (NOEL) is used to calculate the Acceptable Daily Intake (ADI), which is usually one one-hundredth of the NOEL. This is referred to as the "hundred-fold" safety level. This approach works well for noncarcinogens but less well for carcinogens because the safety factor may have to be much higher than 100. Establishment of the safety factor for carcinogens has been criticized because feeding studies use a Maximum Tolerated Dose (MTD), which may increase the degree of cell division (mitogenesis). This in itself may increase the susceptibility to cancer. The current practice of determining whether or not a substance is a carcinogen based on a feeding study at the MTD level is not acceptable. Another criticism is the necessity to extrapolate from high doses to low doses. The shape of the extrapolation curve is important in deciding which extrapolation model is the most valid. In order to estimate risk with a higher degree of validity, more extensive animal data at doses below the MTD are required. A linear extrapolation, from high to low doses, by default due to insufficient data, is a highly questionable practice. Another uncertainty is the degree of accuracy when extrapolating data from animals to humans, particularly when there is a question as to whether the physiology of the test substance is the same in both animals and humans. Current practice of extrapolation, without the assurance of similarity in both groups, is on very shaky ground.

Epidemiological studies are useful in estimating risks. They compare the health of a larger group of persons that probably has been exposed to the test substances to that of a similar group, which probably has not. An advantage of this approach is that it eliminates the uncertainties of animal data. A disadvantage is that they are not usually very precise tools to establish degrees of risk, perhaps because of the size of the sample required, the difficulty in obtaining adequate control populations, and accurate reporting of data.

Difficulties with the interpretation of risk are illustrated by the examples Alar, Great Lakes fish, ethylene dibromide, pesticides, and asbestos. There are those who claim that all these substances are extremely dangerous to human health whereas others insist that the data indicate minimal risk. The methods of estimating risk by regulatory agencies, with the exception of the epidemiology approach, almost invariably are conservative. This is by design because the regulatory agencies usually err on the side of safety.

Advances in analytical methodology have made the Delaney Clause, which states that no amount of cancer causing substances can be added to our food, hopelessly obsolete. It is time to repeal the Delaney Clause and replace it with a "de minimis" concept. This would allow regulatory officials to disregard substances present in such concentrations that they are of no consequence.

The scientific community is concerned about the public perception of food safety. Reassurance of the consuming public in the safety of the food supply is too big a job for the regulatory officials and should be a mandate for the scientific community. We also need to strengthen both the technical capability and the public image of the U.S. Food and Drug Administration.

Introduction

Food safety in our society involves a number of concerns. Probably the most important is the area of food microbiology, but this report is confined to chemicals. The interpretation of risk in the chemical area involves four areas: the accumulation of data on risk, the interpretation of risk, the communication of risk, and the management of risk. All four have been surprisingly difficult. This paper will concentrate on the accumulation of data and the interpretation of risk, primarily from chemicals.

The interpretation of risk depends on who is doing the interpretation. Scientists accumulating and interpreting data may arrive at a vastly different set of conclusions than the "average" consumer. Decades ago, scientists may have enjoyed a popular belief that experts provided the information and interpreted it in a manner to avoid creating conflicts or generating undue public concern. This approach—"trust me"—is no longer publicly accepted and we have a whole new area of risk communication.

Scherer (1991) described the above situation in terms of three assumptions.

1. Science alone can provide "objective truths." Scientific conclusions are expected to be unbiased because they are founded on the scientific process. It has become evident that in the food safety area, some of the methods are liable to value judgements and personal interpretations. The judgements cannot be divorced from the initial weights given to specific data or even the number of observations required to support a reliable conclusion.
2. Scientific and technical experts are the only possible sources of "correct" risk information. This implies that the lay public lacks the information, skills and perhaps the motivation to understand the technical problems. Some have even suggested that their reaction is emotional and irrational. However, the social scientists have indicated that the reactions are neither emotional nor irrational but based on a different set of criteria. For example, risk experts have focused on "hazard," a function of the degree of risk and how likely it is to happen. This can be described as objective or theoretical risk as opposed to subjective or perceived risk. Perceived risk may be influenced by many other factors, which have been combined as the degree of "outrage." Some of these outrage factors are the degree of fairness, familiarity, degree of choice, control, decision making process, and others. The degree of outrage arises when decisions, over which they have no control, are inflicted on individuals and are perceived to be unfair. Examples of high hazard-low outrage may be tobacco and alcohol abuse. High hazard-high outrage could be drunken drivers or nuclear weapons. Low hazard-low outrage could be water chlorination or aflatoxin. Examples of low hazard-high outrage may be pesticides in foods and food irradiation (Groth, 1991). Freudenburg (1988) believes that the dichotomy between "real" and "perceived" risks has been overemphasized particularly in cases involving controversial technologies. Regardless, it is a very real phenomenon in our society.
3. The public is a passive receiver of risk information. By regulating the supply of information, the public behavior can be channeled towards a desirable outcome.

It is becoming evident that all three assumptions are unworkable and unwise and a better method of communication is overdue. We can alleviate the communication problem by attempting to understand the motivation of some groups to interpret the situation for their own purpose. Another complicating factor is a tendency to transform concerns from one area to another. For example, the economic difficulties conceivably faced by milk producers with the introduction of bovine somatotropin (BST) are transferred to concerns about the safety of the milk. Concern about production methods for veal were translated into concerns about the safety of the meat. Concerns about the Chernobyl nuclear power plant disaster have reflected on the safety of irradiated food. Thompson (1990) described the BST controversy as "silly concerns" but they are none-the-less real, and it behooves risk communicators to try to understand these issues. But first, let us look at the accumulation of data.

1 The Principles of Animal Testing

Introduction

Animal testing forms the basis of most of the calculations on hazards and risks in our environment. Animals are chosen because of the obvious moral questions about feeding potentially toxic materials to humans. Usually the animal models for food additives are mice and rats but sometimes chick embryos, rabbits, dogs, monkeys, fish, nonhuman primates, and other species are used. Hopefully, most credibility would be given to experiments using animals that metabolize the test substance in a manner similar to humans, and also have a range of tissue and organ responses similar to humans.

Conventional Testing for Toxicity

When a food or chemical is fed to animals, the effects range from no observable response to beneficial effects, unfavorable results, or death, depending on the nature and quantity of the material ingested. The changes may be gross such as loss of weight or hair, or microscopic as indicated by examining tissues on slides under a microscope. There often may be changes in biochemical activity, such as enzyme action, observable only by chemical analysis.

Figure 1.1 shows a simplistic approach to animal feeding (Francis, 1986a). When dosage is plotted against response, usually a response above the zero dose is considered an adverse effect, whereas responses below the zero dose level are considered beneficial.

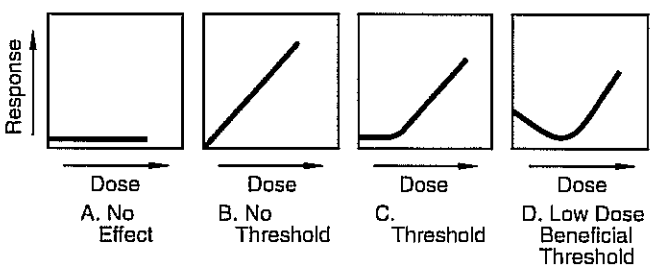

Figure 1.1. Four diagrammatic responses to a toxic chemical (Francis, 1986a).

In Figure 1.1A the compound has no observable effect on the response. Substances such as starch and sugar at reasonable doses would show this effect. There is a toxic effect for both sucrose and starch (the LD_{50} for male rats fed sucrose and starch is 42 g/kg body weight and 200 g/kg body weight/24 hours respectively) (Boyd, 1973). Death caused by sucrose was due to loss of control of bodily fluids and death from starch was due to gastric rupture. Experiments such as these normally are considered outside the realm of conventional toxicity testing. In Figure 1.1C there is a "threshold" dosage below which there is no observable adverse effect. A threshold exists because animals can detoxify, metabolize, or excrete quantities of almost any substance. At higher doses, the animals' ability to handle the compound is exceeded and a toxic effect is observed. Most compounds are in this category. In Figure 1.1B there is no threshold and even an infinitesimally small dose elicits an unfavorable response. Labelled by some as the "one-molecule" hypothesis, it has been argued by some scientists that a "one-hit," i.e., a single molecule change in DNA, is capable of creating a situation leading to the growth of a cancer. Another example of the no-threshold response is the effects of radiation. To a chemist, the one-hit theory is difficult to accept because of the size of Avogadro's number. There are 6×10^{23} molecules in every mole of a chemical. With this number of molecules, and their obvious ubiquity, one would expect considerable interaction. Ames and Gold (1990a) calculated DNA hits per day from an endogenous oxidant to be of the order of 10^5 for rats and 10^4 for humans. Thilly (1991), who believes that at least two genetic changes in a human cell are required before it becomes cancerous, estimated that at birth the human liver has already experienced 450 mutations in every gene. If this is true one has to wonder why cancer is not more prevalent. Also, recent evidence does not support the one-molecule theory. Scientists attempting to insert foreign genes into plant or animal tissue have found a surprisingly large DNase enzyme activity that rapidly removes foreign DNA, including damaged DNA. This is probably one of the most potent human repair mechanisms that mitigates against the one-molecule theory. The existence or nonexistence of the one-molecule theory

is theoretically subject to experimental verification, but it probably never will be because of the infinitely large numbers of experimental animals required to test for the effects of infinitely small doses. In Figure 1.1D there is a range in which the addition of a chemical has a beneficial effect leading to an optimal level. As the dosage is increased a harmful effect is observed. Essential nutrients such as vitamins A and D and selenium are in this category but the classic example is oxygen.

The situation shown in Figure 1.1B is amplified in Figure 1.2 (Food Safety Council, 1982; Francis, 1986b). This illustrates a simplistic situation in which four levels (including zero) of a test substance are fed to rats, with the logarithmic dose plotted as the abscissa and response as the ordinate. The first step is to determine the response above the base level. For example, with tumor production, there is a normal base level at which specific tumors develop regardless of the treatment. The response plus the normal base level is labelled in Figure 1.2 as the total response, sometimes called the Total Adverse Response (TAR). These data are very useful in determining the validity of an experiment because TAR values which differ significantly from normal laboratory experience are indications of problems with the experiments. The next step is to determine the maximum daily dose above the control at which the response is zero or the same as the control. In Figure 1.2 this is labelled as the no-observed-adverse-effect level (NOAEL) or the no-observed-effect level (NOEL), the no-affect level, or the threshold level. The NOEL is then divided by a safety factor to obtain the "acceptable daily intake" (ADI). The ADI is usually expressed as mg of the test substance per kg body weight per day. Expressing the ADI based on body weight minimizes the size differences between animals. Expressing the dose as mg per day minimizes the differences in life expectancy between animals.

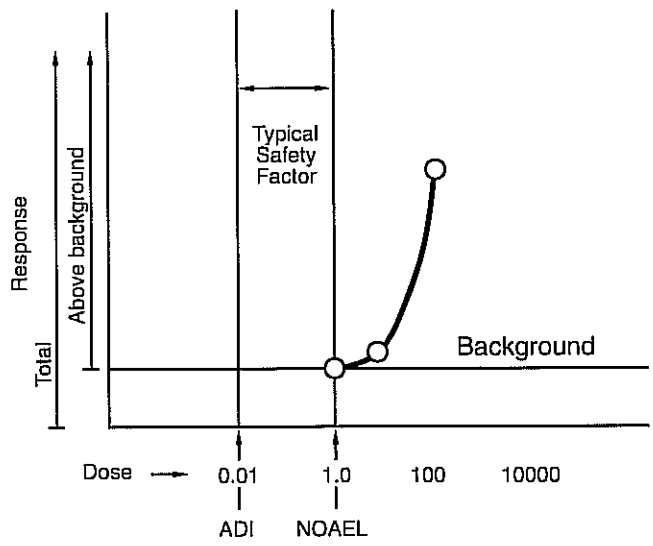

Figure 1.2. A simplified dose response experiment with an animal model (Food Safety Council, 1982). ADI = acceptable daily intake; NOAEL = no observed adverse-effect level.

The safety factor to calculate the ADI from the NOEL is usually understood to be 100. The rationale for using 100 is that humans may be 10 times more sensitive than rats, and humans themselves may vary in sensitivity by as much as 10 times. Thus, $10 \times 10 = 100$ (the 100-fold safety factor). Scheuplein (1989) pointed out that the 100-fold safety factor has to be tempered with judgement. For example, the 100-fold safety factor may not provide a high enough level for some nutrients needed to satisfy nutritional needs to maintain health. Toxicities for vitamins A and D, iron, and certain amino acids may be reached at levels less than 10 times higher than those recommended for optimum nutrition. Scheuplein also stated, "If frank teratogenic effects are observed and confirmed in a second study, judgement would be needed to decide if a larger safety factor should be considered. If the substance was not a carcinogen, the FDA would generally use a 1,000-fold safety factor as an additional margin to ensure against exposing consumers to levels of a chemical capable of producing irreversible developmental effects. If reversible developmental effects are seen, such as retarded skeletal and soft tissue development or decreased fetal weight, the FDA would apply the usual safety factor of 100." There is one more general step. The ADI is an amount but the allowable level in foods is a concentration. Therefore, the FDA has to estimate the probable intake of the food containing the additive and the data are used to calculate the acceptable level. If the quantity of the additive required for good manufacturing practice is lower than the ADI, the additive may be approved for other foods, at a later date, until the ADI is reached. This general approach to food safety testing has had good acceptance worldwide and it is generally believed to be a very successful approach. However, it is not applicable to carcinogens.

Bar (1991) commented that novel foods and other nontraditional substances that could be consumed in significant amounts by humans will require sophisticated safety testing and interpretation of results. Citing lactose and sugar alcohol as examples of secondary carcinogens, calculation of the ADI in the traditional manner is not possible since the usual 100-fold safety factor may not apply. The factor may be closer to one. "An integrated interpretation is

required that takes results from nutritional, biochemical, endocrinological or food technology research into account, if needed."

Testing for Carcinogenicity

The 100-fold safety factor described in the preceding section is not suitable for carcinogens for three reasons. First, the order of magnitude is much greater—up to 5,000 instead of 100. Second, with humans, there could be a lag factor of 20 years or more. Third, some investigators do not believe that a threshold or tolerance level exists. In addition, five concepts introduce uncertainties into the calculations, namely: (1) choice of animal model, (2) mode of exposure, (3) level of dosage, (4) method of extrapolation from high doses to low doses, and (5) need for extrapolation of the data from animals to humans. Because of these uncertainties, the usual procedure in the past has been to adopt a very conservative approach, but all of the above assumptions have been severely criticized in recent years. The conservative approach may lead to serious economic impacts and this has been criticized by the federal Office of Management and Budget (OMB). The OMB (Anonymous, 1990) in an overview section of its regulatory program stated, "Conservatism in risk assessment distorts the regulatory priorities of the federal government, directing societal resources to reduce what are often trivial carcinogenic risks while failing to address more substantial threats to life and health."

The Animal Model

A standard bioassay is performed on both sexes of two species of animals at three dose levels plus a control. Thus, with 50 animals in each group of rats and mice, a total of 800 animals are required (Page, 1977). The whole procedure for testing and evaluation of one chemical takes up to three years at a cost of approximately $1,000,000 (American Council on Science and Health, 1990). With only 800 animals, a relatively weak carcinogen may escape detection. A substance would have to induce cancer in 7 to 10% of the exposed animals in order for there to be a good chance of detecting carcinogenic action having statistical significance with a test of this size. Yet, 800 animals is probably the most that can be used because of the problems and expense in handling very large numbers of animals. Another concern is that even with the assumed close genetic relationship between rats and mice, they do not always react the same. Of the 190 chemicals tested on rats and mice by the National Cancer Institute (NCI), 98 were positive in at least one test species, and of the 98, 54 were positive in only one species (American Council on Science and Health, 1990).

When a given substance is being tested, usually an animal model that has the highest sensitivity to that particular substance is chosen. Yet even within one species, the strains may vary significantly. Wolff and Gaylor (1991) of the National Center for Toxicological Research reported that estimates of carcinogenic potency for 2-acetylaminofluorene (2-AAF) for four mouse hybrids varied by a factor of 2 to 6. They reported that the $B6C3F_1$ hybrid used by the National Toxicology Program generally showed the highest carcinogenic potency. With studies on dioxin, the guinea pig was chosen for prediction purposes because of its sensitivity to dioxin. The LD_{50} values were estimated to be, in terms of μg/kg body weight, one for the guinea pig, 45 for female rats, and 5,000 for hamsters respectively (American Council on Science and Health, 1991). The use of the most sensitive animal model shows a conservative bias in animal testing.

2 The Mode of Exposure

The preferred route of exposure is that which matches as closely as possible the route of human exposure, whether by ingestion of food or water, inhalation, skin, or injection. Chemicals may be injected by intramuscular, intraperitoneal, intravenous, or subcutaneous routes. Chemicals in solution can be painted on the skin, consumed in the diet or drinking water, or inhaled. If a substance is unpalatable it can be given by stomach tube. The administration of chemicals dissolved in corn oil and administered by gavage became suspect several years ago when more problems developed in control groups of rats getting oil without the test chemical as compared with control groups without the oil (Haseman et al., 1985). Historical review of the data indicated that mononuclear cell leukemia in untreated controls had increased from 10% in 1970 to about 50% in 1990, but, apparently the rate of increase is decreasing. Some investigators have attributed this and the reduced survival in long-term rodent studies to the use of "ad libitum" feeding with diets optimized for maximum growth. The elder rats simply get fat, which reduces their chances of survival. The overnutrition also increases their susceptibility to tumor formation. The growing problems of less than 50% survival and significant weight reduction in chemically dosed groups in over 50% of the chronic studies received the attention of the National Toxicology Program (NTP). Unfortunately the 1985 NTP "Workshop to Optimize Diets for Rodents in Chemical Carcinogenicity Studies" was never published. The present situation clearly overstates the risk so there is a need for more research in this area.

3 The Level of Dosage

Usually the Maximum Tolerated Dose (MTD) is used in animal experiments. The MTD is the largest dose that the animals can tolerate without endangering the health of the animals. The National Toxicology Program's Bioassay Program currently defines the MTD as the dose that creates no more than a 10% loss in body weight when compared with the controls. Often the MTD is one-half of the dose at which half of the animals die (the LD_{50}). Many animal experiments consist of three levels, zero (the control), the MTD, and one-half or one-quarter of the MTD. Ames and Gold (1990a,b) reported that more than half of the chemicals tested in rats and mice at the MTD have been found to be carcinogenic. Of the 427 chemicals tested in both species, 350 (82%) were synthetic industrial chemicals and about half (212/350) were classified as rodent carcinogens. About 77 natural chemicals have been tested in rats and mice of which about half (37/77) are rodent carcinogens. Ames and Gold think that this proportion is too high and may be due to the method of testing (Ames et al., 1990a,b; Marx, 1990).

It has been suggested that the high percentage of positives in the testing program was due to an intentional bias in the selection of compounds that have suspicious chemical structures. This may have been true earlier but lately the choice of chemicals for testing has been because of their wide industrial use—i.e., they were high-volume industrial chemicals, pesticides, food additives, dyes, or drugs (Gold et al., 1989a,b).

The use of the MTD in carcinogenic testing that evolved in the 1970s was based on three premises:

1. Only a small proportion of chemicals would have carcinogenic potential.
2. Testing at a high dose would not produce a carcinogenic effect unique to the high dose.
3. Chemical carcinogenesis would be explained by the mutagenic effect of chemicals.

Now, Ames and Gold (1990b) believe that all these assumptions are wrong. They postulate that administration of chemicals at the MTD increases cell division (mitogenesis). This increases the rate of cell mutation (mutagenesis) due to the increased rate of cell activity and, thus, increases carcinogenesis. They claim that any condition that causes cell death and subsequent cell division may predispose an animal to cancer. Examples are liver damage by alcohol, the effect of excess salt on stomach cancer, and chronic inflammation from exposure to asbestos or cigarette smoke. Chronic infections from viruses, bacteria, or schistosomes may cause cell death followed by mitogenesis. The human hepatitis B virus, a major cause of liver cancer, and the human papilloma virus 16, a major risk factor for cervical cancer, both cause cell proliferation. Hormones can cause mitogenesis and are well known as risk factors for breast and other cancers. There are many other examples.

The relationship between mutagenesis and mitogenesis has been used to support the above claims (Ames and Gold, 1990b). About 40% of chemicals that test positive at the MTD level are not mutagenic in *Salmonella*. If mitogenesis itself is mutagenic, the nonmutagens are likely to be acting by this mechanism. Ames and Gold (1990b) state that in rodent cancer tests, mutagens are more likely to be (1) carcinogenic, (2) positive in both rats and mice, (3) toxic at lower doses, and (4) the cause of tumors at multiple sites. The mitogenesis concept was confirmed in ingenious studies with pairs of mutagenic isomers such as 1-vs 2-nitropropane and 2,4-vs 2,6-diaminotoluene in which one was carcinogenic and the other was not. Although both are mutagenic only the carcinogen was mitogenic.

Huff and Haseman (1991) defended the use of the MTD and lower levels in their studies with nearly 400 long-term rodent carcinogenic studies. In pesticide studies, 122 site-specific carcinogenic effects were observed for 31 positive chemicals. For 91% of these effects a numerical increase in these same tumor types was observed at exposure levels below the MTD. "Thus, not one of the 31 positive agrochemicals is a 'high-dose only' carcinogen." Yet, in an assay with only an MTD and one or two lower levels, the dosage is still very high, possibly a thousand times higher than actual human exposures.

Clearly the levels of dosing will influence whether a compound is labelled a carcinogen or not. The use of the MTD is a conservative approach.

4 The Extrapolation from High to Low Doses

The use of high doses in testing for carcinogenicity has been the subject of much controversy but clearly there is no reasonable alternative. The argument is not with the use of animal doses higher than that which would be encountered by humans, but with the concept of how large should the experimental doses be. There is a real problem in designing experiments to detect cancers at a very low incidence. For example, with a U.S. population of 253,000,000 people, an increase of any event of 0.5% represents over 1,000,000 people. This is clearly unacceptable if the event is cancer. However, to identify with statistical confidence a 0.5% increase would require a minimum of 1,000 animals in a test group, assuming that no tumors were present in the control group (Klaassen and Eaton, 1991). If one wishes to decrease the odds, the number of animals required increases very rapidly. For example, suppose the upper limit, using the 90% confidence limits for a group of 1,000 animals yielding no tumors, was 2.3. To reduce the upper limit of risk to two tumors per one million at the confidence limit of 99.9% would require a negative result in a group of over 3 million animals (Lawrence, 1976). It is impractical to use groups of animals this large, so the alternative is to administer a larger dosage to obtain a response with a reasonable number of animals—i.e., 40 to 50 animals. The assumption is that the effects at the high doses can be extrapolated to very low doses. Conventional wisdom has been to draw a straight line from the last data point to the origin—the so-called linear extrapolation concept. However, evidence is accumulating that the effects at very low levels are not linear but are better explained with a curvilinear response. This produces a dosage effect curve that has been described as a "hockey-stick" shaped curve. Figure 4.1 is a diagrammatic representation (Food Safety Council, 1982). Clearly, an extrapolation from high to low doses is needed and the current controversies are concerned with how it should be done.

The main purpose of the extrapolation is to estimate a hazard related to the toxicity of a compound as determined by animal testing. "Hazard" has been used interchangeably with "risk" since both involve consideration of intrinsic toxicity and the circumstances specific to exposure. The process thus becomes "risk

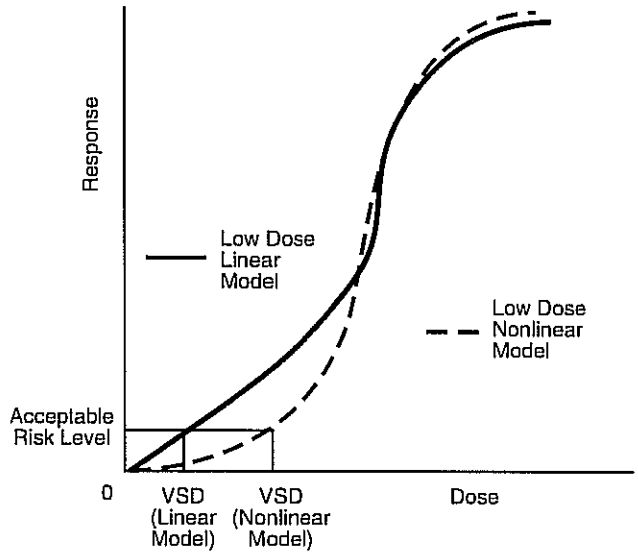

Figure 4.1. The calculation of the virtually safe dose (VSD) with a low-dose linear and a low-dose nonlinear mathematical model (Food Safety Council, 1982).

assessment." The National Academy of Sciences (National Research Council, 1983) has divided risk assessment into four major steps: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization. Risk assessment is followed by risk management, which involves choosing the most appropriate public policy alternative for regulatory action.

The dose-response data can be used to determine the NOAEL as described previously or the lowest-observed-adverse-effect level (LOAEL). The difference between the NOAEL and the LOAEL will depend on the spacing and number of the doses. A number of mathematical models have been developed for extrapolation of the high to low doses (Table 4.1). The reader is referred to Klaassen and Eaton (1991) for a detailed description. A number of mathematical terms for risk have been developed, but one, the "virtually safe dose" (VSD) seems to be gaining acceptance, possibly because it is easy to explain. The VSD represents the daily lifetime dose that would yield a theoretical extra risk above the background risk of some "acceptable" level

Table 4.1. Models used in risk extrapolation (Klaassen and Eaton, 1991)

Statistical or distribution models	Log - probit Mantel-Bryan Logit Weibull
Mechanistic models	One-hit Gamma multihit (k-stage) Multistage (Armitage-Doll) Linearized multistage Stochastic two-stage (Moolgovkar-Venson-Knudsen)
Model enhancement	Physiologically based pharmacokinetics (PB-Pk) Time-to-tumor responses

Table 4.2. Differences in model-derived estimates of virtually safe doses (VSDs) at the 10^{-6} risk level, relative to the one-hit model (Food Safety Council, 1980)

Carcinogen	One-hit	Armitage-poll	Weibull	Multihit
Botulinum toxin Type A	1	1	50,000	150,000
Sodium saccharin	1	8,000	10,000	30,000
Aflatoxin	1	23	1,200	8,000
DDT	1	2	60	180
Vinylchloride	1	1	1×10^{-7}	2×10^{-8}

(often 1 in 1 million). By design, the calculation of the VSD is likely to result in a conservative estimate. Table 4.2 shows estimates of VSDs for five chemicals and four calculation models. Because the dosages vary considerably for each chemical, the VSDs are normalized to the value (one) for the One-Hit model for purposes of calculation. There is obviously a very large variation in VSD depending on the method of calculation. Of the 14 compounds listed by the Food Safety Council (1980), vinyl chloride is the only one that showed a Multi-Hit VSD lower than the One-Hit model. This effect of vinyl chloride was only evident when the highest dose level was considered. In another study Fumento (1990) quoted an 1980 Occupational Safety and Health Administration (OSHA) report as saying that saccharin ". . . shows a range of variation of more than five million-fold in estimates of human risk, although all the estimates were derived from the same set of experimental data on rats. . . ."

There is increasing evidence that the response at very low dosages is nonlinear. In one experiment, the so-called "megamouse" (Anonymous, 1980) or ED01 study, 24,000 female mice were fed a known carcinogen (2-AAF). The experiment was deliberately designed with enough animals to detect a 1% increase in the prevalence of tumors. The dose-response curve for liver cancer was equivocal since the curve was nearly linear down to the lowest level of AAF. In contrast, the curve for bladder cancer was definitely nonlinear. Cohen and Ellwein (1990) attributed the nonlinearity of this genotoxic carcinogen to a combination of carcinogenicity and cell proliferation.

A large double generation study on saccharin involving 2,500 second generation male rats was conducted by the International Research and Development Corp (International Research and Development Corporation, 1983) to determine the shape of the dose-response curve. The incidence of cancers declined sharply with decreases in dosage, and the use of a linear model grossly overestimated the true risk of bladder tumors.

Recent reports on dioxin have supported the sigmoid-shaped response curve (Hansen, 1991b; Roberts, 1991a,c). This was widely circulated by the news media because dioxin had the reputation of being the most potent carcinogen known. It was a contaminant present in the controversial agent—Agent Orange—used to defoliate the jungles in the Vietnam war. The active agents in Agent Orange were a mixture of 2,4-D and 2,4,5-T herbicides. In the absence of relative data on humans, the U.S. Environmental Protection Agency (EPA) assumed the worst and set the ADI at 0.006 picograms per kg body weight per day (one microgram = 1,000,000 picograms). Canada and the World Health Organization set the ADI at 10 picograms/day. Marilyn Fingerhut and coworkers (1991) at the National Institute for Occupational Safety and Health, in an exhaustive study of mortality records of all U.S. workers exposed to dioxin from 1942 to 1984 proved that the response of tumor formation to dioxin concentration was indeed sigmoidal. Furthermore the risk estimates for dioxin at very low concentrations were indeed too high by a factor of 10. A reduction of 10 would remove the concern about the sub parts per trillion amounts of dioxin found in milk from contaminants in cardboard milk cartons. This finding spurred the EPA to search for a new model to predict cancer risk from dioxin (Hansen, 1991b; Roberts, 1991b). Recent risk reevaluation (Keenan, 1991) produced a figure at least 16-fold lower than previous estimates.

An examination of all the large dose-response studies on different chemicals completed by 1981 showed that 27 of the 31 studies indicated a sigmoidal shaped curve (American Council on Science and Health, 1990). More than one-third of the curves indicated that decreasing the dose by a factor of five would decrease the tumor risk by a factor of 25, not the 5 expected from a linear response.

Conventional wisdom indicates that tumor production is a multi-faceted phenomenon and only an understanding of the mechanisms will enable one to choose the appropriate model for dose extrapolation. The current linear extrapolation clearly is conservative.

5 The Receding Zero

The interpretation of the risk in very low concentrations of chemicals in the environment is complicated by the ability of the analysts to detect ever smaller amounts (Figures 5.1 and 5.2). In the early 1900s, analysts could detect milligram quantities of impurities (10^{-3}). Around 1950, the limit had fallen to microgram amounts (10^{-6}). In the 1970s, due to the introduction of High Performance Liquid Chromatography (HPLC), the detection limits were decreased to nanogram quantities (10^{-9}). In the same era, with a combination of gas chromatography and mass spectrometry (GCMS), picogram (10^{-12}) quantities could be detected easily. With extensive clean-up and optimization, the limits could be pushed to femtogram (10^{-15}) quantities. Lately, papers have appeared in the literature reporting analyses at attogram (10^{-18}) levels. Perhaps the ultimate to date is the claim that High Performance Capillary Electrophoresis (HPCE) is capable of detecting milliattograms (10^{-21}) (Stevenson, 1989). Since Avogadro's number is 6×10^{23} molecules per mole, this sensitivity is pushing the analysis to the molecular level. Clearly, there is no way that animal experimentation can cope with the infinitesimally small quantities that modern analytical chemists are capable of finding. The question for interpretations of risk is not "Is the compound present?" but rather "What does it mean?" The ability to analyze for infinitely smaller quantities has rendered the Delaney Clause, which states that no carcinogens shall be added to the food supply, hopelessly obsolete.

The Delaney Clause is an anachronism in food regulation. In the legislative deliberations prior to the passage of the 1958 law, the Delaney Clause was not expected to have much impact, because only about 50 carcinogens were known and these could be easily regulated in food by other sections of the food safety code. When the number of carcinogens reached several thousand, with carcinogenesis defined by the conditions described in this report, the thinking changed. Officials in the FDA developed a number of methods to circumvent the Delaney Clause (Taylor, 1991). Theoretically, the Delaney Clause would apply to all intentional components of the food supply, both natural and synthetic, since nearly all food components become "additive" at one time or another. Congress clearly never intended this, so the prior sanctioned or "grandfather" clause was developed. The second development was the "generally recognized as safe" (GRAS) concept. The third effort, and the FDA's first formal effort to incorporate risk assessment into decision making about foodborne carcinogens, was the DES proviso. This allowed carcinogenic animal drugs and animal feed additives to be approved, provided no residue was found in any edible portion of the animal. The DES proviso in 1962 led to the fourth effort, the sensitivity-of-method (SOM) approach, which defined the meaning of the word zero. The fifth effort involved the "constituents" policy, which allowed regulatory officials to essentially disregard contaminants provided that their risk was low enough, and provided that the major ingredients themselves were noncarcinogenic. The sixth effort involved the development of the "de minimus" concept, which came from the judicial doctrine of *de minimis non curat lex*. Freely translated, this means "the law does not concern itself with trifles." The de minimis principle was challenged in court by Public Voice, a consumer group, and a judge ruled for Public Voice, but only for color additives. The case for other food additives remains for another day. The FDA has been very creative in its efforts to interpret the Delaney Clause in a continuing effort to balance food safety with innovation and food availability. Regardless, the Delaney Clause is an anachronism and should be repealed. There will be opposition, as for example, Haas (1991) predicted a "major confrontation" between industry and consumer groups over the perception that the food safety laws are being weakened. It is unfortunate that this clash between old legislation and new science may be interpreted as positive for human well-being by one group and negative by another. The United States is the only country in the world with a Delaney Clause and it is time to change.

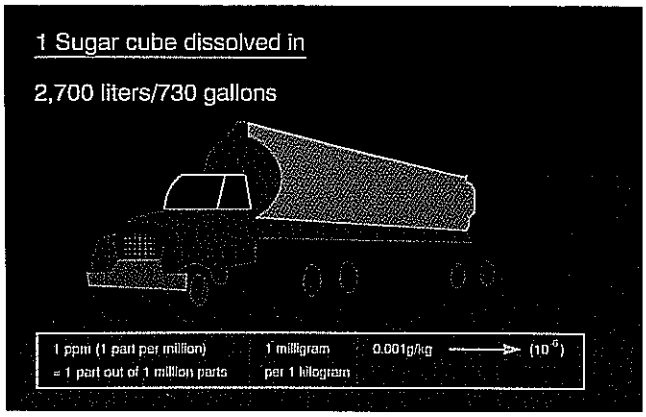

Figure 5.1. Illustration of the meaning of parts per million (ppm). Photograph courtesy of Dr. F. J. Francis, University of Massachusetts, Amherst.

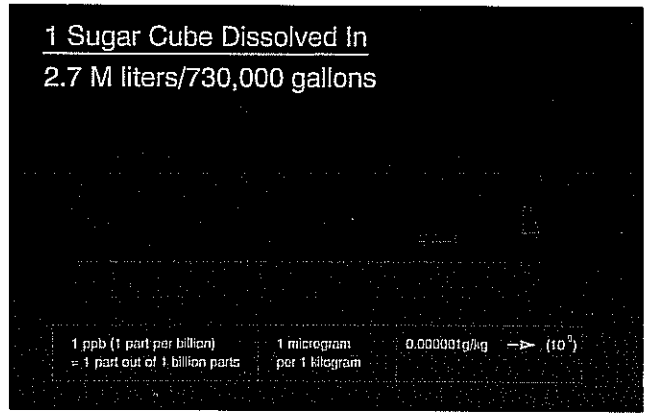

Figure 5.2. Illustration of the meaning of parts per billion (ppb). Photograph courtesy of Dr. F. J. Francis, University of Massachusetts, Amherst.

6 The Extrapolation From Animal to Human Data

The use of animals in testing for carcinogenicity and other toxic effects is based on the conservative assumption that chemicals that cause cancer in animals may also cause cancer in humans. To date, all chemicals known to cause cancer in humans also cause cancer in animals, with the possible exception of arsenic. However, the reverse prediction does not appear to hold. There are hundreds of chemicals that are classified as carcinogens in at least one animal species but it has not been possible to establish that they also cause human cancer. Examples are saccharin, cyclamate, and DDT (American Council on Science and Health, 1990). This may be partially because of the limitations in determining the causes of human cancer. In seven cases (aflatoxin, 4-aminobiphenyl, diethylstilbestrol (DES), bischloromethylether, melpholan, mustard gas, and vinyl chloride), chemicals found to be animal carcinogens were later found to be human carcinogens (Szepsenswol, 1963). To date, of the 54 known human carcinogens, evidence of carcinogenicity was first obtained by animal studies in eight of them (Huff and Haseman, 1991). In view of the hundreds of chemicals (International Agency for Research on Cancer Publications, 1987) suspected of being animal carcinogens, the rate of prediction for human carcinogens is very low. However, in support of the animal data, if a compound produces similar results in several animal species, it is likely that the effect is a basic aspect of metabolism common to most animals including humans. For example, aflatoxin is carcinogenic in mice, rats, fish, donkeys, turkeys, marmosets, tree shrews, and monkeys. DES is carcinogenic in mice, rats, hamsters, frogs, and squirrel monkeys. Benzidine is a carcinogen in rats, hamsters, and dogs. Napthylamine is carcinogenic to mice, hamsters, dogs, and monkeys. Asbestos causes cancer in mice, rats, hamsters, and rabbits (American Council on Science and Health, 1990). It should come as no surprise that all of the above substances are also carcinogenic to humans.

The extrapolation from animal to human data is complicated by a possible species difference. Bar (1991) listed two examples. Increased calcium absorption triggered by polyol consumption (mannitol, sorbitol, xylitol) results in adrenal medullary tumors in test rats. Unlike humans, rats have a genetic susceptibility to adrenomedullary proliferation. "We can dismiss the rat studies as not relevant to humans." Also Leydig cell tumors are spontaneous in rats and lactose drives up the incidence of such tumors due to an effect on the hormone levels. "Lactose is not a human carcinogen: Leydig cell tumors are a one-in-a-million incidence in humans. Overall, these findings are not relevant to humans." Bar (1991) also pointed out four misconceptions:

1. An increased incidence of neoplasia indicates carcinogenesis.
2. All carcinogens are equally dangerous.
3. Increasing dose increases sensitivity.
4. Neoplasia is independent of nutritional and hormonal status.

Clearly, a knowledge of the metabolism of a compound is essential for an understanding of the validity of extrapolating animal to human data.

The species difference may be absolute or a matter of degree. For example, Zeise (1991) pointed out humans are 1,000 times more sensitive to benzidine than are animal models, and conversely, aflatoxin is 20 times more potent in rats than in humans. In the absence of definitive data for humans, a conservative approach assumes that compounds that are carcinogenic to animals are also carcinogenic to humans.

7 The Epidemiological Approach

Epidemiology is the science that attempts to determine the pattern of human diseases by studying the relationships between factors that are suspected to be causative agents. It can identify the association between events that may be risk factors but it usually cannot determine cause and effect.

Epidemiology has been very useful in determining risk factors in humans. For example, the International Agency for Research on Cancer (1989) identified 14 chemicals and industrial processes that they associated with human cancer. This was in addition to cigarette smoking, alcohol, and radiation, which have been identified previously as causing cancer. A number of additional probable causes were noted and about 40 risk factors for various human cancers were listed. Doll and Peto (1981) published an often-quoted epidemiological study of the avoidable risks of cancer in the United States (Table 7.1). Clearly, tobacco and diet are the most important risk factors. The estimates of Doll and Peto for risk factors in the diet agree with those of Wynder and Gori (1977), who placed the proportion at 40% in men and 60% in women. The contribution to cancer of less than 3% from pollution and industrial products (Doll and Peto, 1981) is contrary to public opinion that pesticides cause cancer.

Scheuplein (1990, 1991) used the epidemiological estimates of Doll and Peto to check the estimates of risk from animal data (Table 7.2). Obviously, the epidemiological estimates are not subject to the vagaries for animal data as described in the preceding sections. Cancer accounted for 22% of all deaths

Table 7.1. Proportion of cancer deaths attributable to various factors (adapted from Doll and Peto, 1981)

	Percent of all cancer deaths	
Factor or class of factors	Best estimate	Range
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food additives	<1	−5[a]–2
Reproductive and sexual behavior	7	1–13
Occupation	4	2–8
Pollution	2	<1–5
Industrial procedures	<1	<1–2
Medicine and medical procedures	1	0.5–3
Geophysical factors	3	2–4
Infection	10	1–?
Unknown	?	?

[a]Allowing for a possibly protective effect of antioxidants and other preservatives.

Table 7.2. Risk estimates of various food categories containing carcinogenic substances (adapted from Scheuplein, 1990)

Food category	Amount of food consumed per day	Estimated amount of carcinogens	Risk	Percent of total risk
Traditional food	1,000 g	1,000.0 mg	7.61×10^{-2}	98.8
Spices and flavors	1 g	10.0 mg	7.61×10^{-4}	0.98
Indirect food additives	20 mg	2.0 mg	1.5×10^{-4}	0.20
Pesticides and contaminants	200 μg	0.1 mg	7.6×10^{-6}	0.01
Animal drugs	1 mg	0.1 mg	7.6×10^{-6}	0.01
Food preparation (charred protein)	1 g	0.1 mg	7.6×10^{-6}	0.01
Mycotoxins	10 μg	1.0 μg	7.6×10^{-6}	0.0001
Total risk			7.7×10^{-2}	

in the United States in 1984 (U.S. Department of Health and Human Services, 1988). Assuming a dietary risk of 35%, the risk of death from dietary exposure to carcinogens is $0.22 \times 0.35 = 0.077 = 7.7 \times 10^{-2}$. In order to apportion the carcinogenic risks from food, specific classifications of food are needed, and within each category, the amount consumed, the levels of carcinogens, and the relative potency of each carcinogen. The reader is referred to the original paper (Scheuplein, 1990) for a detailed explanation of the calculations and assumptions in Table 7.2. Surprisingly over 98% of the total risk from dietary exposure to carcinogens comes from traditional food (Ames et al., 1990a,b). A number of reviews have been written on naturally-occurring toxic compounds in foods (e.g., Ames, 1983; Ames et al., 1987; Havender and Meister, 1985; Liener, 1969; National Research Council, 1966, 1973, 1982) and this aspect is well known to experts but apparently not to the general public. This is a very complex area. From hundreds of thousands of known low molecular weight compounds that naturally occur in foods, only about 120 have been identified as carcinogens. This is probably due to the lack of a database. It is inevitable that many more cellular metabolites will be shown to be carcinogens (Scheuplein, 1990). Surprisingly few plant toxins have been tested for carcinogenicity. Among 1,052 chemicals tested in chronic cancer trials, only 52 are naturally-occurring plant pesticides. Of these, 27 are carcinogenic and are present in many foods at levels thousands of times higher than synthetic pesticides (Ames and Gold, 1991). This should be a high priority area for research in the future; however, it has limited consumer appeal.

The naturally-occurring toxins create another dilemma—the double standard between synthetic and natural food components. If standards for safety testing currently applied to synthetic compounds were applied rigorously to natural components of food, there would be chaos in our food supply. Most scientists would agree that this would be a ludicrous development, but it does pose an interesting question.

Epidemiologic studies are an excellent way to predict trends and, thus, point the way toward productive mechanistic studies. However, they do lack precision primarily because of problems in distinguishing adequate control groups with no exposure to the event being studied. This is sometimes referred to as "noise in the system" in electronic parlance. For example, suppose a new treatment can reduce the occurrence of heart attacks by 20%. Since heart attacks kill over 500,000 people in the United States each year, a trial to measure the 20% reduction reliably in one year, would require a placebo-controlled clinical study involving more than 200,000 subjects (Mann, 1990). Accordingly, most of the studies involving a few dozen patients are a waste of time and provide little information, except perhaps to point the way for future research. Peto recognized this when he persuaded 5,000 British doctors to participate in trials to determine the effect of aspirin on heart attacks, since six earlier experiments were too small to give a definitive answer. Clearly, there were not enough medical doctors in Britain to achieve statistical reliability so he assisted Dr. C. H. Hennekin in forming the Physicians Health Study in the United States. This study involved 22,000 doctors and provided conclusive evidence for the beneficial effect of aspirin for heart disease.

Probably the most important information from the heart attack trials was the development of meta-analysis by Richard Peto (Mann, 1990). Simply, this is a statistical method of combining a large number of small related trials into a large clinical trial. Peto is currently applying his approach in a study called the Antiplatelet Trialists Collaboration, which combines over 200 individual studies. Of course, it is possible to run one large trial but they can be very expensive. For example, the Multiple Risk Factor Intervention Trial (MRFIT) (Anonymous, 1982) for coronary heart disease (Kolata, 1982, 1984) was reputed to cost $115 million, and the Coronary Primary Prevention Trial, $150 million (Kolata, 1987). It is interesting that size alone is no guarantee of success since the results of both trials were equivocable. Yet the trials are getting larger. The latest is the Women's Health Initiative, which involves 140,000 postmenopausal women and is reputed to cost $500 million (Palca, 1991). These large clinical trials probably fit the classification of animal testing rather than epidemiological studies, but the requirement for a statistically adequate sample size is common to both. It is unlikely during current economic conditions that many very large multi-million dollar trials will be attempted, thus the meta-analysis approach may be very useful. It surely has a place in toxicity testing for foods and the environment.

The approach to apportion risk as suggested by Scheuplein (1990), or even the ability to determine the risk of a compound in food using animal models, must rely on an accurate data base on food consumption. The single most important survey of eating habits in the United States is the Nationwide Food Consumption Survey conducted approximately every ten years by the United States Department of Agriculture (USDA). It is unfortunate that the $7.6 million 1987–1988 survey was so flawed that the results were almost useless (Marshall, 1991a). It was anticipated that

data from the survey would be used in the allocation of low income benefits, food stamps, school breakfast and lunch programs, and the dietary goals for "Healthy People 2000." Of interest to food safety, the Natural Resources Defense Council used what some have described as inflated figures for apple juice consumption in infants and children in their report on Alar entitled *Intolerable Risk: Pesticides in our Children's Food* (Sewell and Whyatt, 1989). A better data base may have helped to clarify part of this confusion. The USDA should be encouraged to repeat this survey as soon as possible.

8 Alternatives to Animal Testing

A number of procedures have been suggested to partially or completely replace animal tests. These include microbiological tests, tissue culture, plants, chick embryos, fish, computer simulations, and structure determinations. Structure determinations have been very useful since a number of chemical structures have been shown to be carcinogens. Particularly important are those that are genotoxic, i.e., they react with DNA. Some animal rights groups have carried the concept to the point of saying that computer simulations can predict carcinogenicity and we do not need animal testing. However, the procedure does not work very well with nongenotoxic carcinogens and few of us would want to ingest a compound whose safety had been determined entirely by computer. Nevertheless, it is a very useful screening tool.

Another test known as the "Ames Test" has received wide publicity (Ames, 1977). It depends on the ability of a carcinogen to cause mutagenesis, and is based on the supposition that mutagenicity and carcinogenicity are highly correlated. Now it is believed that all chemicals identified as carcinogens are not necessarily mutagens, particularly those which are nongenotoxic (epigenetic) since they do not react with DNA.

Ames and coworkers have developed a procedure for ranking risks, which does not depend on the extrapolation from high to low dose and from animals to humans (Ames et al., 1987; Gold et al., 1989b). It has been called the HERP index from "human exposure–rat potency." The rat potency is determined from the TD_{50} index. This is defined as ". . . the dose rate (in mg/kg/day) that, if administered chronically for a standard period—the "standard lifespan" of the species—will halve the mortality-corrected estimate of the probability of remaining tumorless throughout that period. . . ." (Ames et al., 1987). The TD_{50} is similar to the LD_{50}. However, the TD_{50} takes into consideration the background incidence of tumors and premature deaths that are unrelated to exposure (Klaasen and Eaton, 1991). Table 8.1 shows some selected HERP values. Ames (1988) insists that this index is simply a method of comparing risks and should not be used to calculate risk ". . . because we do not know how to extrapolate to low doses."

The use of small aquarium-type fish, such as the guppy, has been suggested for a number of reasons (American Council on Science and Health, 1990). They reproduce quickly, have a very low incidence of background tumors, and exhibit a high sensitivity to chemicals. Water-soluble chemicals are easily administered and large numbers of fish can be treated in a small space. The disadvantages are a small existing data base and more uncertainty in extrapolating to humans.

It seems unlikely that rodent assays will be displaced in the near future. All existing data should be considered before rendering a final judgement. The ultimate outcome is already subject to considerable judgement and the use of alternative testing procedures may allow for more flexibility.

Table 8.1. The HERP[a] index for some selected foods (Ames et al., 1987)

Substance	Daily exposure	HERP Index
Wine	8 oz	4.7
Beer	12 oz	2.3
Mushroom	1	0.1
Peanut butter	1 oz	0.03
Tap water	1 quart	0.001
PCBs	Average diet	0.0002
DDT	Average diet	0.0003
EDB	Average diet	0.0004
Phenobarbital	60 mg	16

[a]HERP = Human exposure-rat potency.

9 The Interpretation of Data

The preceding chapters illustrate that there is considerable uncertainty about the determination of risk by any approach. Certainly, all the data from animal testing have a statistical range of values above and below the mean. This means that it is possible to choose the most conservative value (worst case scenario) for each step of the process and come up with a high risk value many times higher than the low risk value. And both the high and low values have equal statistical credibility. Thus, it depends on the motivation of the individuals interpreting the data as to whether they wish to emphasize low, medium, or high risks.

The motivations for risk interpretation may vary considerably. At one extreme, a consumer activist organization that depends on public outrage for its success in funding will probably adopt a worst case scenario. At the other extreme, a food company with a sophisticated analytical laboratory and a quality control program to protect the integrity and public image of its products will probably judge its success by the lack of public exposure. Government regulatory organizations, who sometimes judge their success by an equal degree of criticism from either side, probably fall between the two extremes. Regardless there is ample room for mischief-making in all three scenarios. Perhaps five examples will suffice.

Alar

The Alar episode represents a textbook example of how to generate public outrage. The Natural Resources Defense Council (NRDC) hired a public relations firm to generate as much public exposure as possible for their report on Alar in food (Sewell and Whyatt, 1989). The CBS "60 Minutes" television program and subsequent press exposure was considered by NRDC to be a resounding success (Fishbein, 1990). The NRDC predicted that preschool children had a risk of getting cancer from Alar at a rate of 240 per million population. The EPA had already discredited these "old" data obtained before 1985 and established its own risk of 9 per million population. The NRDC sued the EPA to force it to ban Alar, but a Washington State appeals court dismissed the case. The NRDC then decided to take its case to the people via the public media. The "old" data were based on an unsymmetrical dimethylhydrazine (UDMH), a breakdown product of Alar, fed at a level of 28 mg/kg body weight. More recent data from the EPA at 3 mg/kg body weight showed no carcinogenicity. The EPA then ordered Uniroyal, the maker of Alar to quadruple the dose to 13 mg/kg, even though the EPA had estimated the exposure of the U.S. citizen to be 0.000047 mg/kg. Uniroyal complained that it would exceed the MTD and it did. The high dosage rate caused tumors and the EPA banned Alar. Subsequent research in Britain found ". . . no risk to health." A WHO/FAO panel later found that Alar or UDMH was not carcinogenic and set an ADI of 0.5 mg/kg body weight (Marshall, 1991b). It seems clear from recent data that the economic costs of the ban on Alar were unjustified.

Fish in the Great Lakes

Contamination of the Great Lakes is another example of a worst case scenario. The history of the pollutants dumped into the Great Lakes is appalling and a number of environmental associations have resolved to sensitize the public to this situation (Gorrie, 1991; Hanson, 1991a; Myers and Colburn, 1991). The National Wildlife Federation (1989) reported that one meal per week of large lake trout from Lake Michigan created a risk of 1 in 50 for humans to die of cancer. The NWF does not test its own fish. In this case, the data were ostensibly from a 1985 University of Wisconsin study. The NWF reported that the PCB content of 25 large lake trout averaged 8.3 ppm. *Outdoor Life* (Gibbs, 1989) obtained the raw data from the University of Wisconsin and of the 150 lake trout tested, only seven had a PCB content higher than 8.3 ppm. In addition, NWF reported analyses including skin and obvious fat, where most of the PCBs are stored, yet recommended in the same booklet that the skin and fat be discarded. The Center for Environmental Toxicology at Michigan State University was asked to comment on the NWF booklet. They said, ". . . it seems clear to knowledgeable toxicologists at Michigan

State University that the risk is small and likely to be negligible when fish consumption is part of a varied diet" (Gibbs, 1989). The impact of such a report on the sports fishery in the Great Lakes was predictable and unfortunate. The efforts to clean up the Great Lakes are laudable but a questionable interpretation of the data is not the way to accomplish it.

Ethylene Dibromide

The ethylene dibromide (EDB) situation illustrated a different type of problem. EDB had been used for many years as a gasoline additive, soil fumigant for nematode control, fumigant for fruit and processing equipment, and as a means of protecting stored cured grains against insects and subsequent mold growth. In 1983, it became apparent that EDB at levels of 400 ppm in the diet caused cancer (Weisberger, 1984). The EPA set a limit of 30 ppb in ready-to-eat cereal products, 150 ppb in foods that needed cooking before eating (flour, muffin mixes, etc.), 900 ppb in raw grains, and also announced a phase-out of EDB. Even though a case might be made that EDB in the amounts anticipated in the human diet might be "de minimis" or inconsequential, the decision was moot because of the Delaney Clause. The decision was effectively a phase-out or an immediate ban. A number of states called for an immediate ban. For example, Massachusetts called for a limit of 1 ppb even though this level would put 90% of the available flour in violation. The essentially zero level was requested even though workers exposed in the manufacture of EDB to doses up to 10,000 times higher than consumers showed no ill effects. There was no epidemiological data to indicate an adverse effect. Fortunately, the EPA prevailed with a 30 ppb tolerance, and although a large amount of cereal products was destroyed, a catastrophic disruption of the cereal supply did not happen.

Pesticides in Food

The pesticide area, which has probably contributed to many of the current consumers concerns, poses another way of interpreting data. Pesticides are by definition toxic in plant or animal tests and, by analogy, to humans. Consumer concern is understandable, and possibly misplaced (Utt, 1991), but it has led to sophisticated oversight programs by the EPA, FDA, USDA, and many states to ensure safety. The National Cancer Institute (NCI) recently stated that they are ". . . unaware of evidence which suggests that regulated and approved pesticides in foods contribute to the toll of cancer in the U.S." (Adamson, 1990). A more recent review (Henderson et al., 1991) reached the same conclusion. Campt et al. (1991) of the Environmental Protection Agency commented, "What we can say with assurance is that the Environmental Protection Agency does not believe our nation faces an imminent health crisis because of our use of pesticides." Despite many assurances that pesticides are safe, the public concern continues, possibly because of how the risks are calculated. For example, one National Research Council/EPA report calculated the risk of cancer from tomatoes over one human's lifetime to be 859 per million people (Council for Agricultural Science and Technology, 1990). They assumed that all chemicals allowed on tomatoes would be present at the legal tolerance level. Archibald and Winter, using actual residues found by analysis, calculated the risk to be 0.33—a 2,600-fold difference (Council for Agricultural Science and Technology, 1990). Similar data with apples indicated a 21,000-fold difference. In determining theoretical risks, the EPA assumes three factors: (1) all the crop is treated, (2) all residues are at the maximum level, and (3) all consumers eat a fixed proportion of food in their diet (Aidala, 1990). The use of theoretical levels of pesticides rather than actual analyses is surely an example of the worst case scenario.

Asbestos

The asbestos problem provides another twist in the interpretation of data. It is essentially an environmental problem but became a food safety problem when asbestos fibers were found in water, presumably because of general environmental contamination and the use of asbestos-cement pipes for water and sewer mains. They were also found in beverages, ostensibly because of asbestos filters.

From 1900 to 1970, asbestos was a very widespread industrial commodity, used primarily for fire-proofing, insulation, brake liners, and many other products. In the 1970 it was found to cause mesothelioma, a type of lung cancer, in shipyard workers using asbestos for fireproofing and insulation, and in a number of other industrial applications. The problem was mainly with the amphibole type of fibers as compared with the serpentine variety. Ninety-five percent of asbestos used commercially is of the serpentine (chrysotile) type. The undeniable risks associated with exposures for many years to high fiber concentration in the air were extrapolated to low exposures with the predictable public discussion of relevancy. The EPA mandated

that exposure to asbestos fibers be managed and under the Clean Air Act, required that schools submit a plan indicating how they would deal with damaged asbestos. A fine of $5,000 per day would be levied for noncompliance. The EPA said manage, not remove, asbestos but the mandate was interpreted as removal and a new industry was born—the asbestos abatement industry. It even has an institute—the Health Effects Institute-Asbestos Research (Health Effects Institute-Asbestos Research, 1990). The removal of asbestos from homes, schools, and commercial buildings was estimated to cost $50 to 150 billion (Abelson, 1990). Mossman (1990) and others questioned the relevancy of the extrapolation figures and the public debate was joined.

The Manville Corporation, a major merchandiser of asbestos products, was faced with over 100,000 lawsuits to pay for health costs and the potential cost of removal of asbestos insulation. This forced the company into Chapter 11 bankruptcy, from which it emerged in 1988 by setting up a trust fund to settle claims. As of March 1991, the trust had disbursed over $150 million for 25,000 claims but this is only a fraction of the 100,000 impending claims involving over $2 billion. Clearly, the monetary stakes are high in this type of situation.

The EPA hoped to enforce a ban on all asbestos products by 1997, but it is unlikely to be able to do so. A federal appeals court in New Orleans rejected the 1989 EPA regulation in view of the lack of evidence that present uses of asbestos constituted a sufficient risk hazard (Rosewiez, 1991). The public debate on risks did provide some interesting insights.

Aroesty and Wolf (1986) reported up-dated risks of asbestos exposure to median fiber levels in the air (0.0004 fiber/cm^3). They reported that estimated lifetime risk ($\times 10^6$) for male smokers was 292 for lung cancer. The comparable risk for nonsmokers was 27. This is an interesting example of the allocation of risk. Conventional wisdom would say that the current economic costs associated with regulations concerned with very low levels of asbestos are unjustified.

10 Conclusions

The interpretation of risk in most of the conventional methods of calculation is essentially a conservative approach. This is true for the mode of exposure, the extrapolation from high to low doses, the extrapolation from animal to human data, and the interpretation of the data. But over-emphasis on conservatism can be a very costly approach for our society. Clearly the stakes are very high for applications of modern technology to our food production, nutrient, and public health delivery systems.

It is both unproductive and unrealistic to simply suggest to regulators that they use a less conservative approach. We must develop a data base and the methodology that will allow decisions on risk to be made on sound scientific principles. This will involve greater understanding of the metabolism of compounds under review in order that appropriate choices of animal models, mode of exposure, dosage levels, and relevancy to humans can be determined. Better knowledge of the shape of the response curve is vital for extrapolation from high to low doses and this will involve larger numbers of dosage levels particularly in the lower dose ranges. This is an expensive process but the costs of conservative regulation may be much higher.

Clearly, the present use of the MTD in animal feeding is unjustified, as is the use of the linear extrapolation model and the extrapolations from animal data to humans. The defenders of the status quo state that in the absence of data to the contrary, we should adopt a conservative approach. Perhaps, but when multimillion dollar decisions are based on adverse animal responses only at the MTD level, one wonders at their relevance to our society. It would seem logical to accept interpretations more clearly related to reality even if it involves more time and money to obtain more relevant data.

It is likely to continue to be a fact of life that animal experiments will continue to be the main avenue of data accumulation. Then it behooves investigators to choose animal models that metabolize the test substance in a manner similar to humans and also have a range of tissue and organ responses similar to humans. Experiments in which the responses of humans and animals differ are of little, if any, value in predicting human risk. For compounds already in the environment, epidemiology data can be very useful. It is likely that the original risk estimations for Alar, PCB and other contaminants in the Great Lakes, dioxin, some pesticides, and low concentrations of asbestos fibers will be lowered. This will emphasize the need for more realistic interpretation of risk, particularly in view of the enormous economic considerations.

Food and Drug Administration officials have been coping with the Delaney Clause for 34 years in their attempts to create a balance between food safety and innovation and food availability. But the amazing advances in analytical methods have made the Delaney Clause hopelessly obsolete. This creativity in circumventing the Delaney Clause is commendable but it is high time to repeal the clause. The "de minimis" concept has the support of nearly all the regulatory agencies including the EPA, FDA, and USDA and should be supported by the scientific community.

A major concern of regulatory agencies, industry, and academia today is the public perception of food safety. In the food and food production areas, for example, the FDA with their publication, *The FDA Consumer*, and the EPA and USDA through their numerous workshops have tried to address this problem. However, it is not in their mandate to launch major consumer education programs and shoulder most of the effort. The problem is too large and the rest of the scientific community will have to assist. There is a particular need to strengthen both the technical capability and the public confidence in our regulatory agencies.

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