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TOXIC SUBSTANCES CONTROL IN THE 1990s: Are We Poisoning Ourselves with Low-level Exposures?

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INTRODUCTION: THE REASONS FOR CONCERN

The production of synthetic organic chemicals has risen from less than one billion pounds in 1920 to 23 billion pounds in 1945, 75 billion pounds in 1960, to 213 billion pounds in 1988 (Figure 1) (12, 16). Most Americans wake up to synthetic fabrics in their bed cloths and clothing; they eat food (grown with pesticides and fertilizers made from these synthetic chemicals) packed in plastics; they are transported to their jobs in a vehicle that is composed largely of plastics and fueled by organic chemicals; synthetic materials are an essential part of their work. In addition to the synthetic organic materials, most Americans are exposed to large quantities of natural toxins, such as mercury and lead, and eat numerous natural pesticides and cooking-produced toxic compounds (3, 50). Constant exposure to potentially toxic substances is a fact of modern life—and was a fact of life before the first synthetic chemicals.

Toxicology, the science of poisons, is based on the premise stated by Paracelsus in the sixteenth century: "All substances are poison; there is none which is not a poison. The right dose differentiates a poison and a remedy" (quoted in Ref. 31, p. 16). If, however, the adverse effect is cancer, the prevailing theories hold that there is no "safe" level of exposure to a genotoxic

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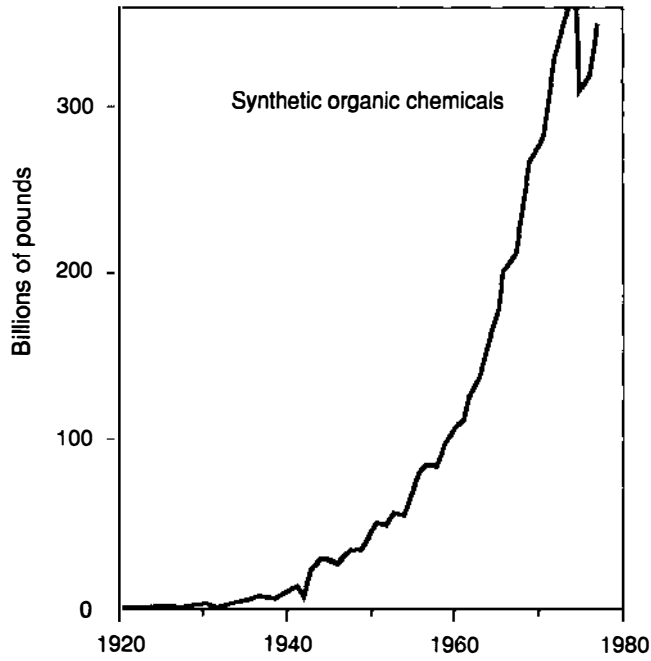

Figure 1 Total synthetic organic chemicals, annual production (excludes tar, tar crudes, and primary products from petroleum and natural gas) (12, 16).

agent, i.e. one that damages DNA (5). For genotoxic carcinogens, any exposure carries a theoretical risk of getting cancer, although the risk may be very small. Two decades ago, it seemed that the ability to cause cancer was the property of only a few chemicals. Yet, of the more than 800 chemicals tested, two thirds have been found to cause or promote tumors in rodents (23–25).

We live in a sea of known (or suspicious) substances, both natural and synthetic. Of the 60,000 synthetic chemicals in use, only a few have received extensive toxicity testing (43b). Thus, the potential health effects of these exposures are largely unknown. Some substances, such as pesticides and chemotherapy drugs, are designed to be poisons; the challenge is to make the chemicals highly poisonous to the target species or cells while attempting to make them harmless to humans (39). Rarely is it possible to attain this goal.

Many people have become concerned that the low levels of toxicants in the environment might cause cancer, reproductive difficulties, or other health effects (19, 20, 53). For example, what are the implications for humans of a few parts per million (ppm) of mercury and PCBs in fish? Of a few parts per billion (ppb) of aflatoxin in corn and peanuts, tricholoethylene in water, or of

benzene in air? Of a few parts per trillion of TCDD in soil? The concern has been fueled by media reports about Love Canal, Times Beach, Woburn, and other incidents, where residents claimed that exposures to low levels of toxicants caused cancer, birth defects, and other damage to health (59). Governments in the United States and other countries have reacted by creating regulatory agencies to prevent health damage due to exposure to environmental toxicants (35, 42).

One simple solution to managing toxic chemicals was to require that they be below detectable levels. The steady improvement in the abilities of analytic chemists to detect toxicants in ever smaller concentrations has paralyzed decision-making. In the 1950s, chemists were able to detect a toxicant in a sample of air, water, or food at concentrations in the ppm range. Since the sensitivity of the tests have gotten one-thousand to one-million times greater in the ensuing 30 years, this solution is no longer feasible. Even a policy of reducing exposures as much as possible is unattractive; the steady improvement in analytic chemistry allows routine detection of toxic substances at concentrations for which there are no scientific data on the health effects.

In parallel with the improvements in analytic chemistry are improvements in the methods to assess the health effects of a chemical. Epidemiologists and toxicologists are able to measure consistently and sensitively a variety of subtle physiological changes and health effects, particularly to exposures at high concentrations (39). Although theories have been developed to infer the effects at low concentrations, they remain theories without convincing data of their validity; the extrapolations are fraught with uncertainty (21).

At present, there are 26 chemicals (or groups of chemicals) that are known human carcinogens (32), more than 600 chemicals that are known rodent carcinogens (23–25), more than two thousand chemicals that are known mutagens (45), and more than 50,000 chemicals with essentially no scientific study of toxicity (43b). These potentially toxic chemicals are found, utilizing the most sensitive tests, to be ubiquitous in the environment. Scientists and regulators have no firm basis in data or accepted theory to predict the effects on humans of exposures at these low concentrations. For example, several chemicals are carcinogens, but also are classified as essential nutrients; at what levels do they stop being beneficial (4, 31)? During the 1990s, it is doubtful that scientific discoveries will lead to definitive predictions of the health effects of human exposures at these low levels. Low-level exposure is an area of vast uncertainty and ignorance where scientists can rely, at best, on only partial understanding of toxicity. There is no basis for assuring the public that absolute safety has been proven. In attempting to estimate the social benefits of decreasing exposure to benzene from, for example, 3 to 1 ppb in air, scientists can do no more than give the roughest estimates of the qualitative and quantitative risks.

Current concern has centered upon the chemicals demonstrated to be carcinogenic to humans or rodents, and also upon new synthetic chemicals as potentially toxic, but virtually all existing (and naturally occurring chemicals) are presumed to be safe (40). Thus, toxic chemical control faces two difficult questions: What are the effects in humans of low-level exposure to carcinogens? Have we identified the greatest hazards?

LIMITATIONS OF THE MODELS USED TO ESTIMATE HEALTH EFFECTS

Three approaches or types of models are used to predict the human health effects of exposures to low concentrations of toxicants: (*a*) structural activity relationships (SAR), (*b*) toxicology, including laboratory experiments with rodents, and occasionally with humans, and (*c*) epidemiology or statistical examination of a human population. Each approach has its comparative advantages. As we show, the approaches should be thought of as complementary, not as substitutes.

Structural Activity Relationships

SAR relies on the chemical structure of a molecule to infer its toxicity (22). The fundamental hypothesis is that identifiable aspects of molecular structure give rise to both acute and chronic toxicity. Any simple hypothesis about the structure leading to carcinogenicity is easily disproved. Thus, researchers have turned to elaborate searches, some using computerized artificial intelligence programs to infer the aspects of chemical composition that are associated with carcinogenicity (46).

The accuracy of prediction from SAR has grown over time (46). Nonetheless, any SAR approach relies on the data used to develop the relationships; even the best SAR predictions of carcinogenicity will have all of the limitations of original data, such as the assumption that chemicals found to be carcinogenic in rodents are human carcinogens.

Toxicology

Toxicology studies poisons, generally by using laboratory animals to predict human effects (34). Its inherent limitation is having to extrapolate from results in laboratory animals (generally rodents) to humans. One consequence of studying rodents in a laboratory setting is that extremely high doses of the toxicant are used; laboratory experiments become prohibitively expensive if large numbers of animals are used; high doses are used to enhance the likelihood that an effect will not be missed in a small group. The high dose used in a carcinogenicity assay is the "maximum tolerated dose" (MTD), the largest dose the animals can receive without displaying signs of acute toxicity.

Thus, in addition to having to extrapolate from rodents to humans, toxicology results must be extrapolated from extremely high to extremely low doses. Often the dose used in the laboratory is more than a 1000-fold greater than humans receive.

The extremely high doses can lead to physiological effects that would not occur at low doses. For example, the quantities of nitriliotriacetic acid (NTA) that produce bladder tumors in rats also produce crystals in the bladders that might be the source of the tumors, rather than the NTA or its metabolites (57). For formaldehyde, high concentrations in air overwhelm the rat's natural defense mechanisms and may produce effects that would not be seen at lower doses (28). Thus, some chemicals that give rise to a physiological response only at extremely high doses, may have a natural threshold below which no tumors would be expected to occur.

To eliminate sources of variation, toxicologists use genetically homogeneous animals and maintain the animals under conditions that shield them from other environmental insults. The human population is genetically heterogeneous and is assaulted by many environmental toxins and toxicants; as a result, the quantitative extrapolation to humans, and even the qualitative characterizations, are subject to uncertainty (10).

Of the chemicals tested, two thirds have been carcinogenic in lifetime rodent bioassays (23–25), if an increase in tumor rate for any experimental group is considered sufficient to classify a chemical as a carcinogen. Empirical justification for the policy of considering a chemical a rodent carcinogen if it is carcinogenic to rats *or* mice is that it eliminates false negatives for known human carcinogens (18; 61); however, false positives are inevitable from such a decision rule (40). Even though the chemicals that have been tested to date are not a random sample of all chemicals in use, the high proportion classified as carcinogens is disturbing (3, 40).

Young (61) catalogues eight general problems that could occur in analyzing and interpreting a lifetime rodent bioassay:

1. data reduction (Is the unit of measurement a specific tumor, any tumor, any tumor bearing animal?)
2. survival (What adjustments should be made for animals that die early because the dose is too high or animal husbandry is inadequate?)
3. which test (Which of a range of available statistical tests should be used?)
4. per comparison error rate (A different statistical test may be appropriate, depending on the rate of spontaneous tumors.)
5. experiment-wise errors (The significance level might be vastly overstated because of multiple comparisons where a single comparison is assumed.)
6. composite test (One way of handling 5. is to do a single composite test before performing multiple individual tests.)

7. use of ancillary information (Rather than examining the data uniformly, it might be aggregated or compared in a special way because of information unrelated to this particular experiment.)
8. vehicle versus untreated controls (Untreated controls might have a lower cancer rate than vehicle treated controls.)

All eight of these problems tend to increase the number of false positives. For purely statistical reasons, the false positive rate was found to range from 9 to 75%, depending on the rules employed.

A final criticism of current rodent bioassays is that the high doses of the test chemicals kill cells and therefore lead to cellular proliferation, particularly in the liver and kidney, and that this proliferation in itself leads to increased cancers (3, 13).

Risk Analysis

Risk analysis was developed to infer the implications for humans of exposures to low levels of toxic chemicals, particularly of carcinogens (5, 43). Studies of the carcinogenicity of ionizing radiation provide the basic principles of risk analysis (43b, 52). The incidence of cancer is dose related, with animal studies providing important evidence about the mechanisms of action. Since ionizing radiation is a mutagen, health physicists assume that damage to DNA is the event that triggers carcinogenesis, although the mechanism is unknown. If so, a single break in a DNA strand could lead to cancer, and so the process is conceived of as a "one-hit" model. The implications of this model are that the incidence of cancer should be approximately proportional to dose at low levels of exposure.

Available data on humans fit this model down to doses of about 100 rem, where it is no longer possible to infer the increase in cancer associated with the radiation dose. The doses of radiation experienced by people in their normal activities are more than 1000 times less than the levels known to cause cancer. For example, a chest X-ray is about 60 millirem, and nuclear power is regulated so that people receive less than 26 millirem annually. In some buildings, the dose to the lungs from radon is high enough that it is estimated to cause about 10% of lung cancers in the United States, primarily among smokers (14, 41). Since the body can repair damage to DNA, there is the possibility that a practical threshold may exist, with the repair mechanisms taking care of DNA damage at the low dose rates. Some scientists contend that low-level exposure extends life by provoking an immune response greater than that needed to handle the challenge (48, 60). Nonetheless, all repair mechanisms are imperfect, and so the original injury or the result of an imperfect repair might lead to cancer. Unfortunately, this argument is purely theoretic, since the limits of epidemiology, including a background cancer

incidence of more than 30%, preclude any practical way of distinguishing between a low risk and a zero risk.

Risk analysis is based on the models of radiation carcinogenesis. The assumption is that the dose-response relationship is a "one-hit" model at low-dose levels. Attempts to use empirical data to verify the linearity of the dose response curve at low doses have been equivocal (62). In addition, risk analysis assumes that any chemical leading to an increase in tumors in laboratory animals (including nonmalignant tumors) causes cancer in humans (5). Again, empirical verification of this assumption has been inconclusive (1, 8).

The standard procedure is to calculate the "potency slope" or proportionality relationship between dose and response from the experiment, rodent species, and dose group that gives the largest potency slope. The assumption is made to ensure that the dose-response relationship for humans is not understated. If more than one lifetime rodent bioassay is done, however, there is bound to be some variation in the number of cancers observed. Taking the group with the greatest potency slope, rather than taking an average of potency slopes, has the effect of using random variation to increase the potency slope.

In addition, the standard method of the Environmental Protection Agency (EPA) calculates the upper bound of the 95% confidence interval of the multistage model that is fitted; it is this upper confidence level that is used (5). Again, this assumption is made in order not to underestimate the risk to humans.

The calculated potency must be extrapolated from rodents to humans. One issue is whether to use body weight or surface area; the latter gives a higher estimate of risk to humans by about a factor of 7 for extrapolations from rats and a factor of 15 for extrapolations from mice (15). Another issue is whether to compare doses on a lifetime or total dose basis; equating lifetimes is standard (43), but using total doses would increase the extrapolated risk by 35 (the ratio of the rodent 2-year lifetime to the 70-year human lifetime). Physiologically based pharmacokinetic models have been developed that take into account differences in metabolism between rodents and humans, although the data needed to use such models are available only for a few extensively studied compounds (11, 51).

Finally, the dose that individuals in the general population receive must be estimated to complete the input data for the risk analysis. No one knows whether a particular source will continue to produce this chemical or whether it will cease to be used in this application. No one knows whether discharges into the environment will rise or fall due to new control technology or changes in the demand for the product. No one knows where individuals will choose to reside or which activities they will choose to pursue. To cut through the

controversy, exposure is characterized by focusing on the highest dose that an individual could plausibly receive (e.g. someone who spends 24 hours each day for 70 years at the spot of greatest exposure). Again, the assumption is made so as not to underestimate human exposure.

Risk assessors and regulators have drawn comfort from being able to assert that their estimates are overstatements of the actual risk that humans experience. Risk extrapolation is an area with such uncertainty, however, that characterizing any estimate as "conservative" (i.e. overstating the risk) is open to challenge.

In addition, each chemical is assessed by itself, although we live in a chemical "stew." Since carcinogens are known to dampen or potentate each other, assessment of one chemical at a time could understate its effects in typical exposures (6). A second argument is that the rodents in the study are genetically homogeneous, whereas humans are genetically heterogeneous. Some people may be susceptible to a chemical to which the test animals were insensitive (10). A lively debate has been sparked by this criticism (1, 21).

Despite these attempts at conservatism, Bailar et al (7) contend that the rodent bioassay, as currently interpreted, may not be conservative. They show that when experimental dose-response curves depart from linearity, some curve-fitting procedures give a higher estimate of risk at low doses than do the "conservative" standard procedures.

Few of these controversies are likely to be resolved in the 1990s.

Epidemiology

Epidemiological studies search for harm, such as an increase in the cancer rate, or at least a physiological change that has resulted from exposure. Since epidemiologists study humans, in general they are searching for situations in which someone has erred in allowing people to be exposed to a toxicant. Human populations are heterogeneous with a high background rate of cancer (30%), thus limiting epidemiological studies to discovering powerful carcinogens in heavily exposed subpopulations (32).

In addition to being retrospective, epidemiologists rarely are able to estimate the dose that people received. For example, Aksoy (2) was able to infer that benzene used as a solvent in glue for shoemakers led to an epidemic of leukemia in Turkey, but he had little ability to infer the doses of benzene that the workers received. Similarly, attempts to regulate asbestos are complicated by the fact that the levels of asbestos exposure can only be inferred retrospectively (47, 58).

A third problem is that people are not exposed to a single toxicant. Was the lung cancer in asbestos workers caused principally by the asbestos or by their cigarette smoking? The concept of "attributable risk" is used when removing one of the agents could reduce the incidence of the disease. For example, a

man exposed to both cigarette smoke and asbestos would have a much greater likelihood of developing lung cancer than someone exposed to only one of the carcinogens (47). Arguably, this individual and society might have found the risks of smoking tolerable, but they would find that adding exposure to asbestos makes the combined risk intolerable. Thus, many of the risks of exposures at present could be increased in a dramatic and unacceptable way if an additional toxicant were added that potentiated existing exposures.

The ability to separate the effects of smoking from those of asbestos is the exception, not the rule. Both chemicals are potent carcinogens, large numbers of people are exposed to both, and many people were exposed to only one of them. The International Agency for Research on Cancer (IARC) (32) categorizes several groups of chemicals as carcinogens without being able to single out the culprit (if there is a single culprit). In these cases, epidemiologists were able to demonstrate a statistically significant increase in cancer but were unable to infer which chemical was the cause.

Finally, although epidemiology is not faced with the difficulty of having to extrapolate effects to humans, it is faced with the problem of extrapolating from high (and often imperfectly known) doses, at which carcinogenicity was observed, to low doses, which are those experienced by the public. For example, what to do about asbestos in buildings, particularly schools, is an extremely controversial issue. There is no question that asbestos causes lung cancer and mesothelioma at high doses. But there is little agreement about whether asbestos causes these cancers at doses 1000 times lower than those experienced by workers (58). Plausible models have extremely different implications of the risks at low exposures. One crucial issue concerns how the incidence of mesothelioma increases with the period since initial exposure. Several models fit data for workers reasonably well but have extremely different implications outside the observed range. In particular, the models have extraordinarily different implications about the risk to 5-year-old children who experience extremely low-level exposures, since they will have an additional 60 to 80 years to develop mesothelioma.

Implications

Society's desire to prevent cancer requires anticipatory action based on models replete with uncertainty (35, 36). The simplest strategy would be to wait until there was evidence that a chemical or group of chemicals causes cancer in humans, and then ban these chemicals. If so, there would be no need for SAR, toxicology, or risk analysis. The only source of uncertainty would be identifying which chemicals are the carcinogens, although some practical problems could arise in implementing a ban on a group of naturally occurring or otherwise unavoidable chemicals.

The desire to find an alternative to banning the carcinogen leads to un-

certainties. Setting a standard to protect people while still using the chemical requires risk analysis. The analysis must estimate the number of cancers resulting from exposing the population at risk in order to estimate the potency of the carcinogen. The number of cancers that would be produced by exposure to regulated levels must be estimated, along with a decision about the social goal for safety. As noted above, there are uncertainties in tabulating past exposures, the number of people at risk, and the number of resulting cancers. There are also uncertainties in the number of cancers that would be expected for each exposure level, and in the amount of exposure that would be expected under alternative standards.

The desire to prevent cancer, to regulate before people are harmed, produces much greater uncertainty. Structure-activity relationships and toxicology are needed to estimate which chemicals are probable human carcinogens. A great deal of uncertainty is introduced by assuming that chemicals positive in lifetime rodent bioassays or in short-term in vivo and in vitro tests are human carcinogens. Still more uncertainty is introduced by estimating the number of cancers likely to result in humans from exposures of particular levels (21, 40).

The desire to prevent cancer leads to the development of models that often cannot be verified with human data. It is not possible to be confident in characterizing some estimates as overstating the risk level. This means that there is no scientific proof that exposure to any particular chemical, or group of chemicals, at an extremely low level either is or is not harmful to a fearful group.

SETTING SAFETY GOALS

We have described the process by which chemicals are tested for carcinogenicity and the processes for estimating the exposures that people might receive and the resulting number of cancers that could occur. Thus, within this set of models and set of assumptions, risk analysis provides estimates of how many cancers might be expected (or rather a plausible upper bound on the number of cancers that might result) from a particular standard (with its implied population exposure). But which standard should be chosen? Given the benefits of using a particular chemical and the costs of losing the chemical or taking measures to reduce exposure, what standard should regulators (representing society) choose? In other words, "how safe is safe enough?"

In some cases Congress has given explicit instructions (9, 35). For example, the Delaney Amendment to the Food, Drug and Cosmetic Act forbids a substance identified as a carcinogen to be added to food. Thus, Congress has set a zero risk goal for getting cancer from food additives. In contrast, the same legislation directs that food contaminants (natural substances in food) be

regulated when they present an "unreasonable risk." Thus, the aflatoxin (due to a mold) contaminating peanuts is regulated on an "unreasonable risk" basis whereas the food colors used with the peanuts are regulated on a "no carcinogenic food additive" basis. The food color might be banned, even if it presented a risk of getting cancer 1000 times smaller than the risk presented by the aflatoxin that is tolerated.

According to Ames et al (4), it would be difficult to have a nutritionally adequate diet if all foods with carcinogenic contaminants were banned. Thus, Congress had no choice but to set a safety goal less stringent than the Delaney Amendment. The discrepancy between the safety goals for a food additive and a food contaminant, and the costly implications of the Delaney Amendment, led the Food and Drug Administration (FDA) to develop risk analysis (31). The notion was that if an additive presented a cancer risk that was trivially small, it would not be banned. FDA set a level of one cancer per million lifetimes as this trivial level. Using the conservative procedures of risk analysis described above, if a carcinogenic food additive would be estimated to cause less than one additional cancer per million people exposed, over their entire lifetimes, FDA deemed the risk to be trivial. This FDA interpretation was the subject of recent litigation (44). The Court asserted that the plain language of the Delaney clause left the FDA with no alternative other than to ban carcinogenic food additives, however unreasonable this might be. However, the FDA approach is still retained for other FDA decisions regarding carcinogens.

Several federal agencies set regulations concerning human exposure to carcinogens, including FDA, EPA, Occupational Safety and Health Administration (OSHA), and Consumer Product Safety Commission (CPSC). For decisions other than those covered by the Delaney clause, Congress has given the agencies little specific guidance as to how safe is safe enough. In some cases the statutory language is that of unreasonable risk; in other cases, the statute is contradictory because it calls for complete protection, but then requires that the resulting regulations must be technically and economically feasible (42). Nonetheless, there is a modicum of consistency in the decisions across different chemicals by different agencies (9, 42a, 52a). Federal agencies rarely regulate a case in which the risk of carcinogenicity is less than one cancer per million lifetimes. In virtually every case in which the risk is greater than one cancer per 1000 lifetimes, the agency chooses to regulate. In some cases, the regulation reduces the risk of cancer to less than one cancer per million lifetimes. In other cases, a high risk remains, even after regulation. The level of risk the agency is willing to tolerate decreases as the size of the exposed population increases.

During 1988 and 1989, EPA asked for public comment on four proposed safety goals (54). The first would offer no guidance to the agency, with each

case considered anew. The second was a safety goal of no more than 100 cancers per million lifetimes. The third was a safety goal of no more than one cancer per million lifetimes. The fourth was a safety goal of no more than one cancer per year in the exposed population. The last proposal takes account, explicitly, of the population exposed, even though it is a flawed goal. EPA has decided to adopt a combination of all four goals; 100 cancers per million lifetimes is the upper bound of tolerable risk, but the agency goal is to reduce the risk to all individuals to one cancer per million lifetimes; EPA will consider the size of the population at risk in arriving at standards, but will consider a variety of additional factors in arriving at a standard (55). EPA has set an explicit safety goal of no more than one cancer per million lifetimes for public exposure to pesticides.

Setting a safety goal, explicitly or implicitly, is a crucial step in managing low concentrations of toxic chemicals in the environment. For example, if a safety goal of 100 cancer per million lifetimes were set, regulation could focus on a small number of cases. If the safety goal were one cancer per million lifetimes, a much larger number of cases would require regulatory attention.

In the absence of any safety goal, every discovery of a potential carcinogen is a candidate for regulation, whether in air, water, food, in buildings, in the workplace, or in soil where people live and play. As analytic chemists are able to measure potentially carcinogenic chemicals in the or parts per trillion or quadrillion range, the lack of a safety goal means that more and more situations are candidates for regulation. Since there is neither time nor resources to deal with all of these situations, some situations must be classified as "unimportant" or others as being of "first priority."

EXAMPLES OF REGULATING ENVIRONMENTAL TOXINS

A large number of toxins and toxicants have been regulated during the past two decades. We discuss saccharin and benzene in order to illustrate the points raised in the preceding discussion.

Saccharin

Saccharin, a nonnutritive sweetener, was tested numerous times in rodent bioassays without a positive result (43a). In 1978, a study found an increase in bladder tumors. Under the Delaney clause, FDA felt it had no option but to ban the chemical. From 1969, when sodium cyclamate was banned, until aspartame was approved by the FDA, saccharin was the only nonnutritive sweetener for sale in the USA. Despite its alleged carcinogenicity, American

consumers wanted saccharin, or rather wanted a nonnutritive sweetener. Consumers protested and Congress forbade the FDA to ban saccharin while the National Academy of Sciences studied the issues.

No epidemiology study has found a statistically significant association between bladder tumors and saccharin consumption, although for two subpopulations of heavy users, the incidence of bladder tumors appeared to increase with use (32).

This pattern of results might occur either if saccharin was a human carcinogen, but an extremely weak one, or if it was not a human carcinogen. In the former case, the signal would be all but hidden in the noise of low doses, interactions with other carcinogens (such as tobacco smoke), the inaccuracy with which cancer is diagnosed, and the possibility that only a part of the population is susceptible genetically. In the latter case, several studies were done that might have under- or over-controlled for interacting factors; it is not strange that a gradient, or even a statistically significant association, would be found in one of the groups. Thus, the epidemiologic studies do not provide definitive evidence that saccharin is not a human carcinogen, although they suggest that it is not.

The lack of significance is not surprising. A standard risk analysis, assuming that humans have the same susceptibility as rats, showed saccharin to pose an undetectable risk to consumers.

The epidemiologic studies do agree that, even if saccharin is a carcinogen, it is of such low potency that the risks of consuming it are low compared to the incidence of cancer, although they could be greater than those of regulatory concern. The lack of support of the epidemiological studies for the rodent bioassay would not allow FDA to back off a ban under the Delaney clause. In 1978 the publicity surrounding the laboratory study, FDA's decision to remove saccharin from the consumer market, and the ensuing campaign that was successful in getting Congress to disallow the FDA ban made nearly all Americans aware of the dangers of consuming saccharin. Since Congress required that products with saccharin be labeled and that warnings be posted in stores, it seems likely that most people understood that they were purchasing products with saccharin and thereby risking cancer. Despite the warnings, most Americans continued to purchase saccharin, deciding implicitly or explicitly that the threat was not sufficient to give it up. Even after aspertame became available, saccharin continued to be consumed in significant quantity. Apparently the benefit of having a nonnutritive sweetener dominated the risk that saccharin is a carcinogen of low potency.

Benzene

When an epidemic of leukemia appeared among adult males in Turkey, Aksoy (2) traced the cause to benzene acting as a solvent in glue used by

shoemakers. Together with case reports from other places, the Aksoy work revealed benzene to be a leukemogen (26).

Benzene is a basic chemical used in many applications. Not only is it a good solvent, it is a constituent in gasoline and a feed stock. Benzene is a "natural" chemical, with about 1 ppb as the background level due to releases from trees and other sources.

Government concern can be separated into that for workers and that for the general public. The Aksoy work made it clear that exposure to high concentrations would lead to leukemia. The recommended and later enforced standards gradually reduced the allowable concentrations to which workers might be exposed; the newly created Occupational Safety and Health Administration (OSHA) adopted the American Council of Governmental Industrial Hygienists' recommended standard of 10 ppm in 1970. In 1977, OSHA published a new standard of 1 ppm. The justification was that benzene was a carcinogen and thus no level other than zero was safe; the social and economic cost of banning benzene was too high to give this possibility serious consideration. In the end, 1 ppm was chosen because it was believed to be achievable.

OSHA was immediately sued by Industrial Unions Department of the AFL/CIO and by the American Petroleum Institute (API) (33). The former contended that the 1 ppm standard was not sufficient to protect workers, and the latter contended that OSHA had failed to show that there was harm at 10 ppm, the existing standard, and that the new standard would be needlessly costly.

Eventually, the plurality of a sharply divided Supreme Court set aside the 1 ppm standard. The Court argued that OSHA had failed to show that the risks to workers at the prevailing standard (10 ppm) was "significant." The Court noted that ignoring *de minimis* issues was a foundation in the justice system; each regulatory agency must show that an issue is "significant" rather than "*de minimis*" before it can take action. OSHA justified its purely theoretical grounds for lowering the standard on the one-hit theory of carcinogenesis; the agency argued that a risk analysis could not be performed. One API witness presented a risk analysis that showed that very few leukemias would result at the current standard, and so lowering the standard ten-fold would involve large costs with little or no decrease in leukemias.

In 1986 OSHA reproposed the 1 ppm benzene standard based on a risk analysis that used conservative assumptions. The standard was not challenged by industry and is in force.

On August 31, 1989, EPA issued a new regulation reducing industrial emissions of benzene by 90% (30, 55). The estimated capital cost is more than $1 billion. According to EPA, the risk to a maximally exposed individual, one living next to the benzene facility 24 hours a day for 70 years,

would be reduced from 1/142 to 1/5000 (given the uncertainties of risk analysis, EPA considers 1/5000 to be equivalent to 1/10,000). For people living near a coke oven, those with the highest exposure to benzene, EPA estimates that current exposure levels lead to 2 leukemias each year among the millions of people exposed. Under the new regulation, there would be one leukemia every 20 years. The cost of bringing coke ovens into compliance is estimated to be $74 million in capital costs and $16 million in annual operating costs. Thus, for coke ovens, the cost of preventing each leukemia is estimated to be more than $15 million. The cost per leukemia prevented is much greater for other industrial facilities covered by the standard. EPA reacts to such a calculation by estimating that the new abatement controls will add less than 1% to the cost of producing coke.

WHAT IS THE RISK FROM ENVIRONMENTAL CARCINOGENS?

In a pathbreaking 1981 study for the US National Cancer Institute, Doll & Peto (17) brought together estimates of the number of cancers that result from tobacco consumption, diet, sexual behavior, occupational exposures, and environmental exposures of the general public. As shown in Table 1, their expert judgment of the epidemiological evidence is that tobacco use generally, but most particularly cigarette smoking, is responsible for about 30% of cancers in Americans. Diet, principally the consumption of high fat, accounts for about 35% of cancers. All environmental carcinogens, including occupational exposures, are estimated to account for about 6% of cancers, with asbestos in the workplace accounting for half of the occupationally caused cancers.

Some people found it shocking that environmental carcinogens were estimated to be responsible for only about 2% of Americans' cancers. Nonetheless, these estimates have come to be accepted widely. For example, the US National Cancer Institute has set a plan for halving the annual number of cancer deaths by the end of the 1990s (56). The focus is on prevention (reducing tobacco use, changing diet, and changing sex habits), with a lesser role for screening to discover cancer at an early stage, and improvements in treatment. Environmental carcinogens are not mentioned; apparently they are too unimportant compared to the other means of prevention.

A recent analysis by Gough (27) attempts to estimate the number of cancers due to environmental exposures. Rather than using epidemiology data, as did Doll & Peto, Gough uses toxicological data and risk analysis. He estimates that about 2% of cancers are due to environmental exposures. The agreement of the two approaches appears to confirm the general accuracy of risk analysis estimates.

Table 1 Proportions of cancer deaths attributed to various different factors (17)

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

[a] Allowing for a possibly protective effect of antioxidants and other preservatives.
[b] Including timing of pregnancy and menstruation.
[c] Only about 1%, not 3%, could reasonably be described as "avoidable."

ISSUES FOR THE 1990s

The stage is set for what might be a divisive battle that consumes enormous resources while doing little to reduce the number of cancers. The dread of cancer that many Americans feel has led to a plethora of legislation creating regulatory agencies and programs to reduce this perceived threat. The increased ability to detect carcinogens in air, water, food, etc. at levels that have unknown implications for health continues to increase pressure on the regulatory agencies. Americans desire to be protected against cancer, but there is no scientific assurance that even one part per quadrillion of tricholoethylene in drinking water might not lead to cancer.

Thus, the perceived problem is likely to grow worse. We will see more and more proof that we live in a sea of carcinogens, however low the concentrations. Risk analysis can be enormously helpful in setting priorities, but there is still a need to set a safety goal: How safe is safe enough? Despite some publicized cases in which some important problems were ignored and some cases in which large amounts of resources were used to control trivial risks, the regulatory agencies have made generally sensible decisions.

The progress in analytic chemistry allows regulators to identify the presence of these toxicants in minute amounts. The progress in measuring physiological responses in humans has made these tests exquisitely sensitive. The

combination of the two scientific advances will impose ever more stringent discharge regulations for toxicants; the regulations will not only impose large costs on producers, they will lead to banning many socially and economically useful chemicals. Although the current regulatory system could continue for a few more years with growing problems, the advances in toxicology and analytic chemistry will make the system nonviable (37).

The 1990s hold ample challenge for public health professionals. Identification of hazards among the thousands of uncharacterized chemicals, both natural and synthetic, will require rational strategies for selecting and using screening tests and evaluating their results (38). Improvements in risk assessment are needed for more consistent treatment of chemicals with varying levels of toxicological information, for more explicit characterization of uncertainty, and for empirical validation of assumptions and procedures (52). Risk communication needs to be improved, which will involve listening to citizens (29), both concerned and unconcerned, as well as talking to them (49). The often-acknowledged theoretical possibility that a chemical carcinogenic to rodents may not be carcinogenic to humans has arisen as a concrete question upon a number of occasions recently; uniform standards for evaluation of evidence need to be developed (13). Finally, virtually every stage in the regulatory process requires scientific data that are inevitably uncertain; thus, there is an urgent need for developing procedures for making decisions in the presence of uncertainty.

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