Saccharin: A Chemical in Search of an Identity

"Anybody who says saccharin is injurious is an idiot," Teddy Roosevelt declared back in 1907. Today, almost three-quarters of a century and several saccharin scares later, 244 members of Congress and 80 percent* of the American public think Roosevelt was absolutely right. But the Food and Drug Administration (FDA) thinks he, and they, are absolutely wrong. At the moment, what the FDA thinks is what counts.

In March, because of the now notorious Canadian findings that saccharin causes bladder cancer in laboratory rats, FDA said it was going to ban saccharin—the last available artificial sweetener (*Science*, 15 April). The public was outraged. Diet food fans by the millions have protested. And the Canadian data, originally advertised as "definitive," on second glance may not be all they were first cracked up to be. But the FDA is sticking to its guns. After 2 days of open hearings on 18 and 19 May at which saccharin users and saccharin sellers pleaded that the agency change its regulatory mind, FDA commissioner Donald Kennedy (who inherited the saccharin decision when he took over at FDA in mid-March) said he will move right along with plans to get saccharin out of the food supply by late summer.

The hearings, something of a first in FDA's attempts to get public input, produced "no blinding flash" of new information, Kennedy said—nothing to alter the agency's basic position. However, he acknowledged that some of the testimony convinced him that FDA should reconsider some of the details of its present proposal. For example, he said that FDA may decide to allow continued use of saccharin in some prescription drugs. But saccharin-laced colas and cookies and ice cream and cake—all of the things people care about most and which account for 70 percent of saccharin use in the United States—remain on the FDA's hit list.

Saccharin's imminent demise has made it a strange yet compelling symbol for a remarkable variety of causes. It is being invoked in the name of everything from rewriting the whole body of food and drug law, to safeguarding the environmental protection movement (if saccharin is allowed to stay, what next), to citizens' "right" to freedom of choice among available risks, to the healthy "psychosocial development" of juvenile diabetics. In addition, saccharin hysteria has provoked fundamental questions about the health value of diet foods and the validity of animal testing in assessing risk to man.

*According to a public opinion poll commissioned by the Calorie Control Council, trade association for the diet food industry, 80 percent of the people think FDA acted "before it had sufficient evidence" against saccharin.

Saccharin: In Need of a Definition

Saccharin is a chemical in search of its identity. Is it a food additive, as the law defines it now? Or is saccharin really a drug that confers some medical benefit? FDA is adamant about getting saccharin out of the food supply, but it will consider reclassifying it as an over-the-counter (OTC) drug. Critics who challenge the idea that saccharin is dangerous see this as an amazingly inconsistent position; the FDA sees it as a practical, lawful compromise—if it can be pulled off. In order for saccharin to become a drug, someone is going to have to prove that it is "efficacious" for some medical purpose, which will not be easy to do.

Indecision about saccharin's real identity has led to considerable discussion of the laws governing foods and drugs, with special emphasis on the Delaney amendment which FDA chose to invoke in announcing its initial proposal to ban saccharin from foods. Delaney is the all-or-nothing 1958 amendment that says "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." Among the current issues are the meaning of the word "appropriate," and the usefulness of the amendment itself, which allows no room for risk-benefit judgments.

In this whole debate about saccharin, a lot of attention has focused on the Delaney amendment. However, as Kennedy has pointed out, even without Delaney "the general provisions of the food safety laws would have required to move to ban saccharin. If you want to save saccharin, you're going to have to change more in the law than the Delaney amendment."

Legally, the FDA is on very solid ground in basing its proposed saccharin ban on rat studies, but from a public relations point of view it is too bad the data are not firmer. Part of the problem has to do with rats. Not everyone agrees that rats are an "appropriate" species for studying saccharin and may wish the case could be bolstered by evidence, which does not exist, that saccharin causes cancer in some other kind of animal.

The immediate impetus for FDA's proposed saccharin ban is data from Canadian scientists who fed saccharin as 5 percent of the diet (approximately 2500 milligrams per kilogram body weight) to two generations of laboratory rats. Among the first generation animals, 3 of 100 developed bladder tumors. Among second generation rats, exposed to saccharin in utero as well as during their lifetimes after birth, 14 of 100 developed bladder tumors. (A special question about the safety of saccharin consumption during pregnancy comes up.) These data, on top of several previous but equivocal rat studies, tipped the balance against saccharin.

Problems with the Canadian Study

But there are problems with relying heavily on the Canadian data. For one thing, according to scientists close to the situation, the Canadians have not yet finished histopathological analyses of all the rats. For another, U.S., British, and other pathologists who are reviewing the slides of the rat bladders do not agree on whether they're looking at cancerous tissue or not. Previous assertions about the number of cancers, therefore, may not hold up. (But Kennedy believes the pathology is really quite sound. Referring to the first group of scientists, including FDA officials, to review the Canadian data, he says, "Not all the pathologists agreed about every slide—that *never* happens—but they did reach consensus about each one.") Third, it is now known that the supposedly contaminant-free saccharin used in the Canadian experiments may not be pure after all. Absolutely pure saccharin, *Science* is told, is not mutagenic in the Ames test—a sensitive new in vitro assay. The saccharin the Canadians used is. Thus, the possibility that cancer was caused by some yet unidentified impurity cannot be excluded as was originally thought.

Two previous rat studies have implicated saccharin as a cause of bladder tumors in rats. However, because the saccharin in those studies was contaminated by OTS (ortho-toluenesulfonamide), the data were set aside. The Canadian study, in which OTS was compared with "pure"

saccharin, seems to have cleared OTS. That being so, some scientists argue, the previous rat studies are validated retroactively, thereby strengthening the FDA's present position On the other hand, it can be said that the contaminants in the Canadian saccharin just muddy things more.

Rats

Complicating the picture even further, there is the question about rats. Many scientists point out that when it comes to bladders, rats are a special breed. Rats concentrate their urine to a very high specific gravity, which means that chemicals in the urine are apt to remain in the bladder for comparatively long periods before being excreted. As a result, rats frequently develop bladder stones which some investigators believe may cause tumors from physical irritation of the bladder wall. Furthermore, saccharin is not metabolized by the body but is excreted unchanged. Although there is no absolute proof, toxicologists interviewed by *Science* said that most known carcinogens are metabolized. In rats fed saccharin in large quantities, this means it is all the more probable that accumulated stores of unmetabolized saccharin could be a physical irritant. (However, Kennedy says—on the basis of information not published in the first draft of the Canadian study—the frequency of bladder stones in the rats was generally low and not all of the animals that had tumors had stones.) Yet another complicating factor is the common presence of certain parasites in rat bladders—parasites associated with tumors.

There have been repeated suggestions that saccharin be tested in other species. As far as *Science* has been able to determine three such experiments are going on in the United States, though others are being conducted abroad. Here, one is being conducted by toxicologist Philip Shubik at the Eppley Institute of the University of Nebraska. Shubik reportedly has found no evidence of tumors in hamsters who have been fed saccharin for a year and a half now. Another study has just been completed at Albany Medical College where Frederick Coulston has been feeding saccharin (200 milligrams per kilogram body weight) to rhesus monkeys for 7 years. He found no tumors or other forms of toxicity. A third monkey study is in its seveneth year at the National Cancer Institute. Richard H. Adamson is feeding saccharin 5 days a week to a group of ten monkeys. At doses of 25 milligrams per kilo, his animals are consuming about 40 times what an average person might consume. Because Adamson intends to follow them for their lifetime, he has no histopathological data, but a variety of clinical tests indicate the animals are perfectly well.

Adamson's studies obviously are not definitive. Neither, for that matter, are Coulston's, involving as they did fewer than a dozen animals. But they are suggestive, and what they suggest is that saccharin does not cause cancer. In addition, a recent report from Britain indicates once again that saccharin is not metabolized in rats, rabbits, or human beings. Epidemiological studies in man, though admittedly imperfect, provide no evidence that bladder cancer occurs more frequently in saccharin users.

Saccharin's Alleged Benefits

A few of these issues were raised at the recent FDA saccharin hearings—especially the point about the validity of rats—but, in general, attention focused on the other important part of the saccharin equation. Is saccharin medically beneficial? Should it be classified as a drug? Should the Delaney amendment be changed or should Congress grant saccharin a special exemption?

Representative James Martin (R–N.C.) led off with a plea to FDA to "allow an extended grace period before the ban falls shut," so that Congress can "refine our food additives policy free from the pressure of the extreme public reaction of which we have had only a taste." Martin, who has received 6000 prosaccharin letters from constituents, estimates that altogether legislators have heard from a million angry citizens. He is chief sponsor of a House bill (193 representatives are cosponsors) that would "modernize" the Delaney amendment

Briefing

Bishops Keep Tabs on Science

Sister Ann Neal comes perhaps as close as anyone to being the Catholic Church's official science-watcher. She is secretary of the Committee for Human Values, a group of bishops which monitors scientific and technical developments likely to raise ethical or religious issues.

The committee, Neal explains, does not go out looking for issues on which to take stands; its purpose is more to keep abreast of what is going on in fields such as energy policy, human experimentation, and recombinant DNA.

Neal took her degree in philosophy, concentrating in bioethics, from Georgetown University in 1976. Her committee, part of the National Conference of Catholic Bishops in Washington, D.C., was established in 1975 by Bishop Mark Hurley of Santa Rosa, California, who serves as its chairman.

Energy policy has been one of the Committee's principal concerns. Wasteful consumption habits, economic justice, and informed citizen participation are among the issues which the committee considers within its purlieu. The concept of energy independence is one that Neal describes as "morally insensitive" because it embodies a greedy attitude to a precious commodity in which other countries find it hard to satisfy even their minimum requirements.

Her committee recently drew up a statement on recombinant DNA research. Approved by the bishops' administrative board at their meeting last month in Chicago, the statement commends several aspects of the debate that has taken place so far, and offers some "guidelines in moral reasoning" about DNA research.

Science is not value-free, the statement observes, but carries ethical and public policy implications that require reflection. "The Church, while recognizing its limitations in scientific matters, has something to contribute to this reflection," says the committee. It warns against judging the research by the strictly utilitarian perspective implied in risk-benefit calculus. While implicitly reserving its position on recombinant DNA research, the committee observes in principle that "There might well be a worthy scientific goal which ought not to be pursued if it unjustifiably violates another human good. In other words, ethical constraints might slow down, or even preclude, some scientific advances." On the other hand it is possible, say the bishops, "to harm future generations by negligently omitting to accomplish some things via science."

By administrative happenstance, Neal also serves as secretary to another committee, one that is in charge of the church's relations with nonbelievers. Asked if there is any significance in her stewardship of the two committees, she says firmly there is no implication at all that scientists are nonbelievers.—N.W.

by introducing the risk-benefit concept to food additives, much the way it now applies to drugs. (Various other pro-saccharin bills also are in the hopper, sponsored or cosponsored by an additional 50 members of Congress.) Martin says that Congress cannot give the matter careful attention during the next couple of months because the House Interstate and Foreign Commerce Committee, which has jurisdiction over the saccharin bills, is busy dealing with President Carter's Comprehensive Energy Act. Therefore, Martin asked the FDA to hold off on its saccharin ban. In addition to pleading for more time, Martin, who holds a Ph.D. in organic chemistry, claimed saccharin is beneficial in "helping people stick to their diets," and he called the rat studies "at best a flimsy scientific basis for predicting any incidence of cancer in humans."

The majority of witnesses at the hearings seemed to be against the FDA and for saccharin, many of them arguing with "anecdotal evidence" that saccharin meets a real need. One woman, unaccompanied by before and after pictures, presented herself as living proof that diet foods help people lose weight. Several witnesses alluded to the virtues of saccharin in reducing obesity, heart disease, and the complications of diabetes.

Representatives of the American Diabetes Association's "Heart of America" affiliate came from the Midwest to testify that diabetics need saccharin to "enhance their quality of life." One of them spoke of "soda without fear." Another, a psychiatrist who treats diabetic children and adolescents, said they need saccharin so they can snack with their peers. It is necessary, she said, to their "psychosocial development."

A spokesman for Procter & Gamble, makers of saccharin-containing Crest and Gleem, told the FDA that if saccharin is banned from toothpaste there could be a "major increase in dental disease," as people by the thousands stop brushing twice a day.

No Evidence Saccharin Works

Countering such testimony were declarations by antisaccharin forces that there is no evidence it is good for anything—scientifically speaking. What few studies have been done to compare dieters or diabetics who use saccharin with those who do not have shown no benefit from saccharin, consumer advocate Sidney Wolfe of the Nader-affiliated Health Research Group rightly pointed out. He added that in some cases saccharin may actually make things worse. Saccharin, Wolfe claimed, has been shown to *lower* blood sugar, which in turn increases appetite and, among diabetics may actually contribute to the onset of hypoglycemia and insulin shock.

In addition to arguing that saccharin has no proven benefit, Wolfe testified

Eschewing Understatement, United Kingdom's

The new Toxic Substances Control Act (TSCA, or Tosca as it's called) was subjected to a withering attack not long ago by British science attaché Alan Smith.

The remarks, which since have enjoyed wide circulation in government and through the diplomatic set, were made at a public meeting staged last March by the Environmental Protection Agency (EPA) on "possible approaches to implementation" of the new act, which went into effect on 1 January.

TSCA, an extraordinarily complex law that took 5 years to get through Congress, requires all "new" chemicals to be proved environmentally safe before they are marketed, and calls for safety testing of many already in use. It will have an important effect on trade because it applies to imports as well as domestically produced chemicals.

At the meeting, Smith, speaking from hastily scribbled notes, complained that EPA had given other governments "ridiculously short notice" for commenting on the act. He also excoriated the law for being, on the one hand, incomprehensible, and on the other, an attempt by the United States to run the world's environment. The little speech was loudly applauded by the audience of over 600, most of whom were representatives of chemical concerns.

Smith's pungent remarks went in part as follows:

"I cannot understand the language of the Act. In its wording, a chemical substance is not a chemical substance; the environment is not the environment; . . . 'manufacture' means 'import'; in short, everything means everything—including everything else.

"We are left in a condition of maximum entropy: in which events and objects are indistinguishable. . . ."

Many interests, said Smith, "could be seriously affected by this absurd piece of gobbledegook," but (theoretically) "how can one comment helpfully about the ravings of a man who . . . does not know what he is talking about, and cannot explain it in everyday language?"

Smith noted that "the United States does not have a monopoly of the environment" and that there already exists international machinery, in the form of the Organization for Economic Cooperation and Development (OECD), to advise governments on such matters. But "You have chosen to ignore that machinery; and instead to embark . . . on this ludicrous charade" of inviting governments to comment on a law they had barely even heard of, much less understood.

"Well, you must take what is coming to you," said Smith. "I believe the situation is too serious to mince words.

"Go back: consult your State Department: have some respect for the international environment of which you are a part. Do not bite off more than you can chew; do not kid yourselves that the words of your mother tongue can be made to carry more meaning than they will bear; do not presume to legislate for the Universe and the whole human race until you have proven to the world that you can run your own affairs; do not try to teach your grandmothers in Europe to suck eggs; . . . and above all, take a thought for your reputation: there is a limit to the number of times even the greatest country in the world can afford to appear ridiculous in international affairs. . . .

"This draft is like the Jabberwocky of Lewis Carroll. . . . The language of chemistry mixes uneasily with the language of metaphysics, and the overlay of legal jargon makes the whole incomprehensible.

"When you know what you want to do . . . approach us through the proper channels. . . . Until then, do not expect the international community to compensate for the defects in your own approach to problems: and do not waste our time."

Smith, a mining engineer who has been at his current post for 2½ years, still sounded angry when *Science* called him up 2 months later. He said he'd had no instructions from his government—"only a great raft of questions"—about the act—"but I have no reason to believe that my

that, in his view, the risks are proven. He referred to 11 different long-term "laboratory studies" in which saccharin has caused cancer. "Some of these studies were less than perfect by today's standards," Wolfe admitted, referring to a continuing problem in evaluating the relatively large amount of saccharin data that have accumulated over the years. "Nevertheless, the consistency of the findings should have compelled a saccharin ban years ago," he said.

In fact, when FDA commissioner Kennedy picked up the ball on the saccharin ban he was handed upon taking office, he went to some effort to point out that it was not *just* the Canadian but the accumulation of evidence that saccharin is hazardous that persuaded him the ban is proper. Furthermore, Kennedy believes a saccharin ban is justified in light of current concern about environmental carcinogens. "We should not," he says, "allow even weak carcinogens in the environment if we can help it. Our systems may already be overloaded."

The many assessments of saccharin give equivocal evidence that it is risky, but there is even less proof that it is safe. As far as the other side of the equation is concerned, there have been no overall assessments of the *benefits* of saccharin, except for a preliminary evaluation of the situation in 1974 by the Institute of Medicine–National Academy of Sciences. At that time, the Academy was completing a study of evidence of saccharin's potential hazards, and the Institute was making ready to consider whether there are grounds for reclassifying it as a drug, were the Academy group to recommend its being banned from food. When the Academy declared the data were not strong enough to ban saccharin, the Institute shelved its saccharin-as-a-drug study. However, reporting for the Institute, pharmacologist Kenneth Melmon of the University of California Medical Center at San Francisco said, "The data on the efficacy of saccharin or its salts for the treatment of patients with obesity, dental caries, coronary artery disease, or even diabetes has not so far produced a clear picture to us of the usefulness of the drug." On the other hand, Melmon says, "There isn't any good evidence that saccharin causes human cancer either."

No one really knows what to make of all of this contradictory and inconclusive information. But many scientists are beginning to join the politicians and the average citizens who think that the FDA may have acted in haste. Whatever the case, it will be unfortunate if a serious—and needed—discussion about possible changes in the food and drug law is clouded by the saccharin debate, with all its ambiguities and emotionalism. The underlying issues about the role of the FDA are too important; saccharin is too trivial a vehicle to carry them.—B.J.C.

Science Attaché Declares Tosca Non Grata

colleagues in Whitehall would dissent from my position." He reiterated that the law was a mess, its definition of "environment" absurd (it's defined as "water, air, land and all living things and the interrelationships that exist" among them) and the apparent intent was "to protect everything from everything anywhere." He added that it would have a horrific effect on trade. "I say it's nonsense and the hell with it."

There have been no official attempts to placate Smith, but he says quite a few people in government have since approached him to say, in effect, "Well done—we don't understand the bloody thing either."

Other foreign representatives sympathize in varying degrees with Smith although they do not share his vehemence. The Canadian science attaché said, "It's time someone said something like that" and agreed with Smith that the law contained "an element of presumption as well as an element of imprecision." A German agreed the law was "unclear" and a French attaché said, "We are very concerned," but unprepared to comment on the law.

EPA Shrugs off Criticism

Irving Fuller of EPA's office of international activities disputed Smith's contention that there was no time to prepare a response to the law, saying he had ample opportunity during all the years the act was going through Congress. Fuller said the agency had tried very hard to get other countries involved in developing strategies to implement the act, that briefings had been held for the diplomatic corps, and that there is to be a meeting with the chemicals group of the OECD this month. (Another EPA official said Europeans felt they had been given inadequate notice but "this is a common complaint in Europe about everything America does.") As for the substance of the act, said Fuller, "That's something that Mr. Smith's government will have to take up with Congress."

An official in the State Department's Office of Oceans and International Scientific Affairs said, "We are involved in a laborious and detailed operation" to inform foreign governments on what the act involves, and that U.S. embassies abroad had recently been deluged with three-volume sets, inventorying some 30,000 existing chemicals, which are to furnish the baseline for determining what chemicals are new.

Although State and EPA officials did not appear to take Smith's criticisms very seriously, all parties acknowledged that other countries do not yet have much idea how the law will affect them. Since "import" does indeed equate with "manufacture" under the new law, any country wishing to trade with the United States will have to pretest any new chemical—and allow evidence of its safety to be publicized—before it can be sold in this country, and will have to supply evidence that any "old" chemical not on the approved list is environmentally safe.

TSCA is not the first American environmental law to have signficant international repercussions—the Clean Air Act, for example, has affected foreign auto manufacturers—but it is undoubtedly the most complex and far-reaching. There are not yet any official prognostications about how the law will affect trade in chemicals. The United States, according to EPA, imports some $2.7 billion worth of chemical substances a year and exports chemicals worth over $8 billion. The potential effects of the law are much wider, however, for EPA's proposed regulations would control all chemicals in all imported articles.

The United States is not alone in having a toxic substances law, but the TCSA seems to be more aggressive than those of other countries—Switzerland, Sweden, Norway, France, Canada, and the United Kingdom—whose basic approach is limited to the control of new substances.

As for the comments by the British science attaché, they may not have been very constructive, but they were refreshingly undiplomatic. One envoy said wryly, "A couple of people are calling it 'the new diplomacy.' "—C.H.