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Food and Drug Administration's Regulation of Food Additives.
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Testimony before Sen. Gaylord Nelson, Chairman, Senate Select
Committee on Small Business; by Gregory J. Ahart, Director,
Human Resources Div.

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Authority: Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301;
21 U.S.C. 348). 21 C.F.R. 121.1(k).

Reviews of color and food additives--Red No. 2,
saccharin and aspartame--included (1) the history of FDA's
regulation, (2) the current status of testing, and (3) whether
the regulatory actions taken complied with the appropriate act.
Red No. 2, the name of dye generically known as amaranth which
meets FDA composition and purity specifications, has been under
suspicion for 15 years as being possibly carcinogenic or toxic
to the reproductive system. Under existing law, action should
have been taken 1 1/2 years after being placed on the
provisional list, but extensions were granted. Red No. 2 was
finally banned in January 1976. FDA limited saccharin use,
because of initial studies indicating possible adverse effects.
No final proof has been obtained. Aspartame, an artificial
sweetener, never was put on the market because of outside
objections to it and discovery of a possible carcinogen in its
makeup, but it did cause its manufacturer's testing procedures
to be questioned and found faulty. The initial regulation for
marketing aspartame has been stayed, but final resolution has
not been made. Continued use of saccharin under the interim food
additive regulation should be justified, and, if justified,
should be used at the conventional level of 100 to 1, rather
than the present 30 to 1, with the level of toluenesulfonamide
decreased. All agencies responsible for protecting the public
from carcinogens should cooperate to develop a uniform policy
for identifying and regulating carcinogenic chemicals and for
allowing public exposure to carcinogens. FDA should be required
to have all approved and proposed food additives tested for
carcinogenicity. (SS)

00521

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STATEMENT OF
GREGORY J. AHART, DIRECTOR, HUMAN RESOURCES DIVISION
BEFORE THE
SENATE SELECT COMMITTEE
ON SMALL BUSINESS
on
FOOD AND DRUG ADMINISTRATION'S
REGULATION OF FOOD ADDITIVES

Mr. Chairman and Members of the Committee, we are pleased to appear here today to discuss our reports on the Food and Drug Administration's (FDA's) regulation of three color and food additives--Red No. 2, saccharin and aspartame. In addition we have issued a report to the Congress on chemical carcinogens including food additives and we have recently initiated a broad scale review of FDA's regulation of food additives. We will discuss these also.

Our reviews concerning the three additives were directed primarily toward developing information on (1) the history of FDA's regulation of them, (2) the current status of testing the safety of the additives, and (3) whether the regulatory actions taken by FDA on the three additives complied with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended (21 U.S.C. 301).

REGULATION OF RED NO. 2

Red No. 2 is the name given to a certified lot of the dye generically known as amaranth. The composition and purity of amaranth varies. FDA has established composition and purity specifications that amaranth must meet before it can qualify for use in food, drugs, and cosmetics. Only amaranth meeting such specifications is classified as Red No. 2.

Since July 12, 1960, the Color Additive Amendments to the FD&C Act have required FDA to establish regulations listing color additives that are safe for use in food, drugs, or cosmetics. Such regulations may list color additives for use generally in food, drugs, or cosmetics or may prescribe the conditions under which the color additives may be safely used.

The act provides that a color additive is deemed unsafe and should not be listed in a regulation permitting its use in food, drugs, or cosmetics if it is found by FDA to induce cancer in man or animal.

The FD&C Act, as amended in 1960, placed all color additives commercially established at that time, including Red No. 2, on a provisional list to allow their use for a reasonable period until their safety could be reviewed and regulations for their use could be issued. The 1960 amendments provided that the provisional listing was to terminate no later than 2-1/2 years from the effective date of enactment (July 12, 1960), or January 12, 1963. The amendments also provided, however, that FDA could postpone the termination date if such action was consistent with the objective of carrying to completion, in good faith, as soon as reasonably practicable, the scientific investigations necessary for making a determination as to the additives' safety.

We found that FDA had permitted the use of Red No. 2 in food, drugs, and cosmetics for 15 years without making a final determination of its safety. FDA postponed termination of the provisional listing for Red No. 2, 14 times on the basis of requests from manufacturers or industry associations to allow completion of scientific investigations concerning its safety.

Since 1970 several scientific studies involving animals, including some performed or sponsored by FDA, raised questions concerning the safety of Red No. 2 in food. In some of these studies Red No. 2 or amaranth was shown in test animals to be toxic to reproductive systems or to be carcinogenic.

Because of its concern about the safety of Red No. 2, FDA in July 1972 issued a proposal to limit human exposure to the color additive. However, at the time our report was issued on October 20, 1975, FDA had not made a final determination regarding its safety.

Because we believed that continued use of Red No. 2 before resolving its safety exposed the public to unnecessary risk, we recommended that the Secretary of the Department of Health, Education, and Welfare (HEW) direct the Commissioner of FDA to promptly establish the safety of Red No. 2 or prevent its use in food, drugs, and cosmetics.

On January 19, 1976. FDA announced a ban on the use of Red No. 2 in food, drugs, and cosmetics. FDA took the action because new evidence showed that Red No. 2 caused a statistically significant increase in the number of malignant tumors in test animals and because of what it termed "the absence of other data to allow a definitive judgment of safety."

REGULATION OF SACCHARIN

In our report on saccharin we pointed out that saccharin was "generally recognized as safe" for use in food until about 1970 when studies raised questions about its potential to cause cancer in test animals.

Saccharin is an acid and pure saccharin 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.

The FD&C 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 by qualified scientists must be approved by FDA.

Food additives "generally recognized as safe" are referred to as GRAS substances. Such substances added to food are not considered food additives and are exempt from the requirement for FDA approval.

Saccharin's safety not established

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 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 removed saccharin and its various salt forms from the GRAS status and issued an interim food additive regulation limiting the use of saccharin in foods.

The interim regulation stated that preliminary results from studies on long-term feeding of saccharin to animals conducted by FDA and others indicated "possible adverse effects." According to the regulation, if the experimental findings indicate that continued use of saccharin poses 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 and for certain technological purposes such as reducing bulk and enhancing flavors in chewable vitamin tablets. This authority for saccharin's use was to expire June 30, 1973.

However, on May 25, 1973, FDA issued a Federal Register notice extending saccharin's interim regulation indefinitely. The Federal Register identified several completed or nearly completed long-term feeding studies made of three different animal species. These study results showed a statistically significant incidence of bladder tumors in the male offspring of test animals fed saccharin.

The Federal Register indicated that these studies were referred to the National Academy of Sciences for review and that a final determination of saccharin's safety would be made after FDA received recommendations from the Academy. In December 1974 the Academy submitted

to FDA its report on the safety of saccharin which pointed out problems with the studies and concluded that existing studies had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." The Academy recommended that certain additional studies be made to resolve the question of whether saccharin is carcinogenic or otherwise unsafe in the human diet.

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."

Safety factor used for
saccharin questionable

The level of saccharin allowed in food under FDA's interim food additive regulation is based on a safety factor of 30 to 1 rather than the conventional 100 to 1 safety factor. Use of a safety factor less than 100 to 1 for saccharin, which was removed as a GRAS substance

because questions were raised about its potential to cause cancer, seems questionable.

In determining whether the proposed use of a food additive is safe, the FD&C Act (21 U.S.C. 348(c)(5)(C)) requires FDA to consider safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data. FDA's regulations provide that except where evidence is submitted which justifies use of a different safety factor, 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.

We believe that 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 regulations.

Impurities in saccharin
should be limited to
lowest achievable levels

We noted also that the levels of o-toluenesulfonamide (OTS), an impurity in saccharin with possible cancer-causing potential, was not being limited to the lowest level achievable under present manufacturing technology. FDA limits the level of OTS to 100 parts per million. We were told that this limit was established in 1974 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.

According to a 1974 National Academy of Sciences report to FDA, impurities in saccharin, especially OTS, may have been the possible cause of the bladder tumors observed in certain studies.

Technology advancements have since made it possible to reduce the levels of OTS in saccharin to less than 50 parts per million and as low as 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.

Conclusions and recommendations

We believe that 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 FIA's intent of permitting use of such additive for a limited period. Potential hazards from the use of saccharin could be further minimized by applying the conventional 100 to 1 safety factor and by reducing

the levels of OTS 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 soon, we recommended that the Secretary of HEW direct the FDA Commissioner to promptly reassess

- the justification for continued use of free saccharin and its three salt forms under the interim food additive regulation and
- the need for issuing a permanent regulation or possibly discontinuing their use in food.

We also recommended that if continued use under the interim regulation is justified, consideration 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.

On December 10, 1976, HEW advised us that the FDA Commissioner had reassessed the justification for the interim listing of saccharin for use as a food additive. He concluded that continuation of the interim listing was appropriate. On January 7, 1977, FDA published two notices concerning saccharin. One extended the interim regulation to permit saccharin's continued use until Canadian studies on its safety are completed and evaluated. The other notice proposed to amend the interim food additive regulation to establish a tolerance of 25 parts per million for toluenesulfonamide. FDA does not believe a change in the safety factor is necessary.

REGULATION OF ASPARTAME

Our third report concerned aspartame, an artificial sweetener that was developed by G. D. Searle and Company.

On February 9, 1973, Searle submitted to FDA a petition proposing the issuance of a food additive regulation to provide for the use of aspartame in foods. The petition included general information on the characteristics and specifications of aspartame, its proposed uses, and summaries of scientific animal and human studies regarding its safety.

After reviewing the petition, FDA considered certain aspects of the animal study data submitted in support of aspartame's safety to be incomplete and suggested to Searle that the petition be withdrawn unless the issues could be promptly resolved. Searle submitted additional support data and on July 26, 1974, FDA published a regulation approving the use of aspartame in certain foods.

Objections filed against aspartame

The FD&C Act provides that individuals adversely affected by a food additive regulation may object and request a formal public hearing. FDA received three statements of objection relating to the aspartame regulation. One statement raised objections to a labeling requirement for cold cereals containing aspartame but did not contain a request for a hearing. The other

statements raised questions about the possibility of aspartame causing brain damage in infants and young children and requested a hearing to resolve those questions.

After reviewing the objections FDA considered the uses of aspartame authorized by the regulations safe but recognized there was a difference of opinion and agreed to convene a hearing to address the safety issues raised by the objectors.

Plans to convene a hearing were suspended, however, as subsequent testing data submitted by Searle indicated that diketopiperazine (DKP), a manufacturing byproduct in aspartame, could be carcinogenic. FDA did not take regulatory action to prevent the marketing of aspartame because Searle and General Foods Corporation, a co-marketer, voluntarily agreed to withhold it from the market until DKP's carcinogenic potential was resolved.

FDA questions data
submitted by Searle

Besides aspartame, Searle also manufactures a number of drugs which FDA has approved for marketing. In July 1975 FDA raised questions about Searle's performance of animal experiments and its reporting of safety data to FDA concerning two drugs--flagyl, used to treat infections and aldactone, an antihypertension drug. Because of the importance and sensitivity of these

questions, the FDA Commissioner, on July 23, 1975, established a task force to

- review the practices followed by Searle in conducting animal experiments, analyzing the experiments' data, and submitting the data to FDA;
- determine if there is evidence that any practices of Searle in carrying out the above functions violated the FD&C Act or any other laws of the United States; and
- recommend an appropriate course of action based on the investigation's findings.

FDA officials said that the investigation was directed primarily toward evaluating drug data submitted to FDA since 1968. They stated that the review of aspartame data was included as part of the investigation, however, because (1) of the additive's recent approval, (2) of its potential for wide use in foods, and (3) its inclusion would provide a broader product base to evaluate Searle's practices.

Aspartame regulation stayed

Preliminary results of the task force investigation indicated possible discrepancies in the data and the research summaries submitted to FDA supporting aspartame's safety. On December 5, 1975, FDA stayed the regulation approving the use of aspartame.

In joint hearings held on January 20, 1976, before the Senate Subcommittees on Health and on Administrative Practice and Procedure, Committees on Labor and Public Welfare, and the Judiciary, the FDA Commissioner disclosed preliminary task force findings. He stated that 11 studies submitted supporting the food additive petition for aspartame had been reviewed and numerous problems had been noted. These problems included poor methods of distribution and identification of control and treated animals, poor records of weighings, poor animal husbandry practices, discrepancies between Searle's pathology sheets and pathology summaries submitted to FDA, and problems in the design of some of the studies. The Commissioner stated that a final decision on whether to revoke the regulation approving the use of aspartame would be made after the task force had officially completed its investigation and added that aspartame would not be permitted to be marketed until all questions about its safety had been aired and resolved.

An FDA Bureau of Foods official told us that as of January 1, 1977, no decision had been made on whether to revoke the regulation.

TESTING FOOD ADDITIVES
FOR CARCINOGENICITY

In addition to these reports, we issued a report to the Congress on June 16, 1976, on Federal efforts to protect the public from cancer-causing chemicals.

In this report we discussed the need for a Federal policy concerning carcinogens. Federal agencies have problems accepting and applying the results of animal tests to people because (1) the National Cancer Institute has only recently developed minimum testing guidelines for determining a chemical's carcinogenicity and other agencies have not officially adopted the guidelines as a basis for carcinogenicity testing and (2) there are no scientific principles to help Federal agencies apply animal test results to humans. As a result, some carcinogens are not regulated at all while others are regulated differently by the various regulatory agencies. All agencies responsible for protecting the public from carcinogens should, we believe, cooperate to develop a uniform policy for identifying and regulating carcinogenic chemicals and the products in which they appear. The policy should also deal with such issues as the conditions under which regulatory agencies will allow public exposure to carcinogens.

We pointed out in the report that under the FD&C Act the safety of certain products and substances, including food additives, is to be assured before they are approved for commercial use. We found that in some cases, however, they did not receive the kind of long-term tests that experts agree are needed to detect cancer-causing potential.

According to officials in FDA's Division of Food and Color Additives, all intentional food additives must receive long-term tests to detect carcinogenicity before FDA will approve them. Intentional additives are to (1) improve nutritional value, (2) maintain freshness, (3) improve esthetic appeal, or (4) aid in processing.

Unintentional additives are used mainly in packaging foods and, according to the FDA officials, receive long-term testing only when the consumer would be exposed to more than 1 or 2 parts per million of the additive in the food unless FDA had valid reasons to suspect that the additive might be carcinogenic. FDA officials explained that the long-term tests were expensive, and because virtually none of the unintentional additives migrate from the packaging material to the food, the amount of the additive which may be ingested is virtually nil. FDA's principle in this regard is the higher the anticipated human exposure, the greater the amount of toxicological data required to assure human safety.

According to an April 1970 report to the Surgeon General
by the Ad Hoc Committee on the Evaluation of Low Levels
of Environmental Chemical Carcinogens

--no level of exposure of a chemical carcinogen
should be considered toxicologically insignificant
for humans and

--no chemical substance should be assumed safe
for human consumption without proper negative
lifetime biological assays of adequate size.

HEW said that, although extending carcinogenicity
testing to unintentional food additives that have only
remote possibilities of risk might be reassuring, it
did not foresee any benefit to the public great enough
to justify the substantial costs of such a policy.

We do not agree that FDA can assure safety for
unintentional additives when the additive migrates to
the food and leaves a residue of less than 1 or 2 parts
per million. Based on the Ad Hoc Committee's criteria,
we do not believe that FDA can assure that all food additives
are safe unless the additives receive carcinogenicity
testing.

Accordingly, we recommended that the Secretary,
HEW, require FDA to have all approved and proposed food
additives tested for carcinogenicity.

CURRENT GAO WORK

Because our work to date on food additives has pointed out certain problems concerning the regulation of food and color additives, we have recently initiated a broad survey of FDA's programs to regulate these additives. During this survey we will attempt to determine whether current legislation and FDA regulatory practices adequately protect consumers with respect to substances which are added to food.

Mr. Chairman, that concludes my prepared statement. We will be pleased to answer any questions that you or other members of the Committee may have.