Of Mice and Mandates:
Animal Experiments, Human Cancer Risk,
and Regulatory Policies

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Executive Summary

Laboratory animals have been used for many years to determine whether chemicals in foods, pharmaceuticals, and other products might cause cancer and other health problems in human beings; and animal testing continues to play a role in determining the safety of products for human use. Yet an increasingly sophisticated understanding of cancer formation (carcinogenesis)—along with growing doubts about how confidently we can infer human health effects from test results in quite different animal species—has begun to change both scientific assessment practices and the legal and regulatory requirements based on them.

In the real world people constantly encounter many known carcinogens, both synthetic and natural, without developing cancer. These substances appear in air, water, and foods; indeed, some are generated naturally within the human body itself. Five hundred years ago the Swiss physician Paracelsus introduced the basic toxicological concept that a substance’s poisonous capacity depends on the dose. Vitamin A, for example, is necessary in small quantities for vision but at much higher doses is toxic to the liver and heart.

This concept is often lost sight of in the interpretation of results from animal tests involving very high doses of a single test agent. A new perspective is warranted in light of the huge cost of animal testing and in light of the all-too-common misinterpretations of the results of animal tests with respect to their predicting of human health risk. In developing that new perspective, we should consider the following points:

- Toxicity testing using animals plays an essential role in the development of drugs, industrial and agricultural chemicals, consumer products, food additives, and cosmetics. When properly conducted and interpreted, animal testing will continue to be a valuable source of information on the potential toxicity of chemicals to humans.

- Differences in physiology and anatomy between humans and mice, rats, and other species often make it difficult to apply animal results confidently and directly to human health. Animal testing should not be viewed as sufficient, in the absence of additional supporting data, to predict risk to humans.

- Some products have been labeled carcinogenic solely as a result of unrealistically high doses having been force fed to laboratory animals. Excessive focus on unrealistic, theoretical carcinogenici-
ty risks of some products diverts resources and attention from documented threats to human health.

• Improved means of interpreting animal test data—along with emerging testing alternatives, increasing understanding of the process of cancer causation, and changes in risk-assessment methodology—will permit a more critical, real-world view of risks to human health.
I. Introduction

It all began with cranberries.

Cranberries disappeared from Thanksgiving dinner in 1959 when the U.S. Secretary of Health, Education and Welfare (now Health and Human Services) announced that an herbicide used in the cranberry bogs could cause cancer. In the years that followed, cyclamates, Red Dye #2, nitrites, formaldehyde in home insulation, and trace levels of pesticides in foods have been similarly implicated. Even coffee has come under suspicion.

These cancer “scares” grew out of tests conducted with laboratory animals. Some critics maintain that these animal assays are the best means we have for assessing human risk, but others argue that results in mice may not be predictive of outcomes in rats, let alone people. These tests form the bases for decisions vital to our health and standard of living. The availability of thousands of products we rely on—including pharmaceuticals—depends on them. Billions of dollars in environmental-remediation and pollution-abatement costs, insurance-premium costs, product-modification costs, and legal fees can hinge on regulatory decisions made based on the results of animal testing.

In 1977, for example, the U.S. Food and Drug Administration (FDA) declared the artificial sweetener saccharin a carcinogen. In making its decision, the FDA relied on laboratory tests showing that saccharin could cause tumors in rats exposed for long periods of time to doses equivalent to a human’s consuming approximately 1,000 cans of diet soda a day. 1

This massive overdosing began with the weaning of the parent generation of rats, and continued throughout the entire prenatal and postnatal lifetime of the animals that ultimately developed tumors. But even under these extreme conditions, only male rats in the second generation developed tumors, and those only in the bladder, with no metastases (migration of cancerous cells) or other tumor types observed. Critics questioned whether the results were applicable to humans; specifically, whether human consumption of ordinary amounts of saccharin posed a significant cancer hazard, particularly since epidemiological studies of long-term users of saccharin (e.g., diabetics) showed no increase in bladder cancer.

The critics’ skepticism was justifiable. Later research demonstrated that only the sodium and calcium salts of saccharin are animal carcinogens at high doses. Tumor development appears limited to rodents and due to physiological conditions that humans do not share. There is no evidence that sac-
charin fosters cancer in humans.

We have only modest understanding of how cancers form. It is believed that cancer is caused by many factors. Current animal testing regimens use very high doses that may be toxic to cells, resulting in cell death; in response, the rate of cell division and proliferation among the surviving cells may increase. A cell’s genetic material is most vulnerable to damage during the process of cell division. Anything that stimulates cell division thus provides greater opportunity for genetic mistakes to occur. If they survive, defective cells produced from such “mistakes” may continue to multiply and, ultimately, to form tumors.

Humans live amidst numerous carcinogens, and we are equipped with natural defense mechanisms against any harm that might come from low-level exposures to both the natural and synthetic chemicals that we encounter in everyday life. Evidence suggests that cancer rates in humans have not increased in the face of the increased presence of both artificial and natural toxicants in the environment.

The American Cancer Society attributes a steady rise in the age-adjusted national cancer death rate to lung cancer, a disease caused predominantly by cigarette smoking. Figures 1 and 2 (at end of doc.) show that the U.S. rates for most cancers have leveled off or declined in the past 50 years, with lung and skin cancer rates the outstanding exceptions. But lifestyle factors—cigarette smoking and increased exposure to sunlight—are major causes of these increases, not exposures to chemical or environmental contaminants. We therefore may question whether the animal tests required by agencies such as the Environmental Protection Agency (EPA) and the FDA—tests that involve testing single agents at very high doses—will (a) accurately identify true health risks and (b) lead to appropriate exposure guidelines.

There is promise on the horizon. The National Toxicology Program (NTP), the EPA, and the Commission on Risk Assessment and Risk Management (CRARM) have called for changes, either in how animal testing is conducted or in how test results are interpreted for the protection of public health. Years of research and of credible scientific investigation provide us with a deeper understanding of the limitations inherent in the extrapolation of animal data to humans.

In this booklet the American Council on Science and Health (ACSH) examines the historical approach to animal testing for predicting cancer and other health effects in humans and discusses the uses and limitations of such testing in protecting public health.
II. Overview of Animal Tests

Why is Animal Testing Conducted?

Information on the toxicity of chemicals to humans comes primarily from two sources: epidemiological studies and animal studies.

Epidemiology is the study of the occurrence of human disease relative to exposure to suspected causative agents. Epidemiological studies are conducted to identify patterns and, depending on study design, to discern significant relationships. The major advantage of epidemiological studies is that they evaluate “real-world” human exposure to chemical substances, thus eliminating the need for animal-to-human extrapolation. Epidemiological studies are limited by difficulties in accurately determining exposures (especially exposures that occurred in the past), and by difficulties in accounting for complicating (“confounding”) variables that may cloud cause-effect relationships. A researcher can account for the effects of confounding variables such as age, sex, and socioeconomic status; but it is difficult to evaluate factors such as genetic susceptibility and little-known lifestyle factors.

Coexposures to other chemical substances particularly complicate exposure-effect investigations of a single agent. These studies require a control, a comparison group of subjects who have never been exposed to the agent being studied. But for a very common agent—caffeine, for example—a nonexposed control group can be hard to assemble.

Epidemiology is a relatively crude science: Even the largest and best designed study usually cannot identify small increases in risk (increases of less than 25 percent above the baseline risk in the control group). And there are practical difficulties inherent in certain types of epidemiological studies—those that require following the health status of large numbers of individuals over long periods of time, for example.

We therefore use animals as human surrogates to test for adverse effects of chemicals, drugs, or other products. Animal toxicology studies provide vital data collected in genetically homogeneous groups of animals under conditions where the dosage (or exposure) can be controlled and the effects measured by precise, reproducible methods. Animal studies alone cannot predict human risks precisely, however.
Who Requires that Animal Testing Be Performed?

Four federal agencies—the EPA, the FDA, the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission (CPSC)—require animal test data to evaluate agents considered to be potential health hazards.

The EPA regulates air pollutants, pesticides, water pollutants, hazardous wastes, and chemical hazards under various laws listed in Table 1 (at end of doc.). Under these programs, the EPA can require animal testing when it is deemed necessary.

The FDA oversees pharmaceuticals, direct food additives, indirect food additives (usually from packaging and processing), color additives, potential contaminants of food or additives, environmental contaminants in foods, and cosmetic ingredients. The FDA requires a variety of toxicity studies in rodent and nonrodent species as prerequisites for the clinical investigation and eventual marketing of new drugs and for marketing approval of new food additives. Food or color additives determined through animal testing to be unsafe cannot be marketed in interstate commerce. (A substance is considered unsafe if it is “injurious to health,” if it contains any added poisonous or deleterious substances, or if it contains food or color additives determined to be carcinogenic.)

The Occupational Safety and Health Administration (OSHA), operating under the 1970 Occupational Safety and Health Act, sets regulatory standards that “adequately assure to the extent feasible . . . that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard . . . for the period of his working life.” OSHA sets maximum airborne chemical concentrations (permissible exposure levels, or PELs) for toxic substances in the workplace. OSHA also identifies chemicals as carcinogens on the basis of human and animal evidence.

The Consumer Product Safety Commission (CPSC) was established in 1972 to consolidate the product safety functions that had been dispersed throughout the federal government. The CPSC has regulatory authority to set safety standards for products that pose an “unreasonable risk” of injury or illness, and to ban or recall products that create “a substantial risk of injury to the consumer.” The Consumer Product Safety Act amendments of 1981 required the CPSC to create a new “Chronic Hazard Advisory Panel” with specific authority to regulate products that present risks of cancer, mutations, or adverse reproductive effects. These amendments expanded the CPSC’s authority to
address hazardous substances in general use in the home; specifically, to protect children from hazardous toys and products. CPSC sometimes relies solely on animal evidence in regulating and restricting human exposures.

What Types of Toxicity Tests Are Conducted with Animals?

Depending on their purpose, toxicity tests vary in duration from short-term tests to identify effects of acute exposure; to subchronic tests (typically three months long); to chronic tests (typically two years long); and to multigenerational tests. Animal testing is used not only to assess carcinogenicity but also to evaluate reproductive, immunological, and other effects.

Toxicity testing ordinarily uses rats or mice, although nonrodent species may be more useful for some agents. There is no perfect surrogate for humans.

How Are Standard Carcinogenicity Bioassays in Animals Conducted?

Carcinogenicity studies (bioassays) usually involve male and female rats and mice. Selection of a particular species depends on the desirability of using outbred (naturally occurring) versus inbred or hybrid strains (products of laboratory controlled mating); species and strain sensitivity to the test chemical; and knowledge of how the test chemical is handled within the body (pharmacokinetics).

The bioassay evaluates tumor incidence at a range of doses of the test agent, which is administered typically in the diet (although studies sometimes use inhalation as the exposure route) over a two-year period (the approximate life span of mice and rats). The route of administration is important in designing and interpreting tests: Ideally, the route should mimic as closely as possible the route by which people would likely be exposed to a substance; i.e., ingestion, skin contact, or inhalation. Administration by stomach tube, or “intubation,” a commonly used method of administering unpalatable test substances to animals, has no parallel in normal human exposure.

Carcinogenicity studies typically include at least three dosage levels and a control (untreated) group. A typical protocol ascertains the number of lesions (e.g., growths) visible to the naked eye, with scientific confirmation of tumor growth. There is periodic monitoring of growth and development, food and water consumption, and illness and mortality, as well as blood sample analysis and urinalysis (among other tests). Some bioassays include euthanasia of some animals, at certain points in the study, for autopsy and pathology analysis.
Increased incidence of benign and malignant lesions in the test animals above that observed in the controls is basic evidence of carcinogenicity. However, classification of an agent as carcinogenic to humans involves both subjective (e.g., scientific opinion) and objective (e.g., increased incidence of malignant tumors when compared to controls) measures.

Why Are Very High Doses Used in Animal Tests? How Does This Affect Applicability to Humans?

Carcinogenicity bioassays typically use three dose levels and a control (unexposed) group. The highest dose is the “maximum tolerated dose,” or MTD, usually determined in a 90-day subchronic study. The EPA defines the MTD as “the highest dose that causes no more than a 10% weight decrement, as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathological lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals’ natural life-span.” Two additional dose levels lower than the MTD are arbitrarily selected, typically at one quarter the MTD and one tenth or one eighth the MTD.

The MTD is used as the highest dose to compensate for the statistical disadvantage of testing a limited number of animals. Some regulatory agencies have believed that the MTD approach maximizes our power to detect weak carcinogens, making animal cancer bioassays valid indicators of human carcinogenicity. For decades regulatory agencies have required testing at the MTD to determine the ability of any substance under any circumstances—including the most extreme—to induce cancer. Inherent in this logic is the assumption that tumor incidence will increase as chemical exposure increases.

A review of the NTP carcinogenicity database on 52 chemicals shows that 62 percent of those chemicals were judged carcinogenic based on effects observed only at the highest dose. None of these chemicals is known to be carcinogenic in humans. One researcher concluded that the highest exposure level in animal carcinogenicity studies could be reduced to 1/2 MTD to avoid both “false positive” results irrelevant to humans and false negative results due to excessive mortality from toxic effects at the MTD. (Excessive mortality is, however, a sign that the MTD has been exceeded and that the study results may be inappropriate for extrapolation to humans.)

Other researchers have also called for revision of the MTD approach, suggesting that other fac-
tors, such as the bioavailability and pharmacokinetics of a test substance, be determined in a test species before the selection of doses for chronic-study purposes.⁹ The American Industrial Health Council (AIHC) stated:

Bioassays using the maximum tolerated dose administered via unexpected [i.e., unnatural] routes of exposure have not been selective in distinguishing chemicals for regulation as carcinogens, and furthermore such studies provide very little guidance for risk assessment.¹⁰

MTDs are often many orders of magnitude—thousands or millions of times—above those doses encountered by people in daily life. Table 2 (at end of doc.) compares the doses of chemicals administered to rodents and found to be carcinogenic with the equivalent human intakes. Clearly, the high doses used in numerous animal studies are not realistic approximations of human exposure; yet the results of these studies remain our primary basis for regulating exposure to chemicals. This testing approach needs to be revisited if we are to trust animal tests to predict cancer risk to humans.

Historically, the way to determine whether or not a carcinogenic response at a lower dose—a dose such as one humans might experience—is simply a proportionally weaker version of the response seen at the MTD has been to conduct a full dose-response study for the substance. Such tests involve numerous doses, often ranging down to doses at a level characteristic of human exposure.¹¹ But such tests also require vast numbers of experimental animals and so are prohibitively expensive for routine screening.

Furthermore, even if results of typical bioassays could be interpreted with confidence, many other factors could limit the human relevance of animal carcinogenicity data (see Table 3, at end of doc.). Today, the use of pharmacokinetic data enables us to better predict tissue dose based on metabolism and aids us in our efforts to determine whether the response or effect of a chemical is proportional across all doses. Unfortunately, such pharmacokinetic data exist for only a handful of chemicals; it is hoped that additional data will be forthcoming in the future.

How Does the Selection of Animal Species Affect Study Results?

The rodent strains most commonly used in the two-year cancer bioassay—the B6C3F1 mouse
and the F344 rat—have high spontaneous rates of certain tumor types, limiting their predictive value in risk estimation for various organ or tissue sites (see Table 4, at end of doc.). The presence of background tumor types must be considered when evaluating risk to humans. Two researchers examined the overall results of 124 consecutive rodent carcinogenesis assays conducted at the MTD on 37 chemicals reported by the NTP. In 31 experiments, in male and female F344 rats and in male and female B6C3F1 mice, results varied bewilderingly with respect to increases and decreases in tumor incidence.

How Does Animal Food Intake Affect Study Results?

Diet and caloric intake have been shown to affect growth, disease development, and the rate and extent of development of spontaneous and chemically induced tumors in animals. Restricted food consumption enhances the health and survival of animals, but it may also affect the expression of toxicity by altering chemical metabolism and disease progression.

The association between animal body weights and tumor incidence was reviewed using individual control animal data from 55 mouse and 53 rat studies conducted by the NTP. Several statistically significant associations with body weight, the strongest of which were for liver tumors in both sexes of mice, pituitary gland tumors in both sexes of rats, and mammary gland tumors in female rats were found. Significant positive correlations between tumor occurrence and body weight occurred in animals at ages as low as 9 weeks.

Recently, the NTP conducted 13-week rat studies using a new diet with the same caloric content, but with less protein and more fat and fiber than the diet traditionally used in NTP studies. The reformulated diet was found to be adequate for growth and maintenance of F344 rats and appeared to prevent or decrease the severity of diet-associated lesions of the heart and kidney. However, we must consider whether tests performed in animals on a calorically restricted or specially formulated diet would be relevant to humans on “unrestricted” diets.

Do Many Chemicals Test Positive for Carcinogenicity?

Of 191 chemicals selected, tested, and reported by the National Cancer Institute (NCI) as of 1980, 52 percent were judged to be carcinogens in at least one out of two species tested. In an update, the NTP reported that 42 percent of the 252 tested chemicals in the combined NCI/NTP series were pos-
itive in at least one species. Finding this high a proportion of positive results was quite unexpected, because the premise of identifying human carcinogens was that they are relatively uncommon.

One explanation for the high frequency of positive results in the NCI/NTP bioassays is that the chemicals were preselected as likely carcinogens in the first place. The preselection process includes clues from chemical structure; mouse skin tumor assays; and short-term screening tests (such as the use of bacterial assays) that show mutagenicity (the ability to cause changes in genetic material) that may be correlated with carcinogenicity.

This explanation alone cannot account for the many common substances that can induce a carcinogenic response in at least one animal species, however: Examples include such common constituents of the human diet as vitamins A and D₂, selenium, and even pepper. Chemicals produced in the human body as normal metabolites, such as tryptophan metabolites and xylitol, are also capable of eliciting a carcinogenic response in animals. Formaldehyde is a potent nasal carcinogen in rodents; but formaldehyde is also a natural by-product of biochemical reactions in mammalian systems and obviously does not present a similar carcinogenic risk to humans. Most likely, formaldehyde is carcinogenic in rodent species because of “portal of entry” effects (i.e., effects observed only at the site of test-substance administration; in this case, the nasal cavity).

The fact that these substances do not cause cancer in humans at the doses at which they are normally present is likely due to the efficiency of the human liver in detoxifying carcinogens present at low concentrations. It is also probable that low-level exposure to many different carcinogens is far less risky than the high-dose, single-agent exposures studied in animal assays.

It is critical to use animal bioassays to distinguish those agents that truly pose health risks to humans from those other substances to which people are exposed but that do not pose a risk of carcinogenicity.

Do Standard Laboratory Animal Tests, Including Carcinogenicity Bioassays, Predict Adverse Effects in Humans?

Human data provide the best experimental evidence for humans. A relatively small number of chemicals have been identified as human carcinogens based on data from epidemiological studies. Two cancer researchers have identified 16 chemicals and 13 industrial processes having a well-estab-
lished elevated cancer risk, based on data on human exposure. The NTP has identified 24 substances, including asbestos, benzene and radon, as human carcinogens.

An analysis was performed on the animal studies for those agents identified as human carcinogens by the International Agency for Research on Cancer (IARC) in 1987. Of all 34 chemicals shown to cause cancer in humans, 31 also induce cancer in animals.

As shown in Table 5 (at end of doc.), properly conducted and interpreted rat and/or mouse bioassays using exposure routes and target organs relevant to humans confirm the carcinogenicity in test animals of 21 of 33 identified human carcinogens. Virtually all of the known human carcinogens are also animal carcinogens as shown by test data. A notable exception to this is arsenic. Thus, the “false negative” rate—the fraction of known human chemical carcinogens that come out negative in well-designed and well-executed animal cancer bioassays—is very low.

The converse, however—that animal carcinogens are predictive of human carcinogenicity—is not well established. Only a limited number of chemicals initially found to cause cancer in animals were found subsequently to be human carcinogens. These chemicals include aflatoxin, 4-aminobiphenyl, DES, bis(chloromethyl)ether, mustard gas, and vinyl chloride. It was concluded that one cannot generalize that the results of long-term, appropriately conducted and interpreted laboratory studies with rats and/or mice correlate with evidence of carcinogenicity in humans.

There are hundreds of chemicals classified as “carcinogens” in at least one animal species that have not been established as human carcinogens, including saccharin and cyclamates. Possible reasons for lack of a better correlation between results in animals and humans include the existence of chemical mechanisms of action that are species-specific (physiological, anatomical, and genetic differences that may significantly alter responses to chemicals) and the use of test conditions (e.g., MTD, lifelong exposure, unusual exposure routes) that are often irrelevant for humans.

An individual animal species may be unique in how it absorbs, distributes, metabolizes, and eliminates a substance—processes collectively referred to as “pharmacokinetics.” No animal closely mimics all aspects of pharmacokinetics in humans. Toxicity testing is designed to elicit adverse effects and is useful in identifying specific endpoints of toxicity from chemical exposure.

The primary purpose of animal testing is to identify hazards, not to evaluate or quantify human health risk. Evaluation of risk requires the consideration of additional factors such as dose-response
relationships, interspecies differences, and human exposure. Extrapolation from animals to human beings assumes that the animal is a good model for human cancer development—an assumption both supported\textsuperscript{27} and contradicted\textsuperscript{28–30} by animal data. This controversy is not recognized in much well-intended legislation.

**Examples of Species-Specific Mechanisms of Toxicity that Are Not Relevant to Humans**

- **Thyroid follicular cell tumors** are perhaps the most common drug-induced endocrine tumors in rat carcinogenicity studies. Increased production of thyroid-related hormones produces a variety of changes in the follicular cell, ultimately including tumor formation. One difference between rodents and primates is the rodents’ lack of a protein that binds and transports thyroid hormones in the blood.\textsuperscript{31} This results in higher levels of free thyroid hormones in rodents than in primates and provides the mechanism for the occurrence of thyroid follicular cell tumors in rats. This species-specific mechanism has profound implications for the relevance or irrelevance of such tumors to humans.

- **Corn oil** is commonly used in rodent carcinogenicity studies to administer water-insoluble substances. NTP studies in F344 rats have shown a dose-related increase in pancreatic carcinoma, related to the use of corn oil.\textsuperscript{32} The mechanism of this effect is not known. However, it is important to evaluate the relevance for humans of studies showing increased pancreatic tumors, in which corn oil was the vehicle of administration of the chemical agent. Such studies should include “vehicle controls” (i.e., a group of animals that receive corn oil not containing the test agent) to determine whether corn oil alone affects tumor incidence.

- **There are several examples of tumors occurring in animal organs that have no counterpart in human anatomy.** For example, butylated hydroxyanisole (BHA) produces tumors in the forestomachs of rats and hamsters, primarily by inducing cell proliferation. No lesions have appeared in species that do not have forestomachs, including dogs and monkeys.\textsuperscript{33–35} (In pigs, another species with a forestomach, the effects of BHA may be masked by spontaneous proliferative changes that normally occur.)\textsuperscript{36} Rodent forestomachs are modifications of the esophagus without any anatomic counterpart in primates, so there seems to be no human relevance of tumors peculiar to that site.

- **A number of drugs and chemicals** (unleaded gasoline, for example) will produce kidney tumors in male rats. These tumors are secondary to kidney damage from the binding of the chemical to a particular protein (alpha-2u-microglobulin) and the resulting accumulation of this protein in the kidney tubules.\textsuperscript{37–39} The chemical-protein complex is toxic and results in cell death, regeneration, and tumor formation. The alpha-2u-globulin–associated kidney damage and kidney tumors are observed only in male rats, but not in female rats, mice of either sex, guinea pigs, or monkeys.\textsuperscript{40,41} Humans do not produce alpha-2u-microglobulin, and they do not experience analogous kidney damage.\textsuperscript{42} Thus, formation of kidney tumors secondary to this species-specific protein seems irrelevant for humans.

- **Nongenotoxic chemicals (“genotoxic” chemicals are those that interact with and damage DNA)** can also produce bladder tumors in rats and mice.\textsuperscript{43} The most common mechanism involves stone (“calculus”) formation in the urinary bladder, resulting in erosion and ulceration of the bladder lining, followed by cell regeneration and tumor formation. Studies using chemically
inert pellets demonstrate that tumors can arise from mechanical damage to the bladder lining, independent of a direct chemical interaction. Chemicals that produce bladder tumors secondary to bladder stones (e.g., chemicals such as oxalates and ethylene glycol) do so at relatively high doses. This mechanism would not apply to lower doses that do not produce calculi; thus, there is a true threshold below which tumors do not occur. There is also little evidence that the presence of calculi leads to an increased incidence of bladder tumors in humans.44

• Several solvents, including chloroform, carbon tetrachloride, and tetrachloroethylene, have been shown to produce liver tumors in mice. Chloroform produces liver tumors in male and female mice, but only at doses that destroy the liver.45 Because chloroform is not genotoxic, its carcinogenicity is considered to be secondary to liver toxicity and subsequent cell regeneration.46–49 Furthermore, recent investigations have convincingly shown that liver tumors observed in female mice after administration of chloroform at the MTD in one bolus (a single dose) through a stomach tube were not observed when the same total dose of chloroform was administered in the drinking water and ingested in small sips throughout the day.50 This shows that the rate of dosing is important. The chloroform ingested in drinking water was delivered to the target tissue at rates low enough to be detoxified. Such scientific evidence must be considered when extrapolating to humans. Cytotoxicity (the death of cells) is an effect that could be expected to exhibit a threshold and thus may not represent a risk at low levels of exposure.

How Can We Make Animal Models More Predictive of Human Risk?

A review conducted on risk comparisons suggest that researchers can enhance the usefulness of animal models for predicting human risk by following certain principles:51

• Comparisons will be more convincing if the studies selected for comparison are well designed and executed.

• Sometimes more than one adequate study will exist in the same species, whether human or laboratory animal, each yielding its own risk estimate. Some attempt should be made to evaluate and reconcile differences in the estimates, rather than just using the one study that yields the highest risk estimate (the procedure typically used by the EPA).

• In general, risks to the same organ or system should be compared in animals and humans if they are reasonably analogous.

• Consistent definitions of endpoints should be used. For example, if benign tumors that do not become malignant are included in the carcinogenic risk assessment for animals, some adjustment to the estimation of malignant tumor risk in humans may be necessary.

• The comparability of exposure regimens with different temporal patterns should be considered. For example, the dosing regimen for one experiment may be intended to simulate occupational exposure; another, to simulate ambient exposures.

Are There Alternatives to Animal Testing?

Researchers are exploring in vitro (cell culture) assays, the use of living tissue removed from embryos (i.e., embryo explants), and tissue-culture techniques. Tests conducted in bacteria and fungi
are well established for preliminary screening. Quantitative structure activity relationship (QSAR) analysis (a type of analysis that attempts to predict the effects of an agent based on its structural similarities to other, known cancer-causing agents) and other predictive tools (such as computer modeling of pharmacokinetics) have also been suggested as alternatives to animal testing. Data on mechanisms of action derived from animal studies can also improve predictive accuracy, although these valuable data are rarely available.

These methods may be valuable adjuncts to—but are not replacements for—animal testing. Animal testing still provides information not available through these other methods.

**How Much Do Animal Tests Cost?**

Table 6 (at end of doc.) shows typical costs of animal toxicity tests. Specialized tests such as immunotoxicity assays, 2-generation reproductive studies, and carcinogenicity bioassays now cost over $1,000,000 for one chemical, in one species, by one route of exposure. Dermal or inhalation exposures, tests in more than one species, and more specialized metabolism and pharmacokinetic studies all involve significant additional expense. A full investigation of the toxicology of one chemical in a single species can easily cost millions of dollars.

Some researchers have concluded that “for almost all of the chemicals tested to date, rodent bioassays have not been cost-effective. They give limited and uncertain information on carcinogenicity, generally give no indication of mechanism of action and require years to complete.”¹⁷ These researchers have proposed a new assessment: one that would consider a chemical’s economic value to society; the potential number of individuals likely exposed; and the likelihood of carcinogenicity, based not on a single bioassay at the MTD, but on additional analyses of the chemical’s structure and its ability to cause genetic mutations in cells.

In addition to the actual costs of the tests are the costs to society of the misuse of animal data: costs of litigation, costs in the form of unwarranted public anxiety, costs related to overly stringent occupational exposure limits, costs related to the loss of viable products in commerce, costs in decreased international competitiveness, costs of environmental cleanups, and costs stemming from the loss of jobs.

The Alar scare of 1989 cost apple growers an estimated $250 million, apple processors $125 mil-
lion, and the American public $15 million. (That last figure represents the amount expended by the
U.S. Department of Agriculture for the purchase of surplus, unsellable Alar-treated apples.)
Economic effects are still being felt in the decimation of apple crops and, ironically, in the increased
need for pesticides, applied to help the apple trees hold their fruit.\textsuperscript{52}

In addition to the economic costs of bans on useful products, manufacturing costs are increased
by the use of engineering controls designed to minimize workers’ exposures to chemicals that, in
reality, are not human carcinogens. These costs are ultimately passed along to consumers.

A prime example of unwarranted environmental clean-up costs involves a commercially impor-
tant solvent, trichloroethylene (TCE). From World War II until 1980 about 13 billion pounds of TCE
were produced in the U.S. and widely distributed. The solvent was used as a degreasing agent at
industrial shops, including those of the U.S. Energy and Defense Departments.

Because of careless disposal, TCE migrated into groundwater. Today it is the substance most fre-
quently found at Superfund and other waste sites. It has been estimated that of the approximately
70,000 hazardous waste sites that are expected to exist in the U.S., roughly one third contain some
amount of TCE.\textsuperscript{53} If the current mandated maximum concentration level of 5 ppb in drinking water
is applied to groundwater generally, the costs of remediation of TCE contamination could be on the
order of $100 billion. But what evidence is there that TCE is a human carcinogen worthy of such a
huge expenditure?

There is no compelling evidence from epidemiological studies that TCE is a human carcinogen.
Careless workplace handling doubtless exposed hundreds of thousands of workers. An EPA risk-
assessment document concluded that epidemiological data are inadequate, either to refute a human
carcinogenic potential for TCE or to demonstrate such.\textsuperscript{54}

The regulatory level for TCE is based on liver cancer induced in B6C3F1 mice, a cancer-prone
strain. The doses were administered by stomach tube (intubation) five times a week over a lifetime.
The results were then extrapolated mathematically to humans, using an arbitrarily selected model.
This is disturbing, given the apparent species- and strain-specific effects of TCE.

Mice, F344 rats, and humans all metabolize TCE to trichloroacetic acid. This metabolism is most
rapid in the mouse. Trichloroacetic acid, when administered directly to mice or F344 rats, gives rise
to liver cancer. However, in F344 rats and humans, the rate of oxidation of TCE to trichloroacetic
acid is limited, and liver cancer is not observed after exposure to TCE.
In summary, the multimillion-dollar expenditures for clean up of TCE-contaminated sites are based on a study that used a single, extremely susceptible test species, and that relied on extrapolation assuming, erroneously, that TCE metabolism is the same in that mouse and in humans.

The financial costs of animal tests pale beside the economic impacts and health trade-offs resulting from inaccurate and misinformed interpretations of animal data. Dr. Ralph Keeney,\textsuperscript{55} of the University of Southern California, and others have linked higher income with lower mortality rates. Keeney has developed a model to estimate the negative impact of governmental regulations on individual disposable income, and hence on fatality risks. The model estimates that every $7.25 million taken out of the economy by government regulations results, on average, in the loss of one life. As Keeney notes, “If the intent of a proposed regulation is to save lives by making some aspect of life safe, then it would seem ridiculous not to consider the potential mortality implications of implementing the regulation itself. These implications include the potential fatalities induced by the cost of the regulation.”\textsuperscript{55}

How many lives have strict environmental regulations saved? The EPA acknowledges that the number may well be zero. The agency’s risk estimates are “upper bounds.” The actual risk at low doses may be zero because the EPA’s risk-assessment procedures often use extremely conservative default assumptions (estimates used in the absence of measured or available data). Dr. Tammy Tengs and associates of the Harvard Center for Risk Analysis\textsuperscript{56} estimate that EPA regulations alone cost $7.6 million per life-year saved, causing more deaths than they are intended to prevent.\textsuperscript{56} (A “life-year saved” is a combined measure of the number of lives saved and the number of years added; for example, a saving of 10 life-years can be achieved by affording one individual 10 more years of life; 10 individuals, one more year of life; 5 individuals, two more years of life, etc.)

Tengs and associates have concluded that environmental regulations are the least cost-effective risk-management intervention. They estimate that, while the median costs per life-year saved for medical interventions and injury-reduction measures are $19,000 and $48,000, respectively, the median cost associated with toxicant-control measures is $2,782,000 per life-year saved.\textsuperscript{56} Thus, saving a life-year through chemical-control measures (the “need” for which is often based exclusively on animal test data) is approximately 150 times as expensive as saving a life through medical risk-reduction practices such as vaccinations. Nine of the ten most expensive lifesaving interventions are related to environmental chemical-control measures.
III. Technical Considerations

How Can Improvements in Our Understanding of Carcinogenesis Increase the Utility of Animal Test Data?

We need to know how substances act as cancer-causing agents in the body: their mechanism of action. Most carcinogens act by damaging the genetic material (DNA) of cells; such substances are called genotoxic agents. Many substances are not carcinogenic in themselves, and the body must change them into “activated” forms before they damage DNA. Furthermore, there are a number of biochemical mechanisms available for repairing damaged DNA.

Some carcinogens do not act by damaging DNA. These agents are referred to as nongenotoxic, or epigenetic, carcinogens. For example, “promoters” are epigenetic carcinogens that are not carcinogenic by themselves but that can promote the carcinogenic activity of other substances. Some promoters facilitate the entry of DNA-damaging chemicals into cells, while others act after initial DNA damage has occurred, causing the damaged cells to divide rapidly. Some nongenotoxic carcinogens, including hormones such as DES, directly stimulate cell division. Indirect or epigenetic mechanisms have four characteristics quite different from the effects caused by genotoxic, or direct-acting (on DNA), agents:

- Epigenetic carcinogens appear to induce cancer only at exposure levels that are near lethal doses.
- Epigenetic carcinogens may increase the incidence of spontaneous tumors but do not appear to induce formation of tumors rarely seen in control populations of test species.
- Cancers generally appear to arise only after a long exposure relative to the life span of the test animal.
- Epigenetic chemicals do not bind with DNA.

An understanding of the mechanisms of chemical carcinogenesis is essential if we are to define accurately and appropriately the risks for human exposure. This is particularly important for nongenotoxic agents, because responses may be unique to the test species or may involve a process with an apparent threshold below which there would be no risk.

Dr. Druckery, a renowned cancer biologist, warned in 1967 that “a proper scientific judgment of the potential risk which may arise from carcinogenic substances wherever they may be present in
the human environment, as well as the possible and necessary measures for cancer prevention, presumes the knowledge of a pharmacological basis governing the carcinogenic action. This applies to the dose-response relationship.” Druckery’s warning echoes Paracelsus, who noted as early as 1564 that nothing is not a poison, and that dose alone determines the poison. This fundamental toxicological principle applies to animal cancer studies, typically conducted at the MTD.

How Are the Results of Animal Carcinogenicity Bioassays Extrapolated to Humans?

Cancer risk-assessment models assume that all carcinogens act similarly, and that there is no threshold for their carcinogenic action. However, cells have repair processes, exemplified by the detoxification capacity of the liver. There is increasing evidence that carcinogenesis is a multistep process involving multiple genes, multiple mechanisms, and multiple causes, which collectively may act to elicit tumor formation. There are several mechanisms by which a substance can influence—or stop—multistep carcinogenesis.

Regulatory cancer risk assessment long assumed that cancer was a “one-hit” process (i.e., that one molecule is sufficient to alter DNA and so lead to the development of cancer), a concept now being questioned. While thresholds exist for each step in the carcinogenic process, the default assumption by U.S. regulatory agencies has always been that there is no measurable threshold for cancer development itself. Most statistical models work on this premise.

The common assumption that all individuals have the same risk of cancer development is also known to be untrue. Given the same exposure, individuals’ genetic predisposition, sex, age, nutritional status, and disease status are important determinants of cancer development.

Several alternative statistical models of cancer formation are used to extrapolate risks from the high doses to which test animals are exposed to the low doses at which human exposure occurs. The linearized multistage model is the most conservative model for predicting risks at low doses—that is, it yields the highest estimate of risk. This model is the one most commonly used in cancer risk assessment by governmental agencies.

The linearized multistage model assumes a dose-response curve, as illustrated by Figure 3a (at end of doc.), although these types of curves are not usually found experimentally. More typical of dose-response relationships is the curve represented by Figure 3b. Depending on the data and assumptions used, the multistage model can either be linear or sharply nonlinear. The EPA has used
an estimation method that forces linearity at low doses, even when the data indicate a nonlinear relationship at known exposure levels.

Very few well-designed dose-response assays support the assumption that cancer risk is linearly proportional to dose. The largest of these studies was conducted by the National Center for Toxicological Research (NCTR): the “ED01,” or “mega-mouse,” study, which used 24,000 mice.\textsuperscript{64}

NCTR exposed groups of animals to the potent carcinogen 2-acetylaminofluorene to measure, with statistical confidence, the incidence of cancer at low doses. NCTR found tumors in two different organs in the test animals—the liver and the bladder. In neither case was the dose-response relationship linear.\textsuperscript{65} In the ED01 study, linear extrapolation of the data for both bladder and liver cancer would overestimate the actual measured risk at the lowest dose. For bladder cancer, the error was more than tenfold; the liver data error was somewhat less.

In an inhalation study of formaldehyde exposure in rats, a threefold decrease in dosage led to a roughly fiftyfold decrease in nasal cancer incidence. Linear extrapolation from the risk observed at the high dose to that at the lower dose leads to a fifteenfold overestimate of the risk at the lower exposure.\textsuperscript{66,67}

The strongly nonlinear nature of the dose-response curve for formaldehyde is important in assessing the human risk from small exposures to this chemical; for example, from trace amounts of formaldehyde that may emanate from urea-formaldehyde foam insulation. In 1982 the CPSC banned this insulation on the basis of linear extrapolation of the high-dose nasal cancer found in rats, only to have the ban overturned in the courts.\textsuperscript{68}

Similarly, a two-generation dose-response study of saccharin in male Sprague-Dawley rats showed, as in previous studies, that large doses produced bladder tumors; however, the shape of the dose-response curve was not linear.\textsuperscript{67,69} The “best fit” curve thru the data points indicated that a hundredfold decrease in dose would result in a millionfold decrease in tumor risk, rather than the hundredfold decrease expected if the dose-response relationship were linear.\textsuperscript{43}

Thus, the assumption of linearity in high- to low-dose extrapolations results in gross overestimation of low-dose risk. Given compelling evidence that carcinogenesis is a multifactorial, multistep process, coupled with the body’s DNA repair capacity, and given the nonlinearity of most dose-response curves, it is scientifically indefensible, inaccurate, and overly conservative to base human carcinogenic risk on mathematical and statistical models that often have little in common with actual
How Do Scientists Account for Nonlinear Dose-Response Curves? Does a Nonlinear Dose-Response Curve Indicate the Presence of a Threshold?

To understand nonlinear dose-response curves, we need to understand that the individual physiological or biochemical processes that underlie carcinogenicity (e.g., uptake, transport, metabolism, DNA repair) can be nonlinear with respect to the administered dose, and that the collective combination of these complex processes is very likely nonlinear with respect to dose.

Nongenotoxic chemicals affect living systems through various mechanisms independent of DNA interaction. Scientific evidence suggests that thresholds exist for many nongenotoxic substances. For such substances to promote cancers, their concentration must be sufficiently high to damage cells. The “no-threshold” assumption is also not borne out: People are constantly exposed to trace amounts of natural carcinogens, as from foods such as peanut butter, nuts, grains, and charcoal-broiled meat. These natural carcinogens exist in amounts and relative potencies much greater than those of the chemical residues present in human food from artificial pesticides or additives. Thresholds obviously exist for many natural—and, presumably, many artificial—genotoxic and nongenotoxic substances we encounter frequently.

If Most Dose-Response Curves Prove to Be Nonlinear, What Are the Implications for Regulatory Policy?

To establish safe exposure levels for noncarcinogenic substances, which presumably have thresholds for effect and whose dose-response curves are nonlinear, we conduct toxicity studies in animals to determine the largest dose level at which no observed adverse effect (NOAEL) occurs. We then divide this number by “uncertainty factors” to reach an acceptable human exposure level. Typically, these uncertainty factors account for metabolic and other physiological differences between humans and test animals, and for genetic and physiological variability in human populations, including the presence of individuals who are particularly susceptible due to age or preexisting medical conditions.

Depending on the type of animal data available, uncertainty factors can range from ten- to ten thousandfold for noncarcinogenic chemicals. Using this approach, regulators have set acceptable
daily intakes (ADIs; the EPA uses the term “reference doses”) for toxic chemicals other than carcinogens. These ADIs may be more than ten- to ten thousandfold lower than the levels at which adverse effects are observed.70

A similar approach can be used to determine acceptable levels for carcinogens. OSHA, the CPSC, and the EPA have, in fact, set levels of permissible exposure for some carcinogens.71,72 The FDA tolerance level of 1 part per billion (ppb) for aflatoxin (from molds) in peanut butter is a good example. In establishing ADIs for carcinogens, large uncertainty factors might be desirable because the consequences of uncertainty are potentially greater than they are for noncarcinogens.

The use of the ADI approach has been hindered, however, by a provision of the U.S. Food, Drug and Cosmetics (FD&C) Act named the “Delaney clause,” after the Congressman (D–NY) whose subcommittee amended the Act in 1958. The Delaney clause prohibited the use of food additives shown to cause cancer in humans or animals—regardless of the substances’ carcinogenic potency, their potential benefit to humans, or the possible existence of thresholds for cancer risk—while not prohibiting trace concentrations of naturally occurring agents in foods.73

Recent Policy Changes Addressing the Delaney Clause

In 1996 Congress unanimously passed the Food Quality Protection Act, replacing the Delaney clause for pesticide residues with a new risk standard of “reasonable certainty of no harm.” This law reflects a more scientifically defensible approach, incorporating risk-assessment methodology. The law sets tolerances for pesticide-chemical residues based either on quantitative risk assessment (for those pesticides for which a threshold of adverse effects has not been identified) or on a level of aggregate exposure determined to be safe. Pesticide uses are permitted in the following circumstances: when the benefit to consumers afforded by the pesticide exceeds the risk posed by the pesticide residue; and when the pesticide is necessary to avoid a significant disruption in domestic production of an adequate, wholesome, and economical food supply.

The Food Quality Protection Act specifically addresses potential exposure to children. In particular, it calls for consideration of consumption patterns among infants and children that are likely to result in disproportionately high consumption of foods containing the residue, in comparison with
the general population. Other factors to be considered include available information on: (a) any special susceptibility of infants and children to the pesticide residues, including neurological differences between infants and children and adults and the effects of in utero exposure to pesticide chemicals; and (b) the cumulative effects of such residues in combination with other substances that share the mechanism of toxicity. There must be a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide residue. The absence of pesticide residues in infant formula subjected to extensive testing by the Infant Formula Council may be comforting (see Table 7, at end of doc.), but millions of dollars continue to be spent in required animal testing in an effort to determine whether trace levels of such pesticides are safe for consumption.\textsuperscript{74}

The law also takes a weight-of-evidence approach to the use of animal-test and other data, considering factors such as: the validity, completeness, and reliability of the available data; the relationship of the results of such studies to human risk; the dietary consumption patterns of consumers; the cumulative effects of the residue and other substances that have a common mechanism of toxicity; the aggregate exposure levels of consumers to the pesticide residue; the sensitivities of major identifiable subgroups of consumers; and whether the pesticide may have an endocrine or other effect similar to that produced by a naturally occurring estrogen.

IV. Use of Animal Data in Risk Assessment

Historically, How Has Carcinogenicity Risk Assessment Been Conducted? Has It Been Effective? Is It Scientifically Defensible?

Cancer risk assessment has been one of the most publicized and controversial areas in federal health, safety, and environmental regulatory policy. In August 1990 the Office of Management and Budget (OMB) noted that then-current policy and risk-assessment procedures often twisted science to produce highly conservative and excessive risk estimates.\textsuperscript{75} Such assessments translate into immediate and long-term unwarranted economic burdens, impacting standards of living and health out of proportion to their presumed benefits.

The OMB commented that the state of the science on carcinogenesis, and, specifically, our inability to define cancer causation, has resulted in the adoption of regulations based on unsupported default assumptions. These assumptions are designed to avoid underestimating risk but result in
maximizing risk estimates. The OMB criticized assumptions that cancer bioassay results in animals are valid predictors of human risk; that the most susceptible animals must be used and challenged with maximum tolerated doses (MTDs); that extrapolations of animal data to below-observed-range doses are based on policy-selected but scientifically unverified and highly conservative mathematical models; and that thresholds for carcinogens do not exist. Furthermore, the OMB objected to the “preempting” of negative epidemiological evidence by positive results in animal tests, and to the use of extreme exposure estimates (corresponding to the most exposed individual) in risk assessments.

The OMB advocated use of all available evidence in decision making. The office implied that risk assessment should be insulated from the value-laden decisions involved in risk management. The OMB stated: “All data from scientific long-term animal studies should be used to assess the possible risk to humans with due regard to biological and statistical considerations.” For dose extrapolation models, the OMB said that “risk estimates should be developed using all biologically plausible models that statistically fit the available data.” Finally, the OMB proposed that “in addition to reporting the possible range of risks, the Agency should report estimates of the likelihood that the actual risk falls within any interval. To the extent possible, the Agency will also provide most likely, or best estimate of risk.”

The OMB concluded that health conservatism is a policy decision; scientific evaluation should present the range of values, not just the most conservative estimates. All too often, numerical estimates of risk based on extremely conservative assumptions are presented to the public as scientific truth.

How Do the Proposed Revised Cancer Risk-Assessment Guidelines Address These Concerns?

On April 23, 1996, the EPA published its “Proposed Guidelines for Carcinogen Risk Assessment” in the Federal Register. This represented a revision of its original 1986 cancer risk-assessment guidelines. The revision takes into account advances in our understanding of the carcinogenic process and allows sufficient flexibility to adapt to future discoveries about carcinogenic processes.
Perhaps the most important change in the proposed guidelines is an increased emphasis on broader, more objective, and complete assessment of data, informed by comprehensive knowledge of carcinogenic mechanisms and the carcinogenic process. According to the proposed guidelines, discussions of hazard, dose-response, and exposure assessments are to include consideration of the extent and weight of evidence, major points of interpretation, alternative conclusions, and uncertainties.

The proposed guidelines represent a fundamental change in the way hazard evidence is weighed to reach conclusions about the human carcinogenic potential of agents. The 1986 cancer guidelines made tumor findings in animals or humans the dominant components of decisions. The proposed guidelines also consider other information, including structure-activity relationships to other carcinogenic agents; physicochemical properties; species differences in metabolism and toxicokinetics; mode of action; and factors affecting expression of carcinogenic potential (for example, an agent might be carcinogenic via inhalation but not by ingestion, or its carcinogenic activity might be secondary to another toxic effect).

The effect of this change on the assessment of individual agents will depend greatly on the availability and quality of emerging data. The proposed cancer guidelines also establish new categories for the weight of evidence for carcinogenic hazard—e.g., “known/likely” human carcinogen; “cannot be determined”; or “not likely”—followed by a discussion of the underlying data.

The proposed guidelines also change the way dose-response assessments are conducted. Significant changes include the use of data on effects of the agent other than tumor incidence in addition to the use of data on tumor incidence, as well as consideration of the apparent dose-response relationship of the agent (linear versus nonlinear).

When the relationship is believed to be linear, low-dose extrapolation is accomplished by extending a straight line through zero (zero dose, zero response). The steepness (slope) of this line is an indicator of how potent a carcinogen the agent is. Slope is used to estimate cancer risks. When the relationship is believed to be nonlinear, a “margin of exposure” approach is used, rather than estimating cancer risks at low doses. This is analogous to the “ADI” approach used to assess risks of exposure to noncarcinogens. It involves comparing the dose at which tumors appear in a predicted number of test animals (commonly 10 percent) with the level of environmental exposure of interest. The higher this ratio, the greater the margin of exposure.
In most cancer risk assessments, default assumptions are needed to bridge gaps in knowledge. The default assumptions in the EPA’s proposed guidelines, although modified to reflect the evolution of scientific knowledge since 1986, remain “public health conservative.” These assumptions include the following.

• Positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans.

• Effects seen at the highest dose tested are appropriate for assessment. However, it is necessary that experimental conditions be scrutinized to insure that tumors are not merely the result of direct toxicity at high doses.

• When cancer effects are not found in well-conducted animal cancer studies in two or more appropriate species, and other information (including human data) does not support the carcinogenic potential of the agent, there is a basis for concluding that the agent is not likely to possess human carcinogenic potential.

• Benign tumors should be included if they have the capacity to become malignant. Benign tumors not observed to progress to malignancy are assessed on a case-by-case basis.

The proposed guidelines are an improvement over the 1986 version in their more comprehensive weight-of-evidence approach, the emphasis they place on the use of toxicological knowledge (including mechanism of action), and their deemphasis of the universal application of conservative and unsupported policy positions. While conservative default assumptions—some of which are based on prudence and policy alone, without any scientific basis—remain in the guidelines, new animal or human data may eventually eliminate the need for them. The proposed guidelines emphasize the need for continuing research. On paper, the EPA is proposing a cancer risk-assessment process supported by a foundation of sound toxicological principles and integrated knowledge. The results remain to be seen.

Have Regulatory or Scientific Bodies Besides the EPA Changed Their Views on the Issue?

The Federal Commission on Risk Assessment and Risk Management (CRARM); the National Toxicology Program (NTP); the National Academy of Sciences (NAS); and, on a state level, the California Developmental and Reproductive Toxicant Identification Committee (DART) and the California EPA (Cal/EPA) have all recognized the limitations of animal data to predict accurately human carcinogenic risk.

On June 13, 1996, CRARM released a draft report, “Risk Assessment and Risk Management in
Regulatory Decision-Making,” that is a broad, two-year examination of the risk-assessment and management policies of the federal government. CRARM found that “some chemicals elicit tumors in rodents through mechanisms that are unlikely to have any corresponding effect in humans. Others elicit tumors only at very high doses that are unlikely to be relevant to human exposures.”

CRARM stated:

The policy of presuming that a chemical that causes cancer when tested in laboratory rodents is potentially carcinogenic in humans is justified by considerable evidence and by the precautionary principles of being protective when uncertain. That policy is undercut, however, when rodent tumor responses that can be shown to be irrelevant to humans are not excluded from consideration. Furthermore, from a risk-management perspective, it is wasteful to expend risk-assessment resources, risk-management time, and public and legal involvement nonproductively revisiting such policy issues chemical by chemical.

CRARM recommends that some rodent cancer responses should be classified as irrelevant to human cancer risk assessment, and that estimates of cancer potency need not be developed for chemicals found to produce only tumors that occur as a result of mechanisms or doses not relevant to humans. The CRARM findings parallel the EPA’s Proposed Guidelines for Carcinogen Risk Assessment.

The NTP’s Board of Scientific Counselors agrees, in preliminary documents, with the important CRARM and EPA recommendations. At its May 8, 1996, meeting the board’s Biennial Report Subcommittee adopted the following criteria for listing chemicals as “reasonably anticipated to be human carcinogens.”

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to metabolism, pharmacokinetics or other data relating to mechanisms of action, or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agents act through mechanisms which do not operate in humans and would therefore reasonably be anticipated not to cause cancer in humans.

The NAS also cautioned in 1994 against classifying substances as carcinogens solely on the basis of animal data if “the mechanisms operative in laboratory animals are unlikely to be operative in
humans.”\textsuperscript{79}

The California DART Committee concluded that sufficient evidence of toxicological effect in experimental animals would be used only “such that extrapolation to humans is appropriate.” On May 24, 1996, the California EPA’s Risk Assessment Advisory Committee recommended that Cal/EPA “use mechanistic data in its hazard identification assessment to upgrade, downgrade, or affirm past decisions. Mechanistic data should continue to be used in making future decisions and Cal/EPA’s risk assessment procedures should be consistent with those of federal agencies.”

These recent reports and policy shifts concerning human cancer risk assessment reflect a consensus that extrapolation of animal data to humans is only appropriate under certain circumstances. There are numerous instances in which the scientific community clearly regards such extrapolation as inappropriate.

V. Conclusions

Animal test data are vital to the evaluation and regulation of chemicals people encounter daily. However, historical use of animal test data for assessment of risk to humans has been flawed (1) by the extreme exposure conditions under which test data are derived; (2) by the lack of inclusion of all relevant scientific data and sound toxicological principles when assessing human health risk; and (3) by the \textit{a priori} insertion of policy decisions made without scientific basis into the process.

Animal cancer and noncancer test data—when they are understood and properly interpreted and applied—are valuable in estimating and predicting human health risk. There are encouraging signs at the federal level concerning the need for a realistic, science-based approach to cancer risk assessment. Similar views must be taken towards noncancer effects. Too often, genuine (if unglamorous) health hazards have been ignored in favor of illusory or trivial ones that nevertheless receive much media attention (exposures to trace concentrations of a pesticide, for example). Animal testing will be fully beneficial and cost effective for the protection of public health only if science-based risk assessment is separated completely from both risk management and policy considerations.

In conclusion, the American Council on Science and Health takes the following positions with respect to animal testing.
• Animal toxicity testing can assist in evaluating and predicting human health effects from potential exposure to chemicals and other substances. When properly conducted, using reasonable routes and concentrations, animal toxicity studies can be valuable in identifying target organs (e.g., kidney, liver), endpoints of concern (e.g., cancer, reproductive toxicity), and estimates of potency in humans.

• Animal toxicity tests have inherent limitations and should not be viewed as sufficient, without additional supporting data, to predict risk to humans. The outstanding flaw in the use of animal toxicity-testing data is the failure to consider toxicological principles when predicting health risk to humans. Factors that must be considered when extrapolating animal data to humans include dose selection (e.g., maximum tolerated dose), test conditions (e.g., chronic exposure and route of exposure), interspecies differences in physiology and metabolism, and mechanism of action.

• Animal testing provides information concerning hazard identification but cannot be equated with determining human health risk. Animal testing uses methods designed to produce adverse effects. Hazard identification of chemical substances should be based on a weight-of-evidence approach encompassing not only animal toxicity data, but also dose-response information and other relevant physical, chemical, or biological data. Prediction of risk from a chemical substance must include not only toxicity information, but also characterization of the dose response in animals and a sound assessment of potential human exposure. It must be recognized that current risk-assessment methods are designed to be protective; i.e., to overstate the true risk in the face of uncertainty; thus, risk estimates should not be viewed as scientific truth.

• It is inappropriate and scientifically indefensible to classify a substance as a “carcinogen” based on a carcinogenic response in a single animal study using the maximum tolerated dose of the test material. However, if a material causes cancer in two or more animal species (one rodent, one non-rodent); if it causes highly lethal or malignant tumors in an animal species, or rare types of tumors that do not occur spontaneously in a particular animal species; if the tumors appear after a short latency period, or if the substance causes cancer at relatively low doses (similar to or lower than anticipated human exposure levels), then the material should be considered to possess human carcinogenic potential.

• False classification of a substance as a human carcinogen and failure to distinguish between true and trivial risks divert attention from important and proven causes of cancer. If we continue to classify chemicals as “probable human carcinogens” solely on the basis of limited animal-test data, even if they pose negligible or no threat of human cancer, we divert attention from greater public health risks; we may needlessly reject new technologies, pharmaceuticals, and consumer products that can increase the quality and longevity of life; and we increase the financial and psychological costs incurred by unrealistic overemphasis on trivial environmental agents.

• Regulatory efforts to reduce human exposure to various chemical substances should clearly indicate when policy, not science, is used in determining a safe level for a particular substance. The establishment of a “safe” exposure level involves public-policy considerations as to how much risk is “acceptable” and how large a margin of safety should be incorporated to address uncertainties in applying animal data to humans.

• Attempts to purge from our environment trace amounts of substances that have caused cancer in laboratory animals at high doses will threaten our standard of living, our economic growth, and our prosperity as a society, while providing no material improvement in public health. In most cases, human exposure to environmental chemicals poses negligible health risk. The common-sense approach to naturally occurring carcinogens ( aflatoxin, for example), whereby acceptable
tolerance levels are established based on scientific methods, offers a model standard for addressing synthetic environmental carcinogens. In the absence of compelling public health justification, our society cannot continue to support the overly stringent control of trace contaminants in the environment.
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25. Jansen, JD. The predictive value of tests for carcinogenic and mutagenic activity, classes of animal and human carcinogens. In Toxicology and Occupational Medicine (WB Deichmann, ed.), Developments in Toxicology and


Glossary

ACSH: American Council on Science and Health
ADI: Acceptable Daily Intake
AIHC: American Industrial Health Council
benign: tumor that does not possess the characteristics of malignancy (see “malignant”)
Cal/EPA: California Environmental Protection Agency
carcinogen: cancer-causing substance
control group: group of subjects (animal or human) that are not exposed to the test agent
CPSC: Consumer Product Safety Commission
CRARM: Commission on Risk Assessment and Risk Management
cytotoxic: causing damage to, or death of, cells
DART: California Developmental and Reproductive Toxicant Identification Committee
DNA: molecule that represents the genetic “blueprint” for the normal structure and function of an organism.
EPA: U.S. Environmental Protection Agency
epigenetic: see nongenotoxic carcinogen
FDA: U.S. Food and Drug Administration
genotoxic carcinogen: carcinogen that interacts with, and damages, DNA
IARC: International Agency for Research on Cancer
in utero: while in the uterus
in vitro: literally, “in glass.” Experiments conducted outside the living organism; e.g., tests conducted on isolated cells (bacteria, animal cells)
latency: time period between exposure and development of cancer
linear dose response: response varies in direct proportion to dose; e.g., doubling of dose will cause doubling of tumor response
malignant: tumor that exhibits uncontrolled growth, invades surrounding tissue, and may spread to distant locations in the body
MTD: Maximum Tolerated Dose; the highest dose at which test animals do not experience reduction of more than 10 percent in weight, mortality, clinical toxicity, or life-shortening pathological lesions
NAS: National Academy of Science

NCI: National Cancer Institute

NCTR: National Center for Toxicological Research

NOAEL: No Observed Adverse Effect Level; the highest experimental dose at which no adverse effect is observed

nongenotoxic carcinogen: carcinogen that acts by a mechanism other than interaction with DNA (epigenetic)

nonlinear dose response: response does not vary in direct proportion to dose; e.g., doubling of dose may cause less than or more than a doubling of tumor response

NTP: National Toxicology Program

OMB: Office of Management and Budget

OSHA: Occupational Safety and Health Administration

pharmacokinetics: how a chemical is handled in the body; includes absorption, distribution among organs and tissues, metabolism, storage and excretion/elimination.

ppb: part per billion

QSAR: quantitative structure activity relationship: relationship between an agent’s molecular structure and its activity (toxicity)

TCE: trichloroethylene

threshold: dose below which no adverse effects occur

TSH: thyroid stimulating hormone
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<tr>
<th>Name of Act and Year Passed and Amended</th>
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<tr>
<td>Food Drug and Cosmetic Act (FDC):</td>
<td>Food, drugs, cosmetics, food additives, color additives,</td>
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<tr>
<td>1906, 1938, amended 1958 (Delaney),</td>
<td>new drugs, animal feed additives, medical devices</td>
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<td>Federal Insecticide, Fungicide, and</td>
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<td>Rodenticide Act (FIFRA): 1948, amended</td>
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<tr>
<td>Toxics Substances Control Act (TOSCA):</td>
<td>Hazardous chemicals</td>
</tr>
</tbody>
</table>

Source: Adapted from Office of Science and Technology Policy (1985).

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Experimental Daily Dose (Rodents Unless Noted)</th>
<th>Equivalent Human Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloates</td>
<td>5% in diet (2.18 gms/day)</td>
<td>138–522 12 oz. bottles of soda (daily) or about 80–240 times typical human intake.</td>
</tr>
<tr>
<td>Saccharin</td>
<td>0.5, 5.0, or 7.5% in diet (a)</td>
<td>40–400 times daily human intake or up to 500 times typical consumption of sweeteners (b)</td>
</tr>
<tr>
<td>DES</td>
<td>One clinical treatment (c)</td>
<td>5 million pounds of beef liver from treated cattle for 50 years</td>
</tr>
<tr>
<td>Sulfate</td>
<td>5,000 ppm in diet (0.5%)</td>
<td>613 12 oz. bottles of root beer daily</td>
</tr>
<tr>
<td>Alar (d)</td>
<td>5,000–10,000 ppm in diet (0.5 to 1.0%)</td>
<td>28,000 pounds of apples daily for 10 years</td>
</tr>
</tbody>
</table>

**Notes:**
(a) Only a few bladder tumors found for high dose animals. European studies at 0.5% intake produced no tumors.
(b) Average sugar consumption is about 150 gms per day. A saccharin dose of 3.35 mg per day per kg. body weight is equivalent to the sweetness of 135 gms of sucrose or sugar per day.
(c) The experimental dose refers to the clinical DES dose given to women, not an animal dose.
Table 3
Factors Confounding Animal Cancer Tests

**Improper test species and strains of rodents**—using inbred strains with high incidence of particular tumors may produce a control group with such a high tumor incidence that the study cannot distinguish the effects of the test substance.

**Failure to consider the role of diet, state of nutrition, and dietary contaminants**—total dietary intake and the nutritional state of the animals influence tumor incidence. Also, many of the commercial rations used in bioassay studies are inescapably contaminated with substances that may alter the degree of response and affect both control and test groups. Finally, administration of substances in a corn-oil vehicle may affect response.

**Strain-specific tumor incidence, genetic drift, and understanding mechanisms for species variation**—over time there is a genetic drift (chance variation in gene frequency) in the rodent colony. Repeated surveillance of the animal type must take place in order to provide a definition of the true and current spontaneous tumor incidence.

**Contaminants in the test chemical**—impurities may affect the final response.

**Animal exposure vs. human exposure**—there may be a wide divergence in exposures that can raise doubt as to the relevance to humans of the animal studies.

**Time to tumor formation**—chemicals with low toxicity may have an induction (latency) period that exceeds the lifetime of the animal, even when the substance is administered in massive doses.

**Threshold**—there may be a point on the dose-response curve where no response to the substance occurs; thus, there may be a biologically defined safe dose of the substance (e.g., the radiation response).

**Metabolic overloading**—the high dose may overwhelm the animal’s ability to handle the test chemical. In addition, different metabolites may form at high and low doses, resulting in different responses (e.g., acetaminophen).

**Epidemiological verification of animal findings**—animal study results that diverge from human evidence should raise doubts as to the conduct of the animal bioassay and its applicability to human exposure.

**Duration of study**—some highly inbred rodent strains are so susceptible to cancer that they will all eventually die of cancer. Study duration must be planned so that test animals are euthanized before the controls succumb to cancer.
### Table 4

<table>
<thead>
<tr>
<th>Site</th>
<th>B6C3F1 Mice Male</th>
<th>Female</th>
<th>F344 Rats Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>10.3</td>
<td>4.0</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Adenoma</td>
<td>21.8</td>
<td>4.1</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0.7</td>
<td>8.3</td>
<td>24.7</td>
<td>47.5</td>
</tr>
<tr>
<td>Pituitary</td>
<td>3.8</td>
<td>1.0</td>
<td>19.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1.3</td>
<td>2.1</td>
<td>10.7</td>
<td>9.3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>12.7</td>
<td>27.2</td>
<td>30.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Hematopoetic</td>
<td>0</td>
<td>1.9</td>
<td>2.5</td>
<td>26.1</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>17.1</td>
<td>7.5</td>
<td>2.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>


### Table 5

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Human carcinogens</th>
<th>Rat and/or mouse</th>
<th>Other animal</th>
<th>Other than human route or target organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component not identified</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Component identified</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Therapeutic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>8</td>
<td>3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Other than antineoplastics</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table 6
Typical Costs of Descriptive Toxicity Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General acute toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Acute toxicity (rat; two routes)</td>
<td>6,500</td>
</tr>
<tr>
<td>Acute dermal toxicity (rabbit)</td>
<td>3,000</td>
</tr>
<tr>
<td>Acute inhalation toxicity (rat)</td>
<td>6,500</td>
</tr>
<tr>
<td>Acute dermal irritation (rabbit)</td>
<td>900</td>
</tr>
<tr>
<td>Acute eye irritation (rabbit)</td>
<td>500</td>
</tr>
<tr>
<td>Skin sensitization (guinea pig)</td>
<td>700</td>
</tr>
<tr>
<td><strong>Repeated dose toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>14-day exposure (rat)</td>
<td>40,000</td>
</tr>
<tr>
<td>90-day exposure (rat)</td>
<td>100,000</td>
</tr>
<tr>
<td>1-year (diet; rat)</td>
<td>225,000</td>
</tr>
<tr>
<td>1-year (oral gavage; rat)</td>
<td>275,000</td>
</tr>
<tr>
<td>2-year (diet; rat)</td>
<td>625,000</td>
</tr>
<tr>
<td>2-year (oral gavage; rat)</td>
<td>800,000</td>
</tr>
<tr>
<td><strong>Genetic toxicology tests</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial reverse mutation</td>
<td>1,850*–13,650†</td>
</tr>
<tr>
<td>Mammalian cell forward mutation</td>
<td>8,400*–13,650†</td>
</tr>
<tr>
<td>In vitro cytogenetics (CHO cells)</td>
<td>8,000*–19,000†</td>
</tr>
<tr>
<td>In vivo micronucleus (mouse)</td>
<td>10,775</td>
</tr>
<tr>
<td>In vivo micronucleus (mouse)</td>
<td>10,775</td>
</tr>
<tr>
<td>In vivo chromosome aberration (rat)</td>
<td>26,500</td>
</tr>
<tr>
<td>Dominant lethal (mouse)</td>
<td>55,000</td>
</tr>
<tr>
<td>Drosophila sex-linked recessive lethal</td>
<td>35,000</td>
</tr>
<tr>
<td>Mammalian bone marrow</td>
<td>26,500</td>
</tr>
<tr>
<td>cytogenetics (in vivo; rat)</td>
<td></td>
</tr>
<tr>
<td><strong>Reproduction</strong></td>
<td></td>
</tr>
<tr>
<td>Segment I (rat)</td>
<td>95,000</td>
</tr>
<tr>
<td>Segment II (rat)</td>
<td>61,500</td>
</tr>
<tr>
<td>Segment II (rabbit)</td>
<td>66,500</td>
</tr>
<tr>
<td>Segment III (rat)</td>
<td>62,000</td>
</tr>
<tr>
<td>Acute toxicity in fish (LC50)</td>
<td>1,750</td>
</tr>
<tr>
<td>Daphnia reproduction study</td>
<td>1,750</td>
</tr>
<tr>
<td>Algae growth inhibition</td>
<td>1,750</td>
</tr>
</tbody>
</table>

* Minimum cost for U.S. registration.
† Worldwide registration.

Table 7
Number of Infant Formula Samples Tested for Pesticides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Milk-based formula</th>
<th>Soy-based formula</th>
<th>Total number of positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alachlor</td>
<td>144</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>Aldicarb</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Atrazine</td>
<td>74</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Benomyl</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Bendiocarb</td>
<td>69</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Captan</td>
<td>134</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Carbofuran</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Carbophenothion</td>
<td>32</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coumaphos</td>
<td>87</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Daminozide/UDMH</td>
<td>29</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diazinon</td>
<td>110</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dicofol</td>
<td>148</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>Dimethoate</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Disulfoton</td>
<td>32</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Ethion</td>
<td>110</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>EBDCs/ETU</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Malathion</td>
<td>46</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Mancozeb</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Maneb</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Methidathion</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Methoxychlor</td>
<td>142</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>Metiram</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Nabam</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Oxamyl</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Parathion Ethyl or methyl</td>
<td>154</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>Phorate</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Phosalone</td>
<td>70</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Ronnel</td>
<td>32</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Thiram</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Zineb</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Ziram</td>
<td>24</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

Totals 2043 1141 0

The data presented in Table 7 represent thousands of samples tested over a number of years by the infant formula manufacturers and contract laboratories. Milk-based and soy-based formulas were tested, as well as the ingredient water (which comprises more than 85 percent of ready-to-feed formulas). The pesticides listed in Table 7 are those that were identified by the Committee on Pesticides in the Diets of Infants and Children of the National Academy of Sciences as being of greatest concern. Table 7 is simply a representative sample of the data that has been collected over the years involving trace levels of pesticides in infant formulas.

Figure 1
Age-Adjusted Cancer Death Rates,*
Males by Site, US 1930-1993

* Rates are per 100,000 and are age-adjusted to the 1970 US standard population.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung, breast, and colon and rectum are affected by these coding changes. Denominator information for the years 1930-1969 and 1991-1993 is based on interracial population estimates, while denominator information for the years 1980-1989 is based on postennial recollution of estimates. Rate estimates for 1980-1989 are not likely of a better quality.

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Figure 2

Age-Adjusted Cancer Death Rates, *
Females by Site, US 1930–1993

* Rates are per 100,000 and are age-adjusted to the 1970 US standard population.
** Uterine cancer death rates are for cervix and corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Ratios for cancers of the breast, ovary, lung, colon and rectum are affected by these coding changes. Denominator information for the years 1930–1953 and 1955–1969 is based on intercensal population estimates, while denominator information for the years 1960–1989 is based on postcensal recalculation of estimates. Rate estimates for 1960–1989 are most likely of a better quality.


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Figure 3
Two Types of Dose-Response Curves

a. Linear Curve
   - Increasing incidence of tumors
   - Measured cancer risk at high dose
   - Increasing dose

b. Nonlinear Curve
   - Increasing incidence of tumors
   - Measured cancer risk at high dose
   - Increasing dose