Saccharin—the sweet and sour saga

Roger D. Middlekauff, Partner, Bonner, Thompson, O'Connell and Gaynes, Washington, DC

At a time when the American public has a widespread concern regarding the food it eats, and a principal concern of the American public is food additives, no food ingredient has been the subject of such prolonged research, such public emotion, such industry support, and specific Congressional action, as saccharin. This focus on saccharin highlights the basic deficiencies in the criteria by which food ingredients are evaluated for safety, particularly when the spector of cancer hangs overhead. The existing evaluation of all aspects of the safety of saccharin has caused an improvement in the safety evaluation proceedings and the benefits have impacted throughout the food industry, its regulators, and the scientific disciplines they rely upon.

Saccharin was discovered in 1879. While various types of studies were performed from time to time, until 1950 no findings were reported that raised any serious questions about the safety of saccharin. However, a chronic study by Fitzhugh and coworkers reported in 1951 produced inconclusive results which encouraged the debate on the safety of saccharin.

In 1955 the Committee on Food Protection of the National Academy of Sciences reviewed the available literature on the safety of saccharin and concluded that "the maximal amount of saccharin likely to be consumed was not hazardous." In 1967, following significant increases in the consumption of saccharin and cyclamates, the FDA asked the NAS to undertake another evaluation. A special Ad Hoc Committee of the NAS reported in 1968 that the consumption of saccharin at the then projected levels would not present a hazard, but the existing carcinogenesis studies on saccharin, by the standards of the day, were inadequate. The Committee recommended that additional studies be conducted.

When cyclamates were banned in 1969 and saccharin consumption was expected to show another major increase, the FDA asked the Ad Hoc Committee of the NAS to undertake yet another evaluation. The NAS report released in 1970 arrived at conclusions very similar to the assessments of 1955 and 1968. The Committee recommended additional chronic toxicity studies, epidemiological studies, comparable metabolism studies, and studies on toxicologic interactions with other selected chemicals. Although the existing studies raised some questions about whether saccharin could cause cancer, no firm conclusions could be reached on the basis of those data.

For many years, saccharin enjoyed a position on the list of "generally recognized as safe" substances. However, its status was modified in 1972 when the Food and Drug Administration announced that a preliminary report from a chronic feeding study indicated certain adverse results which suggested that an interim food additive regulation would be appropriate. The FDA's order was published in the Federal Register on February 1, 1972. The interim regulation placed limits on the use of saccharin with the date of expiration of the regulation to be June 30, 1973. The regulation imposed limits on the use of saccharin to discourage general use by consumers and to inhibit an increase in its use by the general population. On May 25, 1973, the FDA extended the date of expiration of the interim food additive regulation to such time as the FDA "receives a final report and recommendation from the National Academy of Sciences' Committee on Saccharin and publishes an order."

The report from the NAS was released in December 1974. As on prior occasions, its principal conclusion was that the data had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." The NAS again recommended several studies, including an investigation of the toxicological significance of the impurities in saccharin and certain epidemiological studies. The FDA announced that it would evaluate the report and then define the types of tests that it would require to establish the safety of saccharin. Incidentally, the report was issued at a time when the prices of sugar had nearly peaked.

At about the same time the Health Protection Branch of the Department of Health and Welfare

 0361-8587/79/-0001-2301$02.00—

of Canada began several studies on saccharin. The FDA published a revision to the interim food additive regulation in January 1975 limiting further the authorized uses of saccharin pending completion of the HPB's studies. On January 7, 1977, the FDA announced that it would extend the interim food additive regulation until the HPB's studies were final and the FDA had published an order. At the same time, the FDA proposed a limitation on the acceptable level of toluenesulfonamides in saccharin.

On March 9, 1977, the FDA announced its intention to ban the use of saccharin, based on the results of the HPB study.

On April 15, 1977, the FDA published its proposal to revoke the interim food additive regulation of saccharin. This announcement was based on the evaluation of the Canadian study by the FDA. The FDA reported:

> The findings indicate unequivocally that saccharin causes bladder tumors in the test animals. Specifically, 7 male and no female rats in the F_0 generation developed bladder tumors. Twelve male and two female rats in the F_1 generation developed bladder tumors. Thus, of a total of 200 rats fed saccharin, 21 developed bladder tumors.
>
> In sharp contrast, of 100 control animals—those not fed saccharin or OTS—only 1 developed a tumor.

Based on the results of these data, the FDA estimated that the lifetime ingestion of the amount of saccharin in one diet beverage per day results in a risk to the individual of somewhere between zero and 4 in 10,000 of developing a cancer of the bladder. Accordingly, if everyone in the U.S. drank one such beverage a day, this would result in anywhere between zero and 1,200 additional cases of bladder cancer per year.

The FDA proceeded with the proposed revocation of the regulation drawing on its authority under both the general safety requirements of the Food Additives Amendment of 1958 and the Delaney clause. In the preamble to the proposal, the Commissioner noted that "FDA is not empowered to take into account the asserted *benefits* of any food additive in applying the basic safety standard of the act." (Emphasis added.)

You will recall the response from the public. The problem was wrenched out of the hands of the Commissioner and transported by the crowds up to Capitol Hill where it was dropped in front of Congress.

Senator Kennedy was one of the first to react. He declared that the FDA had operated in a "cavalier manner" and that the "saccharin decision was poorly handled." He pointed out that the Delaney clause needed to be reconsidered and suggested "the reevaluation must be a public process."

On June 3, Chairman Rogers of the House Interstate Health Subcommittee introduced a bill to "impose an 18-month moratorium on any action by the Food and Drug Administration affecting the sale or distribution of saccharin." He said that "enactment of this legislation will permit consideration of proposals to amend the Federal Food, Drug and Cosmetic Act in a proper atmosphere, and not on the basis of one decision without adequate consideration of the implications of permanent amendments to the Act." The Bill also requested the NAS Institute of Medicine to undertake another evaluation of saccharin.

A few days later the Senate Subcommittee on Health and Scientific Research conducted a public hearing on the saccharin issue. At the hearing, the Office of Technology Assessment reported the findings of its 60-day study:

- Animal testing provides "valid, reliable predictions that a substance will produce cancer in humans."
- Available laboratory evidence "leads to the conclusion that saccharin is a potential cause of cancer in humans, "but there are no reliable quantitative estimates of the risk of saccharin to humans."
- "Whether or not using a non-nutritive sweetener leads to measurable health benefits has never been tested" in well-controlled scientific studies.
- A comparison of statutory authorities indicates an inconsistency; for example, the Delaney clause precludes a weighing of benefits and risks whereas the Toxic Substances Control Act requires a balancing of benefits and risks.

At the hearing, those OTA Panel members testifying agreed that saccharin was a weak carcinogen.

After considering the results of the hearing, Senator Kennedy on June 10 stated he would support legislation to suspend the ban of saccharin for 18 months. Thereupon, Chairman Rogers started to move quickly with the hearings on his bill in the House of Representatives. Meanwhile, the FDA extended the period for comments on the proposed ban to November 3, 1977.

On September 15, after almost nine hours of debate, the Senate passed S. 1750 to impose an 18-month moratorium on any ban of saccharin. Senator Kennedy voted against the bill. The House passed the Rogers bill on October 15. The Conferees met on November 2; on November 3 the House passed and on November 4 the Senate passed The Saccharin Study Labeling Act, P.L. 95-203.

The Conference Committee Report is very candid as to the dilemma seen by the Congressmen. The report stated that "The saccharin controversy has brought into focus questions about the adequacy of current food additive

safety laws." Specifically, it questioned the "wisdom of requiring all foods containing any food additive which has been shown to cause cancer in man or animals to be banned, regardless of the additive's potential health benefits and regardless of the quantity in which it is found in foods." The Committee expressed the view that the issues raised by the proposed ban on saccharin had implications for the "integrity and effectiveness of our regulatory apparatus."

In this background, what does the Act require?

As it relates specifically to saccharin, the Act specifically prohibits the FDA from removing saccharin from the market for an 18-month period. However, if new information becomes available which, when considered alone or viewed cumulatively with all other existing information, shows that saccharin represents an unreasonable and substantial risk to the public health and safety, then the Commissioner may proceed to remove saccharin from all foods, food additives, drugs, or cosmetics. In addition, the Act made amendments to the Federal Food, Drug and Cosmetic Act regarding certain warning labels.

The Act requires that the Secretary of the Department of Health, Education and Welfare arrange for the conduct of two studies, preferably through the National Academy of Sciences. The first of the two studies mandates an analysis specifically related to saccharin, its impurities, and the health benefits, if any, which can be attributed to saccharin. The Act states that the study is to determine, to the extent feasible:

- "The chemical identity of any impurities contained in commercially used saccharin." The request is based on the representations by several scientists that commercially available saccharin contains impurities which have yet to be identified but which may be active cancer-causing agents.
- "The toxicity or potential toxicity of any such impurities, including their carcinogenicity or potential carcinogenicity in humans." The results of short-term tests on the impurities were positive. Consequently, there remains the question whether the impurities in saccharin or the saccharin itself cause the health hazard.
- "The health benefits, if any, to humans resulting from the use of non-nutritive sweeteners in general and saccharin in particular." Many eminent scientists and physicians stated to the Congress that the availability of a non-nutritive sweetener is beneficial to the health of millions of Americans. That being the case, the benefit should be demonstrated.

Secondly, the Act mandates a broad study regarding the predictability of carcinogenicity, the means for evaluating the health risks and benefits which may accrue from such substances, the existing regulatory authorities governing carcinogenic and other toxic substances in food, and the relationship between existing Federal regulatory policy toward carcinogenic and toxic substances in foods and Federal regulatory policy toward carcinogenic and other toxic substances used as other than foods. The Congressional report was careful to point out that Congress did not want a repeat of the OTA report. They wanted an assessment of federal regulatory policy with recommendations for legislative and regulatory action as appropriate. Specifically, the Act mandates a study on:

"current technical capabilities to predict the direct or secondary carcinogenicity or other toxicity in humans of substances which are added to, become a part of, or naturally occur in, food and which have been found to cause cancer in animals."

"the direct and indirect health benefits and risks to individuals from foods which contain carcinogenic or other toxic substances."

"the existing means of evaluating the risks to health from the carcinogenicity or other toxicity of such substances, and the existing statutory authority for, and appropriateness of, weighing such risks against such benefits."

"instances in which requirements to restrict or prohibit the use of such substances do not accord with the relationship between such risks

and benefits."

"the relationship between existing Federal food regulatory policy and existing Federal regulatory policy applicable to carcinogenic and other toxic substances used as other than foods."

The National Academy of Sciences agreed to undertake the studies. While the deliberations of the NAS are considered confidential, the NAS has released some information which indicates the relative direction and approach being taken.

The studies are being conducted by a coordinating committee and two advisory panels, with the support of the NAS professional staff. Panel I is investigating the risks and benefits of saccharin and other non-nutritive sweeteners. Panel II is charged to investigate the legal and social implications of food safety regulation in the United States.

Panel II has been given the following instructions:

- conduct an evaluation of the adequacy of the existing public and private institutional means of food safety control,
- evaluate the impact of substances in the food supply on the community in terms of health status, economic factors, and political factors, and
- evaluate the impact on the society that any changes in the existing means of technical assessment and regulation of food safety might have.

To carry out these instructions, the NAS stated that the Panel will look into such factors as the routes of entry of substances into the food supply, economic considerations such as value and quantity produced and consumed, average per capita daily consumption, uses by special population groups, types of health risk, aggregate health risks and benefits, particularly to risk or target populations, and the roles of present regulatory groups such as the FDA and the USDA. Panel II will also look into the subject of relative risk and relative benefits, defining those terms to be

> "relative risk is the probability of disease in an exposed population compared with the rate of disease in an unexposed population. Relative benefit, as defined in economics, is a comparison of the use value of different substances in safegarding health compared with their market value in promoting sales."

At the six-month interval of the NAS's study, a report was submitted to the FDA. The coordinating committee and the two panels have proposed to analyze food safety policy on the basis of five prototypic case substances:

saccharin
nitrites (including nitrates and nitrosamines) representing a direct additive as well as a natural toxicant
acrylonitrile, representing an indirect additive
aflatoxin, representing a carcinogenic natural contaminant
methyl mercury, representing a non-carcinogenic natural contaminant

Panel II described its plan of action:

- The legal and regulatory analysis for the study will first involve an inquiry into the statutory framework of the FDA. Then, the Panel will look at food regulation in departments and agencies outside the FDA, particularly the USDA. Finally, it will look at regulation of comparable non-food environmental areas by agencies and departments outside the FDA with emphasis on the Consumer Product Safety Commission, the Environmental Protection Agency, and the Occupational Safety and Health Administration.
- The evaluation of health effects relating to substances in food involves two primary areas: the first is an evaluation of historical and epidemiologic data on the association of diseases, especially cancers, with substances in foods; the second is a comparative evaluation of risks attributed to substances in food compared to risks from other areas of exposure.
- Research in the area of information and education involves examination of the effectiveness of content labeling of foods and non-foods such as tobacco, commercial advertising and its effectiveness, and methods for education and informing the public about safety regulation.
- Regarding the effects on the economy of food safety regulation, discussions are underway with agricultural economists to determine the economic impact of food safety regulations on specific farm and industry food products.

The complex questions under consideration by the NAS have faced the food industry and its regulators for many years, only to be considered and discussed mainly on a case by case basis. The full implications of the extensive animal testing being required by the FDA, the impact of their decisions on the public and the food industry, the social and economic implications—these questions need to be answered, but can they be answered within one year? Is our knowledge regarding toxicology sophisticated enough to permit the questions to be answered at this time? Are the regulators, is congress, is the public ready to accept a risk/benefit relationship in regard to their food products?

At the end of 1977, the Commissioner of the FDA requested that Dr. Morris Cranmer, then the Director of the NCTR, review the data relevant to the question of saccharin carcinogenicity. He was asked to review all the current knowledge concerning the role of direct-action carcinogens versus tumor promoting agents with

respect to the pathogenesis of bladder cancer in experimental animals, to describe the on-going related research by the various Federal agencies, to develop protocol for experiments to identify qualitatively and, to the extent possible, quantitatively the mechanisms involved with saccharin's carcinogenicity with respect to the bladder. On June 7, 1978, Dr. Cranmer completed the report, titled the "Final Report on Saccharin," which consisted of 839 pages. His report provided an insight as to the risk/benefit equation.

First, as it relates specifically to saccharin, the risk/benefit equation would suggest a comparison of saccharin with sucrose.

> When sucrose is fed at 20% in the diet to rats, approximately a 10% incidence of renal adenoma is produced. Saccharin produced approximately a 30% incidence of bladder carcinomas at 5% in the diet. The treatment-related cancers were not extensive enough in either study to produce lifeshortening of cancer-related death. Saccharin is approximately 500 times as sweet as sucrose . . . (I)n other words the risk to cancer in animals is 375 higher for sucrose if they received saccharin or sucrose at equivalent "sweet doses."

In addition to that troublesome view of the risk/benefit equation, Dr. Cranmer pointed out other difficulties that are facing the food industry, the regulators, and the scientists in their evaluations of the safety of food ingredients. He suggested several factors which have to be answered before a risk/benefit equation can be developed with accuracy.

- What consideration should be given to the great variety of substances that individuals are exposed to?
- Why are positive results treated differently than negative results, regardless of the risk/benefit situation?
- What is a biologically insignificant dose?
- How can we distinguish the results caused by chance from the results that are real?

Others have given consideration to the question of relative risk. They have demonstrated that people in their everyday life voluntarily and involuntarily subject themselves to risks of various kinds. The taking of a risk voluntarily is a regular occurrence. There are risks associated with sports, with various occupations, with traveling, as well as with eating and drinking. The consumption of saccharin has been estimated, as it affects the average person, as providing a lower risk of cancer than drinking the water of Miami or New Orleans, and less risky than cancer from natural radiation at sea level, and less risky than death by electrocution.

However, when one starts consuming a can of soft drink per day sweetened with saccharin, the risk of cancer does increase. Nevertheless, it is still estimated as being no greater than the risk of death from bicycle riding, the risk of death from drowning while fishing, the risk of death while a pedestrian, the risk of cancer from breathing air in urban U.S., and less risky than death while living downstream from a dam.

In early November 1978, the first NAS report was completed and released. Rather than answer all the questions of Congress, the report identifies more specific questions, pointing to Panel II as being the source of the remaining answers in its report due early in 1979. The constraints of time had an obvious impact on the Committee's deliberations. Nevertheless, the report focuses attention on the Delaney Clause, and it calls for consideration of such matters as qualitative and quantitative extrapolation of animal data to human, *in utero* exposure, and the mechanisms of cancer promotion. While the report identifies saccharin as a carcinogen of low potency, the raising of these issues indicates that the degree of risk of saccharin consumption is not yet clearly defined.

On the other side of the risk/benefit equation, the report submits that "the committee has found no studies that permit objective assessment of the asserted health benefits of saccharin use." The report recommends that further research be undertaken.

Not surprisingly, the report contains no recommendations "as to whether or not saccharin should be continued in use as a food additive." For this, the committee defers to the second report which will be issued in early 1979.

If the study results in a continuation and support of existing policies of food safety, if it fails to record the limitations of the testing approaches and fails to recommend a consideration of relative risk factors, if Congress is unwilling to legislate regarding the food industry the same way that it has regulated other sources of environmental hazards, we will see a continuation of the over-restrictive testing requirements, a continuation of the view that no risk is acceptable, and a reduction of the number of food ingredients permitted for use in foods.

The study being performed by the National Academy of Sciences could result in a major change in the Federal Food, Drug and Cosmetic Act. It could cause Congress to recognize that the American public is entitled to make informed decisions regarding the risks that it is willing to take in the foods it consumes. It could cause Congress to realize that the only way that the U.S. food industry will be able to continue production of a wide variety of foods is to permit a realistic determination of required food safety.

Acknowledgment

This paper was originally presented at the Flavor & Extract Manufacturer's Association Fall Symposium in October 1978.