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*REPORT OF THE
COMPTROLLER GENERAL
OF THE UNITED STATES*

**Need To Resolve Safety
Questions On Saccharin**

Food and Drug Administration

Department of Health, Education, and Welfare

In February 1972, the Food and Drug Administration published an interim regulation to allow the continued use of saccharin in food for a limited time, to resolve the question of its potential to cause cancer. Resolution of the question is not expected before mid-1978.

Allowing an interim food additive regulation to remain in effect for about 6 years while safety questions concerning the additive are being resolved seems contrary to the Food and Drug Administration's intent of permitting use of such additives for a limited time. Extended use of a food additive, such as saccharin, whose safety has not been established and for which a question of carcinogenic (cancer causing) potential has been raised could expose the public to unnecessary risk.

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AUG. 16, 1976



COMPTROLLER GENERAL OF THE UNITED STATES

WASHINGTON, D.C. 20548

B-164031(2)

The Honorable Gaylord Nelson
United States Senate

Dear Senator Nelson:

This is the last of the three reports you requested on January 30, 1975. It is on the need for the Food and Drug Administration to resolve safety questions on saccharin. Our reports "Need to Establish the Safety of Color Additive FD&C Red No. 2" (MWD-76-40) and "Regulation of the Food Additive Aspartame" (MWD-76-111) were issued October 20, 1975, and April 8, 1976, respectively.

The Food and Drug Administration is part of the Department of Health, Education, and Welfare. As requested by your office, we have not obtained the Department's written comments on the report. However, we have discussed it with Food and Drug Administration officials and have considered their comments in the report.

We invite your attention to the fact that this report contains a recommendation to the Secretary of Health, Education, and Welfare in chapter 5. As you know, section 236 of the Legislative Reorganization Act of 1970 requires the head of a Federal agency to submit a written statement on actions taken on recommendations to the House and Senate Committees on Government Operations not later than 60 days after the date of the report and to the House and Senate Committees on Appropriations with the agency's first request for appropriations made more than 60 days after the date of the report.

We will be in touch with your office in the near future to arrange for copies of this report to be sent to the Secretary of Health, Education, and Welfare and to the four Committees to set in motion the requirements of section 236.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Thomas B. Heath".

Comptroller General
of the United States

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ABBREVIATIONS

FDA	Food and Drug Administration
GRAS	generally recognized as safe
OTS	o-toluenesulfonamide
WARF	Wisconsin Alumni Research Foundation In- stitute, Inc.

COMPTROLLER GENERAL'S REPORT
TO THE HONORABLE GAYLORD NELSON
UNITED STATES SENATE

NEED TO RESOLVE SAFETY
QUESTIONS ON SACCHARIN
Food and Drug Administration
Department of Health,
Education, and Welfare

D I G E S T

Allowing a Federal interim food additive regulation to remain in effect for about 6 years--as in the case of the artificial sweetener saccharin--while safety questions concerning it are being resolved seems contrary to the intent of permitting use of such an additive for limited periods. Extended use of a food additive, such as saccharin, whose safety has not been conclusively established could expose the public to unnecessary risk.

In determining whether the proposed use of a food additive is safe, the Food and Drug Administration is required by law to consider those safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data. The agency's regulations provide that a safety factor of 100 to 1 be used in applying animal experimentation data to man, except where evidence is submitted which justifies use of a different safety factor. Thus, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to laboratory animals. (See p. 15.)

The level of saccharin allowed in foods under the interim food additive regulation is based on a safety factor of 30 to 1. Use of a safety factor less than 100 to 1 for saccharin, no longer generally recognized as safe because of questions raised about its potential to cause cancer, seems questionable.

Saccharin's authorized levels of use in food should be based on the higher margin of safety provided by the 100 to 1 factor while resolution of safety questions is pending. (See pp. 15 to 18.)

Saccharin is intended for use in food for individuals who must restrict their intake of calories. Saccharin is an acid and generally is unsuitable for use in foods and beverages because it is only slightly soluble. It is most often combined with either sodium, calcium, or ammonium salts which neutralize the acid and produce a more readily soluble compound.

Saccharin was generally recognized as safe for use in food until about 1970 when studies raised questions about its carcinogenicity (potential to cause cancer) in test animals.

Food and Drug Administration regulations provide for an interim food additive regulation when new information raises an important question of safety about an additive that was generally recognized as safe. An interim regulation allows the additive's continued use for a limited period while the safety question is resolved.

The Food and Drug Administration is required, promptly upon completion of studies, to

- review all available data,
- terminate the interim regulation, and
- issue a final regulation for the additive's use or require its elimination from the food supply.

The interim food additive regulation for saccharin and its three salt forms was issued in February 1972 because of the questions raised about their potential to cause cancer. Under the interim regulation, saccharin was permitted to be used in foods at the same levels as before, even though the question

of its carcinogenicity is not expected to be resolved before mid-1978. (See pp. 7, 8, 13, and 14.)

The Food and Drug Administration limits the level of o-toluenesulfonamide, an impurity in saccharin, to 100 parts per million. This limit was established because

--substantial levels of the impurity were identified in saccharin samples used in two studies,

--the impurity has possible carcinogenic potential, and

--industry was capable of reducing its levels to 100 parts per million. (See pp. 18 and 19.)

Technology advancements have since made it possible to reduce the levels of o-toluenesulfonamide in saccharin to less than 50 parts per million and as low as 1 to 3 parts per million. Any potential hazard from the use of saccharin could be further minimized by reducing the levels of o-toluenesulfonamide in saccharin to the lowest level practically achievable under present manufacturing technology. (See p. 19.)

Because saccharin has been used under an interim food additive regulation for about the past 4 years and because safety questions about it are not expected to be resolved for about 2 more years, the Secretary of Health, Education, and Welfare should direct the Commissioner of the Food and Drug Administration to reevaluate the justification for saccharin's continued use pending resolution of the safety questions.

If continued use under the interim regulation is justified, the Commissioner should consider the need to increase the safety factor to provide a higher margin of safety and to

reduce the permissible levels of o-toluene-sulfonamide in saccharin to the lowest level achievable under present manufacturing technology.

CHAPTER 1

INTRODUCTION

This report on saccharin is the last of three reports requested by Senator Gaylord Nelson on the Food and Drug Administration's (FDA's) methods for determining the safety of the additives Food, Drug, and Cosmetic Red No. 2; saccharin; and aspartame used in food. As requested, the reports focus on

- the history of FDA's regulation of the additives, including tests conducted within and outside of FDA leading to a change in regulation,
- the current status of testing the additives and FDA's activities affecting the status,
- the extent to which FDA has examined alternatives to the additives in the event their safety is questioned, and
- whether the regulatory action taken by FDA on these three additives, based on the scientific evidence available, complies with the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301).

Our reports "Need to Establish the Safety of Color Additive FD&C Red No. 2" (MWD-76-40) and "Regulation of the Food Additive Aspartame" (MWD-76-111) were issued on October 20, 1975, and April 8 1976, respectively.

REGULATION OF FOOD ADDITIVES

The Federal Food, Drug, and Cosmetic Act, as amended by the Food Additives Amendment of 1958 (21 U.S.C. 348), requires FDA to establish regulations prescribing the conditions under which a food additive may be safely used. The act defines "food additive" as any substance which becomes or may be expected to become a component of food, either directly or indirectly, or which may otherwise affect the characteristics of the food. The proposed use of a food additive whose safety is not generally recognized must be approved by FDA. The act states, however, that no additive be deemed safe if it is found to be carcinogenic (induce cancer) when ingested by man or animal or if it is found, after tests which evaluate the safety of food additives, to induce cancer in man or animal. This provision is commonly known as the Delaney clause.

Substances added to food which qualified scientists have "generally recognized as safe" (GRAS) when used as intended, are not food additives and are exempt from the requirement for FDA approval. This classification of GRAS may be made either on the basis of data derived from scientific procedures or, in the case of substances in use before January 1, 1958, on the basis of either scientific procedures or experience drawn from common use in food.

FDA's food additive regulations (21 C.F.R. 121.1(k)) define GRAS substances as those which experts determine, based on scientific data or reasoned judgment founded in experience with common food use, pose "no significant risk of harm if used as intended." If an important question of safety has been raised regarding a GRAS substance, it may be removed from GRAS status. An interim food additive regulation (21 C.F.R. 121.3(f)(g)) may be issued to permit its use while the safety question is being resolved, provided there is reasonable certainty that the substance is not harmful and that no harm to the public health will result from its continued use.

On February 1, 1972, FDA published an interim food additive regulation (21 C.F.R. 121.4001) for saccharin which had been classified as GRAS based on its use before January 1, 1958.

WHAT IS SACCHARIN?

Saccharin is an artificial nonnutritive sweetener that is about 350 times sweeter than sugar. In its free form saccharin is an acid and is generally unsuitable for use in foods because it is only slightly soluble. It is therefore most often combined with either sodium, calcium, or ammonium salts which neutralize the acid and produce a more readily soluble compound for use in foods.

Saccharin-sweetened foods are intended only for individuals who must restrict the calories in their diets. Sodium saccharin is the form most often used in foods because it is less expensive to produce than the others. Calcium and ammonium saccharin can be used by individuals who must restrict their intake of sodium as well as calories.

Saccharin was first introduced in the United States in about 1900 and its use has steadily increased. The Calorie Control Council, a trade association, estimates that in 1974 approximately 5 million pounds of saccharin were used in foods. About 74 percent of this amount was used in diet soft drinks; 14 percent, in dietetic foods such as canned fruits,

gelatin desserts, jams, ice creams, and puddings; and 12 percent, as tabletop sweeteners. Although most often used in foods, saccharin also has some uses in nonfood applications such as mouthwashes, cosmetics, tobacco, and medical preparations.

Saccharin is produced by either the Maumee Process or the Remsen-Fahlberg Process. The saccharin from these two methods differs primarily in the amount and types of impurities which it contains. One of the most prevalent impurities is o-toluenesulfonamide (OTS). Saccharin produced using the Remsen-Fahlberg Process contains more OTS than saccharin produced using the Maumee Process. OTS levels in saccharin sold in the United States cannot exceed 100 parts per million.

The Sherwin Williams Corporation, the only producer of saccharin in the United States, uses the Maumee Process. According to an official of the Calorie Control Council, Sherwin Williams Corporation produces more than one-half of the saccharin used in the United States; the rest is imported. He stated that in 1974, the latest year for which import data was available, nearly 90 percent of the imported saccharin came from Japan; the remainder, from Korea.

As of June 30, 1976, saccharin was the only artificial sweetener allowed by FDA for use in foods. A possible alternative to saccharin is the artificial sweetener aspartame. On July 26, 1974, FDA published a regulation approving the use of aspartame in food but stayed that regulation on December 5, 1975, because of evidence that data submitted in support of its safety may have been incomplete and/or inaccurate. As of June 30, 1976, the final status of aspartame had not been determined. FDA officials stated that the final decision regarding aspartame's safety must wait until a board of inquiry or a legal evidentiary hearing is held.

CHAPTER 2

SAFETY OF SACCHARIN NOT ESTABLISHED

The Food and Drug Administration's food additive regulations permit interim food additive regulations to be issued when new information raises an important question of safety about the additive (21 C.F.R. 4000). An interim regulation allows its continued use for a "limited period of time" while the question is being resolved by further study. The regulations require FDA, promptly upon completion of the studies, to

- review all available data,
- terminate the interim food additive regulation, and
- issue a food additive regulation or require elimination of the additive from the food supply.

In February 1972 FDA issued an interim food additive regulation for saccharin because certain animal studies raised questions concerning its potential to cause cancer in humans. Later, additional animal study data raised similar questions concerning saccharin. FDA had not resolved the question of saccharin's carcinogenicity as of June 30, 1976, and does not expect to resolve it before mid-1978, about 6 years after the interim regulation was issued.

The extended use of a food additive, such as saccharin, whose safety has not been conclusively established could expose the public to unnecessary risk.

SAFETY OF SACCHARIN QUESTIONED

Because of the increased uses of nonnutritive sweeteners in food, including saccharin, in 1967 FDA requested the National Academy of Sciences to review the safety of these sweeteners. The Academy issued a report on the results of its review in November 1968. The Academy indicated that, based on toxicological (relating to poisons) and consumption data available at that time, saccharin did not present a health hazard. The Academy report recognized, however, that there was limited information on saccharin's toxicological characteristics. Due to increased consumption of saccharin, the report recommended that the carcinogenicity of saccharin be studied, patterns of consumption be determined, and toxicological interactions with drugs be explored.

Until 1969 saccharin was used in foods primarily in combination with cyclamates, another artificial sweetener. As a result of a ban on cyclamates in October 1969, the FDA Commissioner requested in November 1969 that the Bureau of Science and Medicine 1/ assess the safety of saccharin.

On January 26, 1970, the Bureaus submitted a joint report to the Commissioner. The report did not contain recommendations, but it strongly suggested the need for long-term, animal studies on saccharin to evaluate saccharin's potential for inducing bladder cancer. The report noted that the bladder cancer question had been raised by two studies. In one, conducted in England and completed in 1957, paraffin-wax, saccharin pellets were implanted in the bladders of mice. In the other study, completed in early January 1970 at the University of Wisconsin, cholesterol-saccharin pellets were implanted in the bladders of mice. In both studies, mice developed a significant incidence of bladder tumors.

On March 19, 1970, FDA again asked the Academy to review accumulated information on saccharin, including the above FDA report, and to summarize its findings.

On July 20, 1970, the Academy submitted to FDA its report, "Safety of Saccharin for Use in Foods." The Academy's report noted that none of the studies recommended in its November 1968 report had been made. The report stated that the available toxicity studies on saccharin were inadequate to evaluate its carcinogenic potential. Regarding the two saccharin implant studies, the Academy stated: "Tests for carcinogenic effects by * * * implanting pellets into the bladder have no known relevance to the safety of saccharin consumed orally." The Academy added that positive results from those tests cannot be accepted as evidence of a positive effect through dietary intake and stated that

"* * * we feel that negative results in well designed and properly executed long-term feeding tests in two species of animals would indicate the absence of any carcinogenic hazard and would override the finding that bladder cancer is produced by pellet implantation."

1/The functions of the Bureau of Science and Medicine related to food were transferred to the Bureau of Foods when it was established on December 1970.

The report concluded that, based on information available at that time, "the present and projected usage of saccharin in the United States does not pose a hazard." The report recommended that the following additional studies be done and that the question of saccharin's safety be reviewed again when work in progress and the recommended additional studies were completed.

- Long-term studies designed according to present-day standards and including adequate investigation of saccharin's effects on reproduction in at least two species.
- Epidemiologic studies with emphasis on studying diabetics.
- Investigation of patterns and ranges of saccharin consumption to determine the highest levels of average continuous consumption in the most persistent users.
- Studies in man to ascertain the degree to which saccharin metabolism in man and animals are comparable.
- Examination of saccharin-sweetened foods for certain products of decomposition, which result from food storage under a variety of conditions, to determine more precisely what is actually consumed by man.
- Exploration of toxicological interaction with selected drugs and other chemicals.

The Director of FDA's Division of Toxicology, Bureau of Foods and Pesticides 1/, noted in a July 24, 1970, evaluation paper submitted to the Director, Bureau of Foods and Pesticides, that only the long-term and metabolism studies recommended by the Academy were in progress. The paper identified four long-term studies in rats and mice which had recently been undertaken by the (1) National Cancer Institute, (2) Canadian Food and Drug Directorate 2/, (3) FDA, and

1/The responsibility for food, previously under the Bureau of Foods and Pesticides, was given to FDA's Bureau of Foods when it was established in December 1970.

2/In 1972 the Food and Drug Directorate was merged with other health-related divisions of the Canadian Government to form the Health Protection Branch.

(4) Wisconsin Alumni Research Foundation Institute, Inc. (WARF). According to the paper, the metabolism of saccharin and its metabolites (or compounds) were being studied in Canada.

SACCHARIN REMOVED FROM GENERALLY-RECOGNIZED-
AS-SAFE STATUS

On June 25, 1971, FDA published a notice in the Federal Register which stated that, in the interest of safety, limitations on the daily intake of saccharin should be established. Accordingly, FDA proposed removing saccharin from the GRAS status and establishing an interim food additive regulation, pending completion of studies to resolve questions of saccharin's safety.

On February 1, 1972, FDA removed saccharin and its various salt forms from the GRAS status and issued an interim food additive regulation limiting use of saccharin in foods.

The interim regulation published in the Federal Register stated that preliminary results from studies on long-term feeding of saccharin to animals conducted by FDA and others indicated "possible adverse effects." The Register stated that, should the experimental findings indicate that continued use of saccharin does involve a "significant risk" to the public health, action would be taken as warranted to minimize the risk. The regulation authorized saccharin's use as a sweetening agent only in special dietary food as follows:

- 12 milligrams per fluid ounce in beverages, fruit juice drinks, and bases or mixes.
- 20 milligrams for each teaspoonful of sugar sweetening equivalency, for cooking or tabletop use.
- 30 milligrams per designated serving size in processed foods.

Also, the regulation authorized the use of saccharin for the following technological purposes:

- To reduce bulk and enhance flavors in chewable vitamin and mineral tablets.
- To retain flavor and physical properties of chewing gum.

--To enhance flavor of flavor chips used in nonstandardized bakery products.

The regulation stated that the authority for saccharin's use would expire by June 30, 1973.

FDA's news release on the interim food additive regulation stated that the FDA Commissioner "emphasized that the action is an interim step designed to 'freeze' saccharin use at present levels pending final outcome of current research on safety" of saccharin.

After the Academy's July 1970 report to FDA, preliminary results from a WARF long-term feeding study indicated bladder tumor development in laboratory animals. Therefore, FDA awarded a contract to the Academy, effective May 23, 1972, to

- evaluate the scientific validity of all laboratory findings related to saccharin,
- recommend when those findings are sufficient to conclude that saccharin is or is not carcinogenic when administered orally to test animals, and
- prepare and submit a report on the safety of saccharin and its salts in the human diet.

In addition, the Academy was to review and report separately on the chemical nature, metabolism, and toxicity of saccharin and related substances; their role in drug product formulations; and an assessment of their therapeutic value in controlling dietary intake. FDA considered this information necessary to determine if there was a level of safety that would justify the continued use of saccharin to manage medical conditions, such as diabetes and obesity, in the event it was banned as a food additive. The contract identified several ongoing studies that were to be included in the Academy's review. These included long-term feeding studies by WARF, FDA, and others, the results of which were to become available over the next several months.

INTERIM FOOD ADDITIVE REGULATION
EXTENDED INDEFINITELY

On May 25, 1973, FDA issued a Federal Register notice extending saccharin's interim regulation, which was due to expire on June 30, 1973, until the Commissioner received a

final report and recommendations from the National Academy of Science and published an order based on the report. As stated in the Federal Register, the FDA Commissioner concluded that there would be "no significant increased risk to the public health" in extending the effective date of the regulation.

The Federal Register identified several completed or nearly completed long-term feeding studies made of three different animal species. It stated that results for three of those studies had been furnished to the Academy. Two of the studies, conducted by FDA and WARF, exposed test animals to a diet with as much as 7.5 and 5 percent saccharin, respectively, from the time they were weaned until they were mated. The females that became pregnant were fed saccharin throughout pregnancy (known as in utero exposure), throughout nursing (lactation), and during the preweaning feeding of the offspring. The weaned animals were continued on the same saccharin diet throughout their lifetimes. These study results showed a statistically significant incidence of bladder tumors in the male offspring fed saccharin at these levels.

According to FDA's Director, Bureau of Foods, Division of Pathology, "DOSE-RELATED CARCINOGENICITY of administered sodium saccharin for the urinary bladder of rats has been clearly demonstrated."

Several metabolism studies indicated saccharin consumed regularly may accumulate in various body organs and in the fetuses of pregnant animals. One study showed that saccharin fed to pregnant monkeys rapidly crossed the placenta and was assimilated into the fetus, but left the fetus slowly. The slow rate suggested that repetitive maternal ingestion of saccharin during pregnancy might cause the compound to accumulate in considerable quantities within the fetus. The FDA, WARF, and other studies are discussed in greater detail in chapter 4.

In December 1974 the Academy submitted to FDA its report, "Safety of Saccharin and Sodium Saccharin in the Human Diet." The report concluded that existing studies had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." The report stated that:

"Though the results of the FDA and WARF studies suggest that under the circumstances of these tests the bladder tumors observed were related to the

consumption of the saccharin samples used, they cannot be interpreted as showing that saccharin itself was the cause of the tumors."

Concerning the FDA study, the Academy report stated that

"* * * serious consideration should be given to the possibility that the early exposure to saccharin at the 7.5 percent feeding level in the FDA test introduced certain toxicity or stress factors that indirectly influenced the final outcome in terms of bladder tumors."

The report stated that the FDA study could not be accepted, without serious reservations. One drawback of the WARF study, according to the Academy report, was that the tissues studied were so poorly preserved and so inadequately processed that an accurate appraisal of the histologic character (tissue structure) of the lesions was very difficult.

The Academy report added that

"* * * because designs of the many reported negative tests were at fault in not involving in utero exposure of the test animals, the results of these tests cannot be interpreted as showing that saccharin is not a bladder tumorigen. The additional difficulty in interpreting the negative results in these studies arises from the relatively small numbers of animals surviving for final examination, a situation that minimizes the possibility of detecting carcinogenic effects of low incidence."

The Academy recommended that the following studies be made to resolve the question of whether saccharin is carcinogenic or otherwise unsafe in the human diet.

- Investigation of the question of transplacental carcinogenesis of saccharin and its impurities.
- Investigation of the toxicologic significance of impurities in commercial saccharin preparations.
- Comparative studies of the role of bladder stones and parasites in the induction of bladder tumors in laboratory animals.

--Study of the changes in urine composition at high levels of saccharin intake and the relation of such changes to the induction of bladder stones.

--Epidemiologic studies relating the incidence of cancer with the long-term consumption of saccharin.

The Academy report recommended that saccharin's safety be reassessed when most of the data from these additional studies was available.

In March 1975, FDA's Bureau of Foods, Division of Toxicology, recommended that saccharin's interim regulation be continued and that industry undertake the studies recommended by the Academy.

Industry was not asked to make such studies because, according to the Chief of FDA's Bureau of Foods, Division of Food and Color Additives, (1) tests considered by FDA to be sufficient to establish its safety either had been completed or were being made by private or Government organizations and (2) no firm has a protected interest in saccharin since patents on its processes had elapsed.

The Academy did not determine the suitability of saccharin in drug product formulations and its therapeutic value in controlling dietary intake because the Academy's assessment of saccharin's carcinogenic potential in foods was inconclusive and data on saccharin's use in drugs was insufficient. However, officials of the Academy's Institute of Medicine Committee on Saccharin thought saccharin was not required to manage diabetes or obesity, but they thought the presence of saccharin made the lives of individuals with these conditions more tolerable.

EVALUATIONS OF ACADEMY REPORT

FDA and WARF officials expressed certain reservations concerning the conclusions in the Academy's 1974 report. FDA's Associate Commissioner for Science asked FDA's Director of Scientific Liaison and Intelligence Staff to review and comment on the Academy's report. In comments dated December 17, 1974, submitted to the Associate Commissioner, the Director said:

"It must be stated that the overall tenor of the report leaves the unmistakable impression that a group of saccharin defenders were out to beat-back

saccharin accusers no matter what the cost to logic and scientific impartiality. It is, for instance, remarkable that substantially adverse, albeit equivocal, carcinogenesis data was not sufficient to raise even one dissenting voice."

The Director also took exception with several statements in the report. He did not agree with the statement that "the [Academy] Subcommittee cannot judge saccharin to be unsafe for human use solely on the basis of the finding of tumors in the rat bladder under a given set of circumstances." The Director said that this was precisely how the judgment on saccharin's use as a food additive must be made; safety questions are only legitimate if a substance is not carcinogenic. He added that according to the Delaney clause of the Federal Food, Drug, and Cosmetic Act, if a substance were carcinogenic, questions of safe use would not arise.

The Director disagreed with the position of the Academy report that, if the incidence of tumors is considered the critical safety issue, a complete explanation of the cause of the tumors should be sought to determine if there is a "reasonable suspicion of risk, or a reasonable assurance of the absence of risk" in saccharin intake by man. According to the Director, "a statistically significant" excess of bladder tumors in test animals establishes a reasonable suspicion of risk and, although an explanation of their causes would be "interesting mental gymnastics," it would not change the suspicion of hazard from saccharin's use.

In an interview with the Director on June 27, 1975, he said that his views concerning the Academy report were consistent with the above comments to the Associate Commissioner.

The president of WARF on April 2, 1975, wrote to FDA expressing "extreme concern" regarding the Academy evaluation of the WARF study. The president indicated that the Academy report could appear to be a strong effort to discredit data which questions the safety of saccharin and to overemphasize studies which indicate the safety of saccharin. He further said that:

"Apart from the tenor of the report we were very concerned to find some marked differences between the report to [sic] the special panel of pathologists to the [Academy] subcommittee and WARF Institute's pathology report and evaluation.

"Attempting to define the source of differences we discovered that the diagnosis by WARF Institute's pathologists and the subcommittee panel diagnosis of tissues in the report * * * were in complete agreement and the difference in the evaluation was due solely to the failure of the subcommittee panel to evaluate all the pertinent tissues from the WARF study. In short, the panel reported on tissues examined from animals that died or were sacrificed during the course of the study and did not report any examination of pertinent tissues of these animals which were sacrificed at the termination of the study. The most obvious result of this error of omission was failure to examine or report a significant number of tumors that developed in the WARF study."

The president indicated that only one-half of the saccharin-related tumors noted in the WARF study were included in the Academy's examination and therefore the Academy's comments about the WARF findings might be different if all the tumor data had been included. The Academy's report stated that the WARF findings were "of borderline statistical significance."

In an August 18, 1975, letter to the president of WARF, the FDA Commissioner stated that the Academy had apparently not considered the data on the animals killed at the termination of the study. He added that:

"It would seem that the consideration of an increase in significance of the WARF study, occasioned by including the tumors from the animals sacrificed at the termination of the study, would not alter the conclusion of the report."

The FDA Commissioner said he would advise the Academy of the WARF letter and ask the Academy to reply to it. According to the Director, Division of Food and Color Additives, as of June 30, 1976, the FDA Commissioner had not advised the Academy of WARF's April 2, 1975, letter.

CURRENT STATUS OF SACCHARIN REGULATION

In hearings on FDA's fiscal year 1976 appropriations before a subcommittee of the House Committee on Appropriations, the Acting Director of FDA's Bureau of Foods stated that most tests recommended in the Academy's 1974 report were being made by the Health Protection Branch of the Canadian

Government. He estimated that the tests would be completed in 3 years and that in the meantime "saccharin will continue to be interim listed for use as a food additive until such time as conclusive evidence is obtained that saccharin is or is not carcinogenic." According to an official of the Canadian Health Protection Branch, the results of the Canadian studies will not be known before mid-1978.

CHAPTER 3

OTHER SAFETY ISSUES

SAFETY FACTOR USED FOR SACCHARIN QUESTIONABLE

In determining whether the proposed use of a food additive is safe, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)(5)(C)) requires the Food and Drug Administration to consider safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data. FDA's regulations (21 C.F.R. 121.5) state:

"Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1, will be used; that is, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals."

The level of saccharin allowed in foods under FDA's interim food additive regulation is based on a safety factor of 30 to 1 rather than 100 to 1, which is the conventional safety factor. Use of a safety factor less than 100 to 1 for saccharin, which was removed as a generally-recognized-as-safe substance because questions were raised about its potential to cause cancer, seems questionable. While resolution of safety questions are pending, saccharin's authorized levels of use in food should be based on the conventional margin of safety provided by FDA's regulation.

To establish the level of safe use, experiments must be made with animals to determine the maximum amount of the additive which can be fed to them without producing adverse effects (the no-effect level). A daily maximum safe level of saccharin for humans is calculated by applying a safety factor to the no-effect level determined in animal tests. The safe level of daily use is usually expressed in milligrams per kilogram of body weight per day. Regulations are issued to limit the amount of the additive in foods and thus restrict, to the maximum safe level, the amount that probably would be consumed in a person's daily diet.

The Academy's July 1970 report to FDA discussed the results of three long-term feeding studies in which rats or mice were fed diets containing saccharin at levels up

to 5 percent. According to the report, in two of the studies, rats were fed diets containing 5, 1, and .5 percent saccharin. Rats fed saccharin at the 5 percent level in these studies either had a greater mortality rate and a higher incidence of bladder stones and lesions than control rats, experienced bone marrow hyperplasia (abnormal cell growth), or gained less weight than the control rats.

The Academy report stated that

"* * * for rats and mice the no-effect level of saccharin is no less than 1 percent of the diet (equivalent to 500 mg/kg) * * *. Adjusting this figure by the conventional 100:1 safety factor gives a 'safe' level of use by man of about 5 mg/kg/day (equivalent to 0.25 to 0.35 g/day for the adult)."

The report further stated that this estimate of the safe level of use may be "unduly conservative" considering the low level of toxicity of saccharin and the fact that nothing in the 80-year history of saccharin's use by humans indicated adverse effects other than a few instances of photosensitization or allergic response. The report stated, however, that although these observations were "reassuring," additional data on the hazards from long-term consumption of saccharin should be sought by making epidemiologic studies, with emphasis on diabetics.

According to the Academy report, projections for saccharin's likely maximum daily consumption were .2 grams per day for the heaviest users. The report stated that on the basis of the calculated safe level of use saccharin does not pose a hazard.

In a September 8, 1970, memorandum to the Director, Bureau of Foods and Pesticides, FDA's Office of Compliance took exception with the Academy's projected daily consumption estimate. The Office pointed out that if the Academy's calculated safe levels of daily consumption (.25 to .35 grams per day) were accepted, consumption of soft drinks would have to be limited to one or two 16-ounce bottles a day for certain brands. The memorandum listed five brands of diet soft drinks on the market at that time and stated that saccharin amounts in those products were .073, .084, .098, .122, and .196 grams per 16-ounce bottle. The memorandum further stated that the probable maximum use of soft drinks had been estimated at 64 ounces per day (four 16-ounce

bottles) giving an estimated saccharin consumption level of as much as .78 grams per day: two to three times the amount calculated as safe by the Academy, or a safety factor of about 30 to 1. Accordingly, the memorandum suggested that the Academy "may wish to modify their conclusion as to consumption figures."

On September 9, 1970, the Director, Bureau of Foods and Pesticides, brought this to the attention of the Academy, indicating that establishing the safe level of saccharin consumption of .25 to .35 grams per day would reduce the amount allowed in certain diet soft drinks and requested that it "amplify" its position.

In a September 10, 1970, letter to FDA, the Academy stated that only six of the eight members who participated in developing the Academy's position could be reached for comment and that five of them agreed that applying a safety factor of about 30 to 1 to the no-effect level for saccharin would be adequate to protect the consumer. It cited as support past experience of human use and saccharin's low toxicity, both of which had been discussed in its 1970 report. The Academy said nothing indicated that an intake level of up to 15 milligrams per kilogram per day (equivalent to about 1 gram a day) would constitute any appreciable hazard. The one dissenting member believed that the more conservatively derived "safe" level (5 milligrams per kilogram per day) should stand as the Academy's position pending completion of investigations of saccharin underway and of those recommended.

In a memorandum dated November 18, 1970, FDA's Director, Bureau of Foods and Pesticides, Office of Food and Nutritional Sciences, summarized his staff's comments on the Academy's 1970 report. Regarding the safety factor he stated:

"Since the element of doubt in this case is carcinogenesis, we recommend the use of the more conservative safety factor of 1:100 [100:1] * * *. This would only permit the consumption of one to three 8 oz bottles of saccharin-sweetened beverages by 25 kg [55 lb] children and three to nine 8 oz. bottles by 75 kg [165 lb] adults (as the sole source of saccharin). If allocated to enhancing the diet of diabetics, it would permit an adequate, if somewhat restrictive, sweetening of the diabetic menu."

In a memorandum dated June 11, 1971, to the Commissioner, FDA, the chief of FDA's Bureau of Foods, GRAS Review Branch, pointed out that saccharin could no longer be considered generally recognized as safe and cited studies published in late 1969 which reported the induction of bladder cancer in rats administered cyclamate-saccharin mixtures and a report dated March 1970 which noted the induction of urinary bladder cancer in mice administered pellets containing sodium saccharin. He stated that because of these safety questions, the use of saccharin would require "limitations in the interest of safety." He recommended that an interim regulation be issued for saccharin which would restrict its use to 15 milligrams per kilogram per day based on a 30 to 1 safety factor. He stated that this would "silence those persons who point out that saccharin cannot now be considered as GRAS by definition" but would "provide for current uses of saccharin without further restrictions."

On February 1, 1972, FDA issued an interim regulation for saccharin removing it from the GRAS status and restricting its use to a level equivalent to 15 milligrams per kilogram per day.

IMPURITIES IN SACCHARIN SHOULD BE LIMITED TO LOWEST ACHIEVABLE LEVELS

O-toluenesulfonamide, an impurity with a chemical structure similar to known carcinogens, is permitted in saccharin at levels much higher than the lowest level practically achievable under present manufacturing technology.

FDA requires that OTS levels in saccharin conform to those established in the Academy's Food Chemical Codex. The Codex is a compendium of purity specifications for food chemicals based on elements of safety and good manufacturing practices. It established a limit for OTS in saccharin of 100 parts per million. FDA may, through its regulations, establish limits different from those in the Food Chemical Codex.

According to FDA's Bureau of Foods Assistant Director for Petitions Review, specifications for food chemicals should reflect good manufacturing practice and be relevant to toxicological or safety aspects and are subject to change upon the development of new technology, new information, or new safety problems.

According to an Academy official, the limit for OTS was established in June 1974 because (1) substantial levels of OTS were identified in saccharin samples used in the FDA and Wisconsin Alumni Research Foundation Institute long-term feeding studies, (2) OTS might cause cancer, and (3) industry was capable of reducing OTS levels to 100 parts per million.

An Academy publication on a March 1975 forum, "Sweeteners: Issues and Uncertainties," stated that OTS in the saccharin used in the FDA feeding study ranged from about 250 to 5,000 parts per million and in the WARF study OTS ranged from about 200 to 370 parts per million. According to the Academy's 1974 report to FDA, impurities in saccharin, especially OTS, may have been the possible cause of the bladder tumors observed in the FDA and WARF studies. Saccharin used in these studies was produced by the Remsen-Fahlberg process.

Officials of the Calorie Control Council said that, since establishing the Codex limits, technology has made it possible to reduce the levels of OTS in saccharin produced by the Remsen-Fahlberg process to less than 50 parts per million. According to FDA officials, saccharin produced by the Maumee process has been found to contain OTS levels of no more than 1 to 3 parts per million.

The scientific community questioned the prudence of allowing saccharin on the market with levels of impurities that exceeded levels which industry could reasonably achieve.

According to the Academy forum publication, the Director of the University of Nebraska's Eppley Institute for Research in Cancer said that

"* * * in view of the evidence accumulated on the potential importance of OTS, * * * we have been extraordinarily remiss to have had on the market a substance with the level of impurities present in saccharin.

"* * * the levels of OTS in saccharin should be as low as possible and * * * the saccharin with a very low level of OTS should be the only kind that finds its way to the market place."

The Chairman of the Academy's Subcommittee on Nonnutritive Sweeteners expressed the opinion that OTS in saccharin should be reduced to the lowest possible level feasible under good manufacturing practice and suggested the required use of the Maumee process.

CHAPTER 4

STUDIES RELATING TO THE SAFETY OF SACCHARIN

Many studies have been conducted on the safety of saccharin's sodium, calcium, and ammonium salt forms and saccharin's nonsalt form (free saccharin). We reviewed 32 study reports on free saccharin and its salt forms regarding (1) metabolism in the body, (2) long-term effects, and (3) mutagenicity (causing mutations). Some of these studies associated problems found in test animals with the use of saccharin, some indicated no problems, and others were inconclusive.

METABOLISM STUDIES

Metabolism studies determine what compounds (metabolites) a substance may break down to in the body, how fast and into which organs the components are dispersed, and how fast they are eliminated. Metabolism studies aid in understanding results of carcinogenic studies by determining which body organs receive the greatest exposure to the substance or its metabolites.

We reviewed nine saccharin metabolism studies reported since 1970 (see app. I). The results of each were discussed in the National Academy of Sciences' December 1974 report.

In general, the metabolism studies showed that most saccharin is excreted by the body without breaking down into metabolites. Most saccharin is excreted within 24 hours of ingestion. Some studies showed that after repeated use, saccharin tends to accumulate in various organs.

Saccharin accumulation in the bladder and kidney

A 1973 National Institutes of Health metabolism study report noted that with continued use saccharin accumulates in major body organs, with the highest concentration in the bladder and kidneys, but that saccharin is rapidly cleared from the organs when it is withdrawn from the diet. The report stated that "it might be beneficial if regular users of saccharin would occasionally discontinue its use for several days and thus allow for tissue clearance."

The study included three phases in which rats were fed free saccharin at various levels and frequencies. In one

phase a single dose of saccharin was administered to rats, which were then killed in groups of three or more at various periods of time up to 90 minutes after saccharin administration. The study report noted that three to five times more saccharin accumulated in the kidneys of the rats than in the other organs or tissues.

In the second phase, two groups of rats receiving one dose of saccharin each day for 7 days and killed 24 and 72 hours after the last dose were compared with one group of rats which were killed 24 hours after receiving a single dose of saccharin. The study report stated that rats given saccharin for 7 days had accumulated as much as 19 times more saccharin in their bladders than rats receiving one dose. However, most of the saccharin had been cleared from the bladders of rats receiving seven doses 72 hours after the last dose.

Because humans are likely to consume saccharin in small doses rather than one large dose, in the third phase of the study rats were given the same quantity of saccharin, except that some were given it in one dose and others were given it in five doses, each 90 minutes apart. Experimenters killed rats which received a single dose either 90 minutes or 24 hours after they received it. Rats which received five doses were killed either 90 minutes after they received the last dose or 24 hours after they received the first dose. The concentration of saccharin in the bladders of rats killed 24 hours after receiving the first of five doses was almost 10 times that found in the bladders of rats killed 24 hours after receiving the total quantity in a single dose. The concentration of saccharin in the bladders of rats killed 24 hours after receiving the first of five doses was less than 10 percent of the amount in the rats killed 90 minutes after receiving the last of five doses.

A Food and Drug Administration study published in January 1975, compared the excretion patterns for rats which had been on sodium saccharin diets for at least a year with rats on saccharin-free diets. According to the study report, saccharin was widely distributed in the rats' body organs with the highest concentration noted in the kidneys, bladder, and liver. Some saccharin was retained in the rats for more than 7 days after their yearlong saccharin diets.

Saccharin distributed to fetal tissue

On September 15, 1971, the University of Iowa Hospital

and the University of Illinois issued the results of a jointly conducted study in rhesus monkeys entitled "Placental Transmission and Fetal Distribution of Saccharin." One study investigator said rhesus monkeys were used because the structure of their placentas and the transmission of substances between mother and fetus are almost identical to humans. Also, the fetal structures of the monkeys and humans are similar.

Free saccharin was injected into five rhesus monkeys during the last 2 months of pregnancy. Samples of maternal blood, fetal blood, and amniotic fluid (uterine fluid) were collected. Also, samples of fetal tissues were collected for analysis.

The study showed that saccharin rapidly crossed the placenta of the pregnant monkeys. While saccharin levels in the mother were negligible 3 hours after administration, the disappearance of saccharin in the fetal blood was considerably slower. Because the observation period was short (less than 5 hours), the study did not determine how long the fetuses would retain saccharin. However, the study report concluded that:

"The slow rate of fetal clearance found in the present study, however, suggests that repetitive maternal ingestion of saccharin during pregnancy might conceivably lead to accumulation of the compound in considerable quantities within the fetus."

In addition, the study showed that saccharin was widely distributed and present in all fetal tissues. Saccharin was randomly distributed in most tissues; however, it was concentrated in some cells of the bladder and kidney.

LONG-TERM STUDIES

Long-term studies expose test animals to a substance for a lifetime (usually about 2 years for rats) to assess the substance's long-term toxicity. These studies can help assess the substance's cancer-producing potential.

In its report on cancer testing of food additives and other chemicals, a panel of FDA's Advisory Committee on Protocols for Safety Evaluation indicated that the embryo and fetus may be vulnerable targets for carcinogenic substances and that tumors may be produced late in the life of animals

after maternal administration of a carcinogen during pregnancy. The Committee recommended that, ideally, carcinogenesis tests begin before conception by exposing parents of projected offspring to the substance being tested and then continue in the offspring. Thus, animals tested in this manner would be exposed to the test substance in utero to assure "as complete a screening of as many potential deleterious effects as possible."

We reviewed reports for 16 long-term feeding studies on saccharin (see app. I) which were discussed in the Academy's December 1974 report to FDA. Two long-term feeding studies found that saccharin caused cancer in test animals, 1 showed that saccharin is a possible cocarcinogen, and 13 found no evidence that saccharin produced cancer.

Studies show saccharin induced cancer

Two studies--FDA and Wisconsin Alumni Research Foundation Institute studies--showed that some test animals exposed to saccharin in utero developed cancer (see p. 9).

FDA's study was designed to evaluate the effects, especially carcinogenicity effects, of long-term feeding of sodium saccharin to rats. The study involved feeding sodium saccharin to six groups of rats--each half male and half female--at 0, .01, .1, 1, 5, and 7.5 percent of their diets, respectively. Their offspring were divided into 6 groups of 48 males and 48 females each, and these groups were fed at the same levels as their parents. The study report stated that after the offspring on the 5 and 7.5 percent sodium saccharin diets were weaned, the males weighed up to 20 percent less and the females up to 29 percent less than the weaned male and female control rats, respectively. The feeding was terminated after about 28 months and the offspring which had not died or been killed during that period were killed.

The tissues from the offspring in the FDA study were microscopically evaluated by a consulting pathologist. None of the offspring he examined which survived 23 months or less had bladder tumors. However, bladder tumors were reported in offspring surviving over 23 months--6 of 23 males and 2 of 31 female offspring fed sodium saccharin at the 7.5 percent level had malignant bladder tumors; 1 of 21 male offspring fed saccharin at the 5 percent level and 1 of 25 male offspring on a saccharin-free diet had malignant bladder tumors.

An April 9, 1974, final pathology report on the FDA study

noted that the carcinogenicity of sodium saccharin for the bladder of rats was clearly demonstrated and that the potency of sodium saccharin as a carcinogen "appears to be of a low order of magnitude." He added that the cancer might be due to sodium saccharin, o-toluenesulfonamide, a combination of sodium saccharin and OTS, OTS and other impurities acting together, or a combination of sodium saccharin and all of its impurities.

In the WARF study, 160 rats were exposed to sodium saccharin in utero. After birth the rats were divided equally into four feeding level groups, each half male and half female. Sodium saccharin was fed to these groups at 0, .05, .5 and 5 percent of their diet for 100 weeks. The study report showed that 7 of 20 male rats on the 5 percent feeding level had malignant bladder tumors and that 1 of 20 male rats on the .5 percent feeding level had a precancerous type of bladder tumor. No malignant bladder tumors or precancerous type of bladder lesions were found in any other rats.

Study shows saccharin may be a cocarcinogen

A study by the Middlesex Hospital Medical School, London, England, used 4 groups of 50 rats each. Two groups of rats were given daily 2 grams per kilogram of body weight of free saccharin in their drinking water and two control groups were placed on a saccharin-free diet. After 6 weeks, one group of rats fed saccharin and one group of the control rats were given a single dose of N-methyl-N-nitrosourea (a known bladder carcinogen when administered in several doses) directly into the bladder. Twelve rats were killed from each group during the first 56 weeks of the study. Five of the 12 rats administered saccharin and N-methyl-N-nitrosourea had bladder tumors; none of the rats in the other groups had tumors. According to an interim status report published in June 1973, the study showed that saccharin is cocarcinogenic with a single dose of N-methyl-N-nitrosourea. According to FDA records, a final report on this study had not been published as of June 30, 1976.

Studies reporting no saccharin-related cancer

We reviewed 13 long-term animal feeding studies which reported no saccharin-related cancer findings. Except in one case, these studies differed from those which showed cancer in that the test animals had not been given saccharin in utero. In four of these, including the in utero study, test animals were on diets containing less than 5 percent saccharin,

the level of feeding at which cancer findings had been noted in other studies. In the other nine studies the test animals were on diets containing saccharin at various levels including 5 percent.

The validity of the results from six of the nine studies appears questionable. According to the reports on three studies conducted by FDA, the Institute of Cancer Research of London, England, and Boots Pure Drug Company, Ltd., of Nottingham, England, not all bladders of the test animals were microscopically examined. The National Cancer Institute guidelines for carcinogen studies in small rodents point out that microscopic examination of organ tissues is required to identify and provide a description of each type of tumor encountered in a study group. The 1970 Academy report to FDA stated that few test animals in the FDA and the Boots Pure Drug Company, Ltd., studies survived to the end of the study, thus, reducing the credibility of their results.

Another study, conducted by Litton Bionetics for the National Cancer Institute, was designed to insure that sufficient numbers of test animals survived 24 months to allow maximum time for possible tumor induction. During the 18th week of the study, however, many of the test animals died from heat prostration, limiting the number of animals surviving 24 months.

In the remaining two studies, conducted by the Bio-Research Consultant, Inc., for the National Cancer Institute, some dead animals were discarded without autopsy and severe disintegration of tissues or cannibalism often occurred before dead animals were discovered. In a preliminary report on the Litton-Bionetics and Bio-Research studies, the National Cancer Institute stated that: "The number of animals assigned to each test group * * *, while adequate to detect potent carcinogens, is not sufficient to detect small increases in cancer incidence."

MUTAGENICITY STUDIES

Mutagenicity studies are designed to determine if a substance causes mutations. A mutation is any heritable change such as a chemical transformation of an individual gene which may alter its functions or a rearrangement of the structure of or a gain or loss of parts of a chromosome.

We identified eight saccharin mutagenicity studies reported since 1970. Five of these tested sodium saccharin,

while the remaining studies tested free saccharin, calcium saccharin, and ammonium saccharin. A report from one of the eight studies raised questions about possible mutagenicity. Reports from the other seven raised no such questions.

The report for one study, which was conducted by the Osmania University of India, indicated that "a statistically significant number" of embryo deaths occurred in female mice mated with male mice which had been fed sodium saccharin. The study report stated that: "The results suggest the mutagenic potential of sodium saccharin and warrant more careful consideration of its use * * *." Four mutagenicity study reports--one on free saccharin by Stanford Research Institute and three on sodium saccharin, calcium saccharin, and ammonium saccharin by Litton Bionetics--concluded that the four substances were not mutagenic.

FDA's Genetic Toxicology Branch assessed the data on the Stanford and Litton Bionetics studies and stated in a May 1973 memorandum to FDA's Bureau of Foods, Director of Division of Toxicology, that it could only agree with the conclusion of the Stanford study that free saccharin was not mutagenic.

According to the Chief of the Genetic Toxicology Branch, the Litton Bionetic studies indicated that sodium, calcium, and ammonium saccharin might be gonadotoxic (poisonous to reproductive organs) and mutagenic because the studies indicated that pregnancies decreased and early fetal deaths increased in female rats mated to males fed the saccharin salts.

As a result of the questions raised by the Litton Bionetics studies, on June 29, 1973, FDA contracted with the Stanford Research Institute to test sodium saccharin, the predominant type of saccharin on the market. In its November 1974 report to FDA, Stanford concluded that sodium saccharin was not mutagenic. FDA contracts for mutagenic studies on calcium and ammonium saccharin have been awarded and results are expected by June 1977.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATION

CONCLUSIONS

In February 1972 the Food and Drug Administration published for saccharin and its three salt forms an interim food additive regulation because certain animal study results raised questions about their potential to cause cancer. Additional animal study data has since raised similar questions concerning saccharin's safety. The question of saccharin's carcinogenicity is not expected to be resolved before mid-1978.

Allowing an interim food additive regulation to remain in effect for several years while safety questions concerning the additive are being resolved seems contrary to FDA's intent of permitting use of such additive for a limited period. Extended use of a food additive, such as saccharin, whose safety has not been established and for which a question of carcinogenic potential has been raised could expose the public to unnecessary risk.

Moreover, permitting, under the interim regulation, the continued use of saccharin at the same level used as a generally-recognized-as-safe substance, with a safety factor of 30 to 1 rather than the conventional 100 to 1, seems questionable. Potential hazards from the use of saccharin could be further minimized by reducing the levels of o-toluenesulfonamide in saccharin to the lowest level practically achievable under present manufacturing technology.

Because saccharin has been used under an interim food additive regulation for about the past 4 years and because safety questions about it are not expected to be resolved for about 2 more years, FDA should reevaluate the justification for saccharin's continued use pending resolution of the safety questions.

RECOMMENDATION

We recommend that the Secretary, Department of Health, Education, and Welfare, direct the Commissioner, FDA, to promptly reassess (1) the justification for continued use of free saccharin and its three salt forms under the interim food additive regulation and (2) the need for issuing a permanent regulation or possibly discontinuing their use in food.

If continued use under the interim regulation is justified, consideration should be given to the need for increasing the safety factor to the conventional level set forth in FDA's regulations and to reducing the permissible levels of OTS in saccharin to the lowest achievable levels.

CHAPTER 6

SCOPE OF REVIEW

We reviewed legislation, regulations, and practices relating to the Food and Drug Administration's regulation of food additives; examined FDA records relating to the past and present regulatory status of saccharin; and reviewed reports of scientific studies on the safety of saccharin.

We also obtained information from officials of FDA, Rockville, Maryland, and Washington, D.C.; the National Academy of Sciences, Washington, D.C.; the United States International Trade Commission, Washington, D.C.; the National Soft Drink Association, Washington, D.C.; the Sherwin Williams Corporation, Cleveland, Ohio; the Calorie Control Council, Atlanta, Georgia; Health and Welfare, Canadian Government, Ottawa, Canada; and other organizations.

Our review of the regulatory status was confined primarily to the period since 1972 when FDA restricted saccharin's use in foods by establishing an interim food additive regulation. We reviewed reports on scientific studies initiated or reported during or after 1970.

SCIENTIFIC STUDIES RELATED TO THE SAFETY OF SACCHARINDISCUSSED IN THIS REPORT

<u>Title</u>	<u>Date reported</u>	<u>Author(s) or Investigator(s)</u>	<u>Type of saccharin used</u>
Metabolism studies:			
1) Saccharin Metabolism in Macaca Mulatta [Rhesus Monkeys]	July 1971	Pitkin, Andersen, Reynolds and Filer, Jr.; University of Iowa Hospital, Iowa City, Iowa, and University of Illinois at the Medical Center, Chicago, Illinois	free saccharin
2) Placental Transmission and Fetal Distribution of Saccharin (note a)	Sept. 1971	Pitkin, Reynolds, Filer, Jr. and Kling; University of Iowa Hospital, Iowa City, Iowa, and University of Illinois at the Medical Center, Chicago, Illinois	free saccharin
3) Metabolic Fate of Saccharin in the Albino Rat	Apr. 1972	Kennedy, Fancher, Calandra, and Keller; Industrial Bio-Test Laboratories, Inc., Northbrook, Illinois, and Monsanto Company, St. Louis, Missouri	free saccharin and sodium saccharin
4) The Metabolism of Saccharin and the Related Compounds in Rats and Guinea Pigs	July 1972	Minegishi, Asahina, and Yamaha; National Institute of Hygienic Sciences, Tokyo, Japan	free saccharin
5) The Metabolism of Saccharin in Laboratory Animals	June 1973	Byard and Golberg; Albany Medical College of Union University Albany, New York	sodium saccharin
6) The Excretion and Metabolism of Saccharin in Man. I. Methods of Investigation and Preliminary Results	June 1973	McChesney and Golberg; Albany Medical College of Union University Albany, New York	free saccharin
7) Saccharin: Distribution and Excretion of a Limited Dose in the Rat (note a)	Oct. 1973	Matthews, Fields and Fishbein; National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, N. Carolina	free saccharin
8) Excretion and Metabolism of Saccharin in Man. II. Studies with 14 C-Labeled and Unlabeled Saccharin	Apr. 1974	Byard, McChesney, Golberg, and Coulston; Albany Medical College of Union University, Albany, New York	sodium saccharin
9) The Metabolism of Saccharin in Animals (note a)	Jan. 1975	Lethco and Wallace; Food and Drug Administration	sodium saccharin

APPENDIX I

APPENDIX I

<u>Title</u>	<u>Date reported</u>	<u>Author(s) of investigator(s)</u>	<u>Type of saccharin used</u>
Long-term feeding studies:			
1) A Comparison of the Chronic Toxicities of Synthetic Sweetening Agents	Nov. 1951 (reevaluated 1970)	Fitzhugh, Nelson, and Frawley; Food and Drug Administration	free saccharin
2) Feeding Studies on Sodium Cyclamate, Saccharin, and Sucrose for Carcinogenic and Tumour-promoting Activity	Apr. 1970	Roe, Levy, and Carter; Institute of Cancer Research, Royal Cancer Hospital, London, England	free saccharin
3) Carcinogenic and Teratogenic Aspects of Saccharin	Aug. 1970	B. Lessel; Boots Pure Drug Co., Ltd., Nottingham, England	free saccharin
4) Long Term Saccharin Feeding in Rats (note b)	1973	Wisconsin Alumni Research Foundation Institute, Inc.; Madison, Wisconsin	sodium saccharin
5) Chronic Toxic Research towards the Carcinogenicity and Teratogenicity of Cyclamate, Saccharin, and their mixture (notes c and d)	Mar. 1973	Verschuuren, Kroes, Peters, and van Esch; National Institute Public Health, Netherlands	sodium saccharin
6) Carcinogenicity of Chemicals Present in Man's Environment	Jan. 1973	B.M. Ulland; Litton Bionetics, Inc., Bethesda, Maryland (National Institutes of Health contract)	free saccharin
7) Studies on Saccharin and Cyclamate (in rats)	May 1973	Bio-Research Consultants, Inc.; Cambridge, Massachusetts (National Institutes of Health and National Cancer Institute contract)	sodium saccharin
8) Studies on Saccharin and Cyclamate (in mice)	May 1973	Bio-Research Consultants, Inc.; Cambridge, Massachusetts (National Institutes of Health and National Cancer Institute contract)	sodium saccharin
9) Sodium Saccharin: Combined Chronic Feeding and Three-Generation Reproduction Study in Rats (note b)	May 1973	Friedman and Taylor; Food and Drug Administration	sodium saccharin
10) Co-carcinogenic Action Saccharin in the Chemical Induction of Bladder Cancer (note d and e)	June 1973	Hicks, Wakefield, and Chowanic; Middlesex Hospital Medical School, London, England	free saccharin
11) Long-Term Toxicity Study of Sodium Cyclamate and Saccharin Sodium in Rats	undated	Ikeda, Horiuchi, Furuya, Kawamata, Kaneko, and Uchida; National Institute of Hygienic Sciences, Tokyo, Japan	sodium saccharin
12) Chronic Toxicity of Sodium Saccharin: 21 Months Feeding on Mice	undated	National Institute of Hygienic Sciences; Tokyo, Japan	sodium saccharin
13) Lack of Carcinogenic Effects of Cyclamate, Cyclohexylamine, and Saccharine in Rats	1973	D. Schmöhl; Heidelberg, Germany	free saccharin
14) Long-Term Administration of Artificial Sweeteners to the Rhesus Monkey (note d)	1975	Coulston, McChesney, and Golberg; Albany Medical College of Union University, Albany, New York	sodium saccharin
15) A Chronic Study of Artificial Sweeteners in Syrian Golden Hamsters	1975	Althoff, Cardesa, Pour, and Shubik; The Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, Nebraska	free saccharin
16) Carcinogenicity Study of Commercial Saccharin in the Rat	June 1975	Munro, Moodie, Krewshi, and Grice; Health Protection Branch, Health and Welfare, Canada	sodium saccharin

APPENDIX I

APPENDIX I

<u>Title</u>	<u>Date reported</u>	<u>Author(s) or investigator(s)</u>	<u>Type of saccharin used</u>
Mutagenicity studies:			
1) Induction of Dominant Lethals in Mice by Sodium Saccharin (note f)	Apr. 1972	Rao and Qureshi; Osmania University, India	sodium saccharin
2) Study of Mutagenic Effects of Saccharin (Insoluble)	Apr. 1972	Newell and Maxwell; Stanford Research Institute Menlo Park, California (Food and Drug Administration contract)	free saccharin
3) Summary of Mutagenicity Screening Studies	Nov. 1972	Litton Bionetics, Inc.; Bethesda, Maryland (FDA contract)	ammonium saccharin
4) Summary of Mutagenicity Screening Studies	Nov. 1972	Litton Bionetics, Inc.; Bethesda, Maryland (FDA contract)	calcium saccharin
5) Summary of Mutagenicity Screening Studies	Nov. 1972	Litton Bionetics, Inc.; Bethesda, Maryland (FDA contract)	sodium saccharin
6) Dominant Lethal Test in the Mouse for Mutagenic Efforts of Saccharine	Apr. 1973	Machemer and Lorke; Institute for Toxicology, Bayer, Germany	sodium saccharin
7) Study of Mutagenic Effects of Sodium Saccharin	Nov. 1974	Newell, Jorgenson, and Simmon; Stanford Research Institute, Menlo Park, California (FDA contract)	sodium saccharin
8) Progress Report: Study of Mutagenic Effects of Sodium Saccharin	Jan. 1975	I. Oster; Bowling Green State University, Bowling Green, Ohio (FDA contract)	sodium saccharin

a/Study indicated possible accumulation of free or sodium saccharin in body tissues.

b/Study showed sodium saccharin induced cancer.

c/Title is in Dutch and our translation of it may not be exact.

d/Interim study report.

e/Study showed free saccharin is a cocarcinogen.

f/Study showed that sodium saccharin is potentially mutagenic.