AN EVALUATION OF MECHANISMS AND PROCEDURES UTILIZED IN OBTAINING SCIENTIFIC EXPERTISE FOR FOOD AND COSMETIC SAFETY ANALYSES

March 1987

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

under
Task Order #1
Contract No. FDA 223-83-2020
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LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20814
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA) in accordance with the provisions of Task Order #1 of Contract No. 223-83-2020. The report was prepared by the Scientific Steering Group (SSG) with the assistance of Kenneth D. Fisher, Ph.D., Director, LSRO, FASEB. Scientists selected as members of the SSG were chosen for their qualifications, experience, and judgment, with due consideration for balance and breadth in the appropriate professional disciplines. Members of the SSG and others who assisted in preparation of the report are identified in Chapter VII.

The SSG met eight times during the period of the contract. With the completion of each Task Order, the SSG initiated its review and evaluation of the mechanisms by which each Task Order was conducted. As announced by FASEB and FDA in the Federal Register [51 FR 39916], the SSG held an open meeting on November 14, 1986 to provide an opportunity for interested organizations and persons to appear before the SSG to make oral presentations of data, information, and views on the use of scientific expertise in food and cosmetic safety analyses. While no oral comments were received at the open meeting, written statements were received from the two organizations identified in Chapter VIII.

The data, information, and comments received throughout the course of the contract period were considered by the SSG in preparing this report. Copies of transcripts of open meetings and written statements are available for public inspection at either the LSRO, FASEB or the Dockets Management Branch, FDA (Docket No. 85N-0474).

The SSG's evaluation of available information and data was made independently of FDA and any other group, governmental or nongovernmental. The SSG and LSRO accept responsibility for the accuracy of the report; however, listing of the SSG members in Chapter VII does not imply that each individual specifically endorses each study conclusion. This report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Director, FASEB.
While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

March 30, 1987
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
SUMMARY

This report identifies the scientific review mechanisms utilized in the conduct of a series of studies evaluating general scientific issues and specific scientific questions. The procedures used to obtain scientific expertise were selected by a Scientific Steering Group (SSG) and were analyzed subsequently by the SSG to ascertain the efficiency and utility of the several mechanisms. The SSG examined the format of the questions posed by the Food and Drug Administration (FDA), the sources of information used in the conduct of each study, and the appropriateness of the time period available for each study. The SSG also analyzed the ability to obtain appropriate scientific expertise, the responsiveness of the Agency to requests of the study panels, and related aspects of the conduct of extramural review and evaluation studies. The report contains a number of specific observations on the scientific review mechanisms. The report recommends that FDA continue exploration of various mechanisms for obtaining scientific expertise and that FDA consider modification of the contractual mechanisms by which such scientific reviews and evaluations are conducted.
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I. INTRODUCTION

A. BACKGROUND

The legislative and executive branches of the U.S. government have a long-standing tradition of seeking information, advice, data, and views of the scientific community and the public on issues and questions related to applications of scientific knowledge to legislation and public policy. In recent decades, these efforts, coupled with heightened public interest, have exposed the difficulties inherent in formulating legislative guidelines and making regulatory decisions in situations where extant scientific knowledge is either limited or inadequate. Although scientific knowledge is dynamic and constantly evolving, legislative and regulatory decisions which must be based on the best available scientific information, are static. That is, once reached and codified, they can only be changed by legislative mandate or reopening of the regulatory decision-making process.

During the past two decades, the dilemma of limits to extant scientific knowledge and the need for a sound scientific basis for legislation and regulatory decision-making have been subjects of considerable controversy. This was particularly evident in the area of food safety. A number of studies and reports were generated on issues associated with aspects of the scientific basis for regulation of food safety (Food Safety Council, 1980; National Academy of Sciences, 1975; Roberts, 1981; Siu et al., 1977). Partially in response to this debate, the U.S. Congress, in 1981 and again in 1983, considered amendments to and revision of the Federal Food, Drug, and Cosmetic Act (Food and Drug Administration, 1986) that would have established procedures for external evaluation of scientific issues of food and cosmetic safety.

During this period, the Center for Food Safety and Applied Nutrition (CFSAN) undertook an evaluation of the procedures by which the Agency addressed issues of food safety. The FDA recognized that, as a part of the enforcement of the Federal Food, Drug, and Cosmetic Act, its CFSAN is confronted with many scientific problems associated with the safety of foods and is required to evaluate information from diverse sources. Often these problems are complex and involve developments occurring at the frontiers of scientific knowledge. Moreover, the Agency recognized that regulatory decisions made by CFSAN have direct and long-lasting significance for public health.

For these reasons, the CFSAN has for many years made use of various mechanisms for obtaining extramural objective scientific review in addition to that available from Agency staff. Several external scientific reviews and evaluations
have been supported by the Agency and the results are highly regarded both by the scientific community and the general public. These efforts include the Food and Agriculture Organization/World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives, Working Groups of the International Agency for Research in Cancer, the Select Committee on GRAS Substances (SCOGS) of the Federation of American Societies for Experimental Biology (FASEB) and several committees of the National Academy of Sciences that have addressed specific issues related to safety of saccharin and nitrite, as well as interrelationships of diet, nutrition, and cancer. In each of these instances, evaluation panels were selected and organized by the extramural scientific organization. The review process was conducted without direct participation by the sponsoring agency. These committees or expert panels were organized and administered extramurally; that is, outside the sponsoring agency. More specifically, they were typically a recognized scientifically-constituted body, free of vested interest or the appearance of vested interests by virtue of its independent scientific stature. These committees and panels were able to conduct their scientific evaluations with the independence and objectivity of scientific judgment that such separation guarantees (American Chemical Society, 1985).

Federal agency scientists can and do conduct safety evaluations intramurally. Similarly, evaluation panels can be constituted by other organizations, such as trade associations and consumer groups. However, an important distinction is that evaluations of scientific data by independent expert panels constituted by nonfederal scientific organizations avoid unnecessary controversy concerning conflicts of interest and increase public confidence in any subsequent federal agency decisions concerning regulatory matters. Scientific organizations by their nature, should be disinterested parties in regard to proposing or opposing the introduction or use of a substance in food.

The FDA and other federal agencies have a long history of utilizing various mechanisms and sources of external scientific review and evaluation. Typically, these actions have been initiated administratively rather than by legislative direction. During the past decade, support for use of external review mechanisms has been evident in proposals to Congress related to modification of the Federal Food, Drug, and Cosmetic Act. These legislative proposals included statutory authority for use of external scientific expertise.

In its continuing internal review of procedures by which outside scientific expertise is obtained, CFSAN identified a variety of mechanisms by which such reviews might be conducted, such as workshops, conferences, study groups, expert panels, and expert opinion of one or more scientists. CFSAN concluded that it would be useful to explore various mechanisms to ascertain the effectiveness and efficiency of certain approaches to using
external scientific expertise for analyses of questions related to food and cosmetic safety. Such an analysis would also provide further insight into the possible need for the modification of administrative procedures or for development of new legislative recommendations.

B. SCOPE OF STUDY

To assist in the analysis of the various mechanisms for obtaining outside scientific expertise, the CFSAN asked the Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) to explore and critique various scientific review mechanisms for providing counsel on issues in food and cosmetic safety. The analysis was to include an evaluation of the various methods with respect to their effectiveness and efficiency and take into account additional factors such as:

(1) the format of the questions;
(2) sources of information;
(3) timeframes for response;
(4) ability to obtain appropriate experts in various operating formats;
(5) costs associated with various operating formats;
(6) the responsiveness of the Agency to the information and other needs of the contractor;
(7) the responsiveness of the contractor to Agency requests, particularly with respect to the Agency's mission as defined in a statutory and regulatory context.

The LSRO was established in 1962 as an Office within FASEB to analyze specific problems in biology and medicine confronting research program administrators in federal agencies. The Office furnishes expert evaluation of scientific issues through mechanisms involving review of the study topic by qualified scientists who are actively engaged in research. Documented reports are prepared that provide scientific and technological assessment of the subject based upon a comprehensive, critical literature review and the opinions of the scientists who participate in the review. Where appropriate, reports include identification of gaps in knowledge, specific recommendations on research programs, and opportunities for future research. Emphasis is placed on evolving a factual basis for subsequent administrative decisions by the sponsors. Research administrators have found the reports useful in identifying promising areas in the biological sciences for future
programmatic emphasis and as a basis for reaching decisions on issues related to health and environmental safety.

Studies have been undertaken for several federal agencies over the 25-year period of LSRO's existence. Various study techniques have been developed to meet the specific requirements of sponsors including the use of ad hoc consultants for research program or scientific topic review, convening of ad hoc study groups for topical or program evaluations, and formation of quasipermanent panels for extended study efforts. The review and evaluation studies of the LSRO have included a number of general scientific issues as well as specific questions on individual chemical substances. Since 1972, the LSRO has conducted over 40 scientific reviews of general scientific topics and prepared reports on the safety of over 350 specific food and cosmetic ingredients for the FDA.

Because LSRO had used several mechanisms to provide federal agencies with evaluative reviews and scientific reports for over 20 years, scientific review mechanisms already used successfully by LSRO and other organizations formed the basis of the review mechanisms selected for each assigned task. This report addresses the exploration and evaluation of mechanisms of obtaining external scientific expertise that were utilized in responding to seven tasks that were assigned under terms of the contract. It summarizes the opinions and conclusions of the Scientific Steering Group (SSG) that monitored and evaluated the conduct of the seven studies.
II. SCIENTIFIC REVIEW MECHANISMS

A. ASSIGNMENT OF TASK ORDERS

Under terms of contract #223-83-2020, FDA specified assignment of up to nine task orders during a 3-year period. The task orders dealt with either general scientific issues (designated Type I) or specific scientific questions (designated Type II). The FDA provided guidance on definitions of the two types of tasks to be considered in the contract Scope of Work (see Appendix A).

1. General scientific issues

These task orders involve review and evaluation of available scientific data, synthesis of scientific opinion, indication of gaps in scientific knowledge, and, as appropriate, suggestions on research needs or progress on programmatic goals. Typically, general scientific issues do not focus on topics of immediate regulatory concern; rather, they involve evaluation or review of broader topics that provide the sponsoring agency with an overview or "state-of-the-art" synopsis of scientific knowledge and reasoned judgment concerning a generic scientific issue.

2. Specific scientific questions

These types of tasks address more selective topics that are typically of more immediate regulatory concern. The Agency has a continuing need to consider requesting external review and evaluation of scientific information on specific scientific questions with respect to cosmetic ingredients or ingested substances associated with foods, including any substance covered by Sections 402 or 406 of the Federal Food, Drug, and Cosmetic Act or that might be the subject of a pending petition or application or an effective regulation or approval under Sections 409 or 706 of the Act. Reviews of specific substances generally involve special questions or instructions on aspects of safety and use; typically, such questions would be expected to seek evaluation of: 1) the design and conduct of experiments relating to the substance; 2) the factors which could complicate the interpretation of such experiments; 3) the reliability or applicability of particular data, such as animal pathology data concerning the substance; 4) the statistical evaluation of the data; and, 5) how particular studies relate to other studies performed on the substance, particularly when conflicting results are evident.
B. PROCEDURAL ASPECTS

Under terms of the first task order, LSRO established the SSG to recommend approaches to subsequent task orders and to analyze the scientific review mechanisms selected for each. The SSG consisted of six scientists who were selected with due consideration for their recognized expertise in their respective disciplines, freedom from conflict of interest, and balance among the biomedical disciplines. Because the analyses of food and cosmetic safety that were expected to be presented to the SSG in task orders by FDA for subsequent review and evaluation would include a wide diversity of scientific issues, an effort was made to have the SSG represent a wide range of disciplinary expertise including toxicology, pharmacology, clinical medicine, biochemistry, pathology, nutrition, and epidemiology, as well as food and cosmetic sciences. For similar reasons, members of the SSG were drawn from the community of academic scientists who currently hold or have held appointments in institutions of higher learning and who have distinguished careers in research related to the disciplines noted above. (Members of the SSG are identified in Chapter VII).

The primary duties of the SSG were to: 1) examine and discuss scientific aspects associated with the proposed task order studies requested by FDA; 2) recommend a scientific review mechanism or approach to the requested study based on their determination of the type of request (general scientific issues or specific scientific questions); and 3) monitor the effectiveness of the mechanism utilized for each task order. Results of these activities were to be analyzed and included in a formal report at the completion of all contract activities. The operational flow of task order studies and responsibilities of the SSG, LSRO, and study panels are outlined in Figure 1.

The SSG determined in its initial meetings that scientific review mechanisms used for either general scientific issues or specific scientific questions should be designed to evaluate objectively the scientific aspects of each task. They recognized that the 3-year contractual period would allow only a limited number of task orders of either type to be completed. Therefore, the SSG determined that well-established approaches to scientific review and evaluation should be employed rather than experimental approaches. The SSG concluded that regardless of the scientific scope, nature, and immediacy of any task order, the scientific review mechanism selected should include analysis and discussion of evaluation of scientific data and opinions by scientists whose recognized expertise represents the major disciplines associated with the topic.
FIGURE 1. Operational flow of task order studies and evaluation of study conduct by the Scientific Steering Group. See key to processes on following page.
Key to Processes and Operational Flow of Studies Identified in Figure 1.

1. Task order for studies forwarded to LSRO by the Center for Food Safety and Applied Nutrition, FDA, under terms of contract.

2. Task order request transmitted to SSG for determination of type of task and assignment of mechanism to be used for conduct of the study.

3. SSG considers type of task and mechanism for study conduct.

4. SSG decisions and directions transmitted to LSRO for implementation.

5. LSRO organizes panel, provides staff support for conduct of study, arranges meetings, and assists in preparation of study report.

5a. SSG monitors conduct of each task order study and analyzes data and information provided by SSG representative on each study and LSRO staff.

6. Study reports are prepared by each panel in accordance with procedures approved by the LSRO Advisory Committee.

6a. Data and information on the conduct of each study are compiled and transmitted to the SSG by the SSG member on each panel and the LSRO staff.

7. All LSRO reports are reviewed and approved by the LSRO Advisory Committee in accordance with procedures adopted by the Federation Board.

8. Reports approved by the LSRO Advisory Committee are forwarded to the Executive Director, FASEB, for transmittal to the study sponsor.

9. Approved reports are transmitted to the Center for Food Safety and Applied Nutrition, FDA.
Based on these general principles, the SSG determined that the scientific review mechanisms utilized for any task order would involve one of the following approaches:

1. **SSG as ad hoc Panel**: function as an ad hoc scientific review group, with the assistance of special expert consultants if necessary;

2. **SSG as Reviewing Panel**: recommend appointment of an expert scientist whose knowledge of the issue to be reviewed would assist in the preparation of a draft report that would be reviewed and approved by the SSG;

3. **Small ad hoc Panel**: recommend appointment of an ad hoc scientific review panel of less than five persons with one SSG member serving as chairman. Other members of the panel would be selected on the basis of disciplinary expertise required by the task order;

4. **Large ad hoc Panel**: recommend appointment of an ad hoc scientific expert panel of 11 to 15 members including one or more SSG members (with one serving as chairman). Other panel members would be selected from outside the SSG on the basis of the task order requirements;

5. **Symposium/Workshop**: conduct a public symposium and follow the symposium with a meeting of an ad hoc review group. The symposium would include invited papers that provided an overview of the topics included in the scope of work and unscheduled opportunity for presentation of data, information, and views by all attendees. The subsequent workshop would be essentially a large ad hoc panel composed of symposium speakers and other scientists with complementary expertise who would prepare the summary report of both the symposium and workshop discussions.

In addition, the SSG agreed to the following guidelines for the conduct of each task order study (see Figure 1).

1. After the most suitable approach to a topic was determined by the SSG, the designated SSG member and LSRO staff would be responsible for conduct of the study under procedures promulgated by the LSRO Advisory Committee.
2. At the initiation of each task involving general issues and specific scientific questions, additional published and unpublished information, scientific data, and public comment would be solicited by news releases and announcements in the Federal Register.

3. A public meeting would be announced and held to provide an opportunity to obtain written and oral views, information, and data on the subject of each task order study.

4. An attempt would be made to utilize similar mechanisms for two or more task orders so that the SSG would be better able to compare and contrast the efficacy of the mechanism selected.

5. For each specific scientific question, if appropriate, a tentative report would be prepared and released. A public meeting would be held subsequently to provide an opportunity for further public comment on the specific issues addressed in the tentative report. After consideration of public comments, the final report would be prepared.

Finally, it is evident from the foregoing discussions that in each study the SSG relied on an ad hoc expert panel of scientists as a primary resource for obtaining the information needed to answer questions posed in each task order. However, the manner in which the ad hoc scientific review panels operated was varied somewhat to determine similarities and differences in the efficacy of the various approaches. It should be noted that the SSG recognized that they were, in fact, functioning as an ad hoc scientific review panel for the purpose of evaluating the mechanisms used to accomplish the seven other task orders assigned by FDA.

The SSG recognized that their own efforts were funded by FDA, thus creating from the onset, the semblance of an inherent conflict of interest. However, the SSG believes that cognizance of this issue provided a continual reminder of the need for scientific objectivity and separation of SSG activities from those of the several task order panels.
III. ANALYSIS AND CRITIQUE OF SCIENTIFIC REVIEW MECHANISMS

A. DETERMINATION OF TASK ORDER TYPE

During the period December 1984 through September 1985, CFSAN assigned eight task orders including the original request to explore and evaluate scientific mechanisms. These are identified in Table 1. Additional information including the statement of work for each task order is provided in Appendix B. All seven definitive task orders involved aspects of food safety and none was related directly to cosmetic safety.

The SSG initially examined each assigned task order to determine whether it was a general scientific issue or a specific scientific question. As indicated in Table 1, the SSG concluded that four of the tasks were general scientific issues and three were specific scientific questions.

In two cases, the SSG interpretations of the type of study deviated from the FDA suggestions as to the type of question being assigned (Table 2). These were Trans Fatty Acids and Sugar Alcohols. FDA had assigned the two task orders as general scientific issues based in part on their consideration that neither task order was the subject of a pending petition or a pending regulation (or approval) under Sections 409 or 706 of the Federal Food, Drug, and Cosmetic Act. Further, FDA desired a review of scientific issues (see Appendix B) rather than a scientific opinion on possible regulatory status.

However, the SSG considered Trans Fatty Acids and Sugar Alcohols as specific scientific questions because each dealt with a chemically discrete group of substances. In addition, the scope of work for each task order included specific questions about metabolic pathways and effects, analytical methodology, accuracy of data, and statistical evaluation of data. In addition, specific questions were asked about the levels and trends in consumption (Trans Fatty Acids) and the design and conduct of supporting studies and their interpretation (Sugar Alcohols).

These two interpretations by the SSG had little or no effect on the review mechanism selected. However, because neither topic was the subject of a pending regulatory decision or action, the SSG concluded that preparation of a publicly available tentative report was unnecessary. Consistent with review mechanisms used for general scientific issues, the request for additional input from the public via an open meeting was held during the study period prior to completion of the final report of the study rather than after preparation of the publicly available tentative report and prior to completion of the final report of the study.
Table 1. Task Orders Assigned Under the Contract.

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<td>General</td>
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<td>Trans Fatty Acids</td>
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* The abbreviated title is used in the text of this report.
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<td>8-2-85</td>
<td>8-6-85</td>
<td>8-19-85</td>
<td>8-19-85</td>
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</table>

* original proposal
† revised proposal
** feasibility study proposal
†† review study proposal
B. SELECTION OF REVIEW MECHANISMS

Since 1962, the LSRO has been conducting ad hoc review and evaluation studies that utilize the procedures outlined in Figure 1. In most LSRO activities, the review and evaluation of study mechanisms are carried out by the LSRO Advisory Committee. In the case of the seven task orders assigned under this contract, the SSG was responsible for determining the mechanism of study. The LSRO Advisory Committee retained the responsibility for approval of the composition of ad hoc panels and the final review and concurrence on the reports of each ad hoc study panel.

The scientific review mechanisms selected by the SSG for the various task orders were as follows:

1. **SSG and Other Scientists as ad hoc Panel**

   - **Sulfiting Agents** - The SSG functioned with a majority of the members of the previously constituted Select Committee on GRAS Substances and with experts on allergology as the ad hoc Scientific Review Panel. This mechanism was selected to provide SSG members with experience in conducting a specific scientific issue study and to take advantage of the experience and knowledge of the Select Committee on GRAS Substances. Additional experts were added to the panel because hypersensitivity to sulfiting agents was a major issue.

2. **SSG as Reviewing Panel**

   - **Diet and Cancer** - Because this task order involved an ongoing investigation that has yet to be completed, the two principal investigators of the collaborative study provided information and data in progress reports which were used by LSRO in preparation of the draft report. The SSG by itself served as a reviewing panel.

3. **Small ad hoc Panel**

   While originally identified as a possible alternative approach to allow rapid response to a task order request or to provide review of a scientifically narrow scope of work, none of the task orders assigned by FDA was considered suitable for an ad hoc panel of four or fewer persons.
4. Large ad hoc Panel

This basic mechanism has been used by LSRO since 1962. It was the approach used with minor modifications for five of eight task orders. The SSG modified the range of panel size from that originally planned (11-15 members) to 9-17 members and also used reviewing consultants in some cases.

- **National Nutrition Objectives** - An ad hoc panel of nine nutritionists, nutrition education specialists, and clinical nutritionists with broad knowledge of nutrition and public programs in nutrition was selected.

- **Trans Fatty Acids** - Because of the discrete subject matter, an ad hoc panel of nine analytical chemists, food technologists, and nutritional biochemists with research experience directly related to fatty acid metabolism was selected.

- **Sugar Alcohols** - The scope of work required analysis and evaluation of study design, toxicology and pathology data, and interspecies extrapolation. For these reasons, an ad hoc panel of 11 scientists with research experience in these areas was selected.

5. Symposium/Workshop

As noted previously, this review mechanism is a modification of the large ad hoc panel approach. The study procedures were reversed in that a public open symposium was held first and the ad hoc panel, consisting of invited symposium speakers and other expert scientists, met subsequently for a 1-day workshop. Neurotoxicity and Extrapolation were conducted in this manner in an effort to provide a comparison of two broad scientific issues being approached by a similar mechanism.

In retrospect, the SSG recognized that the relatively small number of task orders (seven) limited their ability to derive comparative data on a wide range of approaches to scientific review mechanisms. More importantly, the specialized nature and relative urgency of individual task orders made each unique, requiring some flexibility in establishing the approach.
C. **ANALYSIS OF MECHANISMS UTILIZED**

1. **Synopsis of Data and Information on Assigned Task Orders**

   Table 3 contains comprehensive information on the conduct and results of each assigned task order. Discussions in subsequent sections of this chapter make reference to the data and information presented in Table 3.

2. **Response to FDA Questions on Review Mechanisms**

   The following sections address the eight specific issues requested by FDA in the contract scope of work. The text supplements Table 3 and presents the SSG conclusions on factors influencing the effectiveness and efficiency of the several review mechanisms utilized. The order of presentation on each task order is similar to that noted in Table 3; that is, Type I (general scientific issues) followed by Type II (specific scientific questions) in increasing order of scientific complexity or uncertainty.

   a. **Format of the task order**

   In general, the format of the Agency's requests for study of general scientific issues was sufficiently focused to identify the study topics, yet broad enough to provide the study participants with freedom to introduce related pertinent subjects.

   With respect to **Diet and Cancer**, the scope of work identified six questions. Each question sought an opinion on whether the data being generated in the collaborative study in the People's Republic of China corroborated or established "significant relationships" between nutrient status and data on mortality rates. In retrospect, the questions were too broad and may be unanswerable per se. Furthermore, this epidemiological investigation will probably generate hypotheses rather than corroborate established associations between diet and cancer. In addition, the analyses of data to date suggest that associations are multivariate rather than bivariate.

   The workscope of **National Nutrition Objectives** sought views of the scientific community on seven issues related to 15 National Nutrition Objectives for 1990. While each of the 15 Objectives included aspects of food and nutritional safety, the format of the scope of work provided opportunity for the large number of contributors to make comments, or provide data and information which covered a much broader array of topics than food and nutritional safety. In retrospect, while difficult to manage, the scope of work and responses of the scientific community did provide the ad hoc panel, and subsequently FDA, with a broad perspective on the topics being evaluated.
Table 3. Summary of Data and Information on Assigned Task Orders.

<table>
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<tr>
<th>CHARACTERISTIC</th>
<th>DIET AND CANCER</th>
<th>NATL. NUTR. OBJECTIVES</th>
<th>NEUROTOXICITY</th>
<th>EXTRAPOLATION</th>
<th>TRANS FATTY ACIDS</th>
<th>SUGAR ALCOHOLS</th>
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See footnotes at end of table.
Table 3. Summary of Data and Information on Assigned Task Orders (continued).

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<tr>
<th>CHARACTERISTIC</th>
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<th>NATL. NUTR. OBJECTIVES</th>
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1 Includes 6.5 mo for SSG feasibility study
2 Actual period of effort on task order scope of work after mechanism established
3 Completion of Interim Report
4 *** = primary sources of information
   - = secondary sources of information
   o = not used as a source of information
5 Copies distributed as of 3/1/87
6 Figure is full-time equivalent (FTE) for study period
7 Actual costs within ± 5.0% of projected costs
In the Neurotoxicity study, FDA sought information on scientific issues concerning neurotoxicity and behavioral dysfunction through a series of relatively direct questions (see Appendix B). The SSG considered the questions well formulated. The questions formed the basis for the symposium presentations and provided a working outline for the workshop report. However, symposium and workshop discussions were not limited to the FDA questions alone. Panel members and symposium participants raised specific issues related to individual chemicals or techniques as well as broader regulatory and societal issues. It was apparent that the FDA questions were generic in the sense that other regulatory agencies and interested parties were concerned with selection of appropriate neurobehavioral test procedures for applied toxicology protocols. That is, the scope of work indicated that the Agency sought information to gain a general understanding of methods to improve the current approach to neurotoxicity testing. As a result, the symposium and workshop discussions included (and the report reflects) consideration of information that could be applied over a broad spectrum of circumstances. While workshop discussions identified several substances as unique or exemplary models, the format of the workscope did not focus on specific chemicals of concern to FDA. In retrospect, it might have been helpful to provide each symposium attendee with the detailed scope of work and to restrict the workshop discussions to substances of concern to the Center for Food Safety and Applied Nutrition. On balance, the SSG concluded that the nature of the questions was both adequate and useful, considering the scope of the subject matter, its general interest, and the state-of-the-art in this particular area of toxicological evaluation.

The scope of work for the Extrapolation study proved to be too broad for the proposed study period. Again, the questions asked by FDA in the scope of work were generic and of broad interest to the toxicology and regulatory communities. Because of the wide range of discussions at the symposium, some workshop participants sought to limit the workshop discussions to substances and interspecies extrapolation techniques of more immediate concern to the Center for Food Science and Applied Nutrition. This resulted in disjointed and somewhat superficial consideration of the study topics at the workshop. This in turn, extended the study period and the level of staff effort required to complete the study report.

As might be expected, the workscope for the specific scientific questions (Type II tasks) was quite detailed in each of the three studies. The questions posed in the Trans Fatty Acid task order requested an evaluation of levels in foods, consumption data, metabolic data, and analytical methods. Initially the SSG was concerned that the task order did not seek an evaluation of the safety of trans fatty acids in the diet. This uncertainty was clarified by the FDA contracting officer's technical representatives who presented additional information on FDA's
need for the study. They stated that FDA's interest in trans fatty acids did relate to public health and that the SSG should direct the ad hoc panel to provide a scientific assessment of the information on trans fatty acids. They indicated further that FDA would consider possible regulatory action based on the recommendations of the ad hoc panel report.

The scope of work for Sugar Alcohols was quite explicit and required little discussion or modification.

However, the single question posed in the Sulfiting Agents task order required considerable discussion by the ad hoc panel. Some members were troubled by the constraint identified in the task order that required assignment of sulfiting agents to one of four categories used previously by the Select Committee on GRAS Substances (Siu et al., 1977). This difficulty was related to the increasing frequency of allegations and clinical evidence of human hypersensitivity of a life-threatening nature which had precipitated the issuance of the task order. Some members of the ad hoc Panel on Sulfiting Agents suggested that fewer constraints should have been imposed on the panel in regard to specific conclusions and recommendations on the GRAS status of sulfiting agents. For example, the scope of work provided with Sugar Alcohols was suggested as a more appropriate model. Had the Sulfiting Agents scope of work been somewhat similar and had it contained further explanation of FDA's regulatory questions, the format of the Sulfiting Agents task order would have raised fewer questions. However, other members of the ad hoc Panel on Sulfiting Agents were less concerned and recognized that the ad hoc Panel on Sulfiting Agents should try, if possible, to reach one of the conclusions used previously by the SCOGS (Siu et al., 1977). In retrospect, this dichotomy of opinion reinforces the conclusion that ad hoc expert scientific panels must be provided with adequate background material and explanatory briefings, particularly when specific scientific questions with regulatory implications are being analyzed.

b. Information sources

As noted in Table 3, primary information sources varied widely and included published scientific literature, unpublished studies and reports, FDA scientific documents, and raw scientific data. For Neurotoxicity and Extrapolation, as well as the three specific scientific questions (Trans Fatty Acids, Sugar Alcohols, and Sulfiting Agents), the ad hoc panels relied heavily on unpublished scientific literature provided by FDA and/or obtained by the LSRO staff. In all cases, extensive searching of electronic databases for scientific literature (e.g., Medline, Toxline, etc.) was conducted by LSRO. A significant component of the scientific review process is the ability to continually search and research the primary scientific literature. Secondary
references such as abstracting services, reviews, and annotated bibliographies are useful, but cannot surplant critical analysis of the scientific publication containing primary data.

For Trans Fatty Acids and Sulfiting Agents, the immediacy of the issues and the need for evaluation of recent research resulted in consideration of investigator reports, unpublished manuscripts, and various other sources of data. The National Nutrition Objectives study relied heavily on materials, data, and views submitted by or obtained from various scientific organizations, federal and state agencies, and nutrition scientists. References to cited materials were as complete as possible, and care was taken to inform all persons and organizations providing documents, data, or views, that the materials, once cited by LSRO, were considered publicly available. While identification of information sources was not a problem in any of the studies, staff time in obtaining and delays in receiving reference materials were greater than anticipated. This impacted on budgetary aspects, particularly on studies of shorter duration, e.g., National Nutrition Objectives and Sulfiting Agents.

The Sugar Alcohols study, and to some extent, the Sulfiting Agents study required evaluation of a significant number of published and unpublished studies as well as scientific records that had been submitted to FDA in regard to petitions for food additive or GRAS status. At the insistence of the SSG, the LSRO study proposals included a requirement that FDA provide all pertinent materials on sugar alcohols and sulfiting agents to the LSRO for use by the ad hoc panels. LSRO scientific staff and the FDA contracting officer's technical representatives reviewed FDA files and determined the materials needed in the two studies. Few problems with these arrangements were encountered by the SSG, FDA, or LSRO staff except for the added administrative burden on LSRO technical literature staff to maintain accurate records of the source of individual documents and to develop informative reference citations for unpublished documents that were cited in the study reports.

The nature of the Diet and Cancer task order required that LSRO scientific staff obtain unpublished information and raw scientific data from an ongoing study. The volume and complexity of the data, and the time required for its generation, analysis, and review by the principal investigators were formidable barriers to completing a final task order report in the suggested study period.

c. Timeframes

The SSG is well aware of the fundamental dichotomy of scientific research investigations and regulatory needs. Science is a dynamic process, constantly evolving
new data which lead to reinterpretation of extant conclusions and to the need for more investigation. The development of scientifically sound regulatory decisions requires a reasonable set of scientific data but must be accomplished within finite periods of time. Thus, from a scientific viewpoint, the time allotted for each task order study was insufficient. However, from a regulatory position, either the review study period is too long or the available scientific data not adequate enough to support a regulatory position.

Clearly, the regulatory needs of FDA were more closely associated with the three specific questions than with the four general scientific issues. However, the increasing scientific complexity of the four general scientific issue studies, as judged by the SSG, had a major impact on the perceived appropriateness of the study period. For these two reasons, each task order study is discussed separately after the general observations.

The SSG made several general observations on time requirements based on the data contained in Table 3. First, regardless of the type of task, the quantity of scientific information was typically more extensive than anticipated. Thus each ad hoc panel required more time or sought greater LSRO scientific staff effort than was expected when LSRO submitted a proposal to conduct each study. As indicated in Table 3, only two studies were completed in the predicted study periods; extension of time periods was necessary for most studies. Inasmuch as these activities were conducted under a cost plus fixed fee contract, the need for scientific completeness is continually in conflict with fiscal responsibility (see also section f of this chapter).

Second, the system of obtaining outside analyses of issues in food and cosmetic safety does work rapidly if the FDA's priority for the study is sufficiently high. The SSG notes that for two task orders (Sulfitting Agents and National Nutrition Objectives) for which FDA stated an extreme urgency, the time period from task order request by FDA to acceptance of the LSRO proposal was 1 month or less. For studies with less urgency, the typical time from request to acceptance of the LSRO proposal was about 3 months. Where urgency was indicated by FDA, both the Agency and the contractor moved to expedite the initiation and completion of the study. For example, the Sulfitting Agents and National Nutrition Objectives studies were completed in 7.5 and 6.5 months, respectively.

Third, the number of persons submitting written statements or providing oral views at the open meeting had a major and unpredictable impact on the time required after the open meeting for completion of the study report. This, in turn, affected the level of scientific and support staff effort during this period. For example, the volume of material received on Sulfitting Agents from 53 individuals and organizations exceeded several hundred pages. An equal or greater quantity was received
from five persons or organizations at the open meeting on Diet and Cancer. In the former case, much of the material submitted was pertinent; in the latter case, the majority of materials were marginally related. Nevertheless, in both cases panel members and LSRO scientific staff had to read and evaluate all submitted material. In essence, the quantity, quality, and relevance of submitted materials were unpredictable; yet this had a marked influence on panel and staff level of effort and the actual study period. In each task order proposal, the SSG study time periods were based on the best judgment as derived from experience of LSRO in previous studies. However, experience with the several task orders showed that SSG determinations were incorrect. The SSG observations on the study time periods predicted for each task order are as follows:

- **Diet and Cancer** - The predicted study period (12 mo) appeared reasonable based on information available at the time of study initiation. Delays in data verification, determination of data analysis techniques, and actual data analyses were not anticipated. Consequently, the time allotted for the study was inadequate, and an interim report had to be prepared by the SSG.

- **National Nutrition Objectives** - FDA originally requested a 3.0-month study period; however, the SSG proposed a 6.0-month study period based on delays experienced in scheduling meetings of ad hoc panels, and in publication of required notices in the Federal Register as required in the Code of Federal Regulations [21 CFR 14.15]. Despite outstanding efforts on the part of the ad hoc panel, LSRO staff, LSRO Advisory Committee, FDA scientific staff, and the 37 scientific organizations that provided data and information, the actual study period was 7.5 months. Considering the expressed urgency of the task, the size of the scope of work, and the quantity of data and information evaluated, the SSG concludes that the study period was too short, but was so of necessity with respect to the Agency's needs. Had the task order involved extensive review of scientific data and conflicting interpretations rather than evaluation of scientific opinion concerning limited data, the study period would have been decidedly inadequate. Thus, the time necessary for study completion was, as with other task orders, a function of the task order objectives.

- **Neurotoxicity and Extrapolation** - These studies are considered together as both were conducted by a similar mechanism; that is, a 1-day symposium and a 1-day workshop. Both studies were preceded by a 6.5-month period during which the SSG and LSRO staff explored the feasibility of conducting both studies by an approach which included a large public symposium with invited
speakers, followed by a closed workshop of selected participants. During the feasibility study period, the majority of effort was focused on developing the study processes and details of the seven activity periods common to both studies: a) start-up activities, b) panel selection, c) presymposium activities, d) symposium and workshop, e) preparation of the symposium report, f) preparation of the workshop report, and g) the complete report review process.

In retrospect, too much effort was devoted to the study process and not enough to identification and analysis of the available scientific data. This was more evident for the Extrapolation study than the Neurotoxicity study because of the more extensive and diffuse subject matter in the former. Consequently, it was necessary to rely more heavily on the advice and guidance of symposium speakers and other panelists. The limited period of personal contact and the wide scope of the subject matter led to the need for additional LSRO scientific staff and SSG effort in preparation of the reports. In the case of the Neurotoxicity study, the majority of symposium presentations were received in essentially final form and on time. Such was not the case with the Extrapolation study. Further, the former study had encouraged open discussions during the symposium because time was available, while the latter had more presentation of additional data and views. The extensive, more formal, supplemental presentations at the Extrapolation symposium did constrain the time for informal debate. These factors affected the workshop discussions of the task order scope of work and resulted in considerable additional effort in preparing the drafts of the Extrapolation study symposium and workshop.

The SSG concluded that the symposium/workshop approach is a useful procedure for integrating a broad spectrum of scientific information and opinion from a variety of sources but requires continuing schedule adjustment to accommodate unanticipated events. With the two studies conducted by this mechanism, these unanticipated events and requirements coupled with the broad scope of work resulted in a significantly inadequate timeframe for study completion. Had the workscope of either task order, or an analogous one, been more limited, the timeframe might have been acceptable. Although it may be obvious, the SSG emphasized repeatedly that the scope of work is a major determinant of the timeframe for conduct of a review of a general scientific issue.

- **Trans Fatty Acids** — In planning the scientific review of information on trans fatty acids, a 2-day meeting of the review panel was scheduled for discussions of the questions posed by FDA. However, 1/2 day of the meeting was set aside for an open meeting of the review panel. Even though an evening session was added to the 2-day meeting, time was inadequate to discuss all
available information and, in particular, to develop conclusions regarding the health aspects of trans fatty acids and suggestions for future research.

- **Sugar Alcohols** - The selection of three 2-day meetings over an 11-month period provided adequate time for conduct of the study. The voluminous unpublished data from short- and long-term feeding studies with sorbitol, mannitol, xylitol, lactitol, and lactose would have been difficult to present and difficult for a group of experts to evaluate in any shorter time period. The scheduling of an open meeting of the panel provided ample opportunity for public participation in the review, including participation of interested scientists. Because consumption of the sugar alcohols has not been a public issue, research and interest in these substances were limited to commercial producers and users. If Sugar Alcohols had elicited as much interest as Sulfiting Agents, the quantity of data to be evaluated by the panel would have been too great for an 11-month study period.

- **Sulfiting Agents** - Originally, FDA requested a response in several weeks. The SSG concluded that such a response was neither possible nor scientifically responsible in view of the nature of the problem, the mass of new information to be evaluated, and the rather large size of the panel which was necessary to provide an appropriate disciplinary mix. The time period of 6 to 8 months ultimately agreed to was barely adequate to achieve unanimity on major issues. While there was no disagreement among panel members on the conclusions of the final report, the SSG suspects that some would have been better satisfied if they had had more time to consider the entire report at greater length and to engage in additional discussion.

The SSG observes that this desire to "take one more look" at the conclusions may be an inherent characteristic of studies of this type where urgency, a large number of panel members, and scientific uncertainties interact. Experience with the "law of diminishing returns" suggests that reasonable cutoffs of study periods are a necessity.

The study proposal called for completion in a 6-month period. In preparing the tentative report, the ad hoc review panel and LSRO staff found that they were unable to analyze and interpret data in accordance with the planned schedule. FDA and LSRO agreed to an additional period of 45 days to prepare the tentative report (30 days) and to allow more time for individuals and organizations to request an opportunity to make public comment at the open meeting (15 additional days).
d. **Availability of expert scientists**

The LSRO has developed both a multiplicity of procedures for identifying knowledgeable expert scientists in various biomedical disciplines and a reputation for scientific objectivity which served to attract the interest and cooperation of most scientists contacted for the several task order studies. Little or no difficulty was encountered in obtaining the assistance of expert consultants for all study panels.

In some cases, the proposed study time period precluded participation of certain invited scientists because they had prior commitments (e.g., National Nutrition Objectives, Neurotoxicity) and in other cases the study scope prevented invited participants from presenting both their experimental data and addressing questions in the study scope of work (e.g., Extrapolation).

Despite the general willingness and cooperation of most, if not all, scientists contacted, considerable difficulty was encountered in all studies in scheduling meetings, conference calls, or work sessions because of the schedules of panel members. The SSG concludes that this is an inherent problem in obtaining scientific advice and counsel from research investigators. The most knowledgeable investigators are those most in demand and consequently are those with the most limited availability. Considerable LSRO staff effort was committed to managing meeting schedules, preparing announcements of meetings, responding to inquiries from the public and press, and circumventing conflicts of panel members' schedules in each of the seven studies.

e. **Responsiveness of the Agency**

The contracting officer's technical representative for the overall contract, and those CFSAN scientists also assigned with each task order were the primary Agency contacts with the LSRO staff, the SSG, and the ad hoc panels. In general, responsiveness of the FDA staff to requests for work scope clarification, additional information, availability of reference materials, and identification of other FDA scientists was excellent. The SSG observes that this cooperative attitude was a consequence of the mutual respect of all concerned parties.

However, in a few instances responsiveness of FDA did affect the study conduct adversely because of federal regulations on availability of information. For example, in the Trans Fatty Acids study, LSRO requested information from the FDA SIREN system, the computerized database used for record storage. Because of the nature of the records of information on Trans Fatty Acids, it was determined that retrieved records would need to be scanned to delete proprietary information.
This proved to be a process that was too costly and time-consuming in view of the timeframe for the study. Similarly, in the review of Sulfiting Agents, the ad hoc panel sought consumption data developed by a private contractor and known to be in CFSAN files, as well as information on sulfiting agent usage in drugs, over-the-counter preparations, and other medicinals. In the former instance, CFSAN staff arranged for LSRO scientific staff to examine consumption data. Based on this evaluation, the ad hoc panel concluded that this source of data would not extend or further refine the estimates of sulfiting agent exposure derived from existing data sources. In the latter case, LSRO was required to make requests for materials from the Center for Drugs and Biologics under the Freedom of Information Act. CFSAN staff assisted in expediting these requests for LSRO to obtain printouts of drugs containing sulfites and transcripts of meetings of the FDA Advisory Committee. The need to prepare requests under the Freedom of Information Act resulted in an unanticipated expense and delayed the evaluation of pertinent information sought by the ad hoc panel.

On the other hand, in the Trans Fatty Acid study, the CFSAN staff assisted in obtaining data from the U.S. Department of Agriculture and from various industry sources. In the Sugar Alcohols study, CFSAN staff identified or provided the majority of the unpublished data and studies evaluated by the ad hoc panel. Finally, in the National Nutrition Objectives review, CFSAN staff were instrumental in eliciting the cooperation of various federal and state agencies in providing the ad hoc panel with unpublished data, preliminary reports, and reference materials pertinent to the 15 objectives under review.

f. **Cost comparisons**

Data on numbers of consultants, levels of staff effort, and task order budgets are provided in Table 3. The SSG is uncertain as to whether meaningful cost comparisons can be derived without a detailed audit of each task order expenditures. If such an audit is considered necessary by FDA, it will need to be conducted subsequent to the completion of the contract because of the nature of federal regulations governing audits of direct and indirect costs.

Even with such an audit, the SSG concludes that utility of cost comparisons would be limited because of the relatively small number of task order studies as well as the different effects of a) the scope of work for each task order, b) the urgency of the Agency for a study report, and c) the review mechanism selected.
 responsiveness of contractor's reports to Agency needs

The SSG had only limited information that related to this question. The SSG is aware that the Sulfiting Agents report was used as a basis for formulating revised regulations regarding the use of sulfiting agents in foods. The SSG concludes that other reports are being used similarly even though development of regulatory policies has not been determined yet. Records of the number of study reports distributed (see Table 3) are a reflection of the interests of the scientific community and the general public. The SSG is aware of informal views of FDA staff in regard to the conduct of several studies. The SSG received favorable comments on the conduct of the National Nutrition Objectives review, the Trans Fatty Acids study, and in regard to the concept of a continuing need for independent, extramural review and evaluation of issues in food and cosmetic safety (see Chapter VIII).

The SSG recognizes that four of the seven studies were completed within the last 12 months. Thus, there has been limited time for FDA to react to several of the task order studies in terms of developing and publishing program priorities or publishing regulatory opinions.

After considerable discussion, the SSG concluded that they had inadequate information and data to address this question. Further, the SSG concluded that the FDA itself should address this aspect of the evaluation of the review mechanisms used in this contract.

other considerations

Two additional considerations require identification as they were significant aspects of the conduct of each task order study. These are the procedures associated with open meetings and the related matter of managing, scheduling, and handling public inquiries.

Although LSRO held many open meetings of expert panels in conjunction with the review of GRAS substances, the open meetings held on the several studies under this contract differed in several respects. For example, Trans Fatty Acids and Sugar Alcohols were studies analogous to reviews of the safety of GRAS substances, but did not lead to a recommended regulatory stance. Further, there was no tentative report prepared prior to the open meeting. Thus, both open meetings provided a forum for presentation and discussion of scientific data rather than advocacy of a regulatory position. On the other hand, the Sulfiting Agents open meeting included scientific data as well as views and comments advocating several approaches to regulating the use of sulfiting agents in foods. In retrospect, all open meetings were
characterized by considerable discussion between presenters and panel members. This was facilitated by having each panel seated at a table rather than on a raised dais. In addition, a significant number of presenters were scientists rather than nonscientist representatives of government, industry, or the general public.

In an effort to standardize the management of each open meeting, detailed instructions for submission of materials and oral presentations were prepared for each open meeting. These supplemented information in Federal Register announcements with specific information on location, dates, times, meeting procedures, meeting participants, and other pertinent data. These instruction and information packets proved to be most useful in dealing with media representatives, interested persons, and presenters. They also served to orient panel members and new LSRO staff to the nuances of conducting an open meeting.

Open meetings were a component of the LSRO approach to each task order study because such meetings were required by FDA. The Code of Federal Regulations [21 CFR 14.15] requires public notice of all meetings and provision for interested persons to submit or present their views and opinions. The SSG concurs with these requirements and supports the concept of public meetings as a mechanism for gathering data, views, and information about scientific issues that might not otherwise come to the attention of an expert scientific panel.

However, the SSG noted that the procedures associated with conduct of open meetings did place an unanticipated administrative burden on LSRO staff. This was particularly evident in regard to scheduling of public announcements and open meetings. Because of the schedule for publication of Federal Register announcements and the requirements for review of material for such announcements by FDA legal counsel, draft material about the task order, the location, and the date for each open meeting had to be confirmed 60 to 90 days prior to the actual meeting date. The conflict of these requirements with evolution of a study is most obvious in task order efforts of short durations, e.g., National Nutrition Objectives, 195 days total study period, six panel meetings and Sulfiting Agents, 225 days total study period, four panel meetings. Because executive sessions were scheduled to follow open meetings to reduce travel costs, consultant fees, and time of panel members away from work, open meetings had to be scheduled (to meet Federal Register requirements) before the panel deliberations had confirmed work assignments and other meeting agenda.

Similarly, the SSG observed that the need for critical scheduling dates for submission of Federal Register announcements, executive sessions, open meetings, and panel travel as well as meeting arrangements and interacting with the media and interested persons on several simultaneous task order studies
essentially required the attention of one LSRD staff person full-time. This aspect of managing the contractual activities was greater than anticipated in terms of SSG and LSRD staff time and effort. However, on balance, the SSG concludes that such effort is justified and does contribute to the conduct of scientific analyses of issues in food safety.
IV. ADDITIONAL OBSERVATIONS

A. THE SCIENTIFIC STEERING GROUP

Most organizations that conduct review and evaluation studies have some mechanism to provide a steering or coordinating body. Both the National Academy of Sciences and the Federation of American Societies for Experimental Biology have established procedures for internal review of study reports for scientific merit, objectivity, and completeness in relation to assigned workscope.

With respect to this contractual effort, the SSG functioned as the steering and coordinating body within procedures established by the LSRO Advisory Committee and approved by the Federation Board. The SSG set priorities for responses to FDA's needs, determined the need for clarification of task order workscopes, selected the review mechanisms to be used with each assigned task order, and provided extramural monitoring of study progress by actual participation in each study.

The SSG concludes that their activities were necessary components of extramural scientific evaluation studies, and provisions for the functions they conducted should be included in a similar or analogous manner in future activities of this type. Similarly, a higher level of scientific review such as that of the LSRO Advisory Committee is necessary to address the possible semblance of conflict of interest arising from funding of the SSG's activities by the sponsoring agency.

B. GENERAL COMMENTS

A contract period of 36 months was negotiated to conduct the task order studies. The actual total time period for the seven major review studies was 31 months; however, on one task order, only an interim scientific report was completed for reasons identified previously. The two types of studies conducted under terms of the contract took between 6 and 20 months for completion. Because of the manner in which task orders were assigned under terms of the fixed period contract, the Agency was unable to take full advantage of the contractor's resources. For example, the task order setting up the SSG was negotiated 4 months after award of the contract, and the first scientific study task order was initiated 5 months later. In addition, completion of any study takes at least 6 months. Thus, for all practical purposes, FDA was not able to assign additional task orders during the last 6 to 9 months of the contract period.

These observations are not meant to be censorious, but rather point out that federal regulations on the contracting process do not adequately take into account the possible
continuing and flexible needs of agencies such as FDA for extramural analysis of scientific questions of varying urgency and complexity.

An analogous aspect is the need for contractors such as the Federation to maintain a capacity for flexibility in allocation of resources in response to Agency requirements. For example, the Sulfiting Agents and National Nutrition Objectives studies could not have been completed in 7.5 and 6.5 months, respectively, if schedules for other task orders and other contractual work by LSRO were rigid, precluding assignment of previously committed resources to projects identified as high priority or urgent by the sponsoring agency. Maintenance of flexibility in response to sponsors' needs is absolutely necessary from a scientific point of view. There is a need to alter the provisions of the contractual process to provide a mutually beneficial accommodation of the federal agency's requirements and the contractor's resources.
V. CONCLUSIONS AND RECOMMENDATIONS

A. SPECIFIC OBSERVATIONS

1. Role of the SSG

The SSG functioned as the steering and coordinating body within procedures established by the LSRO Advisory Committee and approved by the Federation Board. The SSG set priorities for responses to FDA's needs, determined the need for clarification of task order workscopes, selected the review mechanisms to be used with each assigned task order, and provided extramural monitoring of study progress by actual participation in each study. These activities are a necessary component of extramural scientific review and evaluation studies that assure scientific objectivity. A scientific steering group or analogous mechanism should be included in contractual activities where analysis and evaluation of complex scientific issues support the federal government's decision-making process.

2. Format of the task orders

While experience of the SSG members was limited to eight task orders over a 3-year period, they observed that the format and scientific detail of each task order were variable. The task order content appeared to reflect the perceived needs of FDA scientific staff at the time of study initiation. The scope of work associated with each of the specific scientific questions was clear, detailed, and well-focused. On the other hand, those requests for studies of general scientific issues were understandably less focused on discrete and identifiable segments of current scientific knowledge. These are recognized complications of the type of general scientific issues. However, in at least one case, the evolution of the study resulted in refinement of the workscope as FDA technical staff became aware of suggestions and recommendations of study participants.

The SSG suggests that for certain general scientific issues, the concept of a biphasic approach would be most useful. In the initial phase (feasibility study or Phase I), the contractor, consultants, and FDA scientific staff can explore the proposed study workscope and develop a more concise or directed work statement that more concretely meets Agency needs. Phase II would include actual conduct of the study based on results of Phase I. The SSG believes that most general scientific issues approached in this manner could be accomplished in 12 to 15 months with a 2 to 4 month initial feasibility study period (Phase I = 2 to 4 months; Phase II = 8 to 13 months). Furthermore, the decision to proceed with Phase II can be made by responsible Agency scientists based on results of the initial study phase as well as evolving needs of the Agency. There is
some evidence to suggest this biphasic approach could be more cost-effective in terms of focusing contractor effort and conserving sponsoring agency resources. Nevertheless, sponsoring agencies which adopt this biphasic approach should also consider the potential adverse effects of interrupted contractor support on continuity and conservation of contractor resources.

3. Information sources

The SSG observes that the LSRO, like other organizations that provide such services, has developed an elaborate series of procedures and mechanisms for retrieving, collating, and documenting published and unpublished scientific literature, information, and data. These procedures and the experience of the staff are quite valuable in the conduct of review studies such as those carried out under this contract. It is extremely important that expert scientific panels have information available from all sources for their review and evaluation. Collection, collation, and documentation particularly of the primary scientific literature containing the first reports of experimental data and/or conclusions, are critical components of the comprehensiveness of the expert panel's evaluation process, and ultimately undergird the acceptability of the panel's report and recommendations.

4. Review and evaluation of scientific data

In theory, the review and evaluation of scientific data can be accomplished by a wide diversity of mechanisms based on techniques grounded in the scientific method. In practice, the mechanisms available to a government agency or any other organization present a series of alternatives that are in part related to the desired outcome.

In selecting of an efficient, objective, acceptable process for the evaluation of data on a controversial or emerging scientific issue one should consider:

• intramural vs. extramural review
• individual vs. group or panel review
• permanent vs. ad hoc evaluators
• advisory vs. binding recommendations
• documentation from published material vs. scientific opinion of experts
• technically qualified panel members vs. unrestricted panel membership
opportunity for public input vs. closed deliberations
preparation of tentative reports and providing time for comment vs. completion of final reports by individuals or panels without additional comments
availability of resources, time, and urgency of the decision making process.

The SSG was closely involved in the application of scientific review techniques developed by the Federation and the LSRO to specific analyses of scientific issues of food safety. These mechanisms, as outlined in Figure 1 (p.7), appeared to serve well the needs of FDA in regard to the several task orders assigned. The SSG recognizes that with any such mechanisms for scientific review and evaluation, opportunities for improvement will continue to arise. An organization such as the LSRO should be alert to the need and opportunity to modify their procedures as required with due regard for continuity and scientific objectivity. As noted previously, continued reexamination of procedures and flexibility of approach within the framework of the scientific method are hallmarks of successful peer review.

5. Study duration

The SSG has already noted that conduct of a scientific analysis of a dynamic and evolving scientific issue in a fixed time period is difficult. As new information becomes available and older scientific data are reinterpreted, the time period for a study becomes more constrained and less adequate. The SSG recognizes the need to balance these two aspects. The SSG suggests that both the Agency and the contractor should recognize that this dilemma may occur and both should be flexible in their approach to each task order. The use of the biphasic approach (see p.33) would assist in controlling this aspect of each study.

Similarly, prediction of appropriate study time periods is markedly influenced by both the Agency's urgency for study results and the availability of scientific resources and information. Considering the types of questions asked in this contract, the minimum timeframe for a well-defined specific scientific question is about 6 months, the maximum for a general scientific issue about 15 to 18 months.
6. Availability of expert scientists

The SSG noted little or no difficulty in finding qualified scientists to participate in the several studies. Scheduling their common availability for ad hoc panel meetings was a continuing problem that impacted on each study and the time required for its completion. Use of the most knowledgeable expert scientists in these types of reviews and evaluations and including provisions for scheduling meetings at mutually convenient times and locations require considerable effort by the contractor. These procedures can be expected to affect the study duration, but is a critical component of the successful outcome of each study.

In several cases, the SSG observed that a second or an additional meeting of the ad hoc panel would have been most useful for the completion of the final report. In the future, consideration should be given to including provisions for additional meetings as appropriate to the workscope. Again, the SSG suggests that the biphasic approach would provide a mechanism to establish the appropriate number of meetings necessary in view of the scope of the work statement requested by the Agency, the urgency of the task order, and the availability of expertise. This is another dimension of the need for both the Agency and the contractor to maintain flexibility in approaching each study topic.

7. Responsiveness of the Agency

As noted previously, the SSG observed few problems with responsiveness of the Agency to specific requests for information, data, or clarification. The SSG and LSRO also benefited from continuity of a single contracting officer's technical representative during the 36-month contract period. On each task order study, a second especially knowledgeable FDA scientist worked with the contracting officer's technical representative in interacting with LSRO staff and the ad hoc panel. In the opinion of the SSG, this system was most efficient, providing continuity on the one hand and specialized knowledge on the other. The SSG recommends that this practice be continued in future efforts that are similar to this series of scientific analyses of issues in food and cosmetic safety.

8. Cost comparisons

As noted previously, the limited number of task orders assigned under the contract and the unique nature of each provided an inadequate basis for meaningful comparisons of costs of the several mechanisms. The SSG is concerned that efforts to derive cost/benefit analysis of these types of scientific reviews and evaluations may be incomplete or misleading if the measurable endpoints of benefit are insufficiently quantitated. Since the
utilization of each task order report by FDA is a continuing activity of the Agency, the SSG suggests this aspect be examined at a later date.

9. **Responsiveness of contractor's reports to Agency needs**

The SSG has concluded that this aspect of the analysis of review mechanisms is more appropriately an Agency function. However, to enhance future work, the SSG recommends that future contractors conducting these types of reviews and evaluations be provided with both this report and the Agency's review and evaluation of responsiveness of contractor efforts to Agency needs.

B. **GENERAL RECOMMENDATIONS**

The SSG is well aware of the possible appearance of conflict of interest in that their analyses and conclusions were conducted under a contract with the FDA. With due consideration of this issue, the SSG holds that the experience garnered under terms of this contract has been useful and productive. The SSG recommends that FDA consider:

1) **Continuing exploration of various mechanisms for extramural scientific review and evaluation both from the viewpoint of scientific impact and cost/benefit analysis.** Specific variations in existing mechanisms should be explored also. Any continuing effort should include provision for an oversight or steering group of scientists whose function would be analogous to that of the SSG.

2) **Continued encouragement of exploration of various mechanisms for extramural scientific review and evaluation under terms of future contracts for such services.** The SSG is aware that the mechanisms utilized in this contract were ones with which LSRO had considerable prior experience.

Only the symposium/workshop combination represented a departure from the format of ad hoc expert panels and scientific staff support. The SSG recommends that further efforts be made to explore additional techniques for obtaining scientific expertise for food and cosmetic safety analyses. Mechanisms that might be explored include: a) use of short-term appointments of expert scientists to the contractor's professional staff under terms of the
Intergovernmental Personnel Act; b) conduct and publication of a symposium followed several months later by a workshop or ad hoc panel evaluation of the symposium results; c) development of a final report by an ad hoc panel that holds a series of open meetings both prior to, and after, preparation and dissemination of a tentative report; d) utilization of computer-conferencing techniques in lieu of ad hoc panel meetings and/or in lieu of review of draft material by mail.

3) Reevaluating the contractual mechanism by which extramural scientific review and evaluation are conducted.

a. The studies completed under this contract were accomplished by several task orders negotiated separately. Federal acquisition regulations require competitive bidding and negotiation of individual task orders. The SSG believes these requirements introduce unnecessary complexity and inefficiency in the conduct of individual studies, particularly in the situation where the federal government is dealing with a nonprofit scientific organization.

b. It would be more efficient to consider early determination of those organizations in the public, private, and nonprofit sectors that can provide the types of services needed in extramural scientific analyses.

c. Subsequently, contractual and/or other agreements could be negotiated with several qualified sources on a continuing basis. Funding of contracts should include provisions for continuity of the contractor's ability to maintain staff and resources. The maintenance of high quality staff is absolutely crucial to the performance of such studies in the shortest timeframe. There are several ways in which this can be accomplished such as overlapping contract periods, longer contract study periods (e.g., 40 to 60 months), and implementation of the opportunity to use the biphasic approach (see p.33) to certain studies as appropriate.
d. In addition to the foregoing recommendations, the SSG suggests that even though a 36-month contract does not provide a full 36-month period for assignment of task orders, the practice of obtaining extramural analyses of scientific issues via a task order-funded contract has a number of distinct advantages to both the federal government and the contractor. For example, the contract establishes a relationship between parties that allows continuous communication on potential needs of the Agency and potential resources of the contractor in responding to those needs. It provides an opportunity to discuss the scope of work of a task order prior to the formal request that a task order be undertaken. Further, it affords both parties the opportunity to discuss possible approaches to the study that reflect both the Agency's urgency and the availability of scientific information and views.
VI. LITERATURE CITED


VII. STUDY PARTICIPANTS

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VIII. INDIVIDUALS AND ORGANIZATIONS PROVIDING MATERIALS

Comments transmitted to the SSG at Open Meeting held November 11, 1985 on Task Order #2, Health Aspects of Dietary Trans Fatty Acids, from:

Robert M. Reeves, President
The Institute of Shortening and Edible Oils
Washington, D.C.

Siert F. Riepma, President
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Letters submitted to the SSG subsequent to the Open Meeting held November 14, 1986 on Task Order #1, A Review of Mechanisms and Procedures Utilized in Obtaining Scientific Expertise for Food and Cosmetic Safety Analyses, from:

Edward Kavanaugh, President
The Cosmetic, Toiletry and Fragrance Association
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Sherwin Gardner, Vice President
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Letters submitted to LSRO subsequent to completion of Task Order #9, A Report of the Scientific Community's Views on Progress in Attaining the Public Health Service National Nutrition Goals for 1990, from:

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APPENDIX A

CONTRACT SCOPE OF WORK


The following scope of work was assigned by the Food and Drug Administration at the initiation of the contract.

The Contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities and otherwise do all things necessary for or incident to the performance of the tasks as generally described below and specifically detailed in each task order:

1. General Scientific Issues Type Task

The contractor shall respond to requests for the study of and recommend appropriate criteria, procedures and scientific methodologies for designing, conducting, or evaluating general scientific issues associated with food and cosmetic safety. Examples of two general issues recently addressed by the Bureau of Foods* involve: 1) developing the framework for the food safety assessment of potential developmental toxicants and 2) establishing the toxicological requirements appropriate for assessing the safety of irradiated foods. The first general scientific issue concerning developmental toxicants involved establishing criteria that could be used for assessing the teratogenic risk from ingested chemicals. The criteria were to indicate the conditions under which evaluation of teratogenicity is required, and were to include the concepts of: (1) hazard identification, (2) evaluation of test results, and (3) the assessment of teratogenic risk to humans. Scientific certainties and uncertainties associated with the determination of potential teratogenic hazards also were to be defined. The second general scientific issue concerning the safety of irradiated foods, focused on how the safety of irradiated foods can be scientifically evaluated, applying scientific principles. Deliberations considered: (1) projected levels of human exposure, (2) qualitative and quantitative estimates of radiolytic products and how these compare with common food constituents in the human diet, and (3) state-of-the-art sensitivity of toxicological tests.

2. Specific Scientific Questions Type Task

The contractor shall review and evaluate scientific information on specific scientific questions with respect to any cosmetics or ingested substances associated with foods, including any substance covered by sections 402 or 406 of the Federal Food, Drug and Cosmetic Act or that is the subject of a pending petition or application or an effective regulation or approval under Sections 409 or 706 of the Act. Examples of substances which have posed specific scientific questions to the Bureau of Foods

* Presently, Center for Food Safety and Applied Nutrition
include Red No. 40, Red No. 2, and butylated hydroxyanisole (BHA). Although specific substances generally present special questions associated with each substance and the studies involving it, the nature of the issues which must be examined can be characterized as involving: (1) the design and conduct of experiments relating to the substance, (2) the factors which could potentially complicate the interpretation of such experiments, (3) the accuracy of particular data, such as pathology data concerning the substance, (4) the statistical evaluation of the data, and (5) how particular studies relate to other studies performed on the substance.

3. **Scientific Review Mechanisms Type Task**

The contractor shall explore and critique various external scientific review mechanisms for providing counsel with respect to their effectiveness and efficiency and take into account factors such as:

a) The format of the questions;

b) Sources of information;

c) Timeframes for response;

d) Ability to obtain appropriate experts in various operating formats;

e) Costs associated with various operating formats;

f) The responsiveness of the Agency to the information and other needs of the contractor;

g) The responsiveness of the contractor to Agency requests, particularly with respect to the Agency's mission as defined in a statutory and regulatory context.
APPENDIX B

SCOPE OF WORK, ASSIGNED TASK ORDERS

This appendix includes the scope of work for each of the four general scientific issue (Type I) task orders and each of the three specific scientific questions (Type II) task orders assigned by FDA under terms of the Contract. Each task order was negotiated separately and the scope of work was provided at the time of task order negotiation. The order of presentation is similar to that in the text of the report. Refer to Table 2 (p.17) for the chronological order of task order assignments.

1. Type I task orders: General Scientific Issues

   a. Task Order #6: "DIETARY CHARACTERISTICS AND CANCER: CHINA COOPERATIVE STUDY"

Scope of Work

Independently and not as an agent of the Government, the contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incident to the performance of the work as described below:

This work is intended to provide an indepth analysis of data to determine, as precisely as possible, the type(s) of cancer that may be affected by various diet characteristics. Specifically, the FDA would like the contractor to address the following questions.

1. To what extent do epidemiological data on cancer incidence and mortality or the overall risk of cancer derived from the China study correlate with information on diet and nutrition?

2. What evidence is there that may relate dietary levels of vitamins A, C, and E with an alteration of cancer prevalence rates in population subsets whose diets contain significantly different levels of such nutrients?

3. What evidence is there that may relate dietary intake levels of selenium and other trace elements with an alteration of cancer prevalence rates in population subsets whose diets contain significantly different levels of such nutrients?

4. What evidence is there that may relate dietary intake levels of lipids (fat and cholesterol) with an alteration of cancer prevalence rates in population subsets whose diets contain significantly different levels of such nutrients? Is there any specificity with regard to type of dietary fat (i.e., saturated and polyunsaturated)?

5. What evidence is there that may relate dietary caloric level and content of dietary fiber with an alteration of cancer prevalence rates in population subsets whose diets contain significantly different levels of calories and dietary fiber? What is known about the effects of the various different forms of fiber?

6. What evidence is there that some food preservation and/or preparation methods alter cancer incidence?
b. **Task Order #9: "A REPORT OF THE SCIENTIFIC COMMUNITY'S VIEWS ON PROGRESS IN ATTAINING THE PUBLIC HEALTH SERVICE NATIONAL NUTRITION GOALS FOR 1990"**

**Scope of Work**

Independently and not as an agent of the Government, the contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incident to the performance of the work as described below:

The Food and Drug Administration requests the contractor to provide answers to the following specific questions:

1. In each of the Objectives as contained in the Supplement to Public Health Reports (Sept. - Oct. 1983) provided to the contractor, are the goals associated with each Objective suitable for the development of programs which will result in achievement of the goal within the remaining five-year timeframe allotted?

2. In each of the Objectives is the information presented as assessment of status valid with respect to what is currently thought by the scientific community to be the actual status (e.g., Is the current level of linear growth retardation seen in this country less than 10% for members of the 1 to 3 year old population?) If the data presented are not correct, what is the correct information?

3. Should any of the Objectives be deleted? If so, which Objectives and why?

4. Should any of the Objectives be modified? If so, which Objectives and why?

5. Should any Objectives be added? If so, which Objectives and why?

6. Should any of the programs associated with any of the Objectives be modified or deleted, or new programs developed to improve the assurance of successful attainment of the Objective? If so, which programs should be altered and why?

7. In what ways can individual objectives be presented so that balance can be achieved between the health aspects of the objective and the social implications of adopting the objective (e.g., How can the goal of increasing the use of breastfeeding be balanced against the desire of women to enter/reenter the labor force where breastfeeding has been ruled inappropriate?)
c. Task Order #3: "PREDICTING NEUROTOXICITY AND BEHAVIORAL NEUROLOGIC DYSFUNCTION FROM PRECLINICAL TOXICOLOGIC DATA"

Scope of Work: PHASE I

The contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities and otherwise do all things necessary for or incident to address the following:

1. To what extent do the various traditional toxicity tests (particularly reproduction, acute, subacute and chronic studies), carried out at exposure levels high enough to produce toxic effects, give information about the nature and scope of potential neurotoxicity or behavioral dysfunction? What particular endpoints in these traditional toxicity tests serve to indicate neuronal dysfunction?

2. To what extent do traditional toxicity tests, vide supra, not give information about the nature and scope of neurotoxicity or behavioral dysfunction? What aspects of neurobehavioral toxicity would or might be missed by relying only on traditional toxicity tests? What type of neurobehavioral test battery would be necessary to complement traditional testing in order to supply this information?

3. If neuronal involvement is indicated by traditional toxicity tests, what type of neuro-test battery would be needed to characterize better the nature and extent of the neuronal dysfunction?

PHASE II

Phase II of this task order shall begin on the effective date of this modification. The contractor shall under Phase II organize and conduct a symposium and workshop to examine the scientific issues relating to Neuro Behavioral Toxicology.
d. **Task Order #4: "THE BIOLOGICAL BASES FOR INTERSPECIES EXTRAPOLATION OF CARCINOGENICITY DATA"**

**Scope of Work: PHASE I**

The contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities and otherwise do all things necessary for or incident to address the following:

1. What are the existing methods for performing interspecies extrapolation?
2. What are the strengths of the data bases supporting these methods?
3. Are there cases (e.g., for a particular route of administration, compound, or other situation) in which one method would be suitable but not another?
4. Is there any reason to believe that a uniform extrapolation methodology for interspecies comparisons can be derived for all substances and species based on existing data?
5. If you believe that existing data would be sufficient to resolve this question, what are the nature and extent of the data bases that must be analyzed?

**PHASE II**

Phase II of this task order shall begin on the effective date of this modification. The contractor shall under Phase II organize and conduct a two (2) day workshop and symposium to examine the following scientific issues relating to Extrapolation of Carcinogenicity Data from Animals to Humans.

In responding to issues, the contractor shall evaluate the information provided to it by the Bureau of Foods. In addition, it may obtain information through other sources, but in no case will it perform original laboratory research.
2. **Type II task orders: Specific Scientific Questions**

   a. **Task Order #2: "HEALTH ASPECTS OF DIETARY TRANS FATTY ACIDS"**

   **Scope of Work**

   The contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities and otherwise do all things necessary for or incident to address the following:

   FDA requires the contractor to address the subject of dietary *trans* fatty acids with respect to three broad issues: (1) the level of *trans* fatty acids in the U.S. food supply and the consumption of these isomers on a per capita basis; (2) the toxicological effects and the nutritional biochemistry and physiology of these substances; and (3) methods for measuring *trans* fatty acids.

   With respect to the first issue, FDA would like the following questions answered:

   1. What information is available about the level of *trans* fatty acids currently in the U.S. food supply and the levels of the past ten to twenty years?

   2. What trends do you predict about levels of *trans* fatty acids in the U.S. food supply over the next five to ten years?

   In addressing these questions FDA requests the contractor to distinguish between fatty acids containing a single double bond (such as elaidic acid) and polyunsaturated fatty acids (such as linolealaidic and elaidodolinolenic acids). FDA also requests that the contractor clearly distinguish between positional isomers (e.g., 6 vs 9 vs 11 in the monounsaturated series and 9,12 vs 12,15 vs 9,11 vs 6,9,12 vs 9,11,13 vs 9,12,15, etc.) in the polyunsaturated series.

   Under the first issue, FDA also requests that a third question be addressed:

   3. What estimate do you make of the U.S. daily dietary intake of *trans* fatty acids?

   In addressing this question, FDA requests the contractor to distinguish between mono- and polyunsaturated fatty acids whenever possible.

   With respect to the second issue, FDA requests the following question be addressed.

   **What is the physiological role of *trans* fatty acids and what are the toxicological, physiological and nutritional effects of *trans* fatty acids?**

   In considering this question, FDA requests the contractor to specifically address the following:

   (1) What are the metabolic pathways involved with the *trans* fatty acids?

   (2) Other than metabolism, what is the fate of the *trans* fatty acids?

   (3) Are *trans* fatty acids deposited in the fat depots, in glycerides, and in vessel-wall structural membranes in sites normally occupied by cis-isomers?
(4) Do relatively high levels of the trans fatty acids dilute or interfere with the absorption of their counterpart cis-isomers?

(5) What information is available concerning the effects of trans fatty acids on the immune system?

In considering the third issue, FDA requests the contractor to discuss the underlying principles and the effectiveness of the methods whenever possible.

Finally, FDA requests the contractor to explain the uncertainties associated with their answers and the data and approaches needed to reduce those uncertainties.
b. Task Order #7: "SAFETY OF SUGAR ALCOHOLS AS FOOD INGREDIENTS"

Scope of Work

Independently and not as an agent of the Government, the contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incident to the performance of the work as described below:

Specifically the Food and Drug Administration would like the contractor to present a plan for addressing the following issues and questions regarding sugar alcohols.

A. Questions Related to Sugar Alcohols and Adrenals

1. Is adrenal hyperplasia and/or pheochromocytoma a characteristic response of certain strains of rats fed high levels of sugar alcohols?

2. Do the lesions seen in the rat adrenal correlate physiologically or biochemically to adrenal lesions occurring in humans?

3. Is there a mechanistic explanation for the occurrence of the lesion in rats?

4. If the answer to question 3 is yes, is there evidence that this mechanism operates in the rat only? In other species?

B. Questions Specific to Xylitol and Mouse Bladder

1. Is there a physiologic or biochemical explanation for the occurrence of oxalate crystals in the bladder of mice fed high levels of xylitol?

2. Is there, in general, a correlation between bladder crystals (stones) and hyperplastic changes in bladder epithelium of rodents?

3. Is the urinary stone formation a reasonable explanation for the occurrence of bladder tumors in mice fed high levels of xylitol?

C. Questions Specific to Xylitol and Dog Liver

1. Are the physiological responses of the dog to high levels of xylitol different from those of other species?

2. If there are differences, are they sufficient to explain the liver histopathology as well as the clinical and biochemical changes noted in dogs fed high levels of xylitol?

3. Would the responses in dogs be sufficiently unique so as to expect that they would not be significant for humans?
D. Questions Specific to Lactitol and Lactose

1. Was there or is there now any information to suggest that lactitol or lactose would have induced testicular tumors in rats fed diets containing 10% lactitol or lactose?

2. Is there a mechanistic explanation for the occurrence of these lesions in rats?

3. What is the relevance of this lesion to humans?

4. Can lactose as it occurs in milk be considered differently from a toxicologic point of view than lactose as a GRAS substance in foods?
c. Task Order #5: "THE REEXAMINATION OF THE GRAS STATUS OF SULFITING AGENTS"

Scope of Work

The contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities and otherwise do all things necessary for or incident to address the following:

"In view of the currently available information relevant to the use and safety of sulfiting agents, which of the five types of conclusions for the appraisal of GRAS substances that were developed by the Committee now applies to the use of sulfiting agents? The conclusion which is reached should be supported by a discussion of the rationale behind the conclusion."
APPENDIX C

Type III task order: Analysis of Review Mechanisms

Task Order #1: "AN EVALUATION OF MECHANISMS AND PROCEDURES UTILIZED IN OBTAINING SCIENTIFIC EXPERTISE FOR FOOD AND COSMETIC SAFETY ANALYSES"

This task was the first assigned under terms of the contract (see Appendix A). It provided for establishment of the Scientific Steering Group (SSG).

The contractor shall exert its best efforts to furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incident to the performance of the work as described below:

The contractor shall establish a means for accomplishing the Scientific Review Mechanisms Type Task. The means established shall include a plan for exploring and critiquing various review mechanisms with respect to their effectiveness and efficiency.