Chemical Carcinogens: How Dangerous Are Low Doses?

Cancer is arguably a unique disease. Its irreversibility, long latent period, and unrestrained growth of cells differentiate it from every other type of human affliction. But if cancer is unique, are the agents that cause it also unique? Are chemical carcinogens subject to the same rules that govern the metabolism of other foreign chemicals, or are they metabolized through unusual pathways that lead directly to the induction of a tumor? Do very small doses of carcinogens retain the capacity to induce tumor formation, or can these small doses be detoxified by mammalian tissues in the same fashion as other toxic substances? The question of what happens after exposure to very low doses of carcinogens is one of the most vexing that regulatory agencies must answer as they try to determine whether any exposure to a carcinogen can be tolerated.

Debate between those who think carcinogens can be detoxified and those who do not has raged for years with all the intensity of a jihad. The analogy to religion is not inappropriate, moreover, since there is little hard scientific evidence to support either point of view. Few investigators have done research in the area, and what little evidence is offered by each side seems to be effectively rebutted by the other. Arguments on both sides of the question often seem to be little more than articles of faith, and it is exceptionally difficult for an impartial observer to decide which faith is more deserving of support.

For the moment, the more conservative view that thresholds do not exist is in the ascendancy. The Delaney amendment to the Food and Drug Act, for example, prohibits the deliberate addition to foods of chemicals that have been shown to be carcinogenic in man or animals. The Federal Insecticide, Fungicide, and Rodenticide Act prohibits use of pesticides that have been shown to be carcinogenic. Proposed rules of the Occupational Health and Safety Administration would prohibit industrial use of carcinogens unless no alternatives are available, and then would require exceptionally strict control of exposures. Nonetheless, an increasing number of scientists now argue that complex metabolic routes can minimize the danger from many carcinogens and that thresholds or no-effect levels can be observed in many cases. It is not yet clear, though, how this knowledge should be applied.

The difficulty arises from the exigencies of animal experimentation. As was discussed in the previous article in this series, results from animal carcinogenesis studies must usually be obtained with high doses of carcinogens in relatively small numbers of animals. Inferences from these results must then be extrapolated to predict what will happen when large numbers of humans are exposed to much smaller amounts (Fig. 1). David B. Clayson of the Eppley Cancer Institute reflects the views of many investigators when he argues that this extrapolation is now so inexact as to be valueless in the predictive sense. Nonetheless, the need for regulation requires that such extrapolations be performed. There are two main ways to go about it.

The threshold hypothesis assumes that there is a no-effect dose of carcinogen below which induction of cancer cannot occur or occurs with an extremely low probability. An alternative statement of the hypothesis is that the dose-response curve is shaped like a hockey stick: the slope of the curve is zero or approaches zero at low doses, but increases sharply as the threshold dose is passed. Proponents of this view thus argue that exposure to limited quantities of many carcinogens may be essentially hazard-free.

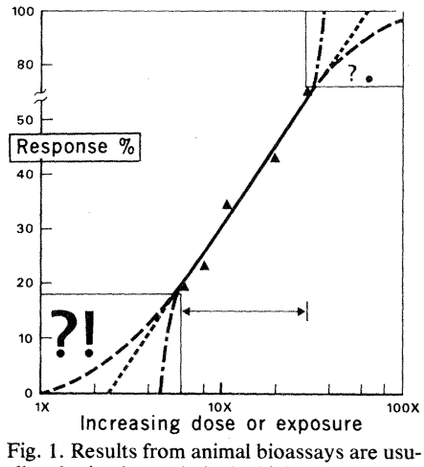

Fig. 1. Results from animal bioassays are usually obtained at relatively high levels of exposure, as indicated by the triangles. The problem in estimating human risks is trying to determine what happens at lower exposures: as indicated on the diagram, there are several possible ways to extrapolate. In most cases, extrapolation of the observed results with a straight line will yield a result suggesting no response at low doses—that is, a threshold. Most scientists, however, now think that the actual response is indicated by the smooth curve passing though zero dose and zero response. [Source: P. J. Gehring, Dow Chemical Company]

The single-event or "one-hit" hypothesis assumes that cancer is an expression of a permanent, replicable change in cellular genetics resulting from the interaction of one molecule of carcinogen with a critical receptor in one cell. In other words, at low doses, the dose-response curve for chemical carcinogens is a straight line that would go through zero dose and, if there were no spontaneous incidence of tumors, zero response. More sophisticated modeling systems assume that two or more events are necessary for induction of a tumor, but that there is no threshold. These models, such as the probit and Mantel-Bryan extrapolations, predict that the dose-response curve is concave upward. At low doses, these multihit models predict a somewhat lower incidence of induced tumors than does the one-hit hypothesis. At the doses of carcinogen generally used in animal studies, however, all the dose-response curves look the same.

The most frequently cited evidence in support of the one-hit theory of chemical carcinogenesis is the exhaustive data on radiation-induced cancer. The induction of leukemia by ionizing radiation from nuclear explosions, for instance, follows a linear dose-response curve down to an induced incidence of about 0.1 percent, below which the statistics are not reliable. Some scientists argue that chemical carcinogenesis must follow the same dose-response curve. Such a comparison is not really appropriate, however, argues Edward E. Pochin of Britain's National Radiological Protection Board, among others.

The entry of radiation into cells is governed by physically predictable laws, Pochin says, and the energy of the radiation—which generates free radicals that can interact with DNA or other cellular components—is as likely to be released in the nucleus of the cell as anywhere else. A chemical carcinogen, in contrast, must generally go through several intermediate steps of transport and metabolism before it can react with DNA. We have much less knowledge of the biochemical laws governing these steps, he argues, and there are many potential roadblocks that could prevent a carcinogen from reaching the nucleus. A better

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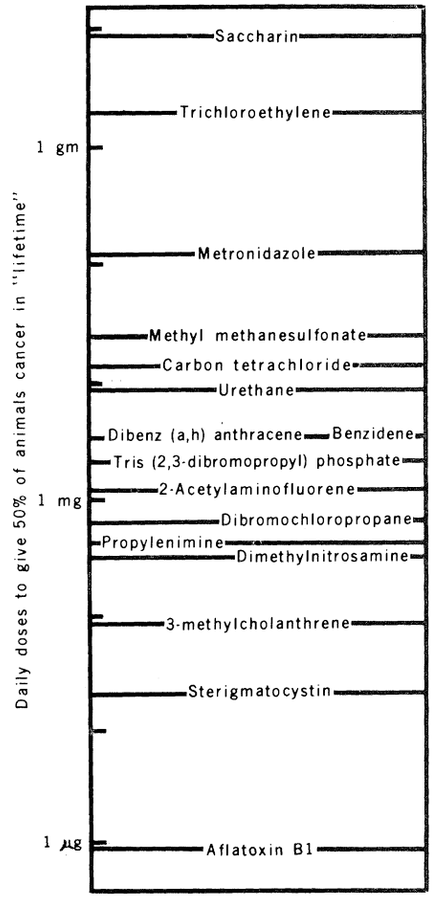
example might be data which show a linear relationship between lung cancer and the number of cigarettes smoked daily. But those data, critics argue, are accurate only down to an incidence of about 1 percent, whereas extrapolations must be performed to predict incidences that are well below 1 percent.

Most of the evidence supporting the one-hit hypothesis is more indirect, however. Paul Craig and his associates at the Franklin Institute, for example, reviewed dose-response curves for 151 chemicals that had been studied at several doses in animals and found that all the curves were consistent with the absence of a threshold. Reviewing these and other data, a 1975 National Academy of Sciences (NAS) Panel on Contemporary Pest Control Practices and Prospects concluded that there is no clear indication of a threshold for any carcinogen. That conclusion was echoed in a 1977 NAS report on Drinking Water and Health. Each of these reports concluded that there is no adequate theory of chemical carcinogenesis that would require

Estimating Potency of Carcinogens Is an Inexact Science

If the balance between risks and benefits is to be considered in regulation of carcinogens, it is important to have some estimate of their potency. Potential benefits of a chemical would have to be very high to justify the risks associated with a potent carcinogen, for example, whereas less substantial benefits might justify use of a weak carcinogen. Unfortunately, the scientific basis for estimating the potency in humans of chemicals shown to be carcinogenic in animals is very limited.

Chemical carcinogens exhibit a wide range of potency in laboratory animals. The accompanying diagram, compiled from the literature by Bruce Ames and his colleagues at the University of California at San Francisco, illustrates the daily dose of a carcinogen (per kilogram of body weight) that is required to induce tumors in 50 percent of a group of rats or mice over the course of their lifetimes. The diagram clearly shows that there is a millionfold difference in potency between aflatoxin B1, one of the most potent carcinogens known, and saccharin, one of the weakest. Most scientists assume that potency in rodents is a rough indicator of potency in humans, but evidence to support this assumption is limited because of the difficulties of obtaining dose information in humans exposed to carcinogens. Estimates of dose levels for substances that have caused cancer in humans are available from epidemiological studies for only six substances —benzidine, chlornaphazin, diethylstilbestrol, aflatoxin B1, vinyl chloride, and cigarette smoke. For each of these chemicals, according to Matthew Meselson of Harvard University, there is a rough correlation between potency in rodents and in humans. This correlation is the justification for most estimates of potency in humans.



But potency is the result of a complex series of biological events and can be altered by many external factors. Significant differences in the observed potency of carcinogens in laboratory animals can be obtained, for example, by exposing the animals to chemical agents that stimulate or depress drug-metabolizing enzyme systems; by modification of the animals' diet; by changing the hormonal balance of the animals; and by stressing the animals in various ways, such as by increasing the number in a cage. Significant differences in potency can also be observed in different animals. Aflatoxin, for example, is a very potent carcinogen in rats, but is not a carcinogen in adult mice; 2-fluorenylacetamide is a very potent carcinogen in one strain of rats, but is not a carcinogen in another strain; and 2-naphthylamine is a potent carcinogen in humans, but is not a carcinogen in rats. Great caution must thus be used in extrapolation of potency estimates between species.

The problem is further complicated when estimates of carcinogenic potency are made from results of short-term mutagenicity assays such as the Ames test. Ames has observed an approximately linear correlation between the mutagenic potency of a chemical in the *Salmonella* test and its carcinogenic potency in animals. Other scientists, however, have reservations about such correlations, particularly since other studies have shown that the correlation does not hold for polycyclic aromatic hydrocarbons and nitrosamines. Some of the problems may arise, say John Ashby and J. A. Styles of Imperial Chemical Industries Ltd. in England, because of the variations in the preparation of rat liver homogenates used to activate mutagens in the Ames and other short-term tests. They recently demonstrated that the observed mutagenic potency of benz-[*a*]pyrene can vary by more than a factor of 100 depending on how the liver homogenate is prepared. Since the Ames test, in their laboratory, is valid only over a thousandfold range of potency, they conclude that acceptance of a linear correlation is premature.

The bottom line, at least for the present, is that it is very difficult to estimate the potency of carcinogens in humans—except in a few cases where the carcinogen is patently very potent or very weak. Until it is possible to make such estimations accurately, any balancing of risks and benefits will necessarily be error-prone. In most cases, then, it seems likely that regulatory agencies will ban carcinogens outright rather than take a chance of underestimating their hazards.—T.H.M.

the general existence of thresholds and no proof that such thresholds exist. In the absence of such proof, they argue, it must be assumed that thresholds do not exist.

Such a conclusion is contrary to common sense, argues Perry J. Gehring of Dow Chemical Company. Man, he contends, lives in a veritable sea of potential carcinogens. Fully 95 percent of all chemicals, whether man-made or naturally occurring, have the capability of reacting with DNA, he says; some 40 percent of them are already in a reactive form and the rest can be converted to a reactive form by mammalian enzymes. The simple fact that not everyone gets cancer indicates that the body has a sophisticated system for dealing with potential carcinogens. Important contributors to that system are membranes that may not permit potential carcinogens to come into contact with DNA, enzyme systems for detoxification of foreign molecules, and other enzyme systems for repair of damage to DNA. Some evidence also suggests that the immune system can identify and destroy many kinds of aberrant cells produced by chemicals that slip through the other defenses.

The constant exposure of man to chemicals is illustrated by several essential metabolites, argues Paul Kotin of the Johns-Manville Corporation. The hormone estrone, for example, has been shown by several investigators to be carcinogenic when given to laboratory animals in large doses and is suspected of being carcinogenic to humans in large doses. Yet estrone is present in very small concentrations in all humans without demonstrable evidence of harm, Kotin contends. Marvin A. Schneiderman of the National Cancer Institute (NCI) argues, though, that estrone is present in much higher concentrations in women than in men, and that this might be at least part of the cause of the much greater incidence of breast cancer in women.

Similarly, Kotin says, large doses of nickel and chromium have been found to be carcinogenic in both animals and man. Any biochemist, however, can cite the importance of trace concentrations of these metals in the functioning of mammalian enzymes. The same argument can be made, says Herman F. Kraybill of NCI, for a number of biological intermediates and other essential chemicals, including xylitol, calcium, selenium, and vitamin D_2. These examples indicate, they say, that the organism is capable of dealing with small quantities of carcinogens and that it is only when these protective systems are overwhelmed that the carcinogen presents a threat. (Conservative investigators such as Schneiderman, though, argue that biological concentrations of such chemicals represent an optimum dose and that mammals must accept a certain low incidence of cancer resulting from them as a fair exchange for the biological benefits.)

One way in which these systems can be overwhelmed is illustrated by vinyl chloride, which has been a subject of great concern since it was demonstrated in 1974 that workers exposed to it exhibit an abnormal incidence of a rare liver tumor known as an angiosarcoma. Gehring and his associates at Dow have shown that inhaled vinyl chloride reacts in the liver with glutathione to form a thioester that is excreted in the urine. In rodents, Gehring says, inhalation of vinyl chloride at concentrations greater than 150 parts per million (ppm) depletes the liver's stores of glutathione, resulting in

How Safe Is "Safe"?

Carcinogenesis studies carried out with reasonable numbers of animals are statistically significant only when the observed incidence of induced tumors is greater than 5 percent. A negative result in an animal bioassay for carcinogenicity, therefore, does not necessarily mean that the chemical is safe.

Consider an animal test in which 100 rodents are fed a chemical. If none of the rodents develop a tumor, then we are 99 percent confident that the actual incidence of tumors that might be caused by the chemical is less than 4.5 percent. If the substance had been fed to the rodents at a dosage of 1 percent of the diet, we can, by direct extrapolation, estimate the risk of cancer in humans at an exposure level of 10 parts per million (ppm) to be less than 5×10^{-5}. That appears to be rather a small risk, but multiplying it by the population of the United States (2×10^8) yields a value of 10^4. Thus, a negative result with 100 animals tells us merely that less than 10,000 people might contract cancer if everyone in this country were exposed to the chemical at a concentration of 10 ppm.

More conclusive proof of safety would require larger numbers of animals. A negative result with 1000 animals, for example, would indicate that the actual incidence is less than 0.45 percent, and so on. Obviously, it is never possible to show complete safety with animal assays. Current testing programs at the National Cancer Institute (NCI) use about 400 laboratory animals. No one has calculated the actual incidence of tumors that could result even if no animals develop tumors, but it is obviously between 1 and 4 percent. (NCI has, however, calculated the probability that a carcinogen may slip through the tests undetected; that probability is about 4 to 5 percent.)

Since there is a finite possibility that a chemical may be a carcinogen even though it tests negative, how does one estimate a "safe" dose? At one extreme, the common practice has been arbitrarily to divide the highest dose tested in animals (D) by 100 and consider that a "safe" dose. This approach leaves much to be desired, particularly if the chemical has been tested in only a small number of animals. At the other extreme, a linear extrapolation based on the "one-hit" principle of carcinogenesis would require the dose to be reduced by a factor of 10 for every tenfold decrease in risk. If the risk were to be reduced from 1 percent (1 in 10^2) to 1 in 10^8, the "safe" level would be $D/10^6$. The danger in this approach is that it will in most instances lead to such low "safe" levels that, in practice, the chemical could not be used.

A reasonable alternative, suggested by Nathan Mantel of George Washington University and Marvin A. Schneiderman of NCI, would be to assume that the risk decreases by one standard deviation (or probit) for every factor of 10 decrease in the dose. If it were determined that an acceptable risk might be one cancer per 100 million exposed individuals, and no tumors were observed in 100 laboratory animals, the "safe" dose can be calculated to be $D/8300$. This approach would have the advantage of rewarding good testing. The higher the dose tested, the higher would be the "safe" dose. Use of more animals would also increase the "safe" dose. If only 50 animals were tested, the "safe" dose would be $D/18{,}000$, but if 1000 animals were used, the "safe" dose would be $D/1000$.—T.H.M.

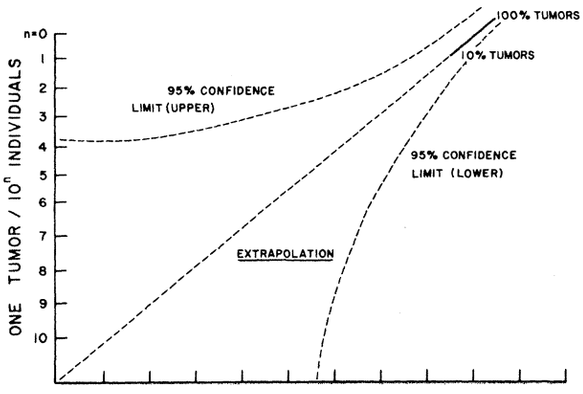


Fig. 2. Extrapolation of bioassay results obtained in animals to predict results in humans at much lower exposures is a very uncertain process. The curved lines in the diagram illustrate the 95 percent confidence limits for a linear extrapolation of the data from animal results obtained between tumor incidences of 10 and 100 percent. A threshold or a variety of other experimental models would fall well within the confidence limits. [Source: David B. Clayson, Eppley Institute for Cancer Research]

less efficient detoxification of the reactive intermediate formed from vinyl chloride and, presumably, giving rise to a disproportionately greater interaction with DNA.

At concentrations of vinyl chloride less than 50 ppm, however, glutathione is not depleted and detoxification can proceed unimpeded. When the results from rodents are extrapolated to humans with appropriate adjustment for metabolic factors, Gehring predicts an incidence of one to two angiosarcomas when 100 million workers are exposed to 1 ppm of vinyl chloride—the current standard—daily for 35 years. This is an incidence most investigators would consider negligible.

A similar situation exists with the toxic—but probably not carcinogenic—chemical bromobenzene. Bromobenzene is eliminated from the body almost entirely by biotransformation, Gehring says. It is converted into a highly reactive arene oxide that reacts with glutathione to produce a nontoxic thioester that is excreted. Bromobenzene does not produce pathologic effects, he says, until glutathione stores are depleted so that the arene oxide is free to react with cellular macromolecules. Other chemicals for which there is evidence that high doses lead to a disproportionate increase in toxicity or carcinogenicity include aspirin, acetaminophen, styrene, ethylene glycol, salicylamide, and aniline.

Were glutathione the only antagonist for carcinogens, it would probably be overwhelmed rather easily. But a variety of other naturally occurring antagonists, particularly antioxidants such as vitamin A, vitamin E, and selenium, can detoxify carcinogens, according to Raymond J. Shamberger of the Cleveland Clinic Foundation. He has identified 16 such antioxidants and suggests that there are probably a great many more that have not yet been discovered. The most important thing to remember about these antagonists, argues Herbert E. Stokinger, who recently retired from the National Institute for Occupational Safety and Health, is that they react with carcinogens in exactly the same way that they react with other foreign chemicals.

Even if the active carcinogen is not detoxified, says Hans L. Falk of the National Institute of Environmental Health Sciences (NIEHS), a large proportion of the carcinogenic molecules will almost certainly be sidetracked by interaction with cellular molecules other than DNA. Then, too, the carcinogen can react with DNA without initiating tumor formation; only interaction with one or a few very specific sites on DNA is likely to induce tumor formation. Reaction with the vast majority of sites on DNA or elsewhere in the cell may be harmless or may cause cell death, but it will not produce the type of transmissible defect that leads to malignancy. The probability of a carcinogen reacting with exactly the right site must be quite low for very small doses.

If the carcinogen should attack the right spot, Gehring argues, cellular repair mechanisms can often restore the DNA to its original state. The kinetics of DNA repair in rodents fed dimethylnitrosamine, he says, show that the chemical causes kidney tumors only when given in doses that overwhelm DNA repair. And if the damage is not repaired (or if it is repaired incorrectly, which can of itself be a cause of tumor induction), the immune system can often destroy the defective cell. Cancer is primarily a disease of old age, Stokinger argues, because that is when the immune system is at its weakest.

Thresholds can also be observed when chemicals are given in doses large enough to produce pathologic responses, such as tissue damage. This is not surprising, Gehring says, because many tumors in humans develop in chronically inflamed tissue or scarred tissue. The effect that such results can have on the actions of regulatory agencies is readily demonstrated by the case of chloroform, says Stokinger. Studies at NCI have shown that chloroform induces tumors in rats and mice when given at very high doses. As a result of these studies, the Food and Drug Administration has banned the use of chloroform in cosmetics and over-the-counter drugs, and the Environmental Protection Agency (EPA) is forcing many cities to install expensive systems for removal of trace quantities of chloroform and related chemicals from drinking water.

The rodents in the NCI study, however, had severely distended abdomens, markedly shortened life-spans, and extensive liver damage, Stokinger says. Tumors were observed only in the most debilitated animals. In more recent studies, Frederick J. C. Roe of the Chester Beatty Research Institute fed chloroform to mice, rats, and dogs at doses that did not produce pathological damage, and these animals show no evidence of malignant tumors. In some strains of rodents, in fact, chloroform-treated animals survived longer than the controls. Because of these results, NIEHS is now conducting new bioassays of chloroform. It would thus appear, Stokinger argues, that chloroform is essentially hazard-free at the concentrations found in drinking water and that EPA's efforts to remove those trace quantities may be misguided.

One other piece of evidence that is frequently cited in support of the threshold hypothesis is the relation between the dose of a carcinogen and the latent period between exposure to the carcinogen and initiation of tumor growth. It is generally recognized that the latent period increases as the dose is reduced. Herman Druckrey of the University of Freiburg in West Germany and Hardin Jones of the University of California at Berkeley have independently found that the product of the dose and a power of time is a constant; that is, dt^n is equal to a constant, where d is the dose, t is the time, and n is 2, 3, or 4. This relation implies the existence of a practical threshold, Jones says, because at very low doses the latent period is several multiples of the animal's lifetime.

This notion of practical thresholds has been severely criticized by other investigators, such as Richard Peto of Oxford University and Schneiderman. The relationship is a mathematical artifact, Schneiderman says, resulting from the fact that the incidence of tumors in animal studies is very high, approaching 100 percent. In humans, the maximum incidence of cancer that is observed is

about 7.5 percent for breast tumors in women. At these low incidences, he says, the relationship simply does not hold. Peto echoes these objections and says that his analysis of the same data used by Jones led him to the conclusion that there is not a practical threshold.

Much more data will be needed to resolve this dilemma, but such data will not be easy to come by. An example of the inherent problems can be found in a large study being conducted by Neil A. Littlefield and his colleagues at the National Center for Toxicological Research; this study is popularly known as the megamouse study, but it is more precisely a kilomouse study. Littlefield's group is trying to find out exactly what happens with low doses of carcinogens. To that end, they subjected 24,192 mice to seven different dose levels of 2-acetylaminofluorene (2-AAF), a potent liver and bladder carcinogen.

The study has not yet been completed, and many of the rodents are still being examined by pathologists. Results obtained so far, however, indicate that more than one mechanism of carcinogenesis may be operating. These results suggest, Littlefield says, that the induction of bladder tumors approaches an apparent threshold at low doses of 2-AAF, but that there is no threshold for the induction of liver tumors.

The megamouse study itself, however, has generated a certain amount of controversy. For one thing, says Clayson, the lowest incidence of observed tumors in that study was about 1 percent, whereas the incidence of concern in discussions of thresholds is much lower. To observe such a lower incidence in laboratory animals, adds Schneiderman, would be virtually impossible, particularly if there is a spontaneous incidence of tumors.

A similar conclusion has been reached by Harry Guess and Kenneth S. Crump of NIEHS. They developed a sophisticated computer simulation to match predictions from various models for the carcinogenic process with results from various types of bioassays. Their results suggest that the "most likely" dose-response curve for chemical carcinogens at low doses is linear. They also conclude, though, that it is extremely unlikely that it would be possible to distinguish between a linear dose-response curve and a highly nonlinear one (threshold), even in a large-scale experiment involving several thousand animals per dose level.

By changing the outcomes for only 11 animals out of 8000 in a set of data, Crump says, it is possible to change the dose-response curve from linear to highly nonlinear. That small number is well within the limits of both experimental variability and human error. It thus seems that statistical analysis of standard animal carcinogenicity experiments, Schneiderman concludes, does not now, and probably never will, resolve the threshold question. There are, he says, simply too many "biologically reasonable" mathematical models, both implying and denying the existence of thresholds, that will fit the observed results.

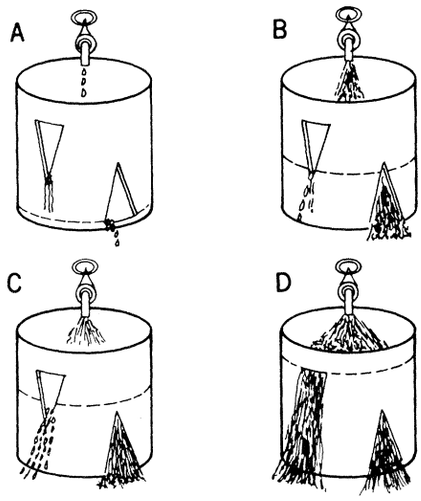


Fig. 3. A schematic representation of one source of thresholds. As increasing amounts of fluid flow into the barrel (as greater quantities of a chemical are ingested), elimination (detoxification) via the lower slit becomes overwhelmed. This results in disproportionate increases in the amount of fluid in the barrel (the amount of carcinogen in the body) and elimination via the upper slip (induction of a tumor). [Source: P. J. Gehring, Dow Chemical Company]

Because there is so little data and so many interpretations, Gehring says, arguing about thresholds is an exercise in futility. But the need for regulation exists, nonetheless. To meet this need, he says, we must describe molecular events as well as possible and do the best risk assessment we can. To Gehring and others, this means that some potential carcinogens, such as chloroform and vinyl chloride, should be considered to be relatively hazard-free at very low doses. Some exposure to such agents could be tolerated if the benefits should be deemed to outweigh the risks.

Others adopt a much more conservative position. An ad hoc committee commissioned by the Surgeon General to consider possible changes in the Delaney clause and chaired by Umberto Saffiotti of NCI reported that

> The principle of zero tolerance for carcinogenic exposures should be retained in all areas of legislation presently covered by [the Delaney clause] and should be extended to cover most [other] exposures as well. . . . Exceptions should be made only after the most extraordinary justification.

It is unlikely that the two sides will be brought closer together in the near future. Some scientists, furthermore, think that they are arguing about the wrong problem. The issue is not one of thresholds or no thresholds, says David F. Rall of NIEHS; the issue is adding a new carcinogen to the present pool of carcinogens. It may indeed be demonstrated in a good laboratory that a mouse exhibits a threshold for any given chemical, he says. But that mouse doesn't smoke, doesn't breathe hydrocarbons or sulfur oxides from fossil fuels, doesn't take medicines, doesn't drink alcohol, and doesn't eat bacon or smoked salmon or well-done hamburgers. Mathematical models developed by Crump and others suggest that each additional exposure to carcinogens, no matter how small, will contribute to the total carcinogenic effect.

Such conclusions about additions to the environmental burden can be misleading, says Gehring. Modern technology, he asserts, generally "replaces" rather than "adds to." The worker in a factory who is exposed to vinyl chloride at 1 ppm, for example, might otherwise be working on a farm, where he might be exposed to pesticides and herbicides, or in mines or in other industries where the risk of injury might be much higher; the vinyl chloride itself is made into pipes, among other things, and replaces pipes made of concrete and metal, each of which has its own hazards. Another good example is soft drink bottles made of acrylonitrile; these were recently withdrawn from the market because there was a slight chance that the acrylonitrile monomer might be leached from the bottle by the soft drink, leading to a very small number of tumors each year. But there are, says Gehring, 100,000 entries to hospital emergency rooms in the United States each year caused by exploding glass bottles. Furthermore, trace metals are adsorbed by the glass and desorbed into the soft drink. A simple ban on use of acrylonitrile in bottles, he argues, does not represent a realistic assessment of the relative risks of the two types of containers.

And so the argument continues, with each side adamantly refusing to recognize the other's position. The hapless observer is left to contemplate the possibility that the actual situation embraces some middle ground and to hope that some kind of consensus will finally be achieved when there is a better understanding of the actual mechanisms of carcinogenesis.—THOMAS H. MAUGH II