Evaluation of health aspects of GRAS food ingredients:

lessons learned and questions unanswered
Evaluation of health aspects of GRAS food ingredients: lessons learned and questions unanswered

R. G. H. Siu
Joseph F. Borzelleca
C. Jelleff Carr
Harry G. Day
Samuel J. Fomon
George W. Irving, Jr.
Bert N. La Du, Jr.
John R. McCoy
Sanford A. Miller
Gabriel L. Plaa
Michael B. Shimkin
John L. Wood

Select Committee on GRAS Substances
Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

May, 1977
CONTENTS

Preface 2525

Background 2527

Organizing operations 2529
  Overall organization 2529
  Composition of evaluation panel 2529
  Panel operations and supporting staff 2531
  Public participation 2531

Assembling relevant data 2532
  Information resources 2532
  Data arrangement 2533

Conducting scientific analyses 2534
  Categories of judgment 2534
  Cause 2535
  Statistical confidence 2535
  Consumption data 2536
  Extrapolation from factory to mouth 2537
  Identification of natural substances 2537
  Natural occurrence 2538
  Fetus 2538
  Neonate 2538
  Animal models 2539
  Hypertrophy of the liver 2540
  Zero level of carcinogens 2540
  Mutagenicity 2541
  Teratogenicity 2542
  Allergenicity 2542
  Enzyme induction 2542
  Interaction with drugs 2543

Arriving at judgments on health hazards 2544
  Consensus 2544
  Subconscious leanings 2544
  Official regulations 2544
  History of use 2545
  Relativity of toxicity 2545
  Check list for conclusion adequacy 2546
  Check list for report adequacy 2546

Translating scientific assessment into official regulation 2547
  Freedom of choice 2547
  Special consumers 2547
  Risk:benefit ratio 2547
  Low-volume substances 2548
  Specifications and contaminants 2548
  Total body burden 2549
  Interaction among dietary components 2549
  GRAS status 2550

Perspective 2553
  References 2554
  Appendix A. Substances evaluated 2557
  Appendix B. Evaluation reports 2561
CONTRIBUTORS

Past and present members of Select Committee on GRAS Substances

Aaron M. Altschul, Ph.D., Professor of Community Medicine and International Health, Georgetown University School of Medicine, Washington, D.C. 20007

Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Virginia Commonwealth University Medical College, Richmond, Virginia 23298

C. Jelleff Carr, Ph.D., Director, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Maryland 20014; Ex Officio Member of Select Committee

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Indiana 47401

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa 52242

George W. Irving, Jr., Ph.D., Research Associate, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Maryland 20014; Chairman of Select Committee

Bert N. La Du, Jr., M.D., Ph.D., Chairman, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48104

John R. McCoy, V.M.D., Professor of Comparative Pathology, College of Medicine and Dentistry of New Jersey-Rutgers Medical School, Piscataway, New Jersey 08854

Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Gabriel L. Plaa, Ph.D., Chairman, Department of Pharmacology, University of Montreal, Montreal, Quebec, Canada

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, University of California School of Medicine, San Diego, California 92093

R. C. H. Siu, Ph.D., Consultant, 4428 Albemarle St, N.W., Washington, D.C. 20016

John L. Wood, Ph.D., Distinguished Service Professor of Biochemistry, University of Tennessee Center for Health Sciences, Memphis, Tennessee 38163

Professional staff of Life Sciences Research Office

Director: C. Jelleff Carr, Ph.D.
Associate Director: Kenneth D. Fisher, Ph.D.

FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), marshals the opinions of knowledgeable scientists in conducting studies and preparing reports on topics in the biomedical sciences. The Office has furnished expert analyses of scientific issues for research administrators, usually through the ad hoc review of the study topic by qualified scientists actively engaged in research in the field.

In the conduct of these studies FASEB is making a noteworthy contribution to societal needs and for this reason it appeared appropriate to undertake the novel task described in this report. The Select Committee on GRAS Substances was organized in June 1972 by LSRO under terms of contract 72-85 with the Food and Drug Administration of the Department of Health, Education, and Welfare. This panel of scientists was asked to assess the potential hazards of some 400 food ingredients that had been "generally recognized as safe (GRAS)" under the provision of the United States Code of Federal Regulations (127) (under number 21 CFR 170.3; prior to recodification this number was 21 CFR 121.1).

Prior to the final editing of this report, the Select Committee has held fifty 2-day executive sessions over a 5-year period. Their evaluations have been supported by extensive literature surveys prepared by other FDA contractors; a generous supply of information and data from governmental, industrial, and academic sources; and intensive individual searches on the part of the Select Committee members in concert with ad hoc consultants and the LSRO staff.

This publication of the Select Committee reviews the nature of its work and the problems encountered in an endeavor to insure the appropriateness of its conclusions, even in instances where the information was very limited. With the encouragement of the Commissioner of Food and Drugs, the Select Committee has compiled this account of its unique experience in food safety evaluation.

The substance of these commentaries by members of the Select Committee is drawn largely from their own experience. Special recognition is due Dr. R. G. H. Siu for his skill and patience in molding the individual efforts of the Select Committee into the present report. So personal a document would not, of course, necessarily express the views of FASEB or any of its constituent societies. However, the members of LSRO consider it a privilege to have joined with the Select Committee in drafting this record of experience and discussion of future needs.

Preparation of this paper was supported by the Food and Drug Administration, Department of Health, Education, and Welfare, contract no. FDA 223-75-2004. The opinions expressed herein do not necessarily reflect the position or policy of the Food and Drug Administration.

C. Jelleff Carr
Director
Life Sciences Research Office

Bethesda, Maryland
May, 1977
PREFACE

As members of the Select Committee on GRAS Substances, we feel privileged to be participants in the first comprehensive scientific evaluation of the safety of a sizable fraction of the number and most of the bulk of the commercially added food ingredients. We wish to express our appreciation for the generous advice and assistance that have been provided by colleagues and strangers alike, here and abroad. Having benefited by this exposure, we believe it useful to pass our experience on to others, especially those who are about to embark on a similar exercise. This report records relevant analyses of some of the more important issues. Every member of the Select Committee and the LSRO professional staff made specific as well as general contributions.

The purpose of presenting these “lessons learned and questions unanswered” is fourfold:

- to illustrate the range of factors to be taken into consideration in the safety assessment of a given food ingredient;
- to offer estimates on the state of the art and commentaries on the nature of the technical dilemmas that are encountered in rendering scientific judgments on food safety;
- to provide suggestions concerning the philosophical, procedural, and scientific ramifications of such an evaluation process;
- to point out needed research to improve the validity and meaningfulness of the associated data.

This contribution should be read and considered together with a sampling of actual evaluation reports of the Select Committee, as given in the Appendix. It was in the generation of these specific reports that the need was felt to write such an article to embrace the many intangibles that could not be appropriately discussed in individual evaluations. With the latter as specific examples, the lessons learned and questions unanswered take on the dimensions and significance we intend to convey.

We are well aware of the tentative and evolving state of information, the limitation of our own expertise, and the differing experiences and viewpoints of others who might come to contrasting positions on the issues discussed. It is our feeling, however, that by adding this account to the public and scientific dialogue in a spirit of candor, we may contribute to the common objective of advancing the nutritional well-being of people throughout the world.

We acknowledge with appreciation the technical, bibliographic, and clerical assistance of the following members of the Life Sciences Research Office: Ann Altman, Kathleen M. Coppola, Kathleen M. Dennis, Elizabeth M. DeWitt, C. Grace Gurtowski, Carolyn A. Paddon, Lee C. Rogers, Jeanne L. Schachter, Gretchen A. Turner, and Evelyn C. Volkman.

Bethesda, Maryland
May, 1977

Select Committee on GRAS Substances
Background

Federal programs assuring the safety of food supplies in the United States began early in the 20th century in the Bureau of Chemistry of the Department of Agriculture. Legal standing was accorded on June 30, 1906 with the passage of the original Food and Drugs Act. The stated purpose was: “For preventing the manufacture, sale, or transportation of adulterated or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein.”

Further impetus was added by the Food, Drug, and Cosmetic Act of 1938, which has been much amended and expanded since then. The law is currently administered by the Food and Drug Administration (FDA) of the Department of Health, Education, and Welfare. It represents the principal, but not the only Federal statute designed to protect consumers from harmful food ingredients in interstate commerce. Regulatory agencies besides FDA include the Department of Agriculture, which continues to be responsible for meat and other products of animal origin; the Department of the Interior, which is responsible for marine food products; and the Environmental Protection Agency, which is responsible for the control of pesticides and environmental pollutants. Individual states have their separate regulations that govern intrastate practices.

Government surveillance of food additives was tightened with the enactment of the 1958 Food Additives Amendment to the Food, Drug, and Cosmetic Act of 1938. This called for prior approval by FDA of new commercially added food ingredients. Petitioners for food additives were required to present evidence of the usefulness and harmlessness of the ingredients when used as proposed. However, the enacted legislation specifically exempted prior sanctions and substances in common use at the time from this regulatory definition of food additives. As such, these substances became known as GRAS (an acronym for “generally recognized as safe”) substances. In presuming that GRAS and prior sanctioned substances were safe, based on data available at the time of the 1958 Amendment, the food additives amendment removed any authority from the FDA to require a demonstration of safety for the continued use of these ingredients, and consequently required FDA to demonstrate them to be unsafe before removal from use. The rest of the commercially added ingredients were legally designated as food additives (115). Figure 1 shows the functional distribution of all ingredients commercially added to foods in 1965.

In order to achieve some uniformity of understanding of GRAS ingredients, FDA published several advisory lists of substances that it believed could be classified as generally recognized as safe for use in foods. After some deletions from the lists through public comments, a final compilation was issued in the United States Code of Federal Regulations (48, 49). In addition, permissions for various uses were granted through unpublished “GRAS letters.” In these communications, FDA officially recognized certain substances as GRAS in response to specific requests by individuals or companies.

The 1958 Amendment did not empower FDA to be the sole judge of GRAS status. It specified that such recognition was to be conferred by “experts qualified by training and experience” to judge food safety. Thus, it came about that the Flavor and Extract Manufacturers’ Association (FEMA) conducted its own independent review of the flavoring substances that made up a majority of the commercially added food ingredients at the time (62). Only those unanimously determined by the members of its expert panel as being safe for human consumption were placed on the FEMA list. After 3 years, approximately 1,200 were

---

Figure 1. Functional distribution of commercially added food ingredients (85).

| Special sweeteners                       |
| Bleaching and maturing agents, starch modifiers |
| Antioxidants                             |
| Preservatives                            |
| Colors                                   |
| Stabilizers, thickeners                  |
| Sequestrants                             |
| Buffers, acids, alkalies                 |
| Surfactants                              |
| Nutrient supplements                     |
| Miscellaneous                            |
| Natural flavoring materials              |
| Synthetic flavoring compounds            |

0 200 400 600 800 Number

EVALUATION OF HEALTH ASPECTS OF GRAS FOOD INGREDIENTS

2527
approved. In 1964 FDA ruled that the FEMA compounds were not to be classified as GRAS substances but were to be given a separate grouping in the Code of Federal Regulations (51, 52). This action was due, in part, to the fact that the information required to make the relevant safety judgments was not widely available to the scientific community.

GRAS substances were administered in the manner described until 1969, when the President directed a full-scale reevaluation. In his consumer message of that year, he indicated that he did not feel it proper to require exhaustive study of the safety of proposed new additives, while accepting the safety of the GRAS substances with little or no specific examination. He therefore instructed FDA to update the GRAS safety assessments based upon currently available data and judgment of scientists. Whereupon, FDA, beginning in 1970, initiated a series of implementing actions, which led in 1972 to the formation of the Select Committee on GRAS Substances as part of an FDA contract to FASEB, the Federation of American Societies for Experimental Biology. The first year’s phase called for the organization of the Select Committee, the development and refinement of evaluation procedures, and the initiation of actual assessments of GRAS substances. Faster rates of review were realized as experience accumulated. To date, 229 substances have been reviewed. These and those in the process of being evaluated are listed in the Appendix.

Judgments on the safety of GRAS food ingredients were rendered on a case-by-case basis. The results were submitted in reports on specific substances. In the process, areas of limiting knowledge were revealed; general approaches and principles were formulated; new perspectives on philosophical issues were acquired. Basic questions were addressed, which went beyond the deliberations immediately pertinent to the particular food ingredient of the moment. We felt that these experiences might be of benefit to others. This report is the outcome.

The body of the document consists of a series of exploratory commentaries on specific issues. Where necessary, the discussions are sharply drawn, rather than diluted into an anemia of consensus with prevailing opinions. Since the evaluations of the Select Committee are part of a decision chain that is expected to eventuate in Federal regulation of commercial practices, the presentation emphasizes operational usefulness.

The report closes with some thoughts on the future of the evaluation of food safety in this country.
Organizing operations

Although the best laid plans of mice and men often go awry, as we have been reminded through sad encounters, a poorly laid plan usually leads nowhere. The Select Committee has reaped the benefit of thoughtful planning and organizing on the part of FDA and LSRO, the Life Sciences Research Office of FASEB. Changes, which we hope were improvements, have been added along the way. Some of the procedures that have worked reasonably well are presented below.

OVERALL ORGANIZATION

The general framework for the evaluation process adopted by FDA appears to be effective in practice. Its central feature was the separation of the consumption surveys, the conduct of special mutagenic and teratogenic tests, the initial collection of toxicological and associated data from the literature, the input of information and opinions by interested parties, and the evaluation itself. The arrangement impressed us as having maximized the chances for completeness in the gathering of raw scientific data and minimized the chances for subconscious and indirect biasing of conclusions.

As a preparatory step, FDA contracted with the Franklin Institute of Philadelphia, Pennsylvania, to compile and abstract the world's literature from 1920 to 1970 on each of the GRAS substances.

Another contract, with the National Academy of Sciences—National Research Council of Washington, D.C., covered a survey of the food industry to determine the extent of use for each GRAS substance and an attempt to estimate its daily human consumption. A third series of contracts was awarded to about nine organizations for mutagenic and teratogenic testing of selected GRAS substances. Considerable teratogenic testing was also conducted within FDA's own laboratories.

Some of the results of these groups were sent directly to the Select Committee; most were made available to a number of other contractors preparing compendiums of scientific literature. These collaborators were responsible for the preparation of updated compilations covering the available data within the past 50 odd years pertinent to the assessment of the health hazard in each case.

Finally, FDA negotiated a contract with FASEB to utilize the services of LSRO to evaluate the material presented in each compendium, supplemented with additional information gathered through its own resources. The Select Committee was organized for this specific purpose. It was assisted by a professional and administrative staff within LSRO. From time to time as needed, the Select Committee retained the services of ad hoc consultants in specialized areas. These consultants did not participate, however, in the formulation of the opinions and conclusions of the Select Committee.

Beginning with the 27th evaluation, the tentative report on each GRAS substance or group of closely related substances was made public through FDA. At the same time, an invitation was announced in the Federal Register for oral and/or written presentation of data and/or views to the Select Committee. If a request for an oral opportunity was received, a public hearing was held.

The final evaluation report of the Select Committee was prepared after consideration of the additional information, including the proceedings of the public hearing. This report was reviewed for policy and professional adequacy by the LSRO Advisory Committee, which was composed of an appointed representative from each of the six constituent societies of FASEB. The document was then submitted by the Executive Director, with the endorsement of FASEB, to FDA.

The conclusion of the Select Committee, together with the supporting data and opinion, constitutes a major element in the subsequent decision of FDA as to whether the GRAS substance in question is to be reaffirmed in its GRAS status or converted to GRAS status with limits, will require additional testing under interim regulation, or will be prohibited from commercial use.

The overall process is diagrammed in Fig. 2.

COMPOSITION OF EVALUATION PANEL

A perusal of the official definition of GRAS substances suggests the necessity of a balanced panel of qualified scientists for the evaluation exercise. But, a more detailed reading reveals the need for equally important qualities beyond purely technical expertise. The nature of these qualities became progressively clearer with each grappling for an appropriate resolution over the safety of a controversial substance.

1 Principal contractors on mutagenic testing include Litton Bionetics of Kensington, Maryland, and Stanford Research Institute of Palo Alto, California.
2 Principal contractors on teratogenic testing include Food and Drug Research Laboratories, Inc., of Maspeth, New York; Mississippi State University of Starkville, Mississippi; Ohio State University of Columbus, Ohio; Saint Louis University of Saint Louis, Missouri; University of Arizona of Tucson, Arizona; and Wisconsin Alumni Research Foundation of Madison, Wisconsin.
3 Principal literature contractors were Informatics, Inc., of Rockville, Maryland, and Tracor Jitco, Inc., of Rockville, Maryland.
4 Members, 1976: Dr. Frederick P. Ferguson, The American Physiological Society; Dr. Willis A. Gortner, American Institute of Nutrition; Dr. Earl R. Stadtman (resigned), American Society of Biological Chemists; Dr. Arthur C. Upton, Chairman, American Society for Experimental Pathology; Dr. Pierson J. Van Alten, The American Association of Immunologists; Dr. Elliot S. Vesell, American Society for Pharmacology and Experimental Therapeutics; Dr. Irwin C. Gunsalus, President, FASEB (ex officio); Dr. E. Leong Way, Vice President, FASEB, (ex officio); Dr. Eugene L. Hess, Executive Director, FASEB (ex officio).
From an operating standpoint for our type of organization, we found a membership of about 10 to 12 to be optimal. This allowed for the occasional but inevitable absences at some of the executive sessions and still left an adequate number of participants for a vigorous and fruitful deliberation.

With less than 10 members, the problem of ensuring the necessary expert coverage of the many disciplines involved became difficult. Occasional shortcomings could be mitigated by the use of ad hoc consultants and professional staff personnel. But firsthand knowledge and experience in the following fields appeared to be essential for representation on the evaluation panel itself: food technology, organic chemistry, biochemistry, nutrition, pharmacology, toxicology, pathology, oncology, and human and veterinary medicine. In this regard, a certain breadth in knowledge, as well as expertise in a given discipline, was preferable to only a narrow depth in a restricted specialty.

Questions concerning the general orientation of the members toward the element of risk assumed considerable significance. Was the panel to be dominated by a strict or permissive attitude? If a balanced orientation was the objective, was this to be achieved by a selection of all members of a balanced stripe or by a selection of equal numbers of opposing polarities?

Since the GRAS concept is judgmental, serving as a legal basis for the control of certain commodities for public consumption, the credibility of the panel's conclusions should not be a matter for unnecessary controversy. This constituted another major factor in the final choice of members. The consideration necessarily imposed certain constraints on their affiliations. Avoidance of even the appearance of a conflict of interest was emphasized. This led to the exclusion of some of the most knowledgeable and talented experts in the field of food technology and additives, because they were associated with industrial concerns producing or using commercially added food ingredients. Members of regulatory agencies were also eliminated from consideration to obviate the suspicion of accommodating the panel's evaluations to current regulatory practices.

One of the more active consumer-interest groups argued that the Select Committee would have good standing with the American community only if one of the members was specifically approved by it as "consumer-oriented." The designation of one of the members as "consumer-oriented" would imply, however, that the rest were not. To produce a balance would have called for the designation of another member as "producer-oriented," presumably approved by a food manufacturers' association. Such a state of affairs would have led to adversarial proceedings, which we had wished to avoid as a means of arriving at the kind of judgments we were expected to make. We preferred the approach of collective reasoning among members with a minimum of bias in either direction.

In fact, we considered the element of judgment to be singularly important. The members were expected to assess not only the scientific rigor of the data reported, but also the reliability of the investigators, the extrapolation of experimental conditions to real-life human situations, the adjudication of conflicting findings, the weight of indicative information, the appropriateness of inferences from in vitro models, and a host of other nebulous considerations.

Finally, there was the practical factor of time. We found that a minimum of 4 full days a month, excluding travel time, was required of the
members. This included 2 days for the monthly executive committee meetings and at least 2 days for the associated home preparation—month after month for several years. Time to analyze the mass of raw data—time to write the original drafts—time to formulate one's own opinions—time to critique the drafts and opinions of others—time, it generally turned out, was the limiting factor in the acquiescence of many outstanding but exceptionally busy scientists to serve.

PANEL OPERATIONS AND SUPPORTING STAFF

The need for an effective supporting staff requires no elaboration. There may be interest, however, in its professional relationship to the Select Committee.

Deliberations on the opinions, conclusions, and interpretation of data were confined to the members of the Select Committee in executive sessions. No representatives of the governmental or nongovernmental sectors were present during these discussions. However, since members of the professional staff were selected in part for their technical balance to the entire effort, they attended all meetings of the Select Committee and joined in discussions regarding the scientific facts of the case under consideration, existing government policies and procedures, information retrieval, and views of various organizations. They also maintained a continuous but free liaison with FDA and attended meetings on food safety sponsored by the food industry, universities, and other institutions such as the National Institutes of Health and the National Academy of Sciences.

To assure the primacy of scientific expertise and reinforce the fact that the opinions expressed in the reports of the Select Committee were entirely those of its members, the initial drafts were written by the members. This was carried out by ad hoc assignments to subcommittees of two members each, serving more or less in random permutations but with some consideration given to matching the subject matter against the professional backgrounds of the individuals. Full committee deliberations were then conducted with these drafts as points of departure. In the meantime, all members of the Select Committee and the LSRO professional staff had the opportunity of studying the same raw data furnished by the FDA contractor-compilers and other sources. The discussions continued until there was agreement among the members of the Select Committee regarding the general adequacy of the draft opinions, conclusions, and supporting data as representing the thinking of all of the members. The draft was then turned over to the staff for final preparation and coordination.

Based on the subcommittee's approved draft and related comments from other members, a second draft was prepared by the staff. Two copies were provided each of the members of the Select Committee for emenda-tions. One marked-up copy was returned to the staff for reworking. All changes were made available to the members and substantive modifications were debated at a subsequent meeting. At times, the second draft was referred back to the subcommittee for further revision, after which the new version was considered at another session of the full committee. One individual in the staff was assigned the responsibility for refining the various drafts and following through as action officer until the submission of the final report.

In preparing the third draft, which reflected the consensus of the Select Committee, the action officer reviewed every statement and figure in the report against the original articles cited and rechecked all calculations. Upon signed approval by all members of the Select Committee, the draft became the tentative report that was submitted to FDA as the basis for public hearing and subsequent processing.

An integration of the efforts of the Select Committee and those of the supporting staff was maintained by means of a full-time scientist, with research and administrative experience in the life sciences, acting in the dual capacity of Chairman of the Select Committee and Director of the supporting staff. He was assisted by several scientists with backgrounds in supplementary specialties. The work of the professional staff was expedited by information aides, skilled in literature searches, bibliography preparation, and library resources; and by an office manager, coordinating clerical and administrative activities.

PUBLIC PARTICIPATION

Particular emphasis was given by FDA toward insuring appropriate public contribution to our deliberations. This input was important for several reasons. The public was the affected party; it was a source of valuable information and views; its confidence in the judiciousness and fairness of the food-safety rule-making process was necessary for efficient implementation of the resulting regulations. Public input was formally requested during three stages along the evaluation process. These were:

a) Upon completion of the compendium of literature pertaining to a given GRAS substance or group of related substances, an announcement was published in the Federal Register of its availability through the National Technical Information Service of the Department of Commerce. In this way the initial information base of the Select Committee was made known to the public. At the same time, an official appeal was included for additional data from all sources.

b) The penultimate draft on each GRAS substance or group of related substances, including the tentative conclusions, was also made available to the public through the same channel. The notice was accompanied by a second solicitation for criticisms and comments to be sent directly to the Select Committee.

c) Before final judgment, beginning in 1974, public hearings were scheduled for anyone expressing a desire for such an opportunity for the presentation of information and opinions on the substance in question.

In addition to these official invitations, the Select Committee and the LSRO staff made a continuing informal effort at gathering relevant data from all sources in both governmental and private sectors.
Assembling relevant data

It was the intention of the original planners of the evaluation exercise to have practically all of the required data assembled by the information compilers. The members of the Select Committee were only to analyze these compendiums. Such a clean separation of functions was not realizable, as we found it necessary regularly to seek out additional articles and unpublished results to fill the perplexing lacunae of knowledge. The situation was one that had to be lived with. It was highly probable that no advance search, however exhaustive, could have anticipated the supplementary needs that inevitably arose during the evaluation process.

INFORMATION RESOURCES

It took more than a year before we began to feel confident about the adequacy of our literature retrieval efforts. By that time a much greater appreciation had been acquired of the problems of timeliness and completeness of information inherent in the system of publication and library services (110), and a compensatory procedure was evolved.

Literature searches usually begin with secondary sources, such as abstracts, reviews, and compendiums (5, 7). The lag between primary and secondary publication in the biomedical sciences appears to be 5 to 8 months or longer (54). The time between the initiation of the toxicological work and the appearance of the results in a secondary source approximates 3 years. During this period the information is limited to a relatively small number of specialists and confreres, who happen to be following the particular journals in which the item of interest was published or maintaining professional contact with the worker concerned.

Theoretically, it should be a straightforward routine to proceed from the secondary sources to the original articles. In practice, we came across many beclouding obstacles. The first related to nomenclature. It was our experience that most scientific sources coded GRAS substances by their chemical names, but this often was not the preferred identity in trade and toxicological designations. For example, in following through on the substance labeled on the GRAS list as corn sugar, it was necessary to recognize that the simple sugar α-D-glucose had been included in a number of secondary sources under dextrose, glucose, α-glucose, d-galactose, corn sugar, corn syrup, Glucol, dextrin, Dextropur, Dextrosol, glycypyrano, and α-D-glycopyranose. Such a multiplicity of synonyms greatly increases the time and difficulty involved in retrospective searches (80).

Regardless of the reputation of the secondary source, we found it prudent to examine the original publications themselves. In one extreme instance, 30 of the 84 references selected for detailed study out of a specially prepared compendium contained mistakes in title citation, journal identification, pagination, author's name, and dates.

A third source of difficulties arose from the differing categorization of information in various data banks. Many of these were discipline-oriented rather than substance-oriented, which was the opposite of our primary interest. Furthermore, the diverse data bases did not necessarily overlap. A toxicity data base might refer to LD₅₀ values and chronic toxicity of a particular study, while a carcinogen data base might not refer to such findings but only to those directly relevant to carcinogenicity. The abstract of an article on animal studies concerning a given substance might include observations on metabolism but omit the key words identifying the substance's use, for example, as a sanitizer in the processing of frozen foods.

A fourth source of difficulties was initially encountered with some of the contractual literature retrieval activities. In a few instances, instead of providing a purely factual compilation of available data, the information specialists were making personal interpretations on the safety of the ingredients involved. It was our feeling that such an expansion of roles might subconsciously warp their selections in the collection of raw data. This was called to their attention and the situation was corrected.

Our own efforts at supplementing the material furnished by FDA contractors emphasized unpublished reports, less widely available documents, and more recent publications. A terminal to the nationwide online bibliographic services, Toxline and Medline, was established at FASEB. The facilities of the Toxicology Information Response Center of the Oak Ridge National Laboratories at Oak Ridge, Tennessee, were also utilized. Independent searches were conducted through various abstract and summary sources (1, 18, 29, 44, 92, 117, 120, 121). Regular combings were made of the files of FDA; food additives standards from other countries, such as England, France, Japan, The Netherlands, West Germany, and Russia; the World Health Organization's food additives report series (134); the National Research Council's contributions (84, 85, 87, 88); and documents from the Department of Health, Education, and Welfare (13, 81, 82, 126), as well as government import (122) and production records (123, 124, 133). Over 30 scientific and statistical reference sources and compilations were routinely consulted.

The number of references obtained for a given GRAS substance varied greatly. A 50-year literature search on carnauba wax uncovered only 23 reports, while a comparable search for vitamin A produced over 20,000. The mass of data per se, however, was no guarantee of adequacy. What was essential was having the significant and critical information at hand. For this, the standard bibliographic services often provided only limited assurance. We found ourselves repeatedly returning to the ways of the researcher, i.e., inquiring of those currently active and productive in the field. This was
an important ingredient for completeness of literature surveys for our purposes.

While all available information was examined, our conclusions were based on that which would have been released to the public at the time the report was issued. The reader was entitled to know not only the manner in which the conclusions were drawn but also the principal raw data from which they had been derived. Only then would he or she be able to assess the validity of the findings. So far, there has been no instance in which our conclusions would have been modified had the confidential information released to us been included in our report. Had there been such a possibility, we would have pressed for the publication of the critical data.

Conflicting reports were found frequently in the literature. In general, we were inclined to believe that well-written accounts with specific and adequately supporting details deserved greater credence than fragmentary notes, that reports in the "refereed" journals were likely to be more reliable than others, and that recent investigations reflected higher sophistication in methodology as a rule than those of decades past. Nevertheless, hours were spent deliberating over even obscure claims of adverse observations. Typical was the report (66) noting significant depression of weight gain, increased liver weight, and enlarged spleens, ovaries, and lungs in mice fed benzoic acid. Other authors contradicted these findings. No communication was dismissed out of hand; all information was weighed. While the extensive data and deliberations could not be detailed in our reports, we hoped that sufficient tracks were provided to enable the reader to follow the line of reasoning that led to the conclusions.

DATA ARRANGEMENT

The following outline for literature compilations had been developed by FDA and LSRO as a guide to the contractor-compiler's. We have found it quite satisfactory for use of the data.

Factual and noninterpretive summary of assembled data, including all references considered by the compiler to be relevant

Identification
Common names
Trade names
Chemical names
Chemical formulas, empirical and structural
Physical description, general characteristics, physical properties
Chemical properties, stability, reactivity
Analytical techniques, accuracy
Production process
Specification, commercial and food grade
Occurrence in nature
Occurrence in foods

Uses
History of human uses in food
Domestic and foreign regulations
Food manufacturing and meal preparation
Amount and manner of addition of ingredient during commercial processing of food commodity
Changes in nature and content of ingredient during manufacturing and storage
Changes in nature and content of ingredient during meal preparation

Human consumption
Totally from all sources
As commercially added ingredient
By food commodity
By age groups
By special consumers

Biochemical studies
Absorption, transport, distribution, excretion
Metabolic transformations
Enzymic interactions
Drug interactions
Nutrient interactions

Animal testing with pathological examinations
Acute toxicity
Short-term feeding
Long-term feeding
Special studies, such as carcinogenicity, fetotoxicity, and mutagenicity

Human responses
Experimental observations
Inadvertent ingestions
Clinical reports
Anecdotal accounts
Special studies, such as allergenicity

Bibliography of all publications, cited above or otherwise, which the compiler believed might be of interest to the Select Committee

Copy of all articles cited in the factual summary
Conducting scientific analyses

This section is intended to convey a picture of the kinds of issues involved in the process of passing scientific judgments on the safety of GRAS substances. Without attempting to amplify the problems inherent in such a procedure, we believe it worthwhile to illustrate the complexities calling for great care in the weighting and extrapolating of indicative observations. This is particularly true in the face of limited data. With relatively few exceptions, the available data on GRAS substances are much less than might be usually regarded as desirable. But since the Select Committee 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. Considerations of relevance, validity, meaningfulness, and significance become increasingly important as data become progressively less complete. It is only fair to state, however, that despite these difficulties, the Select Committee feels confident that the final safety evaluations, having been subjected to the various stages of input and review described in this report, are sound in the light of available data.

CATEGORIES OF JUDGMENT

The review of safety of GRAS substances should be considered in the perspective of the legal requirements imposed by the statutory language of the Federal Food, Drug, and Cosmetic Act as amended. Essentially, FDA has the burden of proof if a GRAS substance is to be declared unsafe for its intended use. Therefore, reasonable grounds must exist in order to question the safety of a GRAS substance and such grounds usually must be supported by substantive evidence derived from scientific data.

FDA guidelines to the Select Committee, therefore, stipulated that credible evidence of, or reasonable grounds to suspect, adverse biological effects had to be present in whatever information was available before the pronouncement of a potential health hazard was to be advanced. This was, of course, the reverse of the premise for the approval of new food additives. In the latter case, there must be sufficient and credible evidence from tests specially designed for the purpose that demonstrates their safety before admission to commercial use.

The judgments on safety of the Select Committee were, therefore, to be stated in the form of one of the following four conclusions:

a) There is no evidence in the available information on that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.

b) There is no evidence in the available information on that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard.

c) While no evidence in the available information on demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies should be conducted.

d) The evidence on is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced.

Only a small fraction of the GRAS substances, such as benzoic acid, vitamin A, and vitamin D, are supported by an array of tests that compare with those required for the approval of new food additives. Some others, such as gum ghatti and clove oil, had not been subjected to oral feeding tests of any kind in the laboratory. Most of the GRAS substances fell in between, with controlled feeding tests often rather limited in scope.

An extreme, but not unique, example of a deficiency in relevant data for a scientific evaluation of potential hazard is Japan wax. Despite the fact that it has been used in food contact surfaces for decades, an extensive search of the literature uncovered no information on its absorption, metabolism, acute or chronic toxicity, or any other biological tests, except for a tangential study on antirachitic agents involving four animals and some in vitro mutagenic tests. Experience with several cases of this kind led to the addition of a fifth category of judgment by FDA, namely:

e) In view of the almost complete lack of biological studies, the Select Committee has insufficient data upon which to evaluate the safety of as a food ingredient.

It may appear that use of this conclusion is inconsistent with the guideline stated earlier in this section, that credible evidence of, or reasonable grounds to suspect, adverse biological effects had to be present in the information available on a substance to permit pronouncement of potential health hazard. However, blind extrapolation of the guideline would lead to the untenable position that the safest substance is one about which nothing is known. Accordingly, the Select Committee used the fifth conclusion when appropriate, believing that for a substance that has not been studied at all, no opportunity has been provided for possible adverse effects to surface.

Not much difficulty was encountered by the Select Committee in placing most of the GRAS substances into one of the assigned categories. About a fourth of the ingredients required considerable discussion before consensus was gained. Some precipitated prolonged discus-
sion. An example of the latter was sucrose. The salient facts appeared fairly straightforward: under certain circumstances, sucrose contributed to the occurrence of dental caries. Should we, therefore, have declared that contribution to dental caries constituted a safety hazard? If so, should we then have recommended that sucrose added in the manufacturing process to certain processed foods be restricted to a stipulated low level, while other commodities, such as candies, are left unrestricted even at a substantially higher level of sucrose content? If sucrose was to be declared a health hazard, what should be done about glucose, fructose, honey, and other caries-promoting substances? Although most of the latter seemed to be less cariogenic than sucrose, the effects were not insignificant. None of the five standard expressions on judgments of safety precisely covered the important nuances of the case. A variant in specific wording had to be composed before consensus could be reached (see Appendix B, 69). Such specially tailored language was required, however, in only a few cases.

**CAUSE**

One of the most facile of assertions heard in the midst of argument over the alleged hazards of a given ingredient is that it “causes” a certain undesirable effect. The term is often loosely employed, which makes it somewhat difficult to link the reported causal factors with dose response.

In the absolute sense, “cause” is a metaphysical abstraction with which Aristotle and other philosophers have grappled with indifferent success. In the mundane world of the biological sciences, “cause” connotes that event B follows event A predictably and that the linkage between them has a rational explanation. The longer the interval between A and B, the more opportunities there are for other modifiers to enter the situation and a causal relationship becomes less evident.

Some authors divide “cause” into subtypes in an attempt to refine its meaning. Others question whether such adjectival qualifiers confound more than they clarify. One of the more commonly used pairs is “sufficient” and “necessary” cause. A is said to be a “sufficient cause” of B, if A alone can bring about the appearance of B. If A is a food ingredient and B is a fetotoxic event, we would then say that the addition of A to foods is a “sufficient cause” for fetotoxicity and therefore represents a hazard. If A alone is not sufficient to bring about B but is “necessary” in conjunction with other ingredients and/or conditions, then the question arises as to the identity of the other necessary factors that must also be present. In this case, the evaluator of food safety needs to examine carefully the similarity of the test conditions to the actual circumstances surrounding the anticipated human consumption patterns.

Another classification of causality is that of “proximal” and “distal” causes. The latter is envisioned as being responsible for inducing a “predisposition” to a given effect, while the former is seen as a “precipitating factor.” When linked as “necessary causes,” they are seen as sequential in nature.

Long ago David Hume had dismissed absolute cause and replaced it with statistical models of the frequency and consistency of occurrences. Striking a match, for example, “causes” a flame. If a flame is not produced, it is assumed that something is wrong with the match or the striking surface. If, instead of a flame, water issues forth, the event is so rare that it may be called a “miracle.”

The word “cause” is not encountered as frequently in the more scientific biomedical journals today as in earlier decades. It is becoming generally recognized that the complex long-term reactions in chronic diseases are better represented by a field of interactions than by a one-directional A-to-B diagram. “Cause” of the latter variety was more commonly encountered among scientific expressions during the classical bacteriological era, with Koch’s postulates becoming enshrined as proof of causality.

“Cause” in the interpretation of biological data, therefore, is a decision based on statistical considerations to the effect that B follows A sufficiently often that one is able to predict with high probability that the same sequence will continue to occur. The conclusion is buttressed by an acceptable explanation of the sequence, called the “mechanism of action.” This recognition pattern is modified or replaced when exceptions are identified or when a better explanation becomes available. “Better” in the biological sciences, however, is not necessarily simpler, a la Occam’s razor, but is encompassing of more related phenomenons or is capable of a more harmonious fit with other scientific data. In such deliberations, consensus among authorities at any given time is not necessarily “truth”—yet another metaphysical concept of an absolute.

Most authors are aware of the need for controlling the independent variable while observing the dependent variable as they attempt experimental demonstration of cause-and-effect relationships. What is overlooked at times is the high desirability of some relatively simple and direct link between the two. When the connection is complex, indirect, and ill-defined without a plausible network of association, restraint is in order in the assertion of causal correlations. It would be boring to repeat the old saw about the high correlation between the wearing of top hats and good health were it not for the fact that claims of causal connections between substance A and physiological condition B continue to appear in print based not only solely on statistics but also solely on statistics involving inadequate numbers and inappropriate analytical procedures.

**STATISTICAL CONFIDENCE**

For many of the feeding tests published on GRAS substances, the number of replicates ran in the range of 5 to 20 animals, instead of the more acceptable practice of about 30 females and 30 males followed in the more carefully conducted experiments. In such instances, our confidence in the reliability of the reported conclusions was proportionally limited.

There is an intrinsic elasticity in statistical reasoning associated with toxicological testing even under the best of circumstances. The dimensions of the problem are laid out very clearly by the FDA Advisory Committee on Protocols for Safety Evaluation (38).
Given a set of experimental conditions with \( n \) number of control and treated animals, respectively, what increase in untoward responses in the latter group over those in the controls should be taken as evidence of toxicity? If \( n \) is 1,000, an upper limit of 2.3 affected animals would give a 90% confidence of the absence of toxicity. Such a degree of assurance, however, would hardly be comforting to the average person as far as cancer is concerned. He or she would prefer a much higher confidence, together with an associated incidence of, say, less than 1 tumor per 500,000 test animals. To obtain such a projection with 0.999 confidence would require negative results in over 3,000,000 test animals.

Brute-force reliance on statistical replications is, therefore, severely limited by practical considerations. Furthermore, indirect adverse effects, such as damaging overextension of the stomach and gut, elicited only at very high levels of testing, may not necessarily be causal under actual conditions of human consumption. A reasoned dissection of the clinical significance of a smaller body of solid experimental data frequently appears to be the only feasible avenue to the evaluation of food safety. To be meaningful, statistical confidence should provide some quantitative insight into the strength of causation at various consumption levels.

**CONSUMPTION DATA**

The hazard to a person from the consumption of a potentially toxic substance is a function of, among other factors, individual susceptibility, average daily consumption, and duration of exposure. With few exceptions, the best available data for GRAS substances fall far short of permitting a fully satisfactory estimate of safety in this refined sense.

Only one survey of GRAS substances added to American food commodities has been conducted. A subcommittee of the National Research Council (NRC) sent questionnaires to food manufacturers concerning the usual and maximum levels of addition of the respective GRAS substances in each of a number of broad food categories (36, 89). To translate the resulting estimates of the amount of each substance used in the manufacturing process into possible human intake, the subcommittee relied on the records of the Market Research Corporation of America on the frequency of consumption of various food items and of the United States Department of Agriculture on the meal portion size of foods in the various categories.

A number of assumptions were made, which usually led to overstated intakes. One of these was that a given ingredient was used in all foods within a specified category, when in fact it might have been used in only one or a few. No adjustments were made for losses during processing, transit, storage, or meal preparation. An additional contribution to the overestimation of intakes of certain GRAS substances reflected misunderstandings. In such instances, the manufacturers appeared to have reported the concentration of the substance in a dry powder rather than in the food as consumed. Thus the concentration of calcium gluconate in baking mixes was listed as 1.59% and the concentration in gelatin, puddings, and fillings as 2.34% (89). Based on these figures, the possible average daily intake for individuals more than 2 years of age was calculated to be 2,665 mg, whereas the daily American per capita intake calculated by the same subcommittee from the total poundage added to food was only $3 mg.

Under the circumstances, the NRC subcommittee recognized that its estimated average total daily intake of the added substance might well be much higher than would be the intake by individuals consuming a diet consisting completely of processed foods in which the GRAS substances were present at the maximum levels. The discrepancies between its estimates and the reality of consumption in many instances were orders of magnitude. As a practical expedient, we sought corroborating estimates by dividing the total production and import of a given substance for food use in the United States by the population, yielding a crude per capita value. Comparative figures by the three methods for representative substances are given in Table 1.

Such figures on average consumptions are beset with further uncertainties with respect to the intakes by actual persons. A specified substance might be consumed by only, say, 10% of the population; the actual consumption by such a segment would be ten times that estimated as the average for the entire population. Surveys of the more common commodities by the Department of Agriculture (125) showed that in the highest consumption category, 10% of the people eat 1.5 to 3.5 times the average consumption of the remaining 90%. The limited data on the national distribution of qualitative and quantitative eating patterns constituted a serious obstacle to the accurate determination of the actual exposure. It would have been helpful to have had acceptable estimates of consumption, both in average quantity per day and duration of related intakes, by the 1% of the population with greatest intakes of the substance in question.

There were cases in which we were able to make fairly satisfactory estimates of consumption. The intake of choline salts by infants was an example. Choline salts were added to certain commercially prepared infant formulas and to no other food an infant is likely to consume. From a knowledge of the concentration of a choline salt per calorie in an infant formula and data concerning high caloric intakes at various ages, reasonable approximations were made of the greatest amount of the compounds likely to be consumed. Such an approach was not feasible with most of the other GRAS substances, however, since they were added to a variety of different foods and little information was available concerning the consumers' patterns of food selection.

A related problem was the parallel estimate of the total dietary load of a given substance from all sources. Examples include iodine and phosphates, which are present in foods both as naturally occurring and as commercially added components.

In many instances, therefore, it was necessary for the Select Committee to offer its opinion about the probable safety of GRAS substances without the benefit of satisfactory estimates on the actual or the highest probable amount likely to be consumed. The formidable difficulties that faced the National Research Council subcommittee were appreciated. There were about 7,000 commercial food prep-
TABLE 1. Comparative estimates by different methods of daily intakes of GRAS substances

<table>
<thead>
<tr>
<th>Substances</th>
<th>NRC subcommittee estimates based on</th>
<th>Estimates based on production and import (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Projected consumption by persons 2–9 year old (mg)</td>
<td>Quantity used in food processing (mg)</td>
</tr>
<tr>
<td>Ammonium carbonate</td>
<td>742</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>2,665</td>
<td>3</td>
</tr>
<tr>
<td>Food starch, modified</td>
<td>11,834</td>
<td>696</td>
</tr>
<tr>
<td>Gum arabic</td>
<td>2,470</td>
<td>108</td>
</tr>
<tr>
<td>Monosodium glutamate</td>
<td>1,106</td>
<td>1,435</td>
</tr>
<tr>
<td>Nutmeg</td>
<td>336</td>
<td>11</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>30,191</td>
<td>79</td>
</tr>
</tbody>
</table>

Arrations in the supermarkets at the time and thousands of new ones, most short-lived, were appearing every year (44). Furthermore, there was no prior experience to learn from; the subcommittee’s survey was the first of its kind ever attempted. Some efforts are already under way to improve the methodology of estimating food consumption.

EXTRAPOLATION FROM FACTORY TO MOUTH

“Many a slip twixt cup and lip”—this old adage came repeatedly to mind as we attempted to estimate the actual amount of GRAS substances consumed from their production, import, and processing data. The information collected in response to the questionnaires by the National Research Council subcommittee provided figures only for the quantities added by the food manufacturers. As shown by the examples given in Table 2, the concentrations span a wide range. No analytical data were given on the quantities of the GRAS substances in the food product as consumed. In most cases, there was little information as a basis for attempting a bridging.

Sulfites and sulfur dioxide represent one of the more difficult problems. These compounds are used as antioxidant, antobrowning, and preservative agents in food processing and as bacterial inhibitors in wine, brewing, and distilled beverage production. They react chemically with certain food ingredients and may become volatilized or otherwise lost in processing. This means that only a fraction of the amount originally added remains in the product consumed.

Potassium iodate used in bread and related baked goods is another case in point. Potassium iodate may be mixed along with potassium iodide or bromate, or calcium peroxide to increase dough stability. A variable but probably smaller amount of iodine is left in the product at mealtime.

A third example is clarifying agents, such as tannins. These substances are generally used to impart a more pleasing appearance to a beverage from the standpoint of brilliance and clarity. They form precipitates that are filtered out; hence the quantities of the agent used are not those ingested with the final product. Nevertheless, certain unknown amounts may be left behind as residue.

A fourth example involved some 70 GRAS substances, listed as migrating to foods from paper, paperboard products, and cotton fabrics used in packaging. In practically all cases, the Select Committee was unable to obtain reliable data on the amounts that were consumed through this avenue. In many instances, even the amounts used in the packaging material itself were unknown.

An illustrative method for the determination of the migration of such substances involved rosin compounds (25). Rosin is used as paper sizing at 1 to 5% by weight. By means of radioactive tracer techniques, the maximum average migration observed in the diet was found to be less than 9 mg per kg. The Select Committee attempted several estimates through back extrapolation. Glucose, as an impurity in starch sizing, may be used to exemplify the range of possible estimates. Reasoning backward from the amount of starch used in the paper, the total paper production, the quantity of paper used in food packaging, the amount of glucose present as a residue in the starch, and an approximation of the amount of migration from paperboard, the Select Committee arrived at a consumption of 8 μg per person per year, if the lowest value for each of the parameters was used. A consumption of 178 mg per person per year resulted if the highest value for each of the parameters was used in the calculations. It so happened that in this particular case, the quantitative difference involved was not critical in altering the final judgment as to the safety of the migrating glucose. One should hope, however, for a relatively more precise estimate for substances that may not be so obviously innocuous.

In addition to information on the substances added during the manufacturing process, therefore, there is need for much more accurate data on the quantities and identities of the related ingredients in foods as consumed.

IDENTIFICATION OF NATURAL SUBSTANCES

A source of constant and considerable uncertainty in the analyses of a

TABLE 2. Representative concentrations of GRAS substances commercially added to foods (85)

<table>
<thead>
<tr>
<th>Percent</th>
<th>GRAS substance and food commodity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>Thiamin in peanut butter</td>
</tr>
<tr>
<td>0.0002</td>
<td>Citric acid in soup bases</td>
</tr>
<tr>
<td>0.0004</td>
<td>Oil of rue in candy</td>
</tr>
<tr>
<td>0.0015</td>
<td>Stannous chloride in canned asparagus</td>
</tr>
<tr>
<td>0.005</td>
<td>Butyl hydroxyanisole in unsmoked dry sausages</td>
</tr>
<tr>
<td>0.005</td>
<td>Nicotinamide in baby cereals</td>
</tr>
<tr>
<td>0.015</td>
<td>Caffeine in soft drinks</td>
</tr>
<tr>
<td>0.02</td>
<td>Oil of clove bud in chewing gum</td>
</tr>
<tr>
<td>0.05</td>
<td>Ascorbic acid in apple juice</td>
</tr>
<tr>
<td>0.1</td>
<td>Sodium benzoate in maraschino cherries</td>
</tr>
<tr>
<td>0.3</td>
<td>Propionic acid in processed cheese</td>
</tr>
<tr>
<td>0.7</td>
<td>Carrageenan in salad dressing</td>
</tr>
<tr>
<td>1.0</td>
<td>Sodium hexametaphosphate in cakes</td>
</tr>
<tr>
<td>2.0</td>
<td>Glycerol in soda-fountain fudge</td>
</tr>
<tr>
<td>3.0</td>
<td>Acetic acid in sherbets</td>
</tr>
<tr>
<td>21.0</td>
<td>Methylcellulose in low-calorie crackers</td>
</tr>
<tr>
<td>50.0</td>
<td>Calcium carbonate in baking powder</td>
</tr>
<tr>
<td>75.0</td>
<td>Sorbitol in confections</td>
</tr>
</tbody>
</table>
number of naturally occurring GRAS substances was their imprecise identification and poorly specified composition. The GRAS listing of "algae" is an example.

"Algae" is recorded in the Code of Federal Regulations (49) as "natural substances or as their extractives that are used with spices, seasonings, and flavorings." The term referred to materials derived from two genera of brown algae (Phaeophyceae), Laminaria sp., and Nereocystis sp., and two genera of red algae (Rhodophyceae), Porphyra sp. and Rhodymenia palmata (L.) Grev. The last species is also given as GRAS under the entry "dulse" (49). Kelp, a synonym for brown algae, is presented separately (49) and, in addition, as a source of iodine in foods for special dietary use (50). In this instance, kelp is identified as the "dehydrated ground product prepared from Macrocystis pyrifera, Laminaria digitata, Laminaria saccharina, and Laminaria cloustoni."

"Mustard" and "mustard oil" represent another example of the need for specificity. There are two kinds of mustard in commerce: yellow mustard from the white Brassica seeds and brown mustard from black Brassica seeds. The two spices differ chemically. Yellow mustard contains the characteristic flavoring ingredient p-hydroxybenzisothiocyanate, while brown mustard contains primarily allylisothiocyanate. It would be an error to extrapolate conclusions on safety from one to the other simply because they are both "mustards."

It seems clear that generic identifications of natural products, such as algae and mustard, are inadequate. Modern taxonomic procedures and analytical methodologies should be employed to provide more delimiting identifications both for regulatory purposes and for assuring toxicologists that they are testing the substance actually used in foods.

**NATURAL OCCURRENCE**

Although this report is concerned primarily with man-added food ingredients, it might be well to remember that Nature herself is the most generous adder of food ingredients. The naturally occurring constituents of foods contribute by far the widest variety of chemical substances in the diet throughout man's lifetime (20). The ordinary potato, for example, whether it is grown "organically" or otherwise, contains approximately 150 distinct chemical substances that have been identified so far, the majority of which serve no known nutritional purposes.

There is a tendency to accord considerable weight on the side of safety to a commercially added food ingredient when it also occurs naturally as a normal constituent of foods that are widely consumed. Many GRAS substances fall in this class. For example, mannitol is present in small amounts in olives, beets, and celery; caprylic acid is found in coconut and palm nut oils and butter fat; traces of tin are widespread in fish and vegetables.

Just because a substance is naturally present in foods, however, is no guarantee of harmlessness. There are some naturally occurring compounds that may be recognizably toxic when ingested regularly and in substantial amounts (88). Typical examples include the goitrogens in cabbage (3), carcinogens in certain spices (78), cyanogenetic compounds in lima beans (27), and radionuclides in a range of foodstuffs (15).

**FETUS**

Information on fetal exposure was deficient for more than four-fifths of the GRAS substances reviewed. We are of the opinion that multigeneration tests alone are not a sufficiently definitive basis for ensuring safety to the fetus. Some fetuses may die early in gestation and be resorbed. In addition, long-term effects are not observed in the usual procedures, inasmuch as the test animals are generally killed when they are no more than 6 months of age.

The fetus is particularly limited in its capacity to detoxify foreign compounds (6, 100). It depends largely on the maternal systems for protection. The placental barrier not only modulates the passage of substances but also contributes to their metabolic detoxication. However, the barriers of maternal metabolism and placenta are usually not completely effective and many undesirable compounds do cross the placenta and enter the fetal circulation. Thus, the female and her fetus may be considered as a two-compartment system, in which the fetus is dependent on the absorptive, metabolic, and excretory processes of the mother (75, 79). This is an important consideration in view of the probability that most of the GRAS substances are consumed by at least some pregnant women.

Appropriate modifications of current toxicological testing protocols are under way to minimize these uncertainties.

**NEONATE**

The neonate stands peculiarly at risk when exposed to food ingredients that may offer only minimal hazard for the adult. In various animal species, hydroxylation, oxidation, and conjugation reactions are depressed in the neonatal period (54, 100). Some tissue formations are incomplete at birth, such as myelination of forebrain structures. Only traces of myelin are evident in the cortical association areas of the 3-month-old infant (141).

Many xenobiotic substances, dietary components, and their metabolites pass readily into human milk (12). The distribution of a substance across the membrane between plasma and milk is influenced by its solubility in lipids and water, its degree of ionization, and poorly understood transport phenomena. In addition, the neonate may be exposed to food additives directly as well as through passage into the maternal milk.

Major shifts in the toxicity of a given compound between the neonate and the adult have been demonstrated (57). In some of the comparative tests conducted so far, young animals appeared more susceptible than the older animals. For example, the neurotoxic effects of large amounts of monosodium glutamate were reported to be much greater in neonatal than in adult animals (74, 91). In other tests, the young were more resistant. For example, caffeine was found to be more toxic for older rats than for younger ones (95). In still others, there seemed to be no difference. For example, the acute L.D.0 values for cottonseed oil in rats of different ages were approximately the same (9).

Feeding tests of GRAS substances have generally been carried out with weaning or older animals rather than with the newborn. Most of the toxico-
logical data were collected before commercially prepared infant formulas and strained and junior baby foods became commonplace. To further complicate the problem of assessing the safety of GRAS substances for neonates, many infants are given table food during the first months of life (37).

For substances intended for infant formulations, therefore, we endorse the call of other workers (69) for toxicological studies on young animals corresponding to infants up to 12 weeks of age. This should begin with newly born animals and continue through the age of weaning and should include the usual battery of toxicological tests. Because the susceptibility of very young animals to a given compound may differ from that of adults, the accumulation of data on very young animals merits prompt attention, especially for those substances commercially added to infant formulations (37).

ANIMAL MODELS

Like others who have been concerned with the meaningfulness of animal test data in terms of human toxicity (83,86), we have come to accept the necessity of qualifying our opinions based on animal models, depending on the particular problem being assessed (76,107).

A constant feedback of test information is necessary to improve the correlation validity of a given animal procedure. The requirements for the rat-beagle-rhesus combinations, for example, which were empirically selected some 20 years ago, are not standing up as reliably for preclinical drug testing as anticipated. Nevertheless, persistent readjustments resulted in quite useful protocols (58). Carefully derived animal results can be highly satisfactory predictors provided, however, identical organ damage is not demanded.

Hope has been entertained that instead of relating the overall toxic response of a given species of test animal to that of man, a closer correlation might be realized if restricted to specific organs or classes of physiological effects. The research literature has shown preferences for the use of the mouse for cancer studies, dog for renal investigations, sheep for fetal research, guinea pig for allergy tests, pig for studies on the gastrointestinal tract, cat for explorations on acute central nervous system effects, and rat for most other categories. Their general usage does not mean, of course, that these particular species are respectively the "best" animal models of human reactions in the specific organs or physiological mechanisms involved. Considerations other than scientific ones played a large role in their selection. The low cost and short life span of mice, as well as the availability of good genetic strains, had much to do with their choice for statistically oriented cancer research.

The fact that the most extensive and creative of the earlier research on the central nervous system was performed on cats must have imparted a momentum to continuing to regard the cat as the species of choice. Such practical factors should not obscure the primacy of their predictive value for human responses relative to other species.

It might be desirable to have an official continually updated list of animal models for various tests on which food safety evaluation can be based. One could envision such a list dividing test species into those showing meaningful, indicative, and poor correlations, respectively, for various organs and physiological functions. However, we do not foresee the necessary consensus on this issue to be forthcoming in the near future.

In the meantime, one might prefer to rely on empirical preliminary observations as being the more reliable basis for the selection of the most relevant species for feeding tests. It might be worthwhile to conduct in vitro biotransformation studies on the test substance using human biopsy material, especially liver, and comparable material from laboratory animals. If the human liver tissue, for example, should metabolize the compound in a fashion similar to that of the rabbit liver, but not the rat liver, then the rabbit should be the adopted animal of choice for the 90-day feeding test. Experience encountered so far in such pathfinding investigations and similar attempts at deriving in vitro information relative to the mutagenicity of drugs and food additives point to a journey of many years.

Even if agreement could be reached on a particular species for a given evaluation, the evaluator is faced with further considerations that lead to additional discrepancies between animal protocols and the human scene.

Typical of these are the source and kind of animals used. Investigators prefer certain genetically defined strains of healthy animals to reduce experimental variability and thereby facilitate interpretation. This is not what the real human world nor for that matter the real rat world is like. People are not an inbred but an outbred population. They do not live under ideal conditions. They are not always completely healthy. It would seem that some comparative toxicological studies should be performed on animals with hypertension, diabetes, acute infectious disease, and several of the other common illnesses that befall human beings. At least a few extensive cross-demonstrations might provide a reasonable point of departure for deliberations on food safety.

The matter of housing of experimental animals represents another factor. Workers in this country usually separate the animals in individual cages in order to observe the respective food intakes and other parameters more precisely. But this is not the way human beings live. They are not hermits but interact. The practice of grouping animals that is followed by other investigators appears to merit consideration. A male and a female or a male with several females are caged together as a group. Although there are no firm grounds to suggest that results obtained under conditions of collective living possess greater toxicological validity than those under conditions of single occupancy, the impact of environmental influences on toxicity test responses deserves much attention. Some studies have shown, for example, that chronic stress increases the incidence of mammary tumors in mice (101) and singlehousing in a cage leads to earlier appearance of tumors than does communal living (2).

Finally, there is the matter of behavioral effects. Present procedures call primarily for physiological and histopathological observations. Biochemical dysfunctions and morphological lesions command prime attention. Equally careful observations on behavioral effects are not regarded.
as essential. The humanness of a human being, of course, is judged by his or her behavior, and there is much common experience on the behavioral influence of chemical compounds, such as ethanol. Only occasionally have we come across records of behavioral effects in relation to GRAS substances. The even greater difficulties in extrapolating such animal data to human behavior are recognized, as compared with those involving purely physiological manifestations. Yet it would appear that toxicologists should no longer continue to ignore the realm of psychotoxicology in defining essential criterions of food safety.

HYPERTROPHY OF THE LIVER

Enlargement of the liver is being reported with increasing frequency in the toxicological literature. Several authors feel that this adaptive change of the liver is not necessarily pathological but rather a normal response to an increased metabolic load. A substance may stimulate proliferation of the endoplasmic reticulum with increased production of enzymes for the required metabolism. The liver returns to its normal size when the administration of the substance is halted. One cannot predict, however, which enzyme will be increased, the level to which the activity will be increased, the time required for the induction, or the duration of the increased activity. Thus, although certain compounds induce liver hypertrophy and others do not, the consequences of such liver hypertrophy are not completely clear.

Butylated hydroxytoluene at high doses, for example, increases the liver weight of animals considerably (119). The consensus among investigators seems to be that the effect is reversible and without toxicological significance. Although some workers regard it as an adaptive mechanism (105), it has been demonstrated experimentally with other compounds that a point can be reached at which adaptation fails (65). The question concerning the challenge to fully adapted livers by compounds that raise the level of microsomal enzymes in the liver thus takes on added significance.

Although many of the leading authorities on liver hypertrophy seem to regard it as without special toxicological concern, it appears that further clarification of its ramifications in terms of food safety should be given emphasis. In view of the increasing use of oral contraceptives, more information should be gathered on the effects of challenging fully adapted livers by compounds that are themselves metabolized by microsomal hydroxylases.

ZERO LEVEL OF CARCINOGENS

Oil of nutmeg was the first of the GRAS substances that led us directly into the Delaney Clause of the 1958 Amendment to the Food, Drug, and Cosmetic Act of 1938.

The Delaney Clause states explicitly that “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal.” Safrole has been reported to be a weak hepatocarcinogen (67,128). A gas chromatographic analysis of East Indian oil of nutmeg was reported to have shown a safrole content of 4.2 to 6.0% (4). Should these findings be corroborated, would the Delaney Clause force a banning of the substance from foods?

Analysis of West Indian oil of nutmeg by the same laboratory, however, failed to demonstrate the presence of safrole. Does this mean that the oil of nutmeg from the West Indian plant should be cleared, while that from East Indian sources should be placed under a cloud?

Implementation of the Delaney Clause is a legal matter. In this instance, the Select Committee was only asked to provide a scientific evaluation of the potential health hazard of the ingestion of less than 1 mg of oil of nutmeg, containing about 4 μg of safrole, per kg body weight per day, when the oral LD₅₀ of nutmeg for the rat is about 2,600 mg per kg, for the mouse about 5,600 mg per kg, and for the hamster about 6,000 mg per kg (40). It is recognized that LD₅₀ values are not well related to carcinogenicity. Nevertheless, the situation raised the same host of questions over the Delaney Clause that remained unresolved within the scientific community after heated sessions during nearly 2 decades (90).

The central issue under discussion concerns the threshold effect for chemical carcinogens. According to one school of thought, there is no evidence that the lower extreme of the dose–response curve for carcinogens differs basically from that of other chronic toxic compounds; therefore, the application of a safety factor is appropriate (21). Others disagree, insisting that although the shape of the dose–response curve is well developed at the higher levels, it is poorly understood at the lower levels. Consequently, there is no evidence of a no-effect threshold (104). Along the same vein, still others claim that unlike the reversible toxic effects of many compounds, those of carcinogens are irreversible (30). This objection, in turn, has met counter objections in the belief that a satisfactory test for carcinogenicity does not require a gross departure from established principles of toxicology (112). Finally, the gnawing perplexity remains regarding the significance of high level testing in animals in terms of the causation of cancer in humans as related to epidemiologic data and dose response. The possibility has been raised that high level testing in animals might elicit expressions of secondary carcinogenic mechanisms, such as alteration in the metabolism of the gastrointestinal flora or tissue cells, thereby facilitating malignant chain reactions from another independent cause that are not operative under low intensity human exposures (73).

The polemics over the question of threshold versus no-threshold (118) can be viewed somewhat in the nature of mathematical games when the extrapolations are carried out to a billionth of the known reactive range. The biological meaning of such extreme dilutions has never been established; whether one billionth of the reactive dose of a carcinogen is metabolized in the same manner is not clear. The dilemma mounts when the question of handling different physiological responses is raised. For example, should all neoplasms, benign as well as malignant, be lumped together, or should hepatomas, skin tumors, and the like be considered separately?

The concept of carcinogenesis as a one-reaction class might have been defensible some 40 years ago, when polycyclic hydrocarbons isolated from tar were the only chemical carcino-
gens known at the time. But soon thereafter it was discovered that the azo dyes produce liver cancers after metabolic conversion. These compounds act very differently from the direct-contact hydrocarbons. Today, many chemicals are known, exhibiting such a wide range of chemical structures and mechanisms of action, and producing so many types of neoplasms in different species that there is need for greater specificity and limitation in the definition of carcinogenesis in the analysis of health hazards.

The rationale of approaching hepatocarcinogens in the same manner as hydrocarbons or ultraviolet light seems tenuous. One is hard put to consider agents that stimulate a wide variety of cancers in all of a group of mice within a few weeks as similar to agents that evoke, or are associated with, a few sarcomas at the site of repeated injections over several years of administration. It is equally difficult to group agents that are active in microgram amounts with those that are active only in amounts comprising a significant fraction of the total diet of the animal over a large part of its lifetime.

The fact is that a conclusion of "carcinogenesis" is either obvious and self-evident in an experimental system or in a human exposure situation, or its characterization is a difficult judgmental matter. The latter requires statistical consideration to determine the probability of an informed group of scientists to decide whether a "significant" and presumably reproducible effect was obtained. Even with this decision in hand, the "true" relevance of animal data to man is subject to considerable debate, as has been discussed in the Section on Animal Models. The correlation between carcinogenic effects on rodents and those on man is not sufficiently consistent for confident extrapolation (86). Societally, however, it seems sensible to avoid potential and probable hazards as defined by animals without actual confirmation in man.

The Delaney Clause had been advanced as a legal barrier against a variety of potential exceptions to and modifications of prohibitions on the use of substances that might otherwise have been designated as noncarcinogenic. What is labeled carcinogenic, however, is often a decision of a group of experts examining specific data. The law can be recorded in absolute terms; fallible human judges must interpret empirical applications.

As far as nutmeg is concerned, whether or not the Delaney Clause does constitute a legal requirement for the banning of GRAS substances is a matter of interpretation among various authorities. Based on a scientific analysis of the available evidence, however, the Select Committee saw no evidence that the current level of consumption of saffrole in nutmeg constitutes a health hazard. It suggests, nonetheless, that appropriate studies be undertaken on other compounds present in nutmeg, such as the methoxy derivative myristicin, which is present in amounts up to 5% and may possibly be converted metabolically into saffrole.

**MUTAGENICITY**

Our attempts at distilling meaning from the findings of some of the current mutagenicity tests were somewhat discouraging.

Beginning with carob bean gum, our very first case in 1972, we were supplied with data from three approved tests for mutagenicity. These were somatic cell cytogenetic technique, dominant lethal assay, and host-mediated assay (59). Long hours were spent discussing the significance of the test results and the weight that should be given to the respective conclusions in the overall evaluation of the safety of a given ingredient.

Carob bean gum showed negative results in all three tests. Did this suggest the absence of mutagenic effects in human beings? Sterculia gum also gave negative results in the cytogenetic and the host-mediated assays, but the dominant lethal procedure gave inconsistent findings. Did this call for an equivocation about the safety of sterculia gum?

Sorbitol did not produce any measurable response in the dominant lethal and the host-mediated assays; but a slight increase was noted in the mitotic recombination frequency for Saccharomyces cerevisiae in the host-mediated assay and a moderate, dose-related adverse effect on human embryonic lung cells scored at anaphase.

Should sorbitol have been marked down on this account?

Around and around we went, as the cases kept coming in with all kinds of combinations and permutations of results. We tried to make the best judgments under the circumstances and included them in our final reports.

Then, a year later, we were informed that the earlier confidence on the predictive value of the tests had been shaken. Experts were far from unanimous in their support of these three tests. Some regarded all three to be unreliable predictors of mutagenicity in human beings (35).

It seemed that the original proponents might have been unduly attracted by their relative simplicity and time economy. Were they probably encouraged by the successful measurements of the mutagenic effects of radiation by similar techniques. Subsequent observations, however, showed vitiating inconsistencies. Known carcinogens, such as nitrogen mustard, were cleared by the dominant lethal test. Even compounds with known potential for reacting with DNA, such as epichlorohydrin, did not respond positively to the same test. Known innocuous compounds failed one or more of them. Statistical difficulties in the interpretation of inconsistent results within a single study also complicated the picture.

The announcement confirmed our suspicions, although we continued to assess the significance of the available data as supplemental information. The downgrading of the status of these three tests, however, left evaluators without an accepted and definitive criterion of mutagenicity for the time being. It is our understanding that FDA plans to fill this void by exploring the feasibility of a "three-tier" approach, involving progressively more complicated techniques that are, it is hoped, more predictive of the human response.

Recent work on mutant strains of bacteria and recessive lethals of drosophila offers interesting new scientific leads (16). Only practice will show, however, whether these and other studies under way will constitute a significantly more promising basis than those that gave rise to the three superseded protocols. In any case, some rather basic investigations on the subject are in order at this time.
TERATOGENICITY

Practically all of the guidelines on toxicological testing for food additives call for teratologic observations. The translation of results from experimental animal teratology to human malformations, however, is still in a primitive state. In the recent most complete comprehensive compilation of over 600 agents producing congenital anomalies in animals, only about 20 are known to cause human defects (111). Not only do different species of animals react differently to a given experimental teratogen, but even different members of the same litter are dissimilar in their reactions (86).

Our examination of the results of tests specially designed to determine teratologic effects of a group of GRAS substances (39) did not obviate uncertainty. In one series of investigations, relatively large quantities of gums dispersed in corn oil were administered by oral intubation for 10 days, beginning with the 6th day of gestation. The translatability of oral intubation of large amounts of a substance in an unusual carrier to conditions of human consumption came under considerable questioning. In many cases, doses approximating the LD₅₀ had to be used to obtain indications of teratogenicity. Maternal deaths occurred at these high intubations even from compounds such as methyl cellulose that showed no teratogenic manifestations in this particular test and no adverse signs in standard toxicological feeding tests.

Various alternative approaches and improvements in teratologic detection have been recommended (19,32,43). One of the more recent is a "four-level" sequence with different species of animals (138). Testing for teratogenic effects should include exposure over the entire gestation period, administration by the oral route, and several levels of intake to provide dose-response curves. These seemingly obvious requirements have not been met by most of the reports in the literature. They are beginning to be adopted as regular practice in current procedures.

ALLERGENICITY

The literature on foods is spotted with references to allergenicity. So far, allergenicity has not constituted a decisive factor in our evaluation of GRAS substances. However, it has been the subject of considerable discussion. The more we delved into it, the more we became concerned over the general state of knowledge regarding some of the most elementary aspects of food allergy.

There are relatively few accurate figures on the prevalence of allergic sensitivity to various food ingredients. Part of the confusion arises from the failure to distinguish between immunologic reactions, which alone are properly definable as allergic, and other adverse reactions of a nonimmunologic origin. Some workers (55) suggest that food allergy is relatively uncommon. Others (31,102) claim it to be more widespread than most people realize. The National Institute of Allergy and Infectious Diseases (33) estimated that about 6% of the population suffer from atopic eczema, angioedema, urticaria, drug allergy, food allergy, or bee sting allergy, excluding migraine. The data did not indicate what fraction is ascribable to food allergy alone. It is impossible to say what fraction of this unknown fraction is related to commercially added food ingredients, such as the GRAS substances corn syrup (98,99) and vegetable gums (10,46).

Detection of allergenicity to a given substance lacks clear-cut diagnostic criteria. Current practice involves a careful history and the selective exclusion of an array of suspected foods or food ingredients from the diet, followed by subsequent provocation testing with the suspected food. This ponderous procedure is fraught with weaknesses and opportunities for inaccuracies. To obtain reliable observations on the prevalence of susceptibility, a dependable and practical test needs to be developed and performed on large numbers of subjects.

Animal experiments may also play a significant contributory role. It was through animal tests, for example, that conclusions were reached that the antigenic property of acacia gum was due to the gum itself rather than a contaminant (113). But if the evaluator is hard pressed to predict allergic response from one group of human beings to another, what confidence would he enjoy in attempting to extrapolate the response from an animal species to man?

Confronted with a discouraging lack of promise for the development of a reliable yet relatively simple test in the near future and the rather crude state of knowledge on the prevalence and basic mechanism of food allergy, one is tempted to strike food allergy from the list of important toxicological symptoms because of its presumed infrequency. This attitude may be encouraged by reports that most of the symptoms and signs of allergy are transient and that most of the reactions, such as urticaria and angioedema, are relatively minor. Yet there are published claims of more serious consequences (56). The fact that food allergens may be cross-reactive, as is apparently the case with gum tragacanth, gum arabic, and karaya gum (47), imparts an additional increment of concern on the subject.

The situation needs much clarification. Research from fundamental laboratory studies to epidemiologic surveys should be fostered.

ENZYME INDUCTION

The demonstration of enzyme induction on the part of some GRAS substances has led to some speculation over its relative importance in the assessment of health hazard. Although the pharmacological implication of microsomal enzyme induction has been recognized for a number of years (16), there is no unanimity on its toxicological significance. As mentioned in the Section on Hypertrophy of the Liver, there is considerable uncertainty concerning the mechanism of the process itself.

Since it is known that the presence of one chemical may affect the toxicity of another through enzyme induction (11,45,63), the question arises as to the weight to be attached to observations such as the induction of hepatic microsomal enzymes by butylated hydroxytoluene and butylated hydroxyanisole. Although no account has come to our attention on microsomal enzyme induction in extrahepatic systems by these compounds, they may theoretically stimulate the activity of steroid hydroxylating enzymes, as is the case with certain other microsomal enzyme inducers (94), and adversely affect
certain reproductive and other biochemical processes.

It would appear that a phenomenon as fundamental as enzyme induction should attract much greater attention than it has in the past, particularly with respect to its place in the hierarchy of warning signals on the health hazards of food additives.

**INTERACTION WITH DRUGS**

The ingestion of foods containing tyramine, such as cheese, producing hypertensive crises in patients taking the antidepressive drug tranylcypromine is a classic example of food–drug interactions. Tyramine-containing foods apparently stimulate the release of norepinephrine, which likely results in the sharp elevation in blood pressure. The release is also accelerated by the drug itself.

We would be surprised if suitable tests on GRAS substances failed to show food–drug interactions to a greater extent than has been reported in the literature to date. A few publications have come to light on the absorption of certain GRAS substances. Relatively small amounts of aluminum-containing antacids, for example, promptly resulted in impairment of the utilization of phosphorus and brought about a secondary loss of calcium (114). One may surmise with some justification that such a concern probably is not as imperative for the general public as for special groups of consumers. Yet in view of the widespread practice of taking numerous medications, often without medical supervision, it would seem appropriate to give this subject some serious consideration in the near future.
Arriving at judgments on health hazards

As can be gathered from the preceding discussions, the literature on GRAS substances represented a wide spectrum of evidential adequacy for the evaluation of health hazards. Not only did the nature of the data vary, but the reliability of the investigators, the rigor of the testing, and the extent of independent confirmations left much to be desired. Many of the earlier observations on toxicity were quite ancillary to the main purposes of the original work.

The conventional lists of criteria for judging the safety of food additives could serve only as an elastic framework for arriving at our own evaluations. Each GRAS substance had to be assessed within its own context and with what data were available.

The "reasoned judgment," which was spotlighted in the Food Additives Amendment of 1958, became our principal thread of consistency in rendering opinions on the various GRAS substances. But, as indicated in the following sections, this was easier stated than implemented.

CONSENSUS

There was considerable latitude for individual judgment as to which of the five categories described in the Section on Categories of Judgment was most fitting for a given substance. At times, we found ourselves in extensive debate, especially regarding which of the first three categories was most appropriate. As a general approach, we eschewed the tactics of resorting to majority and minority opinions, which would evoke protracted disputations. It was our feeling that a statement of consensus, without obfuscating areas of uneasiness, would prove of greater utility to FDA than an elaboration of divergent views without resolution.

In most cases, we were able to arrive at a consensus as to the applicable category after a reasonable amount of discussion. In those instances that involved a lengthy exchange of views, we have, on reflection, noted that some members tended to select that alternative that seemed to reflect the probability of the empirical findings at hand. Others tended to follow the old adage on decision making, i.e., in situations of considerable uncertainty involving matters of great import, select that alternative that, if wrong, would result in the least harm.

As to which direction the Select Committee as a whole has pointed, we, of course, are not in a position to say. Our own belief is that, as a group, we have avoided prior tendency toward one or the other pole, with an opinion being formed separately on each substance as it came along. It is interesting to note, however, that during the early stages of our work, the Select Committee was characterized by one editor (28) as "proceeding on an ultraconservative basis."

SUBCONSCIOUS LEANINGS

Each person brings with him a personal set of experiences and, with it, certain inclinations to the judgment table.

In general, it appears that an industrial scientist is somewhat more impressed with the practical ramifications of a given assessment of safety than an academic scientist and thereby is more susceptible to adding a subconsciously increased weighting on matters of practicality. Scientists with long tenure in a regulatory agency seem to be somewhat more influenced by prior official positions, such as those on labeling, than scientists with an academic background. A basic research scientist is likely to be somewhat more sensitive to theoretical possibilities, such as connotations of enzyme induction, than is an applied research scientist, who may be somewhat more moved by empirical feeding test data and directly associated no-adverse-effect thresholds.

There may also be grounds to suspect that an evaluator with personal affliction to a given illness might give greater or lesser recognition to certain pieces of evidence than another evaluator not so affected, depending upon the situation. A person with hypertension, for example, might add greater weight to the potential contributions of \( \text{F} \text{or} \text{ice} \) to hypertension. On the other hand, should he be sick and tired of tasteless diets, he might well subconsciously minimize the corresponding contributions of salt in the same direction.

A randomly drawn panel of qualified experts might be reasonably well balanced in subconscious leanings. However, should all of the members come from the same professional and experiential mold and vintage, their intuitive biases actually might reinforce each other's and amplify the group's skewness.

Mature judgment implies, of course, self-discipline against such distortions. Special responsibility in being aware of one's own predilections is particularly in order on the part of the members of evaluation panels who have been selected from limited sectors of society.

OFFICIAL REGULATIONS

It is good sense to study the various opinions that have been formulated by others on a given substance before expressing one's own. The Select Committee routinely reviewed the official pronouncements on the safety of food ingredients from as many countries and organizations as available.

A wide diversity in approach is evident. Among the less developed countries, official regulations leave the decision of controlling food ingredients largely to the good offices and social sense of their citizens. The United States seems to have one of the most systematic and tightly enforced procedures.

In those instances in which specific limitations were stipulated as to the levels of commercial usage, we tried to analyze the underlying bases. Here again, considerable variation exists not only from one country to the next, but also from one ingredient to the next within the same country.

When we attempted to find out why an upper limit of 286 ppm for tin in canned foods was established in a cer-
tain European country in 1908 and why it was changed to 250 ppm in
1953, the best explanation we were able to gather was that these concen-
trations constituted “good” manufacturing practices at the respective
times. When we attempted to find out why an upper limit of daily intake of
0.5 mg for butylated hydroxytoluene was recommended by an interna-
tional expert committee in 1964, we were unable to identify the explicit
supporting data and concluded that it must have represented an ad hoc
opinion of the group of individuals involved.

Before accepting the published judgments as anything more than
an intuitive confirmation or contradiction of one’s own conclusions,
it is important to explore the bases for the judgments.

HISTORY OF USE
One of the arguments advanced for the assumption of safety of most of
the GRAS substances is their long history of use. Yet the fact that a
substance is said to have been consumed for a long time without overt
harmfulness does not warrant the conclusion that it is necessarily in-
nocuous, especially in its long-term effects.

The usual clinical reports are associated more with acute than with
chronic observations. The difficulties surrounding attempts at rigorous
epidemiological surveys are well known. A minimum of a lifetime,
some 70 years, would be necessary to eliminate possible effects, such as
arteriosclerosis and prostatic carcinoma. It is unlikely that disease rates
would remain stable over such a time period. The possible role of dietary
substances would remain moot unless their effects were rather striking and
somewhat rapid in development. Nor should a record of consumption of
certain substances by one group necessarily mean that the same level of
intake should be legally adopted as safe by another group. Caution
should also be exercised against the automatic assumption of safety for a
given substance on the basis of its having been in long use in conjunc-
tion with another food commodity and purpose, or of its chemical
analogy having been in long use for the same food commodity and
purpose.

It would be intellectually blind to ignore gross observations, anecdotal
data, and general experience. Yet the inclusion of such notes of evidence
as a theme of safety should always be played against the chord of
tentativeness.

RELATIVITY OF TOXICITY
The fact that a substance has been reported to have exhibited “toxic”
influences in a scientific communication or included in an official list of
“toxic substances” should not in itself constitute a basis for regarding it as
unsafe for human consumption. One needs to consider the quantitative
aspects of toxicity and refrain from drawing black-or-white demarcations.
The GRAS substance hydrochloric acid, for example, is a corrosive
poison at high concentration, but a normal gastric product at lower concen-
trations. To paraphrase Paracelsus, it is the dose that makes the poison.

To evoke dramatic physiological reactions in animal experimentation,
some investigators push the doses to such levels that they border on the
impossible in terms of corresponding human intakes. The literature is
studded with such “toxic” manifestations. In one experiment, for exam-
ple, casein was stuffed into rats until an appreciable mortality re-
sulted from rupture of the stomach. Examples of such lethality thresholds for
common food ingredients are presented in Table 3.

Whether such massive doses are meaningful in establishing safety
criteria is debatable. Different metabolic pathways may be followed when
the dose of a chemical is low and when it is high. This would suggest
that the range of doses for safety evaluations should preferably extend
from low to moderately high levels, rather than extrapolating downwards
from huge levels.

The definition employed in the Registry of Toxic Effects of Chemical
Substances (15), however, has equated all positive responses, including those
at extreme intakes or by other forms of administration, with “toxicity.” To
quote: “A toxic substance is one that demonstrates the potential . . . to
adversely affect the health of a normal or disabled person or any person of
any age or of either sex by producing reversible or irreversible bodily injury or
by endangering life or causing death from exposure via the respiratory tract, skin, eye, mouth,
or any other route in any quantity, concentration, or dose reported for
any length of time.” By this official definition, therefore, a substance
with the potential of eliciting an adverse response at even an absurd
level of human consumption is “toxic.” Taken literally, every existing sub-
stance is “toxic.”

The majority of authors experienced in the field of food additives are careful in gauging human
 toxicity from experimental conditions and concentrations. Instead of taking the lowest level at which an
injury is noted from any route of administration, they usually adopt the highest level of oral consumption
at which no adverse effect is noted in the experimental animals as the point of reference. By applying,
say, a 100-fold margin of safety, a tentative threshold for human safety is obtained. The figure is then refined
upward or downward depending on factors such as reliability of the experimental results, absorption from
the gastrointestinal tract, and uniformity of species responses (86,135). Estimated margins of safety for food
additives in commercial use have ranged from as low as 20- to 500-
fold. It may be less for special groups of consumers (20). Undesirable re-
sponses might be elicited in such persons, for example, from increasing
the normal dietary intake of vitamin A and D only 10 to 40 times and

<table>
<thead>
<tr>
<th>Substance</th>
<th>Lethal range (g/kg)</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum tragacanth</td>
<td>10–20</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Glucose</td>
<td>22–36</td>
<td>Dehydration and tissue inflammation</td>
</tr>
<tr>
<td>Sucrose</td>
<td>25–47</td>
<td>Dehydration and tissue inflammation</td>
</tr>
<tr>
<td>Starch</td>
<td>&gt;336</td>
<td>Bowel obstruction</td>
</tr>
</tbody>
</table>
of iron only 5 to 10 times. Even current levels of sodium chloride might induce untoward effects among more susceptible individuals.

Such an approach at establishing safe limits appears sensible and workable when reliable quantitative figures are available. In the case of most of the GRAS substances, however, the quantitative data on both human consumption and toxicological reactions leave much to be desired. The narrow base of experimental information must then be supplemented with empirical experience over a range of related compounds and discriminating judgment as to the relevant inferences that are permissible. In any case, the semantics of “toxicity” should not becloud common sense.

CHECK LIST FOR CONCLUSION ADEQUACY

Judges and other decision makers usually develop their own personal ways to check the appropriateness of someone else’s or their own conclusions. We have generally followed four points of departure in determining the probable zone of safety. This is then subjected to finer adjustments.

The first point of departure is an examination of empirical data from the battery of toxicological tests (42). The conclusions point to a threshold of maximum intake of the substance in question at which no adverse effects were observed, as described in the previous section, as well as the character of the dose-response curves.

The second point of departure is a study of the nature of the substance itself and its biochemical characteristics, such as absorption, transport, biotransformation, storage, and excretion. Substances that are not absorbed from the intestine, such as methylcellulose (72), are less likely to produce systemic toxicity. Lipid solubility of a substance tends to increase its penetration of body membranes (106), including the placenta (134). The potential formation of free radicals or other reactive metabolites, as might be the case with certain unsaturated compounds, needs consideration (97). These analyses provide some indication to the evaluator as to whether certain specially designed studies are required beyond those conventionally conducted in evaluating the safety of food.

The third point of departure is an estimate of the quantity and nature of the substance or its derivative that is actually consumed. With most GRAS substances, the available data were limited in accuracy. As discussed in the Section on Consumption Data, this has forced greater than desired reliance on presumptive judgments. In any case, the principle of the method still holds. By multiplying the estimated human consumption by a factor appropriate to the substance, perhaps one hundredth, a tentative figure is obtained for comparison against the safety threshold derived from the highest no-adverse-effect dose determined from toxicity and other observations and theoretical considerations.

The three lines of reasoning described so far are related to each other in that they indicate the extent of exposure that may constitute a hazard. The fourth line is different. By itself, it reveals nothing of hazard. It does assist, however, in fleshing out the interpretations of the tentative conclusions on food safety.

The fourth point of departure is a study of the commercial process and the evolving eating patterns of the American people. Based on an understanding of the manufacturing function of a given GRAS substance, the available substitutes, and other related factors, a projection is made as to the probable trend of its usage. The volume would tend to decrease as cheaper substitutes come on the scene. On the other hand, the volume of a given GRAS substance would tend to increase with the dissemination of unfavorable safety reports on other ingredients added for the same purpose. So would the increased variety of foods that might be commercially enhanced through its addition. Finally, the projected future human consumption would also be influenced by changes in the eating habits of the population.

The judgmental interplay around the zone of intersections of these four lines of reasoning further takes into consideration such relevant factors as the adequacy of data, uniqueness of the substance, length of human experience, appropriateness of animal species for human comparison, and credibility of the information sources. In this way, a best estimate of the situation can be refined and the validity of the conclusion tested.

CHECK LIST FOR REPORT ADEQUACY

A simple check list for adequacy of our final reports was developed. The following items were given special attention:

a) Is the opinion clear and convincing, and does it lead logically to the conclusion?

b) Have statements that may be misunderstood or that may lead to unintended inferences been clarified?

c) Has the degree of associated reliability, factuality, or speculation been made explicit in the presentation of comments and data?

d) Have alternative conclusions been given fair and thorough consideration?

e) Although it is not a specific responsibility of the Select Committee, does the report provide a basis for definitive and feasible implementation on the part of the regulating officials?
Translating scientific assessment into official regulation

The translation of scientific assessments into official regulations lies within the authority of the Commissioner of Food and Drugs, operating under the regulatory constraints of current laws, and beyond the purview of the Select Committee. Our deliberations were restricted to a scientific evaluation of the potential health hazards of GRAS substances according to a definite set of guidelines, as has been explained in the Section on Categories of Judgment. Accordingly, we took considerable pains not to permit extraneous factors to interfere with the scientific soundness of our opinions and conclusions on safety. At times, however, considerations regarding the translation of scientific assessments into official regulations became inextricably imbedded within the very context of our legitimate concern. The following discussion represents some thoughts in the penumbra of our focal interest.

FREEDOM OF CHOICE

Encroachment on the freedom of consumer choice constitutes one of the principal arguments for greater regulatory control of commercially added food ingredients over those added in the kitchen. Freedom of choice implies a right of citizens that has gained increasing prominence of late, that of informed consent.

The underlying rationale runs somewhat as follows: in buying a commercially prepared food commodity, the consumer is not as free to exclude a particular ingredient as would be the case had he or she prepared the mixture at home. No meaningful choice is possible if the chooser is unaware of, or cannot distinguish between, alternatives. As the commercial mixtures grow more complex and the manufacturing processes more technical, the buyer finds it extremely difficult to know what he or she is actually getting. The problem becomes progressively more taxing as the range of subchoices in products is increased, while the basic choice between highly processed versus less processed commodities becomes more restricted in practice. The dilemma mounts if information about the product is withheld or obfuscated through advertising allurements.

Within the framework of our current regulatory apparatus, considerable attention is focused on relevant and accurate labeling. The consumer assumes that since all of the ingredients listed had received the prior approval of FDA, the product is safe within the limits of reasonable use. He or she may correctly suppose that recent additives have been subjected to an adequate battery of biological tests and that the degree of assurance of their safety is fairly high or that the best available scientific judgment has been brought to bear in the affirmation of safety.

SPECIAL CONSUMERS

Special consumers require special considerations. As a practical matter, it is difficult to see how the safety of GRAS substances for the general public can be fully determined for those who have peculiar needs, those with metabolic defects, or those who exhibit an inordinate desire for certain substances, such as licorice, clay, and cornstarch.

A number of individuals suffer from allergic reactions, as has been discussed in the Section on Allergenicity, or congenital deficiencies, such as galactosemia, phenylketonuria, or hepatolenticular disease (108), and react adversely to the consumption of certain foods that are harmless to the general population. Persons so affected usually come under medical surveillance at an early age and individual precautions are usually taken.

Some of the serious health problems in the United States have been aggravated not by the ingestion of unsafe food additives but by the overindulgence of natural nonadditive components of foods, which are presumed to be safe. Cardiovascular disease, obesity, and dental caries are subjects of recurring discussions.

When there are many factors contributing to the physiological equation, the question is raised regarding the fair fraction of the total onus that should be placed on the additives alone.

There is an understandable desire to protect individuals against their own idiosyncrasies. Yet in the assessment of the safety of food ingredients, as in all other human matters, a certain degree of prudent behavior has to be assumed for the great majority of the population. Otherwise, regulations would become so detailed and so cumbersome that their execution would paralyze society and the intended beneficial effect would be lost.

RISK: BENEFIT RATIO

As some sage has said, Nature never gives anything to anyone; everything is sold. The risk:benefit ratio has been advanced to add a scientific dimension to this old adage. However, there are so many indirect as well as direct consumer and producer risks and benefits so many nonquantifiable factors that go into the decision to approve or prohibit a particular commercially added food ingredient that the concept of risk:benefit ratio (24) might prove useful only as a broad umbrella-reminder to consider all ramifications of the contemplated action before execution.

One of the primary purposes of the safety evaluation procedure itself, of course, is to minimize the risk element.

A rigorous risk:benefit ratio is intrinsically impossible in the state of our present knowledge about GRAS substances and the complexity of factors associated with their use. The term calls for dividing a very uncertain probability of risk to an ill-defined assemblage of controversially adverse physiological responses in undefined units, confounded with crudely described psychological deviations and pictorial representations of pathological manifestations, by a heterogeneous collection of incongruous entities, such as economic gains expressed in dollars, conven-
ience expressed in nebulous subjectivity, palatability expressed in yet-to-be-agreed-upon measures, aesthetic appeal not expressible in numbers of any kind, and so on.

The apportioning of the total risk: benefit ratio into partial risk:benefit ratios for the various constituent food ingredients added to a single commodity compounds the theoretical problem. In the case of dehydrated potatoes, for example, lye may be used to peel the skin, sulfite to prevent browning, butylated hydroxyanisole to prevent rancidity, and phosphate to accelerate rehydration. There is plausible benefit in the use of each substance; but one would be perplexed as to how they may, respectively, contribute to the nutritionally desirable or undesirable properties of the product as consumed.

There is the further matter of balancing of advantages and disadvantages of the same substance at different levels and to different subgroups of the population. Iodine is a case in point (109). It is an essential nutrient, yet doses of 2.0 mg per day are considered toxic (140). Chronic intakes of iodine below 50 µg per day induce hypothyroidism in ostensibly normal individuals, and chronic intakes in excess of 420 µg per day are known to result in thyrotoxicosis in predisposed individuals (17). Thus, in individuals with normally functioning thyroids, the margin of safety between doses that result in hypothyroidism and hyperthyroidism may be less than 100-fold. Proposals to further fortify foods with essential nutrients have to take into account such balances between essentiality and toxicity.

It is not surprising, therefore, that there is no satisfactory formal analytical methodology for establishing risk: benefit ratios for food additives (96).

LOW-VOLUME SUBSTANCES

A relatively small number of substances account for the bulk of the ingredients added to commercially prepared foods (96). The GRAS substance sucrose is consumed in by far the highest quantity, approximating 46 kg per person per year, of which about 27 kg are used in processed foods. Next in added volume are the three GRAS substances salt, corn syrup, and dextrose. These are followed by about thirty other ingredients, which together account for about 3.4 kg per person per year. Finally the 1,900 remaining GRAS substances and food additives together add up to about 0.8 kg per person per year. When all the commercially added food ingredients are ranked in terms of quantities consumed, the median consumption averages about 0.5 mg per person per year.

The limited toxicological observations involving most of these low-volume substances create a problem in the scientific evaluation of their safety. Oil of rue is an example of the large number of GRAS substances in this class. The flavoring agent is added in amounts of less than 10 ppm in certain baked goods, beverages, and condiments. Less than 50 kg were reported as having been used in the United States in 1970, which averages about 1 µg per person per day. The LD₅₀ for mice was found to be about 2,000 mg per kg (116). No studies on the absorption, disposition, biotransformation, and excretion of oil of rue have come to the attention of the Select Committee. Nor has there been any experiment conducted on long-term feeding, mutagenicity, or carcinogenicity. There was one publication involving two pregnant guinea pigs, each given 12 drops of oil of rue (93), which apparently resulted in abortion of the fetuses. In view of the small number of animals and the extraordinarily large dosage employed, this finding is not taken as indicative of potential hazard in the case of the oil of rue. The actual amount consumed by man is extremely small, especially when viewed in the light of the relatively low acute toxicity.

Were the data in such instances on the borderline of judgment, however, and more testing was required as a consequence, it is conceivable that requirements for large amounts of toxicological data might well drive some of the low-volume GRAS substances off the market within a relatively short time. This consideration should not, of course, distort the scientific evaluation of safety hazards per se.

SPECIFICATIONS AND CONTAMINANTS

There are practical limits to the purity of food ingredients for commercial use. Complete accounting in terms of pure chemical entities is usually not necessary or feasible. Nevertheless, there are many instances where a much clearer product identification and/or specification would be highly desirable.

With the passage of the Food and Drug Act of 1906, official standards for drugs were legally established by recognition of the United States Pharmacopoeia (121) and the National Formulary (120) as the two volumes that set forth the requirements for identity and purity of drugs. No comparable reference standards were adopted for foods at the time. It was not until 1966 that the Food Protection Committee of the National Research Council compiled the first edition of the Food Chemicals Codex (87). This was given a quasi-legal acknowledgment by FDA (129). The second edition of 1972 provides descriptions, specifications of identity and purity, tests for detection of impurities, packaging and storing requirements, and functional use in foods for about 640 substances.

One of the sources of uncertainties in our evaluation of GRAS substances was relating the published biological and consumption data to the ingredients now regarded as GRAS and, in turn, to the product actually added to processed foods. In many reports, the authors have been rather casual about the nature and source of the material investigated. In studies on tannic acid, for example, it was usually referred to simply as tannic acid; occasionally as tannic acid obtained from XYZ Company, or tannic acid, USP; rarely as tannic acid with stated chemical and physical characteristics; never, in our experience, as tannic acid that conforms to the specification in Food Chemicals Codex. Recent literature is somewhat more careful in this respect than the older publications, but still inadequately so. Clinical reports are notably nonspecific. Besides failing to identify the source and quality of the substance used, authors often overlooked mentioning such important facts as the particular isomer involved.
References to gum guaiac offer an example of the imprecision of identification. The Code of Federal Regulations (48) in Section 21 CFR 121.101 (d)(2) lists gum guaiac, source not stated; Section 21 CFR 121.1163 lists guaiac from Guaiacum officinale, Guaiacum sanctum, and Balnesia sarmienti; the meat inspection regulations of the Department of Agriculture (9 CFR 318.7) lists resin guaiac, source not stated; Food Chemicals Codex (87) lists gum guaiac (gum resin) from the wood of Guaiacum officinale or Guaiacum sanctum; the survey of the food industry by the National Research Council subcommittee lists three items, namely, guaiac gum, extract; guaiac wood, extract; and guaiac wood, oil. There is no clear indication as to the degree of similarity among these various substances nor is it clear which was actually used in the particular commodity under discussion.

In general, specifications for the same item are less stringent in Food Chemicals Codex than in either the Pharmacopoeia or the National Formulary. Even though many natural products on the GRAS list meet the specifications set forth in Food Chemicals Codex, their actual composition may be quite variable from batch to batch. Since the purity has not been defined in terms of modern toxicological standards, it remains an open issue whether the permitted variation might constitute an unwitting source of potentially toxic factors.

The specifications in Food Chemicals Codex (87) usually stipulate that a food ingredient should assay not less than 90 to 98% of the named constituents. Limits are placed on the content of contaminants known to be toxic even in small amounts. The usual ceiling for arsenic is set at 3 ppm and for total heavy metals that are colored by hydrogen sulfide under specified conditions (Ag, As, Bi, Cu, Hg, Pb, Sb, Sn) at 40 ppm. Such known toxic elements, however, constitute only a small fraction of the allowable 2 to 10% of impurities. Reliance on “good manufacturing practices” alone might not be sufficient to assure that other unidentified potentially toxic substances are kept within safe tolerances among batches of GRAS substances used by the food producer.

Caramel is an example. Certain caramels prepared with ammonium hydroxide as a catalyst may contain toxic heterocyclic nitrogen compounds (136, 137). Although available information indicates that the level of these compounds in commercial food colors as currently produced and used is well below that which is toxic, a specified limitation has been placed by Food Chemicals Codex (87) with respect to particular nitrogen-containing compounds in its recent specifications in the Second Supplement.

Many instances of loose specifications or inadequate implementation of known assurance techniques have come to our attention during our evaluation efforts. It might not be belaboring the obvious if the point is repeated here that a substance cleared for use as an added ingredient in foods should be accompanied with a sufficiently tight specification so as to preclude the introduction of harmful impurities.

**TOTAL BODY BURDEN**

The possibility of overloading the metabolic system requires consideration in situations involving the addition of nutritional elements to the diet.

The essential nutrient, iron, is an illustration (22, 23). The natural content in some diets is nutritionally marginal, if not deficient, and the element is poorly utilized by many persons. Furthermore, there is a great difference in the bioavailability of different forms of iron, and the nutritional requirements vary among adults, pregnant women, infants, and adolescents. On balance, it appears to be good sense to supplement a few foods with iron as a public health measure (25). In 1971, proposals were made (130) to raise the iron content of enriched flour from around 32 mg per kg to 88 mg and that of enriched bread, buns, and rolls from around 22 mg per kg to 55 mg. Such enrichments could increase the total daily iron intake in this country by 2 to 4 mg per person.

In coping with any nutrient lack through food supplementation, however, there is always the possibility that the total intake might be excessive in some individuals who may have an idiosyncrasy in the absorption or metabolism of the nutrient in question. For individuals with idiopathic hemochromatosis, a rare inborn error of metabolism, consumption of iron-supplemented food could result in some aggravation of their excessive tissue-iron deposits. Should the demonstrated efficacy of supplementation for large numbers of persons then be withheld to avoid the possibility of harming such atypical members of society? The deeply established program of food enrichment, involving milk, flour, bread, and prepared cereals, and the adoption of public water fluoridation in many communities show that such practices have decided advantages. However, society must continue to search for more ways to protect the few individuals for whom the total body burden of a given supplement or additive may be excessive and harmful.

**INTERACTION AMONG DIETARY COMPONENTS**

GRAS substances have been evaluated on an individual basis; yet they are consumed as mixtures of ingredients in varying diets. This is another facet that needs to be taken into account in the extrapolation of scientific findings to regulatory actions.

Zinc is an example. Because of its interaction with certain nutrients and its central role as an activator of certain enzymes and as a coenzyme in many metabolic reactions, the ingestion of large amounts of zinc may bring about a variety of metabolic changes. Some effects noted in the literature include in vitro inhibition of intestinal alkaline phosphatase (a zinc metalloenzyme) (14), increase in urinary excretion of creatinine (103), and reduction in excretion of phosphorus and sulfur. The interaction of zinc with iron, copper, calcium, and other mineral nutrients may lead to a disturbance of their nutritional balance (71). There is much to be learned about the biological involvement of...
zinc; it is desirable to augment our knowledge of the interaction of zinc salts with other essential minerals.

A second example of the interaction among nutrients is that between vitamin E and iron. Vitamin E deficiency appears to be more prone to develop in premature infants receiving iron-fortified formulas than in those receiving similar formulas not fortified with iron (138).

A third example involves calcium and phosphorus compounds. When considered separately, a given amount of calcium and phosphorus compounds added to foods may be without demonstrable harm, but the calcium:phosphorus balance needs to be kept in mind. Substantial deviation from the optimum ratio might lead to physiological dysfunctions. Most of the evidence indicates that the desirable calcium:phosphorus ratio generally lies between 2:1 and 1:1. However, on the basis of standard tables of food analyses from the Department of Agriculture, a ratio of 1:2.8 was calculated for the average human diet (64). Recently, the consumption ratio was estimated to be 1:4 (77). The picture is complicated for regulatory purposes inasmuch as the total intake of both nutrients is determined much more by the amounts naturally present in foods than by those contributed through commercially added components.

GRAS STATUS

As described earlier in the Background chapter, GRAS substances include naturally occurring organic materials and chemical compounds with a long history of use as food ingredients at the time of the 1958 Amendment. Since 1958, these ingredients have been statutorily presumed to be safe until such time as positive evidence to the contrary is uncovered. As such, they have been exempted from the requirement for registration as food additives. The regulatory definitions of "scientific procedures" and "common use in food" suggest two avenues toward the establishment of safety. The law clearly permits "common use in food" as a valid basis, if so recognized by qualified experts. The Select Committee's own review was based on both the history of food use and information generated through scientific and clinical observations. It was conducted to update the judgments that were rendered around 1960, some 17 years ago.

In consonance with the spirit of the 1958 Amendment, the Select Committee accepted the burden of proof of the lack of safety in its deliberations. Although the available data in most cases might not be regarded as constituting "proof of safety," as expected for new food additives, the data provided a sufficient basis for a deliberate judgment as to whether or not reasonable doubts can be raised regarding potential hazards. Several precautions were taken to provide additional assurance as to the soundness of the evaluations. These included an exhaustive combing of the literature, a thorough solicitation of data and opinions through professional and public channels, and a complete freedom from pressures from any quarter.

Of the GRAS substances reviewed by the Select Committee, about 80% were judged as belonging to the first category, 14% in the second category, 3% in the third category, 2% in the fourth category, and 1% in the fifth category. If concurring in by FDA, those GRAS food ingredients judged as belonging to the first category may be affirmed as GRAS, with good manufacturing practices for the intended use as the only limitation, under 21 CFR 121.104.7 Those in the second category may be affirmed as GRAS, with an additional limitation on level of use, under 21 CFR 121.104. Those in the third category may be subjected to an interim regulation in the 21 CFR 121.4000 series. Those in the fourth category may be restricted to safer usage conditions or banned from use in foods (e.g., 21 CFR 121.106). Packaging ingredients falling in either the first or second category may be affirmed as GRAS, with or without limitation of level of use, respectively, under 21 CFR 121.105. Following the current round of review by FDA and the Select Committee, the 1958 list of GRAS substances would have been sorted into appropriate categories of safety with limitations ranging from stipulated uses and good manufacturing practice to outright prohibition. This is part of the FDA program of closer scrutiny of GRAS substances and clarification of related regulatory procedures.

In 1974, the Commissioner of the FDA had proposed to clarify the criteria for recognition of GRAS status. Under these criteria, GRAS substances in common use in food in the United States prior to 1958 were acknowledged not to require the same level of safety data as for new food additives (130). However, to be affirmed as GRAS, the available information on a substance must provide sufficient assurance that there is no evidence of potential hazard through its use in food. These criteria further acknowledged that where significant questions arise on the potential hazards of any existing GRAS ingredient, "the full battery of tests for a new food additive" may also be imposed.

Following the current review of GRAS substances and implementation of appropriate regulatory measures, substances proposed for GRAS status would require "the same quantity and quality of scientific evidence" as for new food additives. After consideration of the comments received from industry and the public, the Commissioner promulgated a revised series of regulations concerning the safety of GRAS substances, effective January 6, 1977 (132). The new regulations and associated commentaries clarified some of the misunderstandings regarding applicable criteria and procedures. The net result is a significant step toward increased assurance of the safety of GRAS substances and awareness by the consumer regarding the attendant bases.

We believe further advances can be made based on a fresh look at the criteria used for GRAS substances. Such a reexamination might even have legal ramifications, leading to a reconsideration of the current statutory provisions.

Several considerations come to mind. The first involves the "common use" in food as a basis for the establishment of safety. The more widespread and the longer the use, the
greater the degree of confidence one would have in assessments based on this criterion. The law, however, does not specify a minimum length of use. Even so, as has been discussed in the Section on History of Use, a history of use is not necessarily a reliable index of safety.

The second question concerns the use of expert panels. Under the GRAS concept, as enunciated in the 1958 Amendment, independent determinations of safety by any group of qualified experts are recognized as valid. As discussed in the chapter on Organizing operations, varying degrees of thoroughness may be expected depending not only on the knowledge of the individual members, but also on the overall balance of the panel as a whole, the amount of technical support, and the level of contribution from the public at large. Considerable variation in these respects has been noted over the years among expert panels that have been assembled here and abroad.

The third consideration involves the regulatory authority on the part of FDA to assure safety of GRAS substances, which is constrained to proof of unsafe use in individual court cases. This legal restriction is different from the legal interpretation held for food additives and would lead the consumer to believe that there are two levels of protection that can be expected from the government with respect to GRAS and non-GRAS ingredients.

The fourth consideration includes a number of misinterpretations, disagreements, and perplexities concerning the implications of the GRAS concept. FDA has done much to clarify the situation, but many uncertainties linger on. A typical misunderstanding is that a substance once cleared as GRAS has no limitations as to its use. A typical puzzlement is that the same ingredient may be controlled as GRAS for one use and also as a food additive in what seems to be a similar use in identical concentrations.

The fifth consideration is a consequence of the advancing knowledge concerning food safety, as discussed in earlier sections. With progress in toxicology, nutrition, food science, and regulatory mechanisms and procedures, what might have once been regarded as sufficient grounds for the pronunciation of safety may no longer be accepted as such by many authorities. It would not be expected that a set of criteria established in 1958 would continue to be valid indefinitely.

It would appear that these and other factors standing in the way of highest confidence on the part of the consumer in the uniform and reliable safety of all commercially added food ingredients, might be considerably reduced by the adoption of a single unified system of regulation. While it may not be true in practice, the very fact that a special category of ingredients (GRAS substances) exists that are handled in a manner different from the rest, leads to the suspicion that there are two levels of safety assurance for food ingredients.

The GRAS concept was necessary at the time of the 1958 Amendment. It has permitted the judicious allocation of scarce testing resources within the country. It might continue to facilitate regulatory actions for another decade or so. There may be cogent reasons even for its indefinite continuation. However, we believe that the dual classification of commercially added food ingredients has served its essential purpose and should be ended at a practicable date.

Should another round of reviews of the affirmed GRAS substances and those falling in the fifth category (see the Section on Categories of Judgment) be implemented, consideration might be given toward basing the safety evaluations more directly on finding "convincing evidence of its general acceptance of safety," as stated in 21 CFR 121.38 of the Code of Federal Regulations (53) for new GRAS ingredients, rather than more indirectly on the absence of evidence that "demonstrates or suggests reasonable grounds to suspect a hazard," as stipulated for the current review by the Select Committee. The following outline represents a feasible scheme:

a) For GRAS substances marketed prior to 1958 and which have now been in widespread use for over 50 years without a scientific basis for suspecting harmful effects, as affirmed in the current series of evaluations, no toxicity tests are required for reaffirmation as safe for human consumption in the manner and at the levels of such use.

b) For GRAS substances marketed prior to 1958 and which have now been in widespread use for less than 50 years without reported harmful effects, as affirmed in the current series of evaluations, a stipulated minimum of toxicity studies is required for reaffirmation as safe for human consumption in the manner and at the levels of such use.

c) For GRAS substances on which there are questionable toxicological observations, as indicated in the current series of evaluations, regardless of the length of usage, toxicological testing is required, similar to that for new food additives (41). We believe the following procedures are especially important:

1) acute toxicity tests with extensive and appropriate description of behavioral and pharmacologic effects, including necropsy of the test animals;

2) subchronic toxicity tests from weaning to sexual maturity on more than one species, including a non-rodent (138), with observations on growth and development, changes in blood and urine, organ function tests, and histopathological evaluation on all appropriate tissues (60);

3) chronic toxicity tests continued for the life of the animal, including the same observations just mentioned;

4) tests for carcinogenic, teratogenic, mutagenic, and reproductive effects;

5) biotransformation and pharmacokinetic studies; and

6) analytical tests on the qualitative and quantitative changes in the ingredient occurring during manufacturing, storage, and meal preparation.

d) The specific array of tests needed in each case is to be tailored to the particular GRAS substance in question. Judg-

---

8 As a result of the recodification of certain food regulations (127), 21 CFR 121.3 has become 21 CFR 170.30.
mental adaptations are required
to determine the desirable addi-
tional evidence in relation to the
nature of the substance, the
proposed manner of use, and
the anticipated human exposure.

(c) For GRAS substances marketed
after the completion of the cur-
rent review, toxicological test-
ing is required similar to that
for new additives.

(f) After such a cycle, further sci-
cific evaluation of GRAS sub-
stances is to be integrated into
the same safety monitoring sys-
tem with non-GRAS food addi-
tives. Newly uncovered signifi-
cant uncertainties as to safety
call for an immediate reexam-
nation of their status and im-
position of clarifying investi-
gations.

Most of such a program of re-
examination has already been car-
rried out or is being considered by
FDA. This is consistent with and pro-
vides an excellent transition from
the current GRAS/non-GRAS dichot-
omy to a unified system of evalua-
tion. We believe that the transition
can be effected even without a second
formal round of GRAS review. We
look 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 commer-
cially added food ingredients.
Absolute safety is the ideal toward which many individuals concerned with food protective measures aspire. Establishing the absence of potential harm, however, entails proving a negative, which is a practical impossibility. We must, therefore, settle for less than perfect testing systems, which we recognize to be so, and with which we are willing to live. The acceptance of a certain degree of risk then becomes the price of eating. The central issue behind the assessment of food safety is in defining this level of socially acceptable risk and, second, but of equal importance, of being clear as to the procedure to be followed in arriving at that threshold.

As can be gathered from the previous pages, many considerations loudly proclaim the imperfectability of evaluation methodologies and the fallibility of expert panels: the voids in information, the restricted resources and budgets for the biological and food sciences, the difficulties in estimating human consumption, the uncertainties over much of toxicological testing, the fuzzy boundaries between physiologic and pathologic responses, the limitations of experimental designs, the tangled web of social consequences associated with the introduction or withdrawal of a commercially added food ingredient, the continuous progression of scientific theories and empirical findings, the subjective interpretations of objectively recorded data, the legal and ethical restraints against the use of human subjects in evaluating food ingredients, the intuitive gaps in extrapolating from animal responses to man, the psychological pitfalls of predictive judgments, the changing cast of interested parties, and the overwhelming pressures of time, economics, and even politics.

As members of such a panel, we have attempted to perform our assigned task as best we could. We have been engaged in a first-level screening of some 400 substances on the basis of the presence of evidence constituting reasonable grounds for the suspicion of hazard. We envision this exercise as marking a transition to a new phase of regulatory procedures. We expect that GRAS substances will eventually be brought into the mainstream of food additives. Gradually the special treatment of being evaluated for the lack of evidence of hazard will give way to being evaluated for the evidence of safety, as is the practice with other commercially added ingredients.

Moving in this direction of uniformity, some toxicologists have called for a standard set of protocols for safety evaluation. These protocols could then be followed across the board for any substance, new or old, that is to be evaluated.

We feel this demand for rigidly standardized protocols fails to recognize the fact that all chemicals do not act in the same fashion. It seems more sensible to tailor the kinds of definitive tests to the nature of the substance at hand and the uses envisioned. What is needed is a set of agreed upon and actionable principles and guidelines. We hope that a generally accepted and officially approved statement will be forthcoming in the near future and continually updated through consensual validation by the community of multidisciplinary health scientists, food technologists, allied workers, and other interested parties.

Several groups of experts are attempting to define the minimum kinds of data necessary for a scientific judgment of safety. Although they find common bases for specifying necessary tests, no overall consensus as to their operational details has emerged. In the meantime, each evaluator must determine for himself or herself the practical question as to what constitutes such an essential minimum for the case at hand.

If there are fairly reliable records that the substance in question has been ingested for a long period of time by many people and no adverse effects have been ascribed to it, one would be inclined to give considerable weight to claims for its wholesomeness. However, this may not constitute a sufficient basis for scientific assurance of safety. There should be a reasonable body of controlled experimental data. The more information there is beyond this minimum, of course, the more credible will be the resulting predictions on safety.

For the present, we need to focus our attention on getting the maximum interpretative value out of the available tests. Too many of the investigations that have been reported in the past have not exploited the full power of these methods. For example, in a large number of instances the reports on LD₅₀ merely stated the number of dead animals in a specified period, usually 14 days. They presented no account of the calculations involved, such as the slope of the mortality curve. Nor have they noted the behavior of the animals, the weight changes, and signs accompanying death. These supplementary data would provide considerably more insight into the possible mechanism of the toxic action of the material under test.

We look forward to improvements in the design and conduct of tests, as well as in the recording of results. Such improvements will greatly facilitate the tasks of subsequent panels in assessing food safety. Of particular urgency are those related to teratogenicity, mutagenicity, and carcinogenicity.

Our association with confreres interested in food safety throughout the world and our study of the biological and toxicological literature of the last decade have given us considerable optimism that the near future will bring progressively more valid predictions of human responses to candidate food additives. A new generation of scientific evaluators with a broad philosophical and operational outlook is appearing on the scene. They are capable of launhing scientific analyses with problem-oriented insights and of meaningfully melding scientific theories and laboratory observations into the realism of the practical world.
The scientific evaluation of food safety is thus becoming well integrated into the common effort of conserving our food resources for the nutritional well-being of man.

REFERENCES


97. Pryor, W. A. Free radical reactions


Appendix A

SUBSTANCES EVALUATED

The following substances, listed alphabetically, had been or were being evaluated by the Select Committee as of June, 1977. Each substance as listed in the Code of Federal Regulations (127) is identified by the appropriate code number(s). Those substances that have been given approval for various uses but have not yet been published in the Code of Federal Regulations are identified by the letter p. A number in parentheses following a substance identifies the specific report of the Select Committee, listed in part B of this Appendix, that covers the evaluation of the substance.

Substances

Acacia (gum arabic) 184.1330, 186.1330 (1)
Acetic acid 182.1005, 182.90, 182.70 (82)
Aconitic acid (achelic acid, equsiitic acid, citric acid) 182.60 (41)
Adipic acid 182.1009 (80)
Agar-agar 182.7115 (23)
Algae, brown 182.40 (38)
Algae, brown (kelp) 182.30 (38)
Algae, red 182.30, 182.40 (38)
Alum (double sulfate of aluminum and ammonium potassium, or sodium) 182.90 (43)
Aluminum ammonium sulfate 182.1127 (43)
Aluminum calcium silicate 182.2122 (61)
Aluminum hydroxide 182.90 (43)
Aluminum oleate 182.90 (43)
Aluminum palmitate 182.90 (43)
Aluminum potassium sulfate 182.1129 (43)
Aluminum sodium sulfate 182.1131 (43)
Aluminum sulfate 182.1125 (43)
Ammonium alginate 182.7135 (24)
Ammonium bicarbonate 182.1135 (34)
Ammonium carbonate 182.1137 (34)
Ammonium chloride 182.90 (34)
Ammonium hydroxide 182.1139, 182.90 (34)
Ammonium phosphate (mono- and dibasic) 182.1141 (34)
Ammonium sulfate 182.1143 (35 & 34)
Ascorbic acid 182.3013, 182.5013 (59)
Ascorbyl palmitate 182.3149 (59)

Baking soda (sodium bicarbonate) p (26)
Beef tallow 182.70 (54)
Beeswax, bleached (white wax) 182.1975 (46a)
Beeswax (yellow wax) 182.1973 (46a)
Bentonite 182.1155 (90)
Benzoic acid 184.1021 (7)
Biotin 182.5159 (92)
Butane 182.1165 (112)
Butylated hydroxyanisole 182.3169 (55)
Butylated hydroxytoluene 182.3173 (15)

Caffeine 182.1180 (89)
Calcium acetate 182.6185 (45)
Calcium alginate 182.7187 (24)
Calcium ascorbate 182.3189 (59)
Calcium carbonate 182.5191, 182.1191 (26)
Calcium chloride 182.6195, 182.1193, 182.90, 182.70 (45)
Calcium citrate 182.5195, 182.6195, 182.1195 (84)
Calcium diacetate 182.6197 (45)
Calcium gluconate 182.6199, 182.1199 (45)
Calcium glycerophosphate 182.5201 (74)

Calcium hexametaphosphate 182.6203 (32)
Calcium hydroxide (lime) 182.1205, 182.90 (72)
Calcium hypophosphite p (73)
Calcium iodate 582.80 (39)
Calcium iodobehenate 582.80 (39)
Calcium lactate 182.1207 (116)
Calcium oxide 182.5210, 182.1210 (72)
Calcium pantothenate 182.5212 (93)
Calcium phosphate (mono-) 182.6215 (32)
Calcium phosphate (mono-, di-, tribasic) 182.5217, 182.1217 (32)
Calcium phytate 182.6219 (45)
Calcium propionate 182.3221 (79)
Calcium pyrophosphate 182.5223 (32)
Calcium silicate, 2% 182.2227 (61)
Calcium silicate, 5% 182.2227 (61)
Calcium sorbate 182.3225 (57)
Calcium stearate p (54)
Calcium sulfate 182.5230, 182.90 (33)
Caprylic acid 182.3025 (29)
Caramel 182.1235 (20)
Carbon dioxide 182.1240 (117)
Carboxymethyl cellulose 182.70, p (25)
Carboxymethylhydroxyethyl cellulose p (25)
Carnauba wax 182.1978 (47)
Carob bean 184.1343 (3)
Carotene 182.5245 (111)
Carotenes p (111)
Carvone, d- or l- (carvone) 182.60 (22)
Casein 182.90, p (96)
Caseinates p (96)
Cellulose (pure and regenerated) p (25)
Cellulose acetate 182.90 (25)
Cholic acid 182.4029 (44)
Choline bitartrate 182.5250 (42)
Choline chloride 182.5252 (42)
Chondrus extract (carrageenin) 182.7255 (6)
Citric acid 182.6033, 182.1095 (84)
Clay (kaolin) 182.90 (90)
Clove bud 182.20 (19)
Clove leaf 182.20 (19)
Clove stem 182.20 (21)
Cloves 182.10 (16)
Coconut oil p (65)
Coconut oil, refined 182.70 (65)
Copper gluconate 182.5260, 582.80 (98)
Copper sulfate 582.80, 182.90 (98)
Corn dextrin 182.70 (75)
Corn silk 182.20 (87)
Cornstarch 182.90, 182.70, p (115)
Corn sugar p (50)
Corn sugar (syrup) 182.90 (50)
Corn syrup p (50)
Cuprous iodide 182.5265, 582.80 (39)

Desoxycholic acid 182.4037 (44)
Dextran (of average molecular weight below 100,000) 182.1275 (83)
Dextrin 182.90, p (73)
Dextrose p (30)
Diacetyl (2,3-butanedione) 182.60 (94)
Diacetyl tartraric acid esters of mono- and diglycerides of edible fats or oils, or edible fat-forming acids 182.4101 (50)
Diatomaceous earth p (61)
Diatomaceous earth filler 182.90 (61)
Dilauryl thiodipropionate 182.3280 (79)
Dill 184.1282 (22)
Dipotassium phosphate 182.6285 (32)
Disodium iron ethylene diamine tetraacetic acid (35)
Disodium phosphate 182.6290 (32)
Dulse 182.30, 182.40 (38)

Erythorbic acid 182.3041 (59)
Ethyl cellulose 182.90 (25)
Ethyl formate 182.1295 (71)
Eugenol 182.60 (19)

Ferric ammonium citrate p (35)
Ferric chloride p (35)
Ferric oxide p (35)
Ferric phosphate 182.5301 (35)
Ferric pyrophosphate 182.5304 (35)
Ferric sodium pyrophosphate 182.5306 (35)
Ferric sulfate 182.90 (35)
Ferrous ascorbate (35)
Ferrous carbonate p (35)
Ferrous citrate p (35)
Ferrous fumarate p (35)
Ferrous gluconate 182.5308 (35)
Ferrous lactate 182.5311 (35)
Ferrous sulfate 182.5315, 182.90 (35)
Fish oil (hydrogenated) 182.70 (66)
Formic acid or sodium salt 182.90 (71)

Garlic 184.1317 (17)
Gelatin 182.70, p (58)
Ghatti gum 184.1335 (12)
Glutamic acid 182.1045 (37a)
Glutamic acid hydrochloride 182.1047 (37a)
Glycerine 182.1320, 182.90, p (30)
Glycerol lactopalmitate p (30)
Glycerol (glyceryl) tributyrate (tributyrin, butyrin) 182.60 (30)
Glycerol monostearate 182.1324 (30)
Glycocolic acid 182.4053 (44)
Glycryrrhiza 182.10, 182.20 (28)
Glycyrhrizin, ammoniated 182.20 (28)
Guar gum 184.1339, 186.1339 (13)
Guam guaiac 182.3336 (64)

Helium 182.1355 (112)
Hydrochloric acid 182.1057 (99)
Hydrogen peroxide 182.1366, 182.70 (113)

Inositol 182.5370 (51)
Invert sugar 182.90 (50)
Iron ammonium citrate 582.80 p (35)
Iron carbonate 582.80
Iron chloride 582.80
Iron citrate (incl. ferrous citrate) p (35)
Iron gluconate 582.80

Iron oxide 582.80
Iron peptonate p (35)
Iron phosphite 582.80
Iron polyvinylpyrrolidone (35)
Iron pyrophosphate 582.80 (35)
Iron, reduced 182.5375, 582.80, 182.90 (35)
Iron sulfate 582.80
Isopropyl citrate 182.6386 (84)

Japan wax 182.70 (46b)
Karaya gum (sterculia gum) 184.1349 (5)
Kelp (algae, brown) 182.30, 182.40 (38)

Lactic acid 182.1061 (116)
Lard 182.70 (91)
Lard oil 182.70 (91)
Lecithin 182.1400 (106)
Lecithin, modified with benzoil peroxide p (106)
Lecithin, modified with hydrogen peroxide p (106)
Lecithin (vegetable) 182.70 (106)
Licorice 182.10, 182.20 (28)
Linoleic acid (from edible fats and oils, free from chick edema factor) 182.5065 (65)
Locust bean 184.1343 (3)
Locust (carob) bean gum 184.1343, 186.1343 (3)

Mace (nutmeg) 182.10, 182.20 (18)
Magnesium carbonate 182.1425, 182.90 (60)
Magnesium chloride 182.90 (60)
Magnesium gluconate p (78)
Magnesium glycerocephosphate p (74)
Magnesium hydroxide 182.1428, 182.90 (60)
Magnesium oxide 182.5431, 182.1431 (60)
Magnesium phosphate (di-, tribasic) 182.5434 (60)
Magnesium silicate 182.2437 (61)
Magnesium stearate 182.1440 (60)
Magnesium sulfate 182.5443, 182.90 (60)
Malic acid 182.1069 (56)
L-Malic acid 182.60 (56)
Manganese acetate 582.80 (26)
Manganese carbonate 582.80 (26)
Manganese chloride 182.5446, 582.80 (67)
Manganese citrate 182.5449 (67)
Manganese citrate (soluble) 582.80 (67)
Manganese gluconate 182.5452, 582.80 (67)
Manganese glycerocephosphate 182.5455 (74)
Manganese hypophosphite 182.5458 (73)
Manganese orthophosphate 582.80 (67)
Manganese phosphate (dibasic) 582.80 (67)
Manganese sulfate 182.5461, 582.80 (67)
Manganous oxide 182.5464, 582.80 (67)
Mannitol 182.5470 (10)
Methyl and ethyl acrylate 182.90 (30)
Methylcellulose 182.1480 (25)
Methylparaben (methyl parahydroxybenzoate) 184.1490 (8)
Monoammonium glutamate 182.1500 (37a)
Mono- and diglycerides of edible fats or oils or edible fat-forming acids 182.4505 (30)
Mono- and diglycerides from glycerolysis of edible fats and oils 182.90 (30)
Mono- and diglycerides, derivatives of sodium sulfoacetate p (30)
Monoglyceride citrate p (30)
Monoisopropyl citrate 182.6511 (84)
Monopotassium glutamate 182.1316 (37a)
Monosodium glutamate 182.1 (37a)
Monosodium phosphate derivatives of mono- and diglycerides of edible fats or oils, or edible fat-forming fatty acids 182.4521 (50)
Mustard 182.20 (16)
Mustard, black or brown 182.10 (16)
Mustard, brown 182.10 (16)
Mustard, white or yellow 182.10 (16)

Niacin 182.5530 (108)
Niacinamide 182.5555 (108)
Nickel p (97)
Nitrogen 182.1540 (112)
Nitrous oxide 182.1545 (112)
Nutmeg 182.10, 182.20 (18)

Oleic acid 182.90, 182.70 (65)
Ox bile extract 182.4560 (44)
Oxides of iron 182.90

Pantothenyl alcohol 182.5580 (93)
Papain 182.1585 (77)
Peanut oil 182.70 (65)
Peanut stearine 182.40 (65)
Pectin p (81)
Pectin and pectinates p (81)
Phosphoric acid 182.1073 (32)
Potassium acid tartrate 182.1, 182.1077 (107)
Potassium alginate 182.7610 (24)
Potassium bicarbonate 182.1613 (26)
Potassium bisulfite 182.3616 (15)
Potassium carbonate 182.1619 (26)
Potassium chloride 182.5622 (102)
Potassium citrate 182.6625, 182.1625 (84)
Potassium gluconate
Potassium glycerophosphate 182.5628 (74)
Potassium hydroxide 182.1631 (85)
Potassium hypophosphite p
Potassium hypophosphate p (73)
Potassium iodate 582.80 (39)
Potassium iodide 182.5634, 582.80 (39)
Potassium metabisulfite 182.3637 (15)
Potassium phosphate, mono- and tribasic p (32)
Potassium polyphosphate (potassium metaphosphate) p (32)
Potassium pyrophosphate p (32)
Potassium sorbate 182.3640, 182.90 (57)
Potassium sulfate 182.1643 (35)
Potassium tripolyphosphate p (32)
Potato starch 182.70 (115)
Propane 182.1655 (112)
Propionic acid 182.3081, 182.90 (79)
Propanoic acid 182.4666, 182.1666, 182.90 (27)
Propylene glycol monostearate p (27)
Propyl gallate 184.1660 (11)
Propylparaben (propyl parahydroxybenzoate) 184.1670 (8)
Protein, animal, hydrolyzed p (37b)
Protein, milk, hydrolyzed 182.1 (37b)
Protein, plant, hydrolyzed p (37b)
Protein, vegetable, hydrolyzed p (37b)
Pulps from wood, straw, bagasse, or other natural sources 186.1673 (40)
Pyridoxine p (100)
Pyridoxine hydrochloride 182.5676 (100)

Rennet (rennin) 182.1685 (71)
Riboflavin 182.5695 (114)
Riboflavin-5-phosphate 182.5697 (114)
Rue 183.1699 (14)

St. John bread 184.1343 (3)
Salt 182.1 (102)
Silica aerogel (finely powdered microcellular silica foam, minimum silica content of 89.5%) 182.1711 (61)
Silicon dioxide 182.90 (61)

Soap (sodium olate, sodium palmitate) 182.90 (86)
Sodium acetate 182.1721, 182.70 (82)
Sodium acid citrate p (84)
Sodium acid phosphate 182.6085 (32)
Sodium acid pyrophosphate 182.1087 (32)
Sodium alginate 182.7724 (24)
Sodium alumininate 182.90 (43)
Sodium aluminosilicate (sodium silicoaluminate) 182.2727 (61)
Sodium aluminum phosphate 182.1781 (43)
Sodium aluminium sulfate 182.1131 (43)
Sodium ascorbate 182.3751 (59)
Sodium benzoate 184.1733 (7)
Sodium bicarbonate 182.1736, 182.70 (26)
Sodium bisulfite 182.3739 (15)
Sodium calcium aluminosilicate 182.2729 (61)
Sodium carbonate 182.1742, 182.90, 182.70 (26)
Sodium carboxymethylcellulose 182.1745 (25)
Sodium caseinate 182.1748 (96)
Sodium chloride 182.1, 182.90, 182.70 (102)
Sodium citrate 182.6751, 182.1751 (84)
Sodium diacetate 182.6754 (82)
Sodium erythorbate (sodium isoascorbate) p (59)
Sodium ferricglycophosphate (35)
Sodium gluconate 182.6757 (78)
Sodium hexametaphosphate 182.6760, 182.90 (32)
Sodium hydroxulfite 182.90 (63)
Sodium hydroxide 182.1763, 182.90, 182.70 (85)
Sodium hypophosphite p (73)
Sodium metabisulfite 182.3766 (15)
Sodium metaphosphate 182.6769 (32)
Sodium pantothenate 182.5772 (35)
Sodium pectinate 182.1775 (81)
Sodium phosphate (mono-, di-, and tribasic) 182.1778, 182.5778, 182.6290, 182.6778 (32)
Sodium phosphoaluminate 182.90 (43)
Sodium potassium tartrate 182.6804, 182.1804 (107)
Sodium propionate 182.3784 (79)
Sodium pyrophosphate 182.6787 (32)
Sodium pyrophosphate, tetra 182.6789 (32)
Sodium sesquisulphate 182.1792 (26)
Sodium silicate 182.90, 182.70 (61)
Sodium sorbate 182.3795, 182.90 (57)
Sodium sulfate 182.90, 182.70 (33)
Sodium sulfite 182.3798 (15)
Sodium sulfaacetate derivatives of mono- and diglycerides p (30)
Sodium tartrate 182.6801 (107)
Sodium thiosulfate 182.6807, 182.90 (52)
Sodium tripolyphosphate 182.6810, 182.1610, 182.90, 182.70 (52)
Sorbic acid 182.3089 (57)
Sorbitol 184.1835, 182.90 (9)
Sorbose 182.70 (49)
Soy protein, isolates 182.90, p (101)
Soybean oil, hydrogenated 182.70, p (70)
Succinic acid 182.1091 (53)
Succrose 182.90, p (69)
Sugar 182.1, p (69)
Sulfamic acid 182.90 (62)
Sulfites, strong alkali p (15)
Sulfur dioxide 182.3862 (15)
Sulfuric acid 182.90, 182.1095 (33)

Talc 182.90, 182.70 (61)
Tall oil 182.70 (68)
Tallow flakes 182.70 (54)
Tallow, hydrogenated 182.70 (54)
Tannic acid 182.20, p (48)
Tapioca starch 182.70 (115)
Tartaric acid 182.6099, 182.1099, 182.70 (107)
Taurocholic acid (or its sodium salt) 182.4105 (44)
Thiamin p (109)
Thiamin hydrochloride 182.5875 (109)
Thiamin mononitrate 182.5878 (109)
Thiodipropionic acid 182.3109 (79)
Tocopherols 182.3890, 182.5890 (36)
α-Tocopherol acetate 182.5892 (36)
Tragacanth (gum tragacanth) 184.1351 (4)
Triacetin (glyceryl triacetate) 182.1901 (30)
Tricalcium silicate 182.1906 (61)
Triethyl citrate 182.1911 (84)

Urea 182.90, 182.70, p (103)

Vinegar 182.1 (82)
Vitamin A 182.5930 (118)
Vitamin A acetate 182.5933 (118)
Vitamin A palmitate 182.5936 (118)
Vitamin B complex and syrup p (104)
Vitamin B₁₂ 182.5945 (104)
Vitamin D₁ 182.5950 (95)
Vitamin D₃ 182.5953 (95)

Wheat starch 182.70 (115)

Yeast p (37b)

Zinc acetate 582.80 (21)
Zinc carbonate 582.80 (21)
Zinc chloride 182.5985, 582.80, 182.70 (21)
Zinc gluconate 182.5988 (21)
Zinc hydrosulfite 182.90 (21)
Zinc oxide 182.5991, 582.80 (21)
Zinc stearate (prepared from stearic acid, free from chick edema factor) 182.5994 (21)
Zinc sulfate 182.5997, 582.80, 182.90 (21)
EVALUATION REPORTS

Evaluation of the substances listed in part A of this Appendix will be found in the following reports of the Select Committee on GRAS Substances. An asterisk indicates that the report has been completed and submitted as of June, 1977. These reports, after release by FDA, may be obtained from the National Technical Information Service, Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

<table>
<thead>
<tr>
<th>Report number</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Evaluation of the health aspects of gum arabic as a food ingredient</td>
</tr>
<tr>
<td>2*</td>
<td>Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient</td>
</tr>
<tr>
<td>3*</td>
<td>Evaluation of the health aspects of carob bean gum as a food ingredient</td>
</tr>
<tr>
<td>4*</td>
<td>Evaluation of the health aspects of gum tragacanth as a food ingredient</td>
</tr>
<tr>
<td>5*</td>
<td>Evaluation of the health aspects of sterculia gum as a food ingredient</td>
</tr>
<tr>
<td>6*</td>
<td>Evaluation of the health aspects of carrageenan as a food ingredient</td>
</tr>
<tr>
<td>7*</td>
<td>Evaluation of the health aspects of benzoic acid and sodium benzoate as food ingredients</td>
</tr>
<tr>
<td>8*</td>
<td>Evaluation of the health aspects of methyl paraben and propyl paraben as food ingredients</td>
</tr>
<tr>
<td>9*</td>
<td>Evaluation of the health aspects of sorbitol as a food ingredient</td>
</tr>
<tr>
<td>10*</td>
<td>Evaluation of the health aspects of mannitol as a food ingredient</td>
</tr>
<tr>
<td>11*</td>
<td>Evaluation of the health aspects of propyl gallate as a food ingredient</td>
</tr>
<tr>
<td>12*</td>
<td>Evaluation of the health aspects of gum ghatti as a food ingredient</td>
</tr>
<tr>
<td>13*</td>
<td>Evaluation of the health aspects of guar gum as a food ingredient</td>
</tr>
<tr>
<td>14*</td>
<td>Evaluation of the health aspects of oil of rue as a food ingredient</td>
</tr>
<tr>
<td>15*</td>
<td>Evaluation of the health aspects of sulfiting agents</td>
</tr>
<tr>
<td>16*</td>
<td>Evaluation of the health aspects of mustard and oil of mustard as food ingredients</td>
</tr>
<tr>
<td>17*</td>
<td>Evaluation of the health aspects of garlic and oil of garlic as food ingredients</td>
</tr>
<tr>
<td>18*</td>
<td>Evaluation of the health aspects of nutmeg, mace and their essential oils as food ingredients</td>
</tr>
<tr>
<td>19*</td>
<td>Evaluation of the health aspects of oil of cloves as a food ingredient</td>
</tr>
<tr>
<td>20*</td>
<td>Evaluation of the health aspects of caramel as a food ingredient</td>
</tr>
<tr>
<td>21*</td>
<td>Evaluation of the health aspects of certain zinc salts as food ingredients</td>
</tr>
<tr>
<td>22*</td>
<td>Evaluation of the health aspects of dill as a food ingredient</td>
</tr>
<tr>
<td>23*</td>
<td>Evaluation of the health aspects of agar-agar as a food ingredient</td>
</tr>
<tr>
<td>24*</td>
<td>Evaluation of the health aspects of alginites as food ingredients</td>
</tr>
<tr>
<td>25*</td>
<td>Evaluation of the health aspects of cellulose and certain cellulose derivatives as food ingredients</td>
</tr>
<tr>
<td>26*</td>
<td>Evaluation of the health aspects of carbonates and bicarbonates as food ingredients</td>
</tr>
<tr>
<td>27*</td>
<td>Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients</td>
</tr>
<tr>
<td>28*</td>
<td>Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycyrrhizin as food ingredients</td>
</tr>
<tr>
<td>29*</td>
<td>Evaluation of the health aspects of caprylic acid as a food ingredient</td>
</tr>
<tr>
<td>30*</td>
<td>Evaluation of the health aspects of glycerin and glycerides as food ingredients</td>
</tr>
<tr>
<td>31*</td>
<td>Evaluation of the health aspects of stannous chloride as a food ingredient</td>
</tr>
<tr>
<td>32*</td>
<td>Evaluation of the health aspects of phosphates as food ingredients</td>
</tr>
<tr>
<td>33*</td>
<td>Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients</td>
</tr>
<tr>
<td>34*</td>
<td>Evaluation of the health aspects of certain ammonium salts as food ingredients</td>
</tr>
<tr>
<td>35</td>
<td>Evaluation of the health aspects of iron and iron salts as food ingredients</td>
</tr>
<tr>
<td>36*</td>
<td>Evaluation of the health aspects of the tocoferols and α-tocopheryl acetate as food ingredients</td>
</tr>
<tr>
<td>37a</td>
<td>Evaluation of the health aspects of certain glutamates as food ingredients</td>
</tr>
<tr>
<td>37b</td>
<td>Evaluation of the health aspects of certain protein hydrolyzates as food ingredients</td>
</tr>
<tr>
<td>38*</td>
<td>Evaluation of the health aspects of certain red and brown algae as food ingredients</td>
</tr>
<tr>
<td>39*</td>
<td>Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients</td>
</tr>
<tr>
<td>40*</td>
<td>Evaluation of the health aspects of pulps as they may migrate to food from packaging materials.</td>
</tr>
<tr>
<td>41*</td>
<td>Evaluation of the health aspects of aconitic acid as a food ingredient</td>
</tr>
<tr>
<td>42*</td>
<td>Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients</td>
</tr>
<tr>
<td>43*</td>
<td>Evaluation of the health aspects of aluminum compounds as food ingredients</td>
</tr>
<tr>
<td>44*</td>
<td>Evaluation of the health aspects of bile salts and ox bile extract as food ingredients</td>
</tr>
<tr>
<td>45*</td>
<td>Evaluation of the health aspects of certain calcium salts as food ingredients</td>
</tr>
<tr>
<td>46a*</td>
<td>Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient</td>
</tr>
<tr>
<td>46b*</td>
<td>Evaluation of the health aspects of Japan wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging</td>
</tr>
<tr>
<td>47*</td>
<td>Evaluation of the health aspects of carnauba wax as a food ingredient</td>
</tr>
</tbody>
</table>
48 Evaluation of the health aspects of tannic acid as a food ingredient
49 Evaluation of the health aspects of sorbose as a food ingredient
50 Evaluation of the health aspects of corn sugar (dextrose), corn syrup, and invert sugar as food ingredients
51 Evaluation of the health aspects of inositol as a food ingredient
52 Evaluation of the health aspects of sodium thiosulfate as a food ingredient
53 Evaluation of the health aspects of succinic acid as a food ingredient
54 Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients
55 Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient
56 Evaluation of the health aspects of malic acid as a food ingredient
57 Evaluation of the health aspects of sorbic acid and its salts as food ingredients
58 Evaluation of the health aspects of gelatin as a food ingredient
59 Evaluation of the health aspects of ascorbic acid and various ascorbates as food ingredients
60 Evaluation of the health aspects of magnesium salts as food ingredients
61 Evaluation of the health aspects of silicates as food ingredients
62 Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials
63 Evaluation of the health aspects of hydroxylamines as they may migrate to foods from packaging materials
64 Evaluation of the health aspects of gum guaiac as a food ingredient
65 Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they may migrate to food from packaging materials, and linoleic acid as a food ingredient
66 Evaluation of the health aspects of hydrogenated fish oil as a food ingredient
67 Evaluation of the health aspects of manganous salts as food ingredients
68 Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials
69 Evaluation of the health aspects of sucrose as a food ingredient
70 Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient
71 Evaluation of the health aspects of formic acid, sodium formate and ethyl formate as food ingredients
72 Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients
73 Evaluation of the health aspects of hypophosphites as food ingredients
74 Evaluation of the health aspects of glycerophosphates as food ingredients
75 Evaluation of the health aspects of dextrin and corn dextrin as food ingredients
76 Evaluation of the health aspects of rennet as a food ingredient
77 Evaluation of the health aspects of papain as a food ingredient
78 Evaluation of the health aspects of gluconates as food ingredients
79 Evaluation of the health aspects of propionates as food ingredients
80 Evaluation of the health aspects of adipic acid as a food ingredient
81 Evaluation of the health aspects of pectin and pectinates as food ingredients
82 Evaluation of the health aspects of acetic acid, sodium acetate and sodium diacetate as food ingredients
83 Evaluation of the health aspects of dextrins as food ingredients
84 Evaluation of the health aspects of citric acid and citrates as food ingredients
85 Evaluation of the health aspects of sodium hyroxide and potassium hyroxide as food ingredients
86 Evaluation of the health aspects of sodium oleate and sodium palmitate as they may migrate to foods from packaging materials
87 Evaluation of the health aspects of corn silk as a food ingredient
88 Evaluation of the health aspects of methyl and ethyl acrylates as they may migrate to foods from packaging materials
89 Evaluation of the health aspects of caffeine as a food ingredient
90 Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients
91 Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials
92 Evaluation of the health aspects of vitamin A as a food ingredient
93 Evaluation of the health aspects of calcium and sodium pantothenate and p-pantothenyl alcohol as food ingredients
94 Evaluation of the health aspects of starter distillate and diacetyl as food ingredients
95 Evaluation of the health aspects of vitamin D, vitamin D₂ and vitamin D₃ as food ingredients
96 Evaluation of the health aspects of casein and caseinates as food ingredients
97 Evaluation of the health aspects of nickel, nickel chloride and nickel sulfate as food ingredients
98 Evaluation of the health aspects of copper gluconate as a food ingredient and copper sulfate as it may migrate to foods from packaging materials
99 Evaluation of the health aspects of hydrochloric acid as a food ingredient
100 Evaluation of the health aspects of pyridoxine (vitamin B₆) and pyridoxine hydrochloride as food ingredients
101 Evaluation of the health aspects of soy protein, isolates as it may migrate to food from packaging materials
102 Evaluation of the health aspects of potassium chloride and sodium chloride as food ingredients
103 Evaluation of the health aspects of urea as a food ingredient
104 Evaluation of the health aspects of vitamin B₁₂ as a food ingredient
105 Evaluation of the health aspects of lecithins as food ingredients
106 Evaluation of the health aspects of tartaric acid and tartrates as food ingredients
107 Evaluation of the health aspects of niacin and niacinamide as food ingredients
108 Evaluation of the health aspects of thiamin, thiamin chloride and thiamin mononitrate as food ingredients
109 Evaluation of the health aspects of carotenes as food ingredients
110 Evaluation of the health aspects of butane, helium, nitrogen, nitrous oxide, and propane as food ingredients
111 Evaluation of the health aspects of hydrogen peroxide as a food ingredient
112 Evaluation of the health aspects of riboflavins as food ingredients
113 Evaluation of the health aspects of starches as food ingredients
114 Evaluation of the health aspects of lactic acid and derivatives as food ingredients
115 Evaluation of the health aspects of carbon dioxide as a food ingredient
116 Evaluation of the health aspects of vitamin A, vitamin A acetate and vitamin A palmitate as food ingredients