BY THE COMPTROLLER GENERAL

Report To The Congress

OF THE UNITED STATES

Need For More Effective Regulation Of Direct Additives To Food

The Federal Food, Drug, and Cosmetic Act requires that the safety of direct food additives be based on scientific evidence and that the evidence be reviewed and approved by the Food and Drug Administration. However, the act exempts from review and approval substances generally recognized as safe by "experts" or approved for use before 1958 and allows the safety determination for some of those substances to be based on experience drawn from common use in food. The safety of several of these exempted substances, including saccharin, cyclamate, and nitrite, has been questioned.

GAO recommends that the Congress amend the law to eliminate the exemptions and that the Secretary of Health and Human Services publish regulations establishing criteria and guidelines for assessing the safety of additives. Regulations listing substances affirmed as generally recognized as safe should be revised to indicate the kinds of evidence that support their safety.

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

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To the President of the Senate and the
Speaker of the House of Representatives

This report discusses the need to amend the Federal Food, Drug, and Cosmetic Act to eliminate regulatory exemptions currently allowed for certain categories of substances directly added to food. The act now exempts from Federal safety review and approval substances generally recognized as safe or sanctioned for use before 1958 and allows safety determinations for some to be based on experience drawn from common use in food. The Food and Drug Administration, Department of Health and Human Services, and the Department of Agriculture are responsible for administering the activities discussed in this report.

Our work in this area followed reviews of the Food and Drug Administration's regulation of several specific substances added to food including, saccharin and FD&C Red No. 2. These reviews had identified several regulatory requirements and administrative practices that we believed warranted closer examination.

We are sending copies of this report to the Director, Office of Management and Budget; the Secretary of Health and Human Services; and the Secretary of Agriculture.

Comptroller General
of the United States

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COMPTROLLER GENERAL'S
REPORT TO THE CONGRESS

NEED FOR MORE EFFECTIVE REGULATION OF DIRECT ADDITIVES TO FOOD

D I G E S T

The Federal Food, Drug, and Cosmetic Act does not provide for uniform regulation of all substances added directly to food, and the Food and Drug Administration (FDA) needs to give the public and industry more information about its regulation of direct additives.

Substances defined by the Act as "food additives" must be approved by FDA after a review of scientific evidence supporting their safety. However, approximately 1,450 substances categorized as generally recognized as safe (commonly referred to as GRAS) or prior sanction (approved before 1958) are exempted from FDA review and approval.

The act provides that the safety determination for a substance used before 1958 can be based on either scientific procedures or experience from common use in food, if the substance was considered GRAS by qualified experts. The determination of safety for a GRAS substance whose use began after 1958 must be based on scientific procedures, but the basis for that determination does not have to be reviewed and approved by FDA before the substance's use.

As a result, safety determinations for many substances used in food before 1958 are based on experience from common use in food, and safety determinations made for most GRAS substances placed in use after 1958 have not been reviewed and approved by FDA.

Tear Sheet. Upon removal, the report cover date should be noted hereon.

FDA's administrative regulations do not clearly define the scientific evidence needed to support the safety of a food additive or explain how it conducts safety assessments. In addition, FDA's regulations, which list some substances it has evaluated and affirmed as GRAS, do not distinguish among the different kinds of evidence which support each substance's safety affirmation. Such evidence can range from history of use to the same scientific evidence required for food additives.

SAFETY OF ALL ADDITIVES NOT BASED ON SCIENTIFIC EVIDENCE

Experience from common use in food has questionable value in assuring that an additive is safe. Over a long period, individuals are exposed to numerous substances, including environmental contaminants, and adverse effects from exposure to harmful substances may not occur for many years.

The safety of three widely used substances--saccharin, cyclamate, and nitrite--has been questioned because of their potential cancer-causing effects. In addition, FDA has taken or is considering regulatory action against at least 50 other substances. Action has been taken to remove 16 substances from the GRAS list because of a lack of scientific or history of use data to support their safety. FDA has also issued food additive regulations establishing maximum safe levels of use for 34 other substances which it has determined can no longer be considered GRAS.

Several Government and private organizations have recognized that a history of safe use is not an adequate basis for determining a substance's safety. They generally believe that history of use data should be considered as only preliminary evidence and not as proof of safety over a lifetime of consumption. (See pp. 8 to 16.)

FDA NOT REQUIRED TO ASSESS THE SAFETY OF ALL ADDITIVES

About 800 substances have been designated as GRAS and are available for use in food without official recognition in FDA regulations. Experts making the designations are not required to notify FDA before the substances' use. An FDA official believes, however, that most of the 800 were first used in food after 1958 and thus their safety should be based on scientific evidence.

Since FDA is not required to review and approve GRAS designations, there is no assurance that consistent criteria are applied in determining the safety of all such substances. In 1971 FDA published regulations requesting the voluntary submission of petitions for GRAS substances. After reviewing each of these petitions, which is to contain the scientific evidence supporting the designation, FDA determines whether it can issue a regulation affirming the substance's GRAS status.

As of October 1979, FDA had received 39 petitions for GRAS substances first used after 1958 and had completed its review of 18. Only 4 of the 18 contained sufficient scientific evidence to support a GRAS affirmation. Substances included in two other petitions were issued food additive regulations that established maximum safe levels of use. FDA denied 1 petition, and 11 were withdrawn by the petitioners. (See pp. 16 to 18.)

SCIENTIFIC ASSESSMENTS USED TO ESTABLISH SAFETY NOT DEFINED

FDA has not published regulations that clearly define the scientific evidence needed to support the safety of a food additive or the criteria it uses to evaluate such information.

The law requires that, before a food additive can be approved for use, a petition must be submitted to FDA containing reports of scientific investigations showing that the substance is safe. While FDA regulations outline the safety information that should be submitted with petitions and the general principles the agency uses in evaluating such information, they do not define the methods and controls appropriate for conducting scientific tests or the criteria the agency uses in evaluating an additive's safety.

During 1978 FDA received 14 petitions formally requesting that food additives be approved. As of October 1979, the agency had not approved or published regulations for any of these substances. GAO's review of 7 of the 14 petitions disclosed that in each case FDA had determined that the scientific evidence supporting the substance's safety was inadequate and had requested additional evidence. In five cases, FDA requested data that were not specifically identified in its regulations.

Within the last few years, FDA has recognized the need to develop and publish definitive scientific testing guidelines and review criteria for determining the safety of food substances, and developmental efforts are underway. Several groups--including the Federal Interagency Regulatory Liaison Group, the Food Safety Council, and the Flavor and Extract Manufacturers' Association--have published their own guidelines or criteria. (See pp. 25 to 30.)

REGULATIONS DO NOT DISTINGUISH BETWEEN LEVELS OF EVIDENCE THAT SUPPORT GRAS AFFIRMATIONS

FDA regulations provide that, for the FDA Commissioner to conclude that a substance is GRAS, its safety must be based on the

same quantity and quality of scientific evidence required as support for food additives or may be based on its history of use, if it was used before 1958.

As of October 1979, FDA had issued final GRAS affirmation regulations for 24 substances. GAO reviewed 15 of these substances and found that only 2 had been subjected to the same type of scientific tests FDA considers necessary for a food additive. The number of scientific tests conducted on the other 13 varied widely. The regulations do not distinguish between the different levels of evidence that support these substances' safety. (See pp. 30 to 33.)

RECOMMENDATION TO THE CONGRESS

The Congress should amend the Federal Food, Drug, and Cosmetic Act to eliminate exemptions for GRAS and prior sanction substances. Changes to the law should provide enough flexibility to encourage the use of information already available and to recognize that different types of scientific evidence may be appropriate to support the safety of food additives. The amendment should also provide a date on which the safety of all GRAS and prior sanction substances must be subject to Federal review and approval.

RECOMMENDATIONS TO THE SECRETARY OF HEALTH AND HUMAN SERVICES

The Secretary should direct the FDA Commissioner to:

--Publish regulations establishing review criteria for assessing the safety of food additives and issue guidance defining the methods and controls to be used in conducting scientific safety tests.

--Revise regulations which list substances that FDA has affirmed as GRAS to indicate the kinds of evidence that support their safety.

AGENCY COMMENTS

The Department of Health and Human Services agreed that the regulation of GRAS and prior sanction substances is an important issue and said it is investigating ways to deal with this complex subject. The Department did not believe, however, that it would be in the public interest to include a mandated time frame for implementing congressionally enacted revisions. The Department indicated that given the large number of ingredients to be tested, constraints on testing, and the current rapid growth of scientific knowledge, it is unlikely that full implementation could be accomplished on a predictable schedule. GAO believes that establishment of a time frame would help ensure that priority is given to this effort.

Regarding the need for better FDA control over the regulation of direct additives to food, the Department said it has drafted protocols and criteria for evaluating tests of additive safety which will be published in scientific literature and the "Federal Register."

The Department did not agree, however, that regulations which list substances FDA has affirmed as GRAS should recognize the different levels of evidence that support their safety because of the volume of information that would be involved. GAO believes that regulations can be published which provide the public with a simple and clear indication of the safety data which FDA uses in affirming a substance as GRAS.

The Department of Agriculture agreed with GAO's recommendations; however, it emphasized the need for gradual implementation of legislative changes to avoid disruptions within the food industry and to permit orderly scientific assessment.

The Departments' comments are discussed on pages 23, 24, 35, and 36 and are included as appendixes I and II.

Contents

		Page
DIGEST		i
CHAPTER		
1	ADDITIVES: BENEFITS, RISKS, AND REGULATION	1
	Why are additives used?	1
	How are additives shown to be safe?	2
	Regulation of food additives	4
2	LEGISLATIVE CHANGES NEEDED TO PERMIT MORE EFFECTIVE REGULATION OF SUBSTANCES ADDED TO FOOD	8
	History of use as a criterion for safety determinations should be eliminated	8
	Status of post-1958 GRAS additives not reviewed and approved	16
	Suggested legislative changes	18
	Conclusions	21
	Recommendation to the Congress	23
	Agency comments and our evaluation	23
3	REGULATIONS NEED TO DEFINE AND DISTINGUISH BETWEEN LEVELS OF SCIENTIFIC EVIDENCE	25
	Scientific assessments required for food additive safety not publicly defined	25
	Safety of substances affirmed as GRAS supported by differing levels of evidence	30
	Conclusions	34
	Recommendations to the Secretary of HHS	34
	Agency comments and our evaluation	35
4	SCOPE OF REVIEW	37
APPENDIX		
I	Letter dated June 20, 1980, from the Inspector General, HHS	38
II	Letter dated July 3, 1980, from the Administrator, Food Safety and Quality Service, USDA	42

ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GRAS	generally recognized as safe
HHS	Department of Health and Human Services
NAS	National Academy of Sciences
NAS/NRC	National Academy of Sciences-National Research Council
USDA	U.S. Department of Agriculture

CHAPTER 1

ADDITIVES: BENEFITS, RISKS, AND REGULATION

Many consumers prefer to buy foods that are ready to serve or easy to prepare. Modern technology has accommodated consumers by developing a wide range of foods that can be prepared quickly.

As the demand for convenience foods and the knowledge of food improvement and preservation have grown, so has the use of additives. The number of additives used intentionally in food increased from about 1,900 in 1970 to about 2,700 in 1979.

WHY ARE ADDITIVES USED?

Some additives prevent or delay food spoilage. Salt, sugar, vinegar, and spices have been used many years for this purpose. However, modern science has developed new preservatives, such as sodium and calcium propionate, which retard the growth of bread molds, and BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole), which retard the spoilage of fats and fatty foods. Additives can also prevent certain illnesses related to food spoilage, such as nitrite's prevention of botulism food poisoning. Foods containing such additives can be transported over greater distances and stored for longer periods.

Other additives improve the nutritive value of certain foods. By helping to ensure that the average diet contains the minimum recommended daily allowance of vitamins and minerals, they help to eliminate and prevent certain diseases attributable to malnutrition. For example, vitamin D added to some dairy products and infant foods has practically eliminated rickets, while enrichment of bread, cornmeal, and cereals has helped eliminate pellagra, a condition caused by niacin deficiency that affects the skin, alimentary tract, and nervous system.

Additives, which include a variety of spices and natural and synthetic flavors, can also enhance the taste of many foods Americans enjoy. Some additives (emulsifiers) improve the texture, homogeneity, and overall quality of food by permitting two or more different liquids to mix completely.

Others stabilize and thicken to give uniform textures and flavors as well as the desired consistency.

Food costs can also be reduced by using certain additives. For example, using sodium benzoate to preserve some beverages eliminates the need for more expensive preservation processes, such as heating or freezing. Sulfite, an antioxidant, is used to prevent potatoes from turning brown during certain food processing steps that require dehydration.

Additives are also used to retain moisture, increase volume, harden, dry, color, leaven, prevent foaming, sweeten, cream, whip, sterilize, prevent sticking, and propel foods from pressurized cans.

According to a 1973 report of the President's Science Advisory Committee, the total per capita annual use of these additives was about 139 pounds. Of this usage, table sugar constituted 102 pounds; salt, 15 pounds; and corn syrup, 13 pounds.

Usage levels for some of the additives that make up the other 9 pounds were infinitesimal. For example, iodized salt contains only 0.2 ounce of potassium iodide for each 100 pounds of table salt. Nevertheless, even at these levels of use, it is important that the safety of such additives be established, since they may be toxic in small amounts when consumed over long periods of time.

HOW ARE ADDITIVES SHOWN TO BE SAFE?

Since consumers are exposed to numerous additives over a lifetime, most in small amounts, questions about their safety do not generally revolve around a clear, immediate, and easily identifiable threat to the public health, but rather relate to potential health effects from long-term use at low exposure levels.

Until about 20 years ago, additives could be used in food if they were not poisonous or deleterious to health. Most substances were determined to be safe based on history of use rather than scientific tests. The adequacy of the tests that were conducted varied considerably in the absence of incentives for manufacturers to improve their quality. Current law requires, however, that the determination of an additive's safety be based upon scientific procedures. Scientific procedures include conducting experimental studies of the effects, if any, a substance has on humans or animals.

The ideal subject in which to study the safety of additives for human consumption is a human being; however, experiments in which humans are intentionally exposed to a substance of unknown safety and monitored for health effects are rarely conducted because of the risk. Epidemiology studies that evaluate health effects in humans after exposure to a specific substance can also be used to evaluate safety. For example, cancer deaths in groups of diabetics have been studied to determine if there is a relationship between saccharin use and bladder cancer. In most safety studies, however, animals are substituted for human beings, since their cell and tissue responses to toxic substances are similar to humans.

Animal studies enable toxicity testing of a substance under controlled experimental conditions, using the animal specie, dosage, and method of administration which most nearly duplicates human exposure. Effects from exposure to such a substance are followed over time by periodically killing the animals and examining their organs and tissues. Several groups of animals may be used in the experiment with one or more not exposed to the substance, thus serving as a control group. A wide range of health effects can be evaluated depending on the study's design and length.

Acute or short-term animal tests provide a relatively rapid and inexpensive means of establishing a substance's level of short-term toxicity, tracing the movement of a chemical in the body, examining the body's disposition of the chemical, and evaluating changes in body processes and functions, including reproduction, resulting from its use. Such tests include acute toxicity, metabolism, mutagenicity (potential to cause hereditary changes), and reproductive studies.

Chronic or long-term tests are more expensive to conduct, but must be used to detect carcinogens (cancer-causing substances) or other toxic substances that show effects only after long periods at low exposure levels. These tests, which cost about $500,000 each, generally involve one generation of small animals, from conception to death, such as rats or mice, which have lifetimes of 2 to 3 years. Such tests approximate human exposures of more than 70 years.

When a substance is shown to produce an adverse effect in exposed animals, the information must be converted to an estimate of possible human risk. Since uncertainties remain as to how data from animals can be extrapolated to humans,

several long-term studies are usually conducted, using different animal species, thereby increasing the confidence level of reported findings.

An October 1977 U.S. Office of Technology Assessment report that discusses testing for carcinogenic potential states:

> "Animal tests are the best current method for predicting the carcinogenic effect of substances in humans. All substances demonstrated to be carcinogenic in animals are regarded as potential human carcinogens; no clear distinctions exist between those that cause cancer in laboratory animals and those that cause it in humans."

REGULATION OF FOOD ADDITIVES

The Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et seq.), as amended on September 6, 1958, by the Food Additives Amendment (21 U.S.C. 321(s), 342(a) (2)(c), and 348), requires the Food and Drug Administration (FDA) to establish regulations for substances that are used in food and are defined as food additives. With certain exceptions discussed on page 6, the act defines a food additive as

> "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food * * *."

The act (21 U.S.C. 348(b)) provides that any person may file a petition with FDA proposing the issuance of a regulation prescribing the conditions under which a food additive may be safely used. A petition must contain:

--The name and all pertinent information concerning the food additive, including where available, its chemical identity, and its composition.

--A statement of the conditions of the additive's proposed use, including all directions, recommendations, and suggestions for its proposed use, and specimens of its proposed labeling.

--All relevant data on the physical or other technical effect the additive is intended to produce and the quantity of the additive required to produce such effect.

--A description of practicable methods for determining the quantity of the additive in or on food and any substance formed in or on food because of its use.

--Full reports of investigations made about the additive's safety, including full information on the methods and controls used in conducting the investigations.

FDA may initiate, on its own, a proposal to issue a food additive regulation.

In determining whether a proposed use of a food additive is safe, FDA is required (21 U.S.C. 348(c)) to consider

--the probable consumption of the additive and of any substance formed in or on food through use of the additive;

--the cumulative effect of the additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in the diet; and

--safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data.

FDA must also determine that the food additive accomplishes the effect for which it is to be used--for example, preservatives must preserve.

The act states that no food additive shall be deemed safe, if it is found to be carcinogenic when ingested by man or animal, or if it is found, after tests which are appropriate for evaluating food additive safety, to induce cancer in man or animal. This provision is commonly known as the Delaney Clause. Under this provision, once a food additive in use has been shown, based on adequate scientific analysis, to induce cancer when ingested by man or animal, it must be banned.

After FDA's review of the petition shows it contains all the data prescribed in the act, FDA is required to publish in the "Federal Register" a notice of the food additive regulation proposed by the petitioner. FDA then evaluates such data, and if it determines the substance is safe, the agency must publish in the "Federal Register" a final regulation that describes the proposed uses of the additive and conditions under which it may be safely used. Within 30 days after publication of this regulation, persons adversely affected by it may file objections and request a public hearing which could result in the amendment or revocation of the regulation.

Two categories of substances which are exempt from the food additive provisions of the act are:

1. Prior sanction--Substances used in food in accordance with sanctions or approvals granted by FDA or the U.S. Department of Agriculture (USDA) before enactment of the Food Additives Amendment of 1958.

2. Generally recognized as safe (GRAS)--Substances which "experts qualified by scientific training and experience" have generally recognized as safe when used as intended in food. The basis for such findings may be (1) scientific evidence or (2) in the case of substances used before January 1958, either scientific evidence or experience based on common use in food. These findings can be made by any qualified expert and GRAS substances can be used in food without FDA approval.

When the Food Additives Amendment was enacted, there was much confusion over which direct substances should be considered GRAS. In response, FDA published regulations in the "Federal Register" that contained a partial listing of substances it considered to be GRAS. FDA's first regulation, published in November 1959, listed 168 substances. As of June 1979, 623 GRAS substances had been listed. FDA's regulations list neither substances, such as vinegar, sugar, and salt, that are recognized as GRAS by most everyone nor numerous substances that have been designated GRAS by experts from the food additives' industry but not officially recognized by FDA.

FDA's Bureau of Foods is responsible for establishing regulations, performing safety evaluations, and administering other provisions of the act relating to food additives and other substances used in food. Most of these activities are performed at the agency's headquarters in Washington, D.C., and Rockville, Maryland.

This report does not deal with the regulation of color additives. Our review also did not cover the regulation of substances which get into food indirectly through production methods, manufacturing processes, or packaging (indirect food additives).

CHAPTER 2

LEGISLATIVE CHANGES NEEDED TO PERMIT MORE EFFECTIVE REGULATION OF SUBSTANCES ADDED TO FOOD

The FD&C Act does not provide for uniform regulation of all substances added directly to foods. For substances defined as food additives, the act requires FDA to review scientific evidence of safety and to approve their use before they can be added to foods. Substances categorized as GRAS and prior sanction are exempted under the act from prior FDA review and approval.

Prior sanction substances were approved before September 6, 1958, and their use in food was allowed to continue based on those approvals and a continuing history of safety. The act also exempted GRAS substances used before 1958 from the food additive provisions by stating that their safety could be based on scientific evidence or experience from common use in food. The safety of substances designated GRAS after 1958 was required to be based on scientific evidence; however, such designations could be made by any qualified experts. Thus, newly developed substances can be designated GRAS by such experts and used in food without prior FDA review and approval.

Approximately 1,450 of about 2,700 substances FDA knows are added directly to food are GRAS and prior sanction substances. Because of legislative exemptions, most GRAS and prior sanction substances have not been subjected to the same safety review procedures required for issuing a food additive regulation and the adequacy of the evidence which supports their safety has been questioned by some government and private organizations.

HISTORY OF USE AS A CRITERION FOR SAFETY DETERMINATIONS SHOULD BE ELIMINATED

The FD&C Act requires that, before a direct food additive can be marketed, FDA must establish regulations prescribing the conditions under which it may be safely used. Any person may file a petition with FDA proposing the issuance of such a regulation and submit scientific evidence supporting the substance's safety. FDA is required to issue a food additive regulation, if it determines that the evidence submitted supports the safety of the proposed use.

The FD&C Act permits the safety of GRAS substances used in food before January 1, 1958, to be based on scientific procedures or experience from common use in food. FDA regulations (21 CFR 170.30) interpreting this provision state that experts qualified by scientific training and experience may base general recognition of safety for substances in use before 1958 on a history of use without requiring the quality and quantity of scientific procedures needed for approval of a food additive regulation. The regulations further provide that safety "shall ordinarily be based upon generally available data and information."

We could not determine the exact number of GRAS substances which were used before 1958. The branch chief, Division of Food and Color Additives, Bureau of Foods, who has responsibility for reviewing the safety of GRAS substances, stated that the agency does not know the total number of such substances since the law allows any qualified expert to make GRAS designations. He and another official of his division stated that many of these substances were GRAS because their history of use did not disclose any adverse effects. GRAS substances are preservatives, emulsifying agents, nutrients, food sweeteners, and perform other functions.

In addition other substances used before 1958 were granted prior sanction approval by USDA and FDA. The Federal Meat Inspection Act of 1907 (21 U.S.C. 601 et seq.) and the Poultry Products Inspection Act of 1957 (21 U.S.C. 451 et seq.) authorized the Secretary of Agriculture to inspect and otherwise regulate the processing and distribution of meat and poultry products to ensure that they were free of adulteration when delivered to consumers. In accordance with these legislative authorities, the Secretary prescribed regulations which approved the use of substances in the preparation of meat and poultry products to ensure that these products were not adulterated.

The FD&C Act of 1938 (21 U.S.C. 342) provided that food would be deemed adulterated if it contained any poisonous or deleterious substance which may render it injurious to health. FDA used this authority before 1958 to sanction the use of certain substances in food.

The purpose of the prior sanction category exemption in the Food Additives Amendment was to permit continued use of such substances in food after 1958 without requiring scientific testing. After 1958 no substance was to be granted prior sanction status.

USDA sanctioned the use of about 100 substances added directly to meat and poultry and included them in its regulations before September 1958. About 80 of these have since been recognized by FDA as GRAS or regulated as food additives. These substances performed several functions, including color fixing, flavoring, sweetening, and preserving meat or poultry. USDA officials stated that the Department's basis for granting sanctions to many of these substances was a history of use without adverse effects.

FDA, however, did not publish regulations listing the substances which it sanctioned, and we were unable to determine the number of such substances. According to the special assistant to the FDA Commissioner, such substances were not published for fear of violating trade secrets. FDA officials stated that, because the sanctioned substances were not listed in its regulations, and a central file of documents granting the sanctions was never maintained by the agency, it does not know how many substances were actually sanctioned. Also, the special assistant to the FDA Commissioner stated that the safety for many of its prior sanction substances was based primarily on history of use.

History of use is generally no longer considered a sound basis for safety judgments because over a long time individuals are exposed to numerous substances, including environmental contaminants, and any adverse effects from exposure to these substances may not be manifested for many years. Furthermore, it is difficult to conclude that one specific substance may have caused an adverse effect when many substances may be the cause.

The following government and private organizations have recognized the need to reevaluate the safety of prior sanction and GRAS substances used before 1958. These organizations believe that scientific testing rather than history of use should support safety.

In a 1970 report "Evaluating the Safety of Food Chemicals," the National Academy of Sciences (NAS) stated that man is the ideal subject in which to study safety of substances added to food. NAS in its discussions about the use of man in such studies stated:

> "The ultimate assessment of the safety of a food chemical derives from years of widespread consumption by man under given conditions of use. Even here, however, the absence of known

adverse effects does not, by itself, constitute adequate assurance of safety. The possibility always exists of adverse effects that, because of their subtle or slowly developing nature, are not recognized as being caused by the chemical in question."

The President's Science Advisory Committee in its 1973 report "Chemicals and Health," commented on the data used to support the safety of GRAS designations for substances used before 1958 and stated:

"One of the criteria for judgment of general recognition of safety was a record of apparent safety associated with the use of the chemical by the general population. * * * The majority of food additives [referring to GRAS substances] are permitted for use through judgments based on data [history of use] which were considered adequate at one time but must now be ranked as 'preliminary.'"

The director of the Division of Food and Color Additives, Bureau of Foods, stated the agency's position on history of use before an industrial group in 1975. He said that "Toxicity testing has become much more sophisticated and we are now aware that we cannot rely on the lack of reported adverse effects as a sole measure of safety."

In addition, the Federation of American Societies for Experimental Biology, representing 15,000 biological and medical scientists, was awarded a contract by FDA to develop criteria for evaluating the GRAS status of flavoring substances added to food. In a June 1976 report "Criteria for Evaluation of the Health Aspects of Using Flavoring Substances as Food Ingredients," the Federation discussed the evidence which was needed to assess the safety of substances and concluded:

"A long history of use of a food additive [referring to GRAS substances] without evident harm resulting may be useful in setting priorities for detailed toxicological examination; but alone has limited value in providing an adequate assurance of the safety of lifetime consumption."

The Federation, in another report dated October 1977, "Evaluation of Health Aspects of GRAS Food Ingredients: Lessons Learned and Questions Unanswered," which was based upon the Federation's analysis of data used in conjunction with FDA's GRAS review (see p. 31), commented on the quantity of scientific data available to prove the safety of substances in this review. The Federation reported:

> "Only a small fraction of the GRAS substances, * * * are supported by an array of tests that compare with those required for the approval of new food additives."

The Flavor and Extract Manufacturers' Association is the flavor industry's trade organization which has designated numerous substances as GRAS. Its counsel told us that the Association believes it is not necessary for good public health to have chronic toxicity studies made on common food chemicals, such as salt, sugar, vinegar, baking soda, and many other materials that have been in common use for a long time. The counsel noted, however, that if evidence of a question of safety arises concerning a GRAS substance, it is not immune from review.

In 1970, FDA published regulations (21 CFR 170.6) which stated that, in the interest of public health, substances which FDA had previously considered safe and for which it had issued prior sanction approvals must be reexamined in light of current scientific information and current principles for evaluating the safety of the additives if their use was to be continued. These regulations further state that, because of the length of time, FDA may no longer have the documents in its files, which expressed FDA original opinions, and in the absence of such data their safety of use could not be reexamined. For this reason the regulations state that the original opinions about the safety of prior sanction substances are revoked. However, the regulations provide that, if copies of the original sanctions are submitted to FDA, they would be replaced with qualified and current opinions. Agency officials told us that this effort to identify and reexamine the safety of prior sanction substances was not pursued because FDA's chief counsel had reservations about the agency's legal basis for unilaterally revoking prior sanction approvals.

The following GRAS and prior sanction substances' safety, which was originally based on history of use, has been questioned after those substances were subjected to new scientific tests or existing data were reviewed. Three such substances have been widely used.

Saccharin

Saccharin, an artificial nonnutritive sweetener, was initially classified as GRAS based on its use before January 1, 1958. Because certain long-term animal studies questioned the potential for this substance to cause cancer in humans, FDA proposed in 1977 a complete ban on its use in food. Before the ban became effective, the Congress enacted the Saccharin Study and Labeling Act (Public Law 95-203) in 1977 imposing an 18-month moratorium (ended May 23, 1979), on the proposed ban to study existing data, gather new information, and consider the impact of the ban. This act required mandatory warning labels on all saccharin-containing foods shipped in interstate commerce after February 21, 1978.

Under authority of the act, a contract to study the saccharin data was awarded to NAS and it concluded in a 1979 report that, based on available scientific information, saccharin has the potential to cause cancer in humans. The report stated that most study committee members believed that there should not be a total, immediate ban on the use of saccharin because of its potential benefits in managing diabetes and obesity and in preventing tooth decay. However, because the large number of persons exposed to saccharin justifies a serious continued public health concern, these committee members believed that its use should not be freely allowed without special labeling. All members agreed that FDA should take action to educate users as to saccharin's risks and encourage the search for an alternative artificial sweetener.

On June 17, 1980, the President signed legislation (Public Law 96-273) which further extends the moratorium on FDA's proposed ban of saccharin until June 30, 1981. According to FDA's Deputy Associate Commissioner for Public Affairs, the agency, during the moratorium, will continue its evaluations of findings from three recently completed epidemiology studies--especially a $1.5 million bladder cancer study performed by the National Cancer Institute, National Institutes of Health, whose findings were published in early 1980. In our August 16, 1976, report (HRD-76-156), we discussed the need to resolve safety questions on saccharin.

Cyclamate

Cyclamate, an artificial nonnutritive sweetener, was first manufactured and used in food in the early 1950s. Since saccharin alone left a bitter aftertaste with some

people, cyclamate was often used in combination with saccharin to combat that effect. In 1959, FDA determined cyclamate to be GRAS and included it in the agency's regulations as such a substance. However, in October 1969 after several scientific studies showed that cyclamate could cause adverse health effects, FDA issued a regulation which stated that the substance could no longer be regarded as GRAS and banned its use in food.

In November 1973, a major producer of cyclamate submitted a petition to FDA requesting that the substance be regulated as a food additive. FDA denied the petition in October 1976 on the basis that the scientific evidence did not establish that cyclamate was safe for its intended uses. Subsequently the petitioner requested a public hearing. An administrative law judge has reviewed the case twice, and in September 1978 and February 1980 decisions stated that the petition should be denied on the basis that cyclamate has the potential to cause harm. The February 4, 1980, decision states that evidence presented "tends to increase the likelihood that cyclamate is a carcinogen." The judge concluded that

> "In view of the evidence of the potential carcinogenicity of cyclamate, the evidence of record will not support the requisite finding that its safety has been established."

According to the FDA official responsible for processing the cyclamate petition, the final ruling on approval or denial of the petition will be made by the FDA Commissioner.

Nitrite

Nitrite is classified by USDA as a prior sanction substance when used to fix colors and preserve meat and meat products, including bacon. This sanction was initially granted in 1925, and according to a department official, the safety of nitrite was based on its history of use. In addition, FDA has issued food additive regulations permitting the use of nitrite as a preservative and color fixative in fish and home-cured meats, poultry, and wild game and as a botulism toxin inhibitor during the commercial processing of smoked chub fish.

Nitrite's safety was first questioned in the late 1960s when scientists found that it combined with certain other chemicals in food to form nitrosamines, a compound known to cause cancer in test animals. However, it was not until the

1970s that two FDA-sponsored long-term scientific feeding studies raised the possibility that nitrite, alone, may cause cancer in laboratory rats.

As a result of these findings, FDA and USDA were faced with two kinds of health risks. First, if nitrite is omitted from food, botulism toxin, a deadly poison, is more likely to form in food. Secondly, if nitrite is added to food, the public may be exposed to a potential cancer-causing substance. In an attempt to solve these risk problems, in 1978, FDA developed a plan, with USDA concurrence, for gradually phasing out nitrite's use. This plan was contingent upon confirmation of the scientific validity of the two long-term feeding studies. In response to the Department of Health and Human Services (HHS) 1/ request for a legal opinion on the phaseout plan, the Department of Justice concluded on March 30, 1979, that such a plan is not permissible under FD&C Act's Delaney Clause which, it stated, does not permit a delay in removing from food any substance found to cause cancer.

On this same date, the Secretaries of HHS and Agriculture announced their intention to propose legislation which would prevent banning nitrite until May 1, 1980, and after that would permit nitrite's use in food to be phased out if the findings of the two studies are confirmed. As of June 30, 1980, this or similar legislation had not been enacted.

FDA efforts to confirm the validity of the two studies are currently being performed by a private contractor, and FDA should complete its work by mid-1980. On January 31, 1980, we reported (HRD-80-46) on FDA and USDA efforts to to regulate nitrite, including the conduct and evaluation of the two FDA-sponsored studies.

Other additives

Nordihydroguaiaretic acid (NDGA) is another GRAS substance whose use was later prohibited because of safety issues. It was included in FDA's 1959 GRAS list as a food preservative. In April 1968, after evaluating the Canadian

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1/On May 4, 1980, the Department of Health, Education, and Welfare was abolished and two departments--the Department of Education and the Department of Health and Human Services--were created. The Department of Health and Human Services is responsible for the FDA activities discussed in this report.

Government's ban on NDGA's use in food and other relevant data, FDA determined that the substance could no longer be classified as GRAS and issued regulations removing it from the GRAS list. The regulations stated that the substance was being reclassified as a food additive, and indicated that, before further use could be permitted, a petition must be submitted supporting the substance's safety and a food additive regulation authorizing its use would need to be issued.

As a result of FDA's GRAS review (see p. 31), the agency has taken or is considering regulatory action against at least 50 other GRAS substances because they can no longer be regarded as GRAS. FDA has initiated or completed regulatory action to remove at least 16 substances from its GRAS list because there was no scientific or history of use data to support their safety. FDA regulations provide that future use of these substances in food is contingent on the submission of scientific evidence of safety. FDA has also issued food additive regulations establishing maximum safe levels of use for 34 other substances which it has determined can no longer be considered GRAS.

STATUS OF POST-1958 GRAS ADDITIVES NOT REVIEWED AND APPROVED

The safety of GRAS substances initially used after 1958 must be supported by scientific evidence, the same as required for food additives. However, the support for these GRAS substances does not have to be submitted to FDA for its review and approval. Qualified experts can review this evidence and designate the substance as GRAS. The term qualified experts and the level of scientific training and experience needed for one to be considered an expert has not been defined.

The FD&C Act (21 U.S.C. 321(s)) provides that a substance first used in food after 1958 can be designated as GRAS, if its safety is based on adequate scientific evidence and if it is generally recognized safe among experts qualified by scientific training and experience to evaluate an additive's safety. Authority for making GRAS designations rests not only on FDA, but under the act's provisions qualified experts may designate a substance as GRAS. The act does not define what an expert is, the level of scientific training and experience needed for one to be considered an expert, or what scientific evidence experts may use in making a GRAS designation. Furthermore, the act does not require that such experts inform FDA of the evidence supporting the designation or that the agency review and approve the evidence before a substance's use in food.

Of the approximately 1,430 substances which FDA has identified as GRAS, about 800 have been given this designation and are available for use in food without those designations being officially recognized in FDA regulations. Over 450 of the 800 substances are flavors which the Flavor and Extract Manufacturers' Association had determined safe and had designated as GRAS. While we were unable to determine how many of the 800 GRAS substances were given this designation since 1958, the director of the Division of Food and Color Additives, Bureau of Foods, told us that he believes most of these are post-1958 GRAS designations and that their safety should be supported by scientific evidence.

Because the act does not state the level of scientific training and experience expected of qualified experts who designate a substance as GRAS and does not define the scientific evidence required to support a substance's safety, no central control exists over these substances. Central control would allow for the establishment of criteria to be used in determining the safety of these substances and would require that all GRAS substances meet the same safety standards.

FDA attempted to establish better control over the safety of GRAS substances in 1971, when it published administrative regulations (21 CFR 170.35) establishing a voluntary review and affirmation procedure for GRAS substances. A GRAS affirmation, like a food additive approval, is initiated by the FDA Commissioner or by a petition from an interested party. The regulations require FDA to publish in the "Federal Register" a notice requesting public review and comment on proposals to affirm GRAS substances after which the agency must review the various data, including evidence of safety for these substances. Following this review, FDA is required to publish regulations affirming the GRAS status of these substances or notices that they must be considered food additives and be subjected to section 348 of the act.

As of October 31, 1979, FDA had received 75 petitions from parties requesting the agency to affirm as GRAS, substances added directly to food. Thirty-nine of these petitions concerned post-1958 GRAS substances whose safety was required to be supported by scientific evidence. As of October 31, 1979, FDA had completed its review of 18 of these petitions and has published GRAS affirmation regulations for 4 substances and food additive regulations establishing maximum safe levels of use for 2 other substances. For the other 12 petitions, FDA's review disclosed that insufficient

scientific evidence was included in the petitions to support the substances' safety, causing the agency to deny 1 petition because the substance could not be affirmed as GRAS or approved as a food additive. Petitioners voluntarily withdrew the other 11 petitions from further FDA consideration when they were requested to submit additional information.

FDA's refusal to affirm these substances as GRAS under its own criteria does not in itself prevent their continued use in food because industry can establish its own criteria for making GRAS designations. However, if a manufacturer persists in marketing a substance that FDA does not consider GRAS, the agency can initiate an enforcement action in Federal court to remove it from commerce. FDA must prove, however, that the substance is not GRAS.

Since manufacturers and users are not obligated to submit GRAS affirmation petitions to FDA, the number of petitions that were withdrawn by petitioners or denied by FDA compared to the total number submitted is significant. The fact that these petitions were voluntarily submitted would seem to indicate that petitioners believed the safety of these substances was properly supported and FDA's safety affirmation would be a routine procedure. When FDA found the scientific evidence to be insufficient and requested additional evidence, however, petitioners withdrew their petitions.

FDA's findings that the safety of these substances was not properly supported is also important, since it indicates that scientific evidence which some experts are willing to use in making GRAS designations may not meet FDA's standards. Legitimate differences of opinion can occur in the evaluation of scientific evidence, and some experts may be willing to accept less scientific evidence of safety than FDA considers adequate.

SUGGESTED LEGISLATIVE CHANGES

Because questions have arisen about differences in additive regulation, private and government organizations have expressed concern about the need to amend the present FD&C Act. These organizations have suggested changes to the act which would require all substances added directly to food to be regulated consistently.

The Federation of American Societies for Experimental Biology reported in October 1977 on the GRAS review (see p. 31) that, if another round of reviews of the affirmed GRAS substances occurs, toxiological testing should be performed on substances marketed after completion of this review similar to that required for new food additives. The report stated that the Federation looked

> "* * * forward to the disappearance of the term, GRAS, from the regulatory vocabulary by the year 1990, as heralding the full implementation of a single completely integrated system for insuring the safety of all commercially added food ingredients."

NAS in its March 1, 1979, report on food safety policy authorized by the Saccharin Study and Labeling Act stated that the FD&C Act places substances into different classifications, which serve to focus regulatory attention on certain types of food substances to the neglect of others. The report noted that substances defined as food additives must be tested for safety and approved individually while many other food substances remain unregulated.

NAS' report recommended the following legislative changes:

--Abolish the differences in the statutory standards among categories of substances.

--Create a single standard for food safety regulation applicable to all food substances.

--Provide FDA with authority to assess the risk of all substances in the food supply. The assessment process must incorporate contemporary science and technology as their most reliable source of information, especially since rapid changes in scientific knowledge and procedures may enhance recognition of previously unknown risks.

The FDA Commissioner established a Food Safety Policy Task Force in October 1978 to fully explore a broad range of issues in connection with food safety policy and formulate new food safety legislation to be considered by the Congress. The Commissioner's special assistant, chairman of this effort, told us that the task force is considering, among other things, whether GRAS and prior sanction substances

should continue to be exempt from the food additive provisions of the FD&C Act. According to the special assistant, the major effect of eliminating this exemption would be to require that scientific tests be performed on GRAS and prior sanction substances to determine their safety.

The special assistant said, however, that performing scientific tests on all GRAS and prior sanction substances equal to those required for food additives is not feasible due to the lack of laboratory facilities. He said that FDA would have difficulty justifying from a logical point of view the expenditure of a large amount of its resources to conduct tests on substances that have been declared GRAS or granted sanctions and are currently used in food with apparently no harmful effects.

The special assistant stated that scientific testing of all such substances could be partially overcome through the use of information already available to FDA. He said that the agency has determined the safety of certain substances and affirmed them as GRAS. These substances could automatically be transferred to food additive status. For other GRAS substances, FDA, through a computer matching process, could compare the composition and uses of these substances with already regulated food additives. GRAS substances which are found to be similar to food additives could be transferred to food additive status. Also he said that there were other substances which because of their multiple uses in food were approved as prior sanctions and were regulated as food additives. These substances could be regulated as food additives based on the petitioned safety evaluations. The other GRAS and prior sanction substances, which he believed to be a relatively small number, would need to be individually tested for safety. He stated that, while he believes any new legislation should set a time limit for the regulation of all substances as food additives, he believes that FDA should be permitted to determine how best to accomplish that task.

The special assistant stated that FDA had forwarded legislative suggestions to the Secretary of HHS concerning amendment of the food additive provisions of the FD&C Act. However, we were told that there has not been any proposed legislation drafted on this subject as of February 29, 1980.

Several bills to amend the FD&C Act were introduced during the first session of the 96th Congress. Proposed changes included allowing FDA to consider benefits and risks when approving food additives rather than basing such approvals

on risks alone, requiring that approvals based on benefit be considered by an advisory committee of experts, deleting the Delaney Clause from the act, and permitting the continued use of saccharin and nitrite in food. However, these bills did not propose that GRAS and prior sanction substances added directly to foods should be subjected to the food additive provisions of the act.

CONCLUSIONS

The FD&C Act should be amended to require that the food additive provisions apply to all substances added directly to food. Such a change should state the period in which scientific testing, evaluation, and issuance of food additive regulations for GRAS and prior sanction substances must be completed.

Permitting the continued use of GRAS and prior sanction substances whose safety was based on history of use may have been necessary in 1958 to avoid a sudden disruption of the food supply when the Food Additives Amendment was enacted. However, continued acceptance of history of use as the sole basis for safety determinations does not seem appropriate in view of current concerns about additive safety and advances in safety evaluation methods. The need for legislative authority to require that substances be subjected to scientific tests is demonstrated by safety questions about such substances as saccharin, cyclamate, and nitrite.

While the safety of additives first used after 1958 must be based on scientific evidence, they can be designated as GRAS by qualified experts without governmental review or approval of such evidence. The food additive provisions of the law should be amended to require FDA to review safety evidence for all GRAS substances. Such a change would ensure the use of consistent criteria in determining the safety of these substances.

We recognize that increasing FDA's regulatory responsibilities concerning food additives may appear contrary to the current trend of reducing, wherever possible, government regulation and control over the marketplace. We also recognize that the additional testing, review, and regulatory requirements placed on industry and FDA by such a change in the law will inevitably add costs. We did not attempt to assess the economic impact of the changes we propose. However, we believe a procedure, such as suggested by the special assistant to the FDA Commissioner (see p. 20), which uses information

already available to the agency for determining the safety of GRAS and prior sanction substances, would make the impact of amending the FD&C Act less costly because the number of new scientific tests could be significantly reduced.

We believe that FDA's food additive regulatory responsibilities need to be expanded for several reasons. First, the public's exposure to such substances has greatly increased since the 1958 amendment was passed because their use has allowed the development of convenience foods demanded by the present day eating habits of most Americans. Secondly, current legislative provisions allow more than half of the direct additives to food to be used without FDA review and approval of their safety. Qualified experts can designate a substance to be GRAS using whatever safety criteria they believe are appropriate. There is no requirement that the same safety criteria be applied by all experts making such designations.

Third, virtually everyone consumes food which contains additives, and that consumption can extend over a lifetime. Even small risks associated with these substances are magnified when exposure extends over long periods. Fourth, consumers who are exposed to additives cannot reasonably provide their own protection since the knowledge and resources necessary to determine safety are difficult and costly to develop and the large number of additives in use makes it extremely difficult, if not impossible, for consumers to educate themselves about each additive. It, therefore, should be the responsibility of the Federal Government to provide food additive protection.

Finally, several substances not subjected to FDA safety review and approval under the FD&C Act have been found unsafe when subjected to scientific studies. Some, which have been widely used and are well known to consumers, have been or are being removed from use and the evaluation of others is continuing. Thus, we believe all additives should be determined safe by FDA based on scientific data and regulated as food additives under the act.

While our review covered only substances added directly to food and the following recommendation applies only to these substances, we believe a similar conclusion could be reached about the need to amend the FD&C Act as it relates to GRAS and prior sanction substances which get into food indirectly through shipping, manufacturing, or processing steps. Such substances are also exempt from the act's safety review requirements.

RECOMMENDATION TO THE CONGRESS

We recommend that the Congress amend the FD&C Act to eliminate exemptions currently allowed for GRAS and prior sanction substances. Changes to the law should provide for sufficient flexibility to encourage the use of information already available and to recognize that different types of scientific evidence may be appropriate to support the safety of food additives. The amendment should also provide a date on which the safety of all GRAS and prior sanction substances directly added to food must be subject to Federal review and approval.

AGENCY COMMENTS AND OUR EVALUATION

HHS said that the regulation of GRAS and prior sanction substances is an important issue to the Department and that it is investigating alternatives that will deal with this complex issue.

HHS stated, however, that it does not believe that it would be in the public's best interest to include a legislatively mandated time frame for fully implementing revisions the Congress may enact. The Department stated that any implementation plan would be based upon a system of establishing priorities for conducting additive evaluations, testing them according to up-to-date scientific procedures, and publishing regulations regarding their status. HHS concluded that, because of the large number of additives to be tested, the time required for each test, the limited number of toxicity testing facilities available, and the current rapid growth of scientific knowledge, it is unlikely that full implementation could be accomplished on a predictable schedule.

Our concerns about the need to set a time frame in which to implement the proposed regulatory changes stem from a general recognition of the time required to do safety analyses, as HHS has pointed out, and FDA's past performance. For example, the Color Additive Amendments of 1960, which amended the FD&C Act (21 U.S.C. 376), required FDA to establish regulations listing color additives that are safe for use in food, drugs, and cosmetics. Color additives commercially established before July 12, 1960, were allowed to continue in use for "a reasonable period," which was generally defined as no longer than 2-1/2 years pending completion of scientific investigations to determine their safety. FDA has repeatedly extended this interim period for some colors on the basis of requests from manufacturers or industry associations to allow

time to complete safety investigations. The review of some color additives is not expected to be completed until 1981. Twenty-one years does not seem to be "a reasonable period" for completing such scientific investigations, and use of such substances over extended periods could expose individuals to unnecessary risk.

We believe the same situation could occur in regulating GRAS and prior sanction substances as food additives unless the Congress establishes some control over the period of implementation. We recognize that there will be disagreement on whether the Congress should set a date by which legislative changes must be implemented, and on what that date should be. We further believe, however, that the establishment of such a date is desirable for the following reasons.

A specific date would represent a stronger congressional statement on the importance of regulating all substances as food additives. It would establish a time frame in which the mandatory changes must be accomplished, thus setting a level of priority within agency programs. Failure to set a deadline would likely result in a lower priority for such an effort. Establishing a deadline would provide a basis for congressional oversight on the progress of the effort. The agency would be required to gauge and report on progress being made and, if the original date proved to be too optimistic, the Congress would be aware of the reasons. Finally, since the funding for such an effort will be, by necessity, spread over several years, the establishment of a completion date could establish the intent of the Congress to provide the funding necessary to complete the project within the given number of years.

USDA stated that, since eliminating regulatory exemptions for GRAS and prior sanction substances from the FD&C Act could disrupt the food industry, an economic impact evaluation is essential to assess public benefit. However, they generally supported a gradual implementation of the recommended legislative changes to avoid unnecessary disruption and to permit orderly assessment of available scientific evidence.

We recognize that the recommended legislative changes will have an economic impact; however, page 22 discusses the reasons we believe increased regulatory costs are justified.

CHAPTER 3

REGULATIONS NEED TO DEFINE AND DISTINGUISH BETWEEN LEVELS OF SCIENTIFIC EVIDENCE

FDA has not provided the public and industry with sufficient information about its regulation of substances added directly to foods. Regulations which clearly define the scientific evidence needed to support the safety of a food additive have not been published. Furthermore, FDA's regulations affirming substances as GRAS do not distinguish between the different levels of evidence which have been used to support their safety. FDA's failure to communicate such information may have delayed the processing of the seven food additive petitions received by FDA during 1978 that we reviewed, and may give the public an incorrect impression of the level of evidence which supports GRAS affirmations.

SCIENTIFIC ASSESSMENTS REQUIRED FOR FOOD ADDITIVE SAFETY NOT PUBLICLY DEFINED

FDA has not published regulations clearly defining the scientific evidence needed to support a substance's safety or the criteria used in reviewing such evidence for issuing food additive regulations. Although FDA requires that certain scientific safety tests be performed, the agency believes that the safety of each substance should be evaluated separately using the best available assessment guidelines.

The FD&C Act requires that, for substances to be marketed as food additives, reports of scientific investigations must be submitted to FDA in food additive petitions showing that the substance is safe under the conditions of proposed use and describing the methods and controls used in the investigations. The act requires that FDA make a fair evaluation of these investigations to establish that the substances' proposed uses will be safe. In determining whether these uses are safe, the act states that the agency shall consider

> "safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data."

FDA has issued regulations (21 CFR 171.1) outlining the safety information which should be submitted with petitions and the agency's general principles used in evaluating such information. These regulations require that full investigative reports showing that a substance is safe for its intended use be submitted as part of food additive petitions. These reports should include detailed data derived from appropriate animal and other biological experiments in which the methods used and results obtained are clearly set forth. The regulations state that FDA in reviewing the scientific evidence will give full consideration to the specific biological properties of a substance and the adequacy of the methods employed to demonstrate safety for its proposed use, and they will be generally guided by principles and procedures for establishing the safety of a food additive which are set forth in the current publication of the National Academy of Sciences/National Research Council (NAS/NRC).

According to an FDA official, the current NAS/NRC publication is its 1970 report entitled "Evaluating the Safety of Food Chemicals." The report is a review of the general procedures for evaluating the safety of substances added to food. It does not provide definitive guidelines on the scientific tests and evaluation criteria needed to accomplish this objective.

While FDA does not provide petitioners with written definitive guidelines on what scientific evidence is needed to support the safety of a food additive, it informally furnishes this information on an ad hoc basis through correspondence and meetings with petitioners based upon their request for such information, or when FDA finds petitions scientifically inadequate. FDA corresponds individually with petitioners explaining to them what data are needed to complete their petitions.

The branch chief, Division of Food and Color Additives, Bureau of Foods, who has responsibility for controlling the review of a food additive petition, stated that meetings are the primary method used by FDA to communicate what information is required to support a food additive regulation, and they are held before and after submission of most food additive petitions. He said that petitioners who have submitted petitions before will request an early meeting with FDA to

learn what data are required, but parties submitting petitions for the first time rarely request such meetings. Other Bureau of Foods' officials said that there is no established format for such meetings which would assure that all petitioners are furnished the same type of information. They stated, however, that consistency is achieved since experienced agency personnel attend these meetings.

During 1978, FDA received 14 food additive petitions requesting issuance of food additive regulations. As of October 31, 1979, the agency had not approved or published regulations on any of these substances.

We reviewed FDA files for 7 of the 14 petitions and found that in each case the scientific information submitted with the initial petition data was ruled inadequate by FDA to determine the safety of the substances for their proposed use. The agency found that either the quantity of data was insufficient or the quality of scientific studies was unsatisfactory. In each case, FDA requested additional information from the petitioners.

In five of the seven instances the agency requested data not specifically identified in Federal regulations. For example, for each of the five, FDA requested specific data on either the impurities in the additive or the anticipated level of its use. FDA regulations provide no detailed guidance as to what specific data should be submitted.

In addition, in three of the five cases FDA requested that data from a specific kind of animal study be submitted before the petition could be approved. FDA regulations only state that information submitted should include "detailed data derived from appropriate animal and other biological experiments" and do not specify the kind of studies needed.

As of October 31, 1979, FDA had received additional information on one of the seven petitions and was proceeding with its review. The agency had not received any additional information on the other six petitions and had placed them in an inactive status.

FDA has not published regulations establishing review criteria for assessing the safety of food additives. While the agency requires that certain tests be performed to support the safety of food additives, it evaluates each substance's safety on an ad hoc basis. Informal review

criteria are provided to FDA personnel, who are responsible for evaluating evidence that is submitted in support of an additive's safety. These criteria list, according to a substance's proposed use, the type of scientific tests necessary to support additive safety and provide a suggested format for documenting a safety evaluation. The branch chief, Division of Toxicology, Bureau of Foods, who is responsible for evaluating food additive toxicity studies, stated that FDA has provided petitioners with references to publications upon which its informal criteria are based.

This FDA official stated that the agency generally requires as support for direct food additive regulations two core studies--a reproduction/teratogenic study in one rodent specie and a long-term feeding study which includes two different rodent species. In addition, he said that there are preliminary studies--mutagenic, LD50 (Lethal Dose-50--dosage sufficient to kill 50 percent of animals) and short-term continuous feeding--which FDA does not require but which must generally be performed to develop protocols for the core studies. He said that these are minimum requirements in that other studies may be required depending upon the data produced from the preliminary studies or obtained elsewhere.

Within the last few years, FDA has recognized the need to develop and issue definitive scientific testing guidelines and review criteria for determining that substances used in food are safe.

In 1977, FDA's General Counsel presented a paper on toxicology decisions at the First International Congress on Toxicology in which he expressed the need for documenting the rules used in making toxicological evaluations. He stated:

> "If they [government personnel] are in fact applying consistent rules, then those rules obviously can be put in writing. * * * The alternative is to risk quite different rules by each individual toxicologist or government agency, a lack of any knowledge by the regulated industry of the toxicological requirements to be imposed, and a resulting distrust and loss of confidence by the public, legislators, and the courts."

Because of advances in safety evaluation techniques, FDA recognized that conclusions about food additive safety based on earlier scientific studies could not be relied on indefinitely. As a result, in 1977 FDA initiated a cyclic review with the objective of reevaluating the safety of all food additives, flavors and spices, and other substances added directly to food in terms of current safety criteria.

To meet the cyclic review's objectives, FDA formed two committees to develop definitive minimum protocol guidelines for making scientific tests required to support a substance's safety and review criteria to be used in evaluating a substance's safety once the tests are made. FDA is developing minimum scientific test protocol guidelines and plans to make them available to the public on an informal basis. In addition, following an approximately 2-year developmental effort, which included a pilot study of 88 substances to test the feasibility of review criteria, FDA has begun drafting proposed regulations for the cyclic review program. These regulations will be discussed in an advanced notice of proposed rulemaking to be published in the "Federal Register" for public comment in the summer of 1980. While these issuances were prepared specifically in conjunction with the cyclic review, FDA officials stated that these issuances will also apply to the safety review and approval process for new food additives.

The Interagency Regulatory Liaison Group--FDA, the Consumer Product Safety Commission, the Environmental Protection Agency, the Food Safety and Quality Service, USDA, and the Occupational Safety and Health Administration, Department of Labor--was established in August 1977 to improve public health by sharing information, avoiding duplication of effort, and developing consistent regulatory policy. This group recognized that minimum scientific test protocol guidelines were not always uniform among these agencies when testing chemicals for toxicity. In August 1979, the group published draft guidelines in the "Federal Register" which are to be used as a basis for regulations to be published by individual agencies. According to an FDA official, the liaison group's draft guidelines which apply to scientific tests for substances added directly to food are being adopted by FDA.

Two private organizations--the Food Safety Council and the Flavor and Extract Manufacturers' Association--have recognized the need to develop safety review criteria for substances added to food. The Council was organized in 1976 to develop criteria for assessing the safety of food and its additives. It is composed of representatives from government, academic science, consumer organizations, and industry. The Association has also developed criteria which it believes are appropriate in conducting evaluations. Both organizations have recently published their review criteria in technical journals.

In our report on nitrite (see p. 15), we noted that FDA does not have guidelines for design, data collection, and reporting of long-term toxicity studies for determining the safety of food additives. We recommended that FDA develop such guidelines. FDA officials agreed that guidelines can be helpful in designing such studies, but pointed out the difficulty in developing a single set that would receive universal approval by the scientific community.

SAFETY OF SUBSTANCES AFFIRMED AS GRAS SUPPORTED BY DIFFERING LEVELS OF EVIDENCE

FDA regulations listing affirmed GRAS substances do not distinguish between the differing levels of evidence which support their safety. The safety of some substances included in FDA's regulations is supported by scientific evidence similar to that required for food additives, while the safety of others is supported by little more than a history of use.

FDA administrative regulations provide that the FDA Commissioner either on his own initiative or on the petition of an interested person may affirm the GRAS status of a substance. (See p. 17.) These regulations provide that, to be determined as GRAS, a substance's safety must be based on either the same quantity and quality of scientific evidence needed to obtain a food additive regulation, or if the substance was used before 1958, history of use. Recognition of safety through history of use is based on whatever data, including scientific evidence, is generally available.

When new substances are affirmed by FDA as eligible for GRAS status, they are published in the agency's regulations as affirmed GRAS substances (21 CFR 184). Most substances listed in FDA's regulations as affirmed GRAS substances, however, are supported by evaluations made under FDA's GRAS review, and the safety of many of these substances is based on a history of use.

In 1969, FDA banned the use of cyclamate after it was found to cause cancer in test animals. (See p. 13.) Because this substance had been classified as a GRAS item before it was banned, public concern was raised about the safety of all substances which had been designated GRAS. To restore public confidence in the GRAS category, the President, in his 1969 consumer message to the Congress, directed the Secretary of HHS to begin a safety evaluation of GRAS substances.

In 1970, FDA began this evaluation of the safety of GRAS substances. About 350 nonflavor GRAS substances listed in the agency's regulations were selected for the first phase (known as the GRAS review), and of this number about 310 were substances added directly to food. The purpose of the review was to evaluate by current standards all existing safety information about each substance. Since the law exempts GRAS substances from food additive regulation, FDA's review was not intended to evaluate these substances in relation to food additive requirements, but to affirm their GRAS status based on a review of existing literature.

As a result of this review of direct GRAS additives, FDA had published as of October 31, 1979, final GRAS affirmation regulations for 24 substances and proposed affirmed GRAS regulations for an additional 58 substances. FDA has published final food additive regulations which establish maximum safe levels of use for 34 substances, which can no longer be considered GRAS. In addition, the agency published regulations removing the GRAS classification from 21 more substances, 5 of which were permitted to be used temporarily until scientific safety studies were completed. The other substances were prohibited from direct use in food because there was no scientific or history of use data to support their safety. The remaining direct GRAS substances (about 175) were in various stages of review by FDA.

Because the agency had almost no consumption and toxicological data on these substances, and it lacked the staff necessary to develop such information, FDA used contracts to obtain most of the needed data. FDA contracted with NAS to survey the food industry for human consumption data, and several firms were awarded contracts to abstract the world's scientific literature from 1920 to 1973 for each substance. Because many GRAS substances had never been studied for teratogenic and mutagenic effects, a third series of contracts was awarded to test selected GRAS substances to determine the potential for such effects.

In addition, FDA awarded contracts to the Federation of American Societies for Experimental Biology to analyze the accumulated information and to issue advisory opinions on most substances in this review.

FDA instructed the Federation that evidence of adverse effects had to be present in the information available for a GRAS substance before a health hazard could be declared. In response to this instruction the Federation, based upon an evaluation of its performance under the contract, reported in 1977 that:

> "With relatively few exceptions, the available data on GRAS substances are much less than might usually be regarded as desirable. But since the Select Committee [of the Federation] had been asked to make assessments based on whatever information was available, it tried to be responsive whenever there was at least a modicum of evidence."

The Federation found that most GRAS substances' safety was based primarily on history of use, not scientific evidence. Also the Federation reported weaknesses in the quantity and quality of data supplied to it. For example:

--Consumption data were not very reliable because many assumptions were made which usually led to overstatements of use. If a GRAS substance was added to a food in a given category, it was assumed to be added to all substances in that category. For example, a preservative used in a specialty cracker was assumed to be used in all baked goods.

--The teratogenic and mutagenic studies on selected GRAS substances were of little use in the evaluation process. The Federation stated that it had difficulty interpreting the test results because, at this time, there was no generally accepted way to extrapolate test results from experimental animals to humans.

--Other chemical and toxicological data were found to be inadequate in that (1) not enough animals were tested at each feeding level in some studies and (2) test animals were not examined for all possible

adverse effects. In addition, the chemical composition of naturally occurring substances (e.g., mustard) tested were not precisely identified.

We reviewed 15 substances used before 1958 which were included in the GRAS review and for which the agency had published GRAS affirmation regulations to determine what scientific tests were performed on these substances and whether the same level of evidence supported the safety of each. While the safety of these substances could be based on history of use, we compared the scientific tests to which FDA said these substances had been subjected with the tests which FDA considers necessary for approval of food additive regulations. (See pp. 27 and 28.)

Only 2 of the 15 substances were subjected to the tests FDA considers necessary to support a food additive regulation. Little consistency existed in the types of scientific tests to which the other 13 substances had been subjected. Three of the substances were subjected to both core--reproduction/teratogenic and long-term feeding--tests, but they lacked other tests. Nine substances were not subjected to a long-term feeding study, three substances were not subjected to the reproduction/teratogenic test, and two substances were not subjected to either test. In addition, 6 of the 13 substances were not subjected to a mutagenic test, 2 lacked a short-term continuous feeding test, and 3 had no LD50 test.

The fact that a substance has been issued a food additive regulation authorizing its use means that it has met the same basic level of evidence as all other substances which have been issued food additive regulations. Placing substances in a regulatory category called "affirmed as GRAS" also implies that the evidence supporting the safety of all those substances meets a basic level of evidence common to all.

FDA regulations provide that, for a substance to be affirmed as GRAS, scientific evidence equal in quantity and quality to that required for food additives must be available, or if the substance was used before 1958, may be based on history of use. FDA's regulation which lists affirmed GRAS substances includes in one list, substances designated under both criteria and does not state the levels of evidence which support each substance's safety.

CONCLUSIONS

Guidelines are needed that describe the appropriate methods and controls for making scientific tests of safety, and regulations are needed that define the criteria that FDA uses in evaluating an additive's safety. Such guidelines and regulations would improve the industry's and public's understanding of FDA's safety decisions in regulating these substances. FDA's GRAS affirmation regulations should recognize the different levels of evidence which support the safety of GRAS substances.

Until FDA defines scientific test guidelines and review criteria for food additive regulations, only general information is available to the public and industry about the scientific evidence considered necessary and evaluation criteria used by the agency for issuing of such regulations. We realize that test guidelines cannot be rigid and will need to be revised periodically to allow for advances in science technology; however, such guidelines must be issued to help ensure that food additive safety is substantiated by studies of uniform design and execution. Formal publication of review criteria would help ensure that petitions are reviewed consistently. Establishing formal criteria would also help to improve industry and public confidence in FDA's program to regulate food additives.

In addition, including substances whose safety is supported by much less evidence than others in the same affirmed GRAS regulations may give an incorrect impression as to the level of evidence supporting the safety of these substances. To fully inform the public as to the level of evidence which supports each affirmed GRAS substance, FDA's regulations should distinguish between the levels of evidence--history of use or scientific evidence--which support the safety of each affirmed GRAS substance.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We recommend that the Secretary direct the FDA Commissioner to:

--Publish regulations establishing review criteria for assessing the safety of food additives and issue guidance defining the methods and controls to be used in conducting scientific safety tests.

--Revise regulations which list substances that FDA has affirmed as GRAS to indicate the kinds of evidence that support their safety.

AGENCY COMMENTS AND OUR EVALUATION

HHS said that as part of its programs to reevaluate the safety of additives to food, FDA has drafted a series of protocols for biological studies and criteria for evaluating these tests. These will eventually be published both in scientific literature, where they can undergo the scrutiny of peer review, and in the "Federal Register" as guidelines.

HHS stated, however, that these guidelines and standards will provide only general descriptions of what is usually required to demonstrate the safety of a host of possible food additive uses. The agency pointed out that it is not possible to develop standards specific enough to anticipate all situations, nor is it desirable to preclude the exercise of scientific judgment as to the appropriateness of specific tests relating to particular additives or their uses.

We believe that, when issued, such guidelines and standards will represent a significant step toward implementing our recommendation. We recognize that development of standards which are specific to all situations may not be appropriate. We believe, however, that these standards should be specific enough to insure the application of consistent criteria in conducting food additive safety evaluations and the conduct of studies which are of uniform design and execution.

HHS did not concur with our recommendation that regulations which list substances FDA has affirmed as GRAS should recognize the different levels of evidence which support their safety. HHS agreed that the nature of the evidence FDA relies on in affirming the GRAS status of an additive varies depending on the specific circumstances of each case. HHS stated, however, that simple generalized statements about the levels of evidence that support a GRAS affirmation would not provide a clear picture of the basis for particular decisions. Also, HHS said that, if regulations were revised as suggested, each of the regulations would have to recite the kind of detailed discussion of the basis for the regulation that FDA now presents in the "Federal Register" preambles to proposed and final regulations.

HHS did not believe the small degree of added consumer awareness that might result from such an expansion of the regulations would justify the considerable administrative

cost FDA would incur. The Department stated that, by publishing the affirmations as regulations, FDA is recording its conclusions that there is an adequate legal basis to support the GRAS determination, and that, based upon available information, there is no reason to expect any harm to the public from the use of these substances in accordance with the regulations. HHS pointed out that the entire administrative record underlying FDA's GRAS determinations is put on public display in the FDA hearing clerk's office at the time of publication, and copies of these records are available to interested parties under the Freedom of Information Act. HHS believed FDA's present procedures adequately insure that the bases for determining that additives are GRAS are generally available to interested parties.

In response to HHS' comments we have attempted to clarify our recommendations. We would not expect FDA to include in its GRAS affirmation regulations the preambles which are already available in the "Federal Register." However, we believe that regulations can be published which provide the public with a simple and clear indication of the safety data which FDA uses in affirming a substance as GRAS. For example, the GRAS affirmation regulations could be divided into three categories. The first category might include GRAS substances whose safety is supported by scientific evidence, the second might include substances whose GRAS designation is based on a combination of scientific evidence and a history of safe use in food, and the third category might include substances whose evidence of safety is limited to a history of safe use.

A method like the example given would require only a definition of the affirmed GRAS categories. It would not require a restatement of detailed information already available in regulatory preambles. Such a change would be relatively inexpensive to implement but would make important information about the level of evidence supporting the safety of substances added to the food supply readily available to the public.

USDA agreed with our recommendations in this chapter. It stated that the Interagency Regulatory Liaison Group has recognized the lack of uniform scientific testing guidelines among its member agencies and that this is one of several areas USDA is trying to improve.

CHAPTER 4

SCOPE OF REVIEW

This review was directed toward determining whether current legislative authority and FDA regulatory practices adequately protect the public against hazards from substances added directly to food.

We examined provisions of the FD&C Act which exempt about 1,450 substances from food additive regulation by FDA. We reviewed several exempted substances whose assumed safety was later questioned and whose removal from use has been proposed or completed. We also evaluated the potential impact these exemptions could have on the level of evidence supporting the safety of these substances. We discussed with FDA and USDA officials and private associations the reasonableness and practicality of changing the law to require that the evidence of safety for all substances be established as that currently required for food additives.

We evaluated FDA's direct additive regulations and practices and the effectiveness with which they are communicated to the food industry and the public. Also, we examined food additive petitions FDA received during 1978 to determine whether petitioners were submitting safety information which the agency considers necessary to support a food additive regulation. Furthermore, we reviewed the types of scientific tests that supported the safety of GRAS substances FDA had affirmed as GRAS from 1974 to 1979 to determine the consistency of such scientific evidence.

We also reviewed USDA's legislation, regulations, and practices. We discussed the regulation of additives with FDA and USDA officials, and representatives of the Flavor and Extract Manufacturers' Association, the Federation of American Societies for Experimental Biology, and the Food Safety Council--all are located in the Washington, D.C., metropolitan area.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

Office of Inspector General

JUN 20 1980

Mr. Gregory J. Ahart
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Need for More Effective Regulation of Direct Additives to Food." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard B. Lowe III

Richard B. Lowe III
Acting Inspector General

Enclosure

APPENDIX I

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT ENTITLED: "NEED FOR MORE EFFECTIVE REGULATION OF DIRECT ADDITIVES TO FOOD"

In general, we find this report to adequately address the Food and Drug Administration's (FDA) regulation of ingredients directly added to foods. We suggest, however, that the attached technical comments be incorporated to clarify the statutory distinctions between food additives, generally recognized as safe (GRAS) ingredients, and prior sanctioned ingredients and to more accurately portray the current status of FDA's food additive program. It should also be noted that this report omits color additives and indirect food additives, which account for approximately 85 percent of the food additive petitions submitted to the agency. The quality of the report would also be enhanced by a brief discussion of the full implications and consequences of adopting the proposed legislative changes to eliminate the GRAS and prior sanction exemptions to the food additive requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

GAO Recommendation To The Congress

We recommend that the Congress amend the FD&C Act to eliminate regulatory exemptions currently allowed for GRAS and prior sanction substances. Changes to the law should provide for sufficient flexibility to encourage the use of information already available and to recognize that different types of scientific evidence may be appropriate to support the safety of food additives. The amendment should also provide a date on which the safety of all GRAS and prior sanction substances directly added to food must be subject to Federal review and approval.

HHS Comment

In recommending changes in the regulation of GRAS and prior sanction substances, GAO has identified an issue of importance to the Department. In this regard, the Department is investigating alternatives that would deal with this complex issue.

In addition, we do not believe it would be in the best public interest to include a legislatively mandated timeframe for fully implementing any revisions that the Congress may enact. Any implementation plan would, of necessity, be based upon a system of establishing priorities for conducting required ingredient evaluations, testing them according to the most up-to-date scientific procedures, and publishing regulations regarding their status. Given the large number of ingredients to be tested, the length of time required for each test, the limited number of toxicity testing facilities available, and the current rapid growth of scientific knowledge, it is unlikely that full implementation could be accomplished on a predictable schedule.

APPENDIX I

GAO Recommendation

The Secretary of Health and Human Services should direct the FDA Commissioner to publish regulations establishing review criteria for assessing the safety of food additives and issue guidance defining the methods and controls to be used in conducting scientific safety tests.

HHS Comment

As part of the Agency programs to reevaluate the safety of ingredients added to food, FDA has drafted a series of protocols for biological studies and criteria for the evaluation of these tests. These will eventually be published both in the scientific literature where they can undergo the scrutiny of peer review and in the Federal Register as guidelines.

One must keep in mind, however, that these guidelines and standards will provide only general descriptions of what is usually required to demonstrate the safety of a host of possible food additive uses. It is not possible to develop standards specific enough to anticipate all situations, nor is it desirable to preclude the exercise of scientific judgement as to the appropriateness of specific tests relating to particular ingredients or uses.

GAO Recommendation

The Secretary of Health and Human Services should direct the FDA Commissioner to revise regulations which list substances that FDA affirmed as GRAS to recognize the different levels of evidence which support their safety.

HHS Comments

We do not concur. As the report recognizes, the nature of the evidence FDA relies on in affirming the GRAS status of a food ingredient varies depending on the specific circumstances of each case, e.g., the extent and nature of pre-1958 experience with the use of the substance, the amount and nature of available data on the substance derived from scientific studies, etc. Simple generalized statements about the "levels of evidence" that support a GRAS affirmation would, thus, not provide a clear picture of the basis for particular dicisions. To revise the regulations as GAO suggests, FDA would have to recite in each of the regulations the kind of detailed discussion of the basis for the regulation that FDA now presents in the Federal Register preambles to proposals and final regulations. We do not believe the small degree of added consumer awareness that might result from such an expansion of the regulations would justify the considerable administrative cost FDA would incur. By publishing the affirmations as regulations, FDA is recording its conclusions

APPENDIX I

that there is an adequate legal basis to support the GRAS determination, and that, based upon available information, there is no reason to expect any harm to the public from the use of these substances in accordance with the regulations. The entire administrative record underlying FDA's GRAS determinations is put on public display in the FDA hearing Clerk's office at the time of publication, and copies of these records are available to interested parties under the Freedom of Information Act. We believe FDA's present procedures adequately insure that the bases for determining that ingredients are GRAS are generally available to interested parties.

APPENDIX II

United States Department of Agriculture
Food Safety and Quality Service
Washington D C 20250

Mr. Henry Eschwege, Director
Community and Economic Development Division
United States General Accounting Office
Washington, DC 20548

JUL 3 1980

Dear Mr. Eschwege:

Thank you for the opportunity to review your draft report on the regulation of substances added directly to food. Although your report does not deal directly with programs of this Agency, your recommendations for amendment of the Federal Food, Drug, and Cosmetic Act (FD&C Act) would have a major impact on our activities regulating additives used in meat and poultry products.

Since amending the FD&C Act to eliminate regulatory exemptions for Generally Recognized As Safe (GRAS) and prior sanction substances could be disruptive for the food industry, an economic impact evaluation is essential to assess the public benefit. However, we generally support a gradual implementation of the recommendations in Chapter 2, to avoid unnecessary disruptions, and permit orderly assessment of available scientific evidence.

We also agree with your recommendations in Chapter 3. The Interagency Regulatory Liaison Group (IRLG) has recognized the lack of uniformity in testing guidelines within and among the IRLG agencies and has, as you mentioned, published draft guidelines. This is one of several areas we are trying to improve in regard to substances of mutual concern and shared responsibilities.

For clarity, the Cover Statement should reference the report's conclusions. The first paragraph of the Digest could also be made clearer by separately presenting the two key provisions in current law.

It would be helpful if statistical references to 15 out of 24 substances (page ix) were briefly explained in the Digest. After looking at the pages of the text referenced in the Digest (pages 48-54), assumptions still were necessary to confirm why the 15 were reviewed. Both the text and the Digest could benefit from more clarity in justifying the sample.

On page 20, paragraph 3, sentence 1, and on page 22, paragraph 2, sentence 1, "nonnutritive" should be used instead of "nonnutritious." The action on nitrites described on page 24, in paragraph 3, should be noted as a joint action by the Food and Drug Administration and this Agency. On page 54 in the first sentence under Conclusions, it would be helpful if the two ideas were presented in two statements: one for guidelines needed and one for regulations needed.

I hope you will find these comments helpful in preparing your final report.

Sincerely,

Donald L. Houston
Administrator

GAO note: Page references in this appendix may not correspond to page numbers in the final report.

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