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### INTRODUCTION

The Food, Drug, and Cosmetic Act requires that safety of food additives be established “provided that 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 animals.”

This statement of special treatment for food additives, emphasizing the risk of cancer, is commonly known as the “Delaney clause,” named for the legislator who introduced it into what became the Food Additives Amendments of 1958. The clause prohibits the marketing of a food additive that has been shown to be carcinogenic, that is, capable of inducing cancer. It allows no balancing of the risks and benefits of the food additive. In contrast, governmental regulation of other substances has tended to require assessment of both risks and benefits.

Saccharin, a non-nutritive sweetener, has recently been identified by the Food and Drug Administration as a carcinogen. Under the “Delaney clause,” its use in foods must therefore be prohibited. Saccharin is the only non-nutritive sweetener currently available to the American public, and it is widely used. The proposed ban of saccharin has prompted debate about the appropriateness of the “Delaney clause.” Many people are asking whether a demonstration of carcinogenicity in animals is sufficient reason to keep a substance off the market, regardless of its benefits.

Regulatory decisions concerning substances that have been available to the public for some time (like saccharin) are especially difficult to make. Once a substance is in use, two phenomena commonly occur: (1) additional groups of people are exposed, intentionally or unintentionally, and (2) the use itself becomes perceived by some people as a benefit. Thus, once a substance is introduced into the market, additional information on risks and benefits accrues. In some instances, the information refines the evidence for or against appropriate use. In other instances, risks and benefits become known that are different from those originally examined.

The current debate about saccharin and the “Delaney clause” has also raised questions about the validity of cancer testing technology. The carcinogenicity of a substance is tested by laboratory experiments and epidemiological studies, methods susceptible to scientific protocols and statistical verification. Controlled animal experiments, which test the ability of a substance to cause cancer in animals, provide the most reliable laboratory evidence of carcinogenicity. Animal experiments are expensive and require several years to conduct. Short-term laboratory tests, which are inexpensive and usually require only a few weeks to conduct, have been developed to aid

in evaluating the potential of substances to cause cancer. These short-term tests examine the capacity of a substance to cause mutations or other genetic alterations. Epidemiological studies examine whether exposure to a particular substance causes cancer in humans. Positive epidemiological results are the most convincing of all evidence, but negative results are less certain. Epidemiological studies are very difficult to conduct because they require data from a large number of people, sometimes over a long period of time.

Complicating an evaluation of the risks of cancer is the fact that testing technology is rapidly changing, and standards are constantly being revised. Advances are being made in the amount and quality of data available and in methodologies used to gather that information. In many cases, alterations, in standards occur between the time a test is begun and completed. For example, guidelines for animal studies of carcinogenicity presently call for experiments that require 2 to 3 years to conduct, and changes in the guidelines are being considered. Thus, data from recently initiated and ongoing experiments may not meet testing standards when the experiments are completed. Similarly, short-term tests are in varying stages of development, and they have not been fully validated.

Testing saccharin for carcinogenicity reflects the advancing nature of cancer testing technology. Data about saccharin are available from a number of laboratory experiments and epidemiological studies. However, only the most recently completed studies approach current standards for testing. Data about the carcinogenicity of saccharin from short-term tests are still limited.

Although the “Delaney clause” does not allow the weighing of risks and benefits of a food additive such as saccharin, the current debate has raised the question of benefits nevertheless. Possible benefits of saccharin involve cultural and psychological considerations. Various hypotheses have been advanced about the effect of saccharin’s sweet taste. Some of these hypotheses predict beneficial effects; others predict detrimental effects.

Except when the chemical properties of a specific non-nutritive sweetener are at issue, the potential benefits of these sweeteners lie in their possible contribution to the reduced consumption of sugar. On the other hand, enumerating hypothetical benefits of saccharin does not eliminate the possibility that its use promotes practices that constitute health risks. Conceivably, continuing to provide the sweet taste may lead to greater, not lower, consumption of sugar.

The benefits of saccharin are more difficult to test than the risks. The kinds of questions asked about risks have never arisen for benefits. Specific benefits of saccharin have neither been studied in isolation from other sweeteners nor examined as carefully as the risks from carcinogenic substances. Because of the general lack of relevant literature, the kind of detailed analysis applied to the assessment of risks is not possible for the assessment of benefits. Thus, the analysis of risks is narrower but more thorough than the analysis of benefits,

Because the possible benefits of saccharin are primarily related to its use as a sweetener, the analysis of its benefits also applies to other non-nutritive sweeteners. Therefore, the availability of other artificial sweeteners does not affect the analysis of the benefits of saccharin.

## FINDINGS AND CONCLUSIONS

1. Because carcinogenicity cannot be tested directly in humans, indirect methods are necessary. Current methods can predict that a particular substance is likely to cause cancer in humans. The technology for making quantitative extrapolations from animal experiments to human risk is progressing and has been verified in the few cases for which data are available. But this technology does not currently permit reliable estimates of the numbers or locations of cancers that might occur in humans.
2. Three methods are employed:
  - A. Animal tests are accepted as valid, reliable predictors that a substance will produce cancer in humans.
  - B. Short-term tests provide presumptive evidence of a substance's risk to humans. A positive result in any of the short-term tests warrants suspicion and calls for tests in animals. A negative test indicates that carcinogenicity is less likely, but does not rule it out.
  - C. Human epidemiological studies attempt to answer two questions: (1) Is there a positive association between a particular exposure and the occurrence of cancer in humans, and (2) If there is, is it causal? Positive results can clearly show that human populations are at risk. Negative results are more difficult to interpret, but they do not eliminate the possibility of risk.
3. Statutory authorities for regulating carcinogenic substances to which humans may be exposed are not consistent. Unlike the Food and Drug Administration's (FDA) authority under the "Delaney clause," other agencies regulate carcinogenic substances under general authorities relating to toxic substances. Although attempts are made through implementing regulations to apply consistent standards, such efforts are voluntary, often discretionary, and the legislation sometimes precludes consistency:
  - A. The "Delaney clause" reflects the present state of technology in which laboratory methods can predict that a specific substance is likely to cause cancer in humans, but cannot reliably quantify this potential effect.
  - B. Other legislative authorities that allow risks to be balanced against other factors in decisions to regulate carcinogenic substances implicitly permit quantitative extrapolations to be made from animal testing to humans.
4. The National Cancer Institute (NCI) guidelines do not provide criteria for classifying an agent as a potential risk to humans. Although they provide criteria for judging whether specific experiments have been properly conducted, they are not mandatory for all Federal agencies.
5. Laboratory evidence demonstrates that saccharin is a carcinogen.
  - A. Prolonged ingestion of saccharin at high levels caused a significant increase in the incidence of bladder cancer in rats in three independent experiments. Earlier experiments were not sensitive enough to detect this carcinogenic effect.

- B. This evidence leads to the conclusion that saccharin is a potential cause of cancer in humans.
  - C. There are no reliable quantitative estimates of the risk of saccharin to humans.
6. Epidemiological studies of human experience have not been sensitive enough to determine whether or not saccharin is a carcinogen when ingested.
7. As part of this study, a battery of 12 short-term tests was conducted on pure saccharin, impure saccharin, and impurities in commercial saccharin.
- A. Pure saccharin was mutagenic in 3 of 10 completed tests.
  - B. Impurities were mutagenic in the one system in which they have been tested. These impurities could possibly account for the observed carcinogenicity of saccharin in animals, but they are present in commercial saccharin.
8. Because of its widespread use, the availability of a non-nutritive sweetener is of perceived psychological benefit to many people.
9. Claimed benefits of non-nutritive sweeteners were identified for five groups of users:
- A. Diabetics. A non-nutritive sweetener may help in avoiding consumption of sugar and in complying with prescribed dietary therapy.
  - B. Persons with long-term, low calorie requirements. Substitution of a non-nutritive sweetener for sugar by people on restricted diets could permit them to consume greater amounts of foods containing vitamins and minerals without reducing the consumption of sweets and without increasing total calories.
  - C. The obese and those concerned with avoiding obesity. A non-nutritive sweetener may help in avoiding excessive consumption of sugar.
  - D. Persons particularly susceptible to dental caries. Non-nutritive sweeteners may aid in reducing exposure to sugared foods, which are highly cariogenic.
  - E. Persons who must take certain drugs. A non-nutritive sweetener may have benefit in improving the palatability of certain essential drugs, including fluoridated dentifrices and other fluoridated oral health preparations.
10. Whether or not using a non-nutritive sweetener leads to measurable health benefits has never been tested. The Food and Drug Administration has proposed limited use of saccharin as a single-ingredient, over-the-counter drug and as a component of certain drug products, but these uses will be allowed only if such health benefits are proven.
11. The availability of alternative non-nutritive sweeteners is uncertain at this time. The Food and Drug Administration began new hearings on cyclamate

on July 13, 1977. Petitions for four other non-nutritive sweeteners have been filed with the FDA. No predictions on availability can be made on the basis of these petitions.

## SCOPE OF THE STUDY

Questions of benefits and risks were the major issues behind the congressional request for this study. The Office of Technology Assessment was asked to undertake four specific tasks:

- (1) To assess the capacity of current testing methodology to predict the carcinogenic potential of chemicals consumed by humans, with special reference to the validity of extrapolating from results of animal tests to possible human effects.
- (2) With respect to that assessment, to evaluate and quantify insofar as possible the potential risks that saccharin consumption might cause cancer in humans.
- (3) In view of current methods for measuring health benefits of dietary behavior, to evaluate the potential health benefits, including any psychological benefits, of saccharin availability to the general public and to diabetics and other groups with special medical problems.
- (4) To assess the potential availability of alternative artificial sweeteners.

The request asked the OTA to evaluate saccharin for only one risk, carcinogenicity (which is the only one known or suspected), but to identify all potential health benefits of its availability. This study is, therefore, not a comprehensive risk/benefit analysis of saccharin. Such an analysis would attempt to weigh all relevant risks against all relevant benefits. The Office of Technology Assessment was asked not only to examine the evidence for the one specific risk and to quantify it, but also to examine critically the testing methods used to generate that evidence.

In addition to the four tasks listed in the request, the OTA commissioned a battery of 12 short-term tests to be conducted on saccharin as part of this study. This study marked the first time that saccharin had been tested by most of these methods. The purpose of conducting these tests was to demonstrate to the Congress the nature of the tests, the speed with which they can be conducted, and their usefulness in regulatory decisions. It also seemed possible that conducting a full battery of short-term tests might help to clarify some of the uncertainties regarding the carcinogenicity of saccharin.