RUMINATIONS ON A RAT: SACCHARIN AND HUMAN RISK

William R. Havender

THE HUBBUB began in earnest when Canadian scientists claimed in 1977 that saccharin caused cancer in rats and the Food and Drug Administration, invoking the Delaney amendment, then proposed to ban the use of saccharin in foods and soft drinks. This evoked a vociferous public protest, and Congress, swamped with angry letters, voted an eighteen-month moratorium on the proposed ban to allow the National Academy of Sciences to complete its own evaluation of saccharin's risks and benefits. That evaluation is now in hand, and the moratorium ends in May, so Congress will shortly have to make its final decision. It is thus timely to see what we know about the benefactions and malefactions of saccharin, and what these imply for shaping a wise regulatory policy. We are venturing, of course, upon dark and bloody ground where battles have raged, but we will emerge with quite firm conclusions about the form that responsive regulation ought to take.

Does saccharin cause cancer in rats? The answer is doubtlessly yes, since this has been shown in three independent experiments. But the effect was always weak and could only be demonstrated at the limit of these tests' sensitivity. There is little dispute over these facts, but the consensus evaporates altogether over the problem of extrapolating human risks from rodent tests.

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Of Rats and Men

Let us take a brief look at the experiments. It is customary to use whopping doses of a suspect substance in animal cancer tests, because there are financial and logistical limits to the number of animals that can be used in any single test. A typical test for a suspected carcinogen (cancer-causing substance), for example, might consist of 50 animals of each sex exposed to each of two different doses of the substance, with 50 undosed animals of each sex for comparison (300 animals in all). This would cost more than $250,000 and would last not less than four years (the two-year lifetime of the animals, plus the time for the preparatory experiments to determine dosage, plus the time for a pathologist to examine the microscope slides from some *forty* different tissues from *each* animal for signs of cancer). But the smallest number of tumor-bearing animals

that could be detected in such a test (assuming we detect any) would be one animal at the highest dose, or only 1 percent. An incidence of 1 percent in a population of 200 million persons is 2 million cases; that is, a substance capable of causing some 2 million cases of cancer in the United States might well go undetected if it were tested only at doses that simulated human usage. However, since the number of tumorous animals will usually increase as the dose of a carcinogen increases, the test's sensitivity can be magnified by using very high doses. And in fact, the normal practice is to include the highest dose that will not poison the animals to death (the maximum tolerated dose, or MTD) in order to make the test as sensitive as possible.

It is this practice that has engendered public impatience with the saccharin tests, since the rats developing tumors had been fed the equivalent of 800 diet sodas every day of their lives. FDA spokesmen have tried to soften this impatience by explaining what I have explained here—that there *is* a valid reason why such doses are employed and that feasible experiments in the dose range of human usage would not be sensitive enough to detect agents that might still cause numerous cases of cancer. Nevertheless, there *is*, too, a valid question at the core of the public's skepticism about such enormous doses—namely, can things happen at such high doses that do not happen at all, or at least not in proportion, at the low doses typical of human usage? This is a profound rather than naive question, and the short answer is that no one knows and there is no simple way to find out.

When considering the three critical saccharin tests, one is made uneasy, however, by the fact that tumors were observed only in the rats receiving the highest dose (MTD). While these animals had normal life spans,* they were still clearly suffering metabolic distress, as shown by the fact that they had lower weights or smaller weight gains (between 10 and 20 percent less, on the average) than their undosed counterparts. This introduces a tinge of doubt in interpreting these results, because the observed tumors could well be a side-effect of metabolic stress that would not develop at all in the absence of debilitation. In any case, weakened animals might be more susceptible to cancer than healthy ones, so that *quantitative* extrapolations of risk to humans (that is, attempts at estimating the number of cancer cases expected in humans from the numbers seen in rats) are made somewhat dubious.

Two other features of these experiments also bring human risk estimates into question. One is that tumors have, with a single exception, been observed only in tests that lasted for *two* successive generations. Thus, most of the animals developing tumors had not merely been fed saccharin from the time they were weaned but had in addition been conceived, gestated, and suckled by mothers whose own tissues had been saturated with saccharin. Since fetal tissues are generally much more sensitive to injury than adult tissues (recall thalidomide!), it is primarily this exposure during a supersensitive stage that leads to cancer. This view is supported by the fact that no cancers were seen in five out of six *one*-generation rat-feeding tests (where saccharin doses started only at weaning), nor in two similar tests in mice. This fact—that animals exposed to saccharin *in utero* are far more susceptible to cancer than those exposed only after weaning—adds further uncertainty to risk estimates for human *adults* made from animals thus exposed. Perhaps the easiest way to see this is to realize that the sensitivity of fetally exposed rats would not predict the cancer rate even among *rat* adults that had been exposed only since weaning!

Finally, only the *males* developed tumors in all three rat tests, not the females. Such sex differences are not uncommon, but in this context they mean that male rats could not be used to predict the risk even for females of the same strain raised under identical conditions—thus further weakening the reliability of estimates of human risk.

These uncertainties are, of course, superimposed upon the more general uncertainties involved in all animal cancer tests. One of these is: do rats metabolize saccharin the same way humans do (at least when corrected for differences in body size and lifetime), or are they perhaps special in some pertinent way? We do not know; rats could be less, more, or as sensi-

*It is noteworthy that the animals did *not* die prematurely from the tumors. The induced tumors were described in all cases as "of low invasiveness" with "no reported metastases." Thus, saccharin induces only a very weak form of cancer in rats.

tive as humans. Scientists assume for simplicity that there are no important differences in metabolism, but this is merely a convenience, not an unassailable fact.

Nor are we sure how to estimate the risk at low dose from determinations made at high dose. The usual procedure is to assume that the low dose risk is simply proportional to the decrease in dose, but no one knows if this is true over the entire thousandfold range from the MTD to the levels of human use. However, the assumption is fundamental to quantitative risk estimates, and in particular to answering the question whether there exists a "safe dose," or "threshold." Although the described limitations of animal tests prevent us from answering this question directly, we can specify certain requirements that would have to be met for the response at low dose to be proportional. One is that the organs and processes that clear saccharin from the body must function as efficiently at near-lethal doses as at doses a thousand times lower. (If, for example, they became overloaded at high dose and were less effective at removing saccharin, then the assumption of proportionality would *over*estimate the true risk at low dose.) The same restriction—no overloading at high dose—must hold as well for any biochemical mechanisms that might repair the chemical damage caused by saccharin (such repair processes are quite common for other kinds of chemical damage that lead to cancer). We have no evidence that these conditions are *not* met, but it is merely supposition —not established fact—that they are. And because we are extrapolating over a large dose range, even a small inaccuracy in our assumptions would reduce the cancer incidence at low dose appreciably below what it would be if the reduction in risk were proportionate to the reduction in dose.

Another complicating factor is that the length of time that passes between first exposure and the appearance of an induced cancer (called the latent period) may itself depend upon dose, being longer at low dose than at high dose. Since the rat cancers developed late in the life of the animals, only a small increase in the latent period at low dose would result in the animals' dying first of ordinary old age. We could thus define a "practical" safe dose as the one at which the latent period exceeded the life span of the animals. We have no evidence for or against such an effect with saccharin, and the evidence for such a process with other carcinogens is disputed. But again, only a small effect of this type would lead, given the thousandfold dose reduction, to a large decrease below proportionality in the cancer incidence at low doses.

The final problem in making low dose predictions arises because laboratory animals are bred to be *uniform* in their genetic sensitivities, whereas human populations have enormous genetic *diversity*—which means there is probably a great variety in human susceptibilities to any carcinogen. The incidence of cancer in such a varied group could not decrease simply in proportion to the decrease in the dose, because not *only* is the dose declining, but so also is the *segment* of the population that is sensitive to it. Thus, the incidence at low dose must be lower than would be predicted by assuming a reduction in incidence proportional to the reduction in dose. And since we are talking about a thousandfold decrease in dose, this effect is probably not negligible. (Only one of the various methods of dose extrapolation—the Mantel-Bryan probit model—takes this natural variation in sensitivity into account.)

In sum, then, there seems little reason to doubt that rats can indeed be made to develop tumors in response to saccharin, when we stand on tiptoe to do it. But saccharin is an extremely weak carcinogen—it is "among the weakest carcinogens ever detected in rats," as the Office of Technology Assessment put it. Also, quite precarious assumptions are entailed in estimating the probable cancer incidence in humans. Specifically, it is simultaneously assumed that

(1) visibly toxified animals have the same susceptibility as healthy ones, *and* that

(2) the sensitivity of animals exposed *in utero* is the same as animals exposed only after weaning, *and* that

(3) no unanticipated metabolic differences exist between rats and humans—and, in particular, that the susceptibility of male rats, though clearly different from that of female rats, is nonetheless the same as human adults (including women), *and* that

(4) the chemical effect of saccharin and the rats' physiological response is the same over the entire relevant dose range, *and* that

(5) there is no change in the latent period when doses are changed, *and* that

(6) human populations have no greater genetic diversity in saccharin sensitivity than inbred rats.

Given these assumptions, the calculation of human risk from the rat data is quite straightforward. The resulting numbers range (depending on the particular body size, dose, and lifetime corrections employed) from less than a dozen cases of bladder cancer per year to at most a few thousand, with most estimates falling near several hundred cases per year. (Bladder cancer was the only kind seen in significant numbers in rats, so it is assumed that if saccharin causes any kind of cancer in humans, it is most likely to be this kind.) These figures are calculated for 50 million persons who have been steadily consuming saccharin in amounts equivalent to one 12-ounce can of diet soda each day of their lives. They may be compared with a current annual incidence of about 30,000 bladder cancer cases.

The risk might be higher than this if saccharin could also act by "promoting" the action of *other* carcinogenic agents to which people are exposed (such as smoking). There is, in fact, a small amount of evidence from animals and tissue-culture systems suggesting that saccharin at high dose can enhance the cancer-inducing potency of certain other chemicals. But even less is known about the mechanism(s) of "promotion" than of direct cancer induction—most importantly, how the effect might depend upon dose. If, for instance, enhancement resulted simply from the general debilitation that near-lethal doses of saccharin can produce, the effect should disappear entirely at nondebilitating doses. Given the paucity of our knowledge about promotion, its effect on human risk cannot now even be intelligently guessed.

Tests on Man

Let us turn from studies in animals to studies in man. Has there been an increase in bladder cancer rates that can be shown to be due to the increase in saccharin use that has occurred since World War II? There has not. However, this is not conclusive, because we probably could not detect a small effect (such as we would expect from the animal data), because other causes of bladder cancer have also increased in the period (smoking and occupational exposure to certain industrial chemicals together cause about 60 percent of currently diagnosed cases), and because not enough time may have elapsed for the latent period to have fully passed. Suppose, then, we look specifically among diabetics (who have been heavy users of saccharin since early in this century) for an elevated rate of bladder cancer. None has been found, but diabetics tend to smoke less than the rest of us (which might compensate for the cancer risk from their increased saccharin use), and also have elevated mortality risks from *other* causes than cancer and so might be dying first of these other things before the latent period for bladder cancer had passed.

A more sensitive procedure would be to query people with diagnosed bladder cancer in order to see if they had a history of excessive saccharin use when compared with a matched group of cancer-free persons. This is called a retrospective, or case-control, study. The two largest and most careful studies of this type on saccharin gave conflicting results: one completed recently in Baltimore on some 500 bladder cancer patients and a matched cancer-free group found no significant difference in saccharin use between the two groups, while the other,

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carried out in Canada, found *less* usage of saccharin among women with bladder cancer than among women without it, and a small *excess* of use in men with bladder cancer compared with men without it. All other retrospective studies were negative.

It is this single study in humans that, together with the rat results, supplies the evidential base for a saccharin ban. It is worth a look. The salient feature is that the difference in saccharin use among males was small: out of 480 men with cancer, 69 had "ever" used saccharin, while among the cancer-free group of 480 men, 43 had done so; thus, the difference consisted of only 26 men. The small size of this difference is significant. For unless the two groups are matched meticulously on all other factors that might be associated with saccharin use, we cannot securely rule out the possibility that so small a difference came about through association with some other dissimilarity between the two groups. There might be, for example, a chance, small excess of obese persons in the group with cancer, or a small excess in alcoholic consumption (diet sodas are often used for mixing cocktails), or a small increase in income (saccharin use increases with income and education); or there might be some other factor not yet identified. It is exceedingly difficult to match groups so perfectly as to eliminate all possible confounding factors. When the difference between the two groups in exposure to a suspected disease-causing agent is large, this problem can usually be ignored. (In this same Canadian study there was, for example, an enormous excess of heavy smokers in the group with cancer.) But when the difference is small and concerns only a small fraction of the matched samples, any conclusion suggested by it must be accepted with caution.

The wisdom of caution here is suggested by two additional facts. First, as mentioned, the effect among women in this same study was precisely opposite to the effect among men: there was *less* saccharin use among those with cancer than among those without it. (The actual numbers were 18 users of saccharin in a group of 152 women with cancer and 30 in the comparison group, also consisting of 152 women. This is a *larger* proportional difference than was seen in men, but it suggests the contrary conclusion.) It could be, of course, that a sex difference exists in humans as in rats. But it could also be that there are uncontrolled factors in the matching that produce false signals when we have such small numbers. And second, the equally good Baltimore study, which could have confirmed this difference in males, contradicted it instead.

Despite this disagreement, we can still draw a strong conclusion: the contribution of saccharin to bladder cancer rates in humans is,

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if not zero, so small that it cannot be reliably distinguished from zero within the sensitivity of this type of study. That sensitivity is not overly high, but it is probably fair to say that if saccharin in its past patterns of use caused 10 percent or more of the 30,000 bladder cancer cases diagnosed each year (through initiation and promotion combined), it should have been securely seen in these studies. (Note that, because of the long latency between the exposure to a bladder carcinogen and the clinical appearance of cancer—typically twenty to forty years for the two potent agents we know about—the rates we now see reflect usage patterns of at least twenty years ago. Thus these results cannot assure us that no risk at all will become manifest in the future from increased saccharin use.)

How Sweet It Is

So much for the risks from saccharin. What are its benefits? It has minor uses as a flavoring agent in toothpastes and certain drugs, and it is believed by some to help reduce tooth decay. But its primary use is in diet control. Diabetics and their doctors, for example, view saccharin as a major aid in diet maintenance. It is not merely saccharin as a table-top sweetener that is valued here, but *specifically* the widespread marketing and easy availability of diet desserts, fruits, and drinks. These give variety to a diabetic's diet, permit him to travel widely without worrying about the availability of safe foods, and enable diabetic children to lead less

dry and parsimonious lives than they would otherwise.

And saccharin is widely believed to be helpful in weight control. Some 22 percent of our population—more than 40 million people—are twenty-five pounds or more overweight. Some people may use saccharin products to lose weight, but a much larger number use it to avoid a weight gain that, all things being equal, would otherwise occur. Again, it is precisely the wide availability of foods containing saccharin that makes it not merely possible but also convenient to stick with a diet. And since obesity aggravates many diseases, a substantial health benefit may well result from having saccharin widely obtainable in varied forms.

These are the purported benefits of saccharin, but are they real, and how large are they? Unfortunately, there is a dearth of "scientific" evidence on these points. No one knows how many cavities might be prevented through consumption of saccharin-sweetened foods in place of sugared ones. No one has measured how much "quality" is added to the life of a diabetic by the ready accessibility of diabetic foods as compared with having only pills available. And no one knows how much weight would be either gained or not lost if saccharin (or some other artificial sweetener) were not available, nor how many more cases of heart disease, stroke, late-onset diabetes, and other weight-related illness would be diagnosed each year if foods containing saccharin were banned. We may note, however, that these benefits need not be very large to offset the risks of saccharin entirely: a few thousand heart attacks, strokes, and diabetic crises avoided per year among the tens of millions of saccharin users would do. That is a number so small that we could not exclude it by any conceivable study. It is, in short, as difficult to prove that small benefits do *not* exist as it is to prove that a small risk of cancer does.

Thus, in making the benefit/risk judgment on saccharin, the benefits must be assigned the value, not of zero, but of a wild card. The net effect that a saccharin ban would have on the public's health therefore cannot be known.

We do, however, have other forms of testimony about saccharin's benefits. Not only has Congress been flooded with letters—as *Science* magazine writes, "diet food fans by the millions have protested" the proposed ban—but we have as well the evidence of people's market actions *after* the saccharin risk was widely publicized. This is not insignificant, because consumers have first-hand knowledge (not always apparent to the "scientific" observer) of the value of diet foods to them, and their actions tell us that they find the benefits of saccharin worth the risk as this has been set forth to date.

Prohibition or Free Choice?

Given this situation, what would be an intelligent regulatory response? Two considerations greatly clarify this matter. First, this is *not* a situation similar to air pollution or to the contamination of the land with pesticides, where externalities prevent individuals from taking independent action to control their own fates, and hence require that a collective, unitary judgment on the overall risks and benefits be enforced. Instead, it is a *user-risk* situation, where the user is generally the only person exposed to danger and where he can choose whether to take the risk.

Second, there are great variations in the risk/benefit circumstances of individuals. We can, for instance, identify groups that may have elevated risks from saccharin: pregnant women, since their unborn children might be unusually sensitive (as the two-generation rat tests suggest), and children, who not only might be more sensitive but who also have such a long life expectancy before them that an induced cancer would have ample time to develop. We can as readily identify groups that are likely to have zero risk. All persons fifty-five years of age or older, for example, can probably use saccharin with impunity since the latent period for cancer induction would be longer than their remaining life expectancy. Also, adult women suffer no apparent risk to themselves: none of the epidemiological studies have found any risk to women, and none of the rat studies have shown significant numbers of tumors in females. Women and those over fifty-five, be it noted, comprise well over *half* the population! (The same kind of variation exists on the benefit side, too. There obviously are groups of people—the obese and the diabetic—who *already* have more than ordinary health hazards that can be reduced by saccharin and who hence can derive a more than ordinary benefit from it.)

Any sensible regulatory effort must, then, take these wide variations in personal circumstances into account: what is needed is a variegated solution rather than a uniform one. This consideration should carry us far away from simple thoughts of banning all uses of saccharin-containing products, including good ones, and toward solutions that are aimed at specific groups with high relative risk or that rely on incentives to encourage the desired pattern of use. Consider these possibilities:

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(1) Pregnancy is a temporary condition, so that temporary abstinence from saccharin use would eliminate all hazard to unborn children. This is a narrowly focused policy problem. Presumably, informing pregnant women, nursing mothers, and their doctors would largely solve it, as it does for other substances (such as certain drugs) that pose a danger to fetuses and infants.

(2) Childhood, too, is temporary. A prohibition on saccharin sales to minors (as we now prohibit alcohol), coupled with an educational program to convince parents of the hazard, would be one way to reduce this risk. Once again, this policy problem has a narrow scope and would not be efficiently addressed by a uniform ban on all uses of saccharin products.

(3) One solution relying upon incentives would be to put a tax on saccharin-sweetened products, thereby introducing an optionally large price difference between these and their sugared substitutes. This would discourage frivolous consumption of saccharin products, while still permitting persons with special needs for diet foods to obtain them.

(4) Finally, one could simply supply information about the risks and benefits of saccharin to consumers as the information becomes available, and let them make their own decisions.

Let us examine this last alternative in more detail. It envisions that people would evaluate their own risk/benefit situations and determine their saccharin use accordingly. Presumably, people with the greatest risk from other health problems would be primary users of saccharin. We *would* thus obtain a variegated solution that allowed for differences in individual circumstances and that also had the general form we want. Too, it would be *self*-adjusting, so there would be no administrative costs other than those involved in assembling and communicating the information needed for making intelligent judgments of net risk. (This information should, of course, include a description of bladder cancer symptoms, so that the chances of early detection among saccharin users could be improved. This cancer, like many others, is highly curable in its early stages.) And changes in the state of our knowledge could be rapidly accommodated; if, for instance, a great danger *were* ultimately proven, there is little doubt that consumers would cease using diet foods of their own accord. A simple program of providing information, then, has by itself many of the features of a desirable and workable solution, and it is already largely in place.

We might now ask what it is about saccharin that distinguishes it from other, greater risks we leave to individual choice. Why, for example, do we find ourselves serenely contemplating a person's plan to climb a dangerous Himalayan peak at the same time that we propose making it illegal for her to buy a can of Tab? The answer is simple: it is the 1958 Delaney amendment to the Food, Drug, and Cosmetic Act which, in its crucial phrases, runs as follows, "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal."

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Consider those words in light of the facts just reviewed. Several defects are apparent:

(1) The words presume a fine clarity in the

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judgments of science that is not always there. There is no "proof," for instance, that cancer has ever been caused by saccharin when "ingested by man." Nor can anyone irrefragably assert that exposure of rat fetuses to near-toxic doses is "appropriate" for the evaluation of the safety of this additive. And is exposure through the umbilical cord what is meant by "ingestion"? Too, nowhere in this confident phrasing is there allowance for a situation that is very common when scientific techniques are stretched to their limit, namely, that equally well-performed experiments can give *conflicting* results. Five one-generation rat tests, for example, produced no tumors, while one did; and one major epidemiological study found a slight cancer risk in males, while all the others did not. Being able to repeat a result is, of course, the sine qua non for converting an isolated (and possibly aberrant) observation into a secure scientific fact, and in the absence of this replicability, there is no basis for making a decision.

(2) As has often been pointed out, the amendment takes a curiously one-sided view in ignoring offsetting gains: an additive would still have to be banned even if there *were* proven counterbalancing benefits!

(3) The words require that a *single* decision for the entire society be made even in the face of uncertainty concerning judgments of net risk. A more prudent course would permit people to make choices either way on an ambiguous issue so as to limit the damage from the wrong guess.

(4) The passage ignores the person-to-person *variations* in risk/benefit situations that any sensible public policy in a user-risk context would accommodate.

(5) Moreover, the Delaney amendment aims to solve another problem than the one at hand. It seems to presuppose a situation where businessmen (acting to maximize short-term profits and oblivious to the insidious long-term harm their products might cause) expose the public to needless risk. Yet the true situation here is that there is a *legitimate* disagreement in interpreting the information we have, and it is evidently the public's will rather than manufacturers' greed that the words of the amendment frustrate.

There is, then, a reasonable question whether this state of affairs truly is the intent of Congress rather than an unforeseen and unintended consequence.

Let us now sum up. Science cannot tell us how many potential human cancers swim in a can of diet soda, though it has made some guesses. What *can* be shown is that a weak cancer can be induced by saccharin in rats, but only under unusual conditions whose relevance to human risk is obscure. From epidemiology we learned that the number of human bladder cancer cases that might currently be caused by past patterns of saccharin use is certainly small, and perhaps zero. We know, on the other hand, that it is at least *plausible* that saccharin offers substantial health benefits to certain groups of people, that these benefits need not be large in order to offset saccharin's slight risk, and that, unless we know *for sure* that the benefits are imaginary, it would be a reckless gamble with the public's health to compel a ban on diet food products. We know that a simple program of informing the public would accomplish by itself most or all of the aims of wise policy. And we know that the impetus for a ban does not issue from a proven public injury but from a well-intentioned legalism whose full consequences probably were not foreseen. Finally, we know that the public has spoken against a ban not just patiently and politely, but with a mass roar.

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Indeed, the contradiction between what the public wants and what FDA officials think, in a somewhat Pharisaic exercise, they are obliged to do should give pause to those who wish to secure the public's true well-being. For behind this lies a profound question: *Is* the public always right, after all? This question, of course, concerns not only saccharin but the heart of democracy as well. ■