GUIDELINES FOR
SAFETY EVALUATION OF NUTRIENTS

June 1980

Prepared for
BUreau of Foods
Food and Drug Administration
Department of Health and Human Services
Washington, D.C. 20204

under
Contract Number FDA 223-75-2090

by
Richard G. Allison, Ph.D.
C. Jelleff Carr, Ph.D.
T. Colin Campbell, Ph.D.

Life Sciences Research Office
Federation of American Societies
For Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
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 active in specific areas of biology and medicine.

This technical report was prepared for the Bureau of Foods, Food and Drug Administration (FDA), by Richard G. Allison, Ph.D., Staff Scientist, C. Jelleff Carr, Ph.D., Director Emeritus, and T. Colin Campbell, Ph.D., Senior Scientific Consultant, in accordance with the provisions of Contract No. FDA 223-75-2090.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study (see Section VII). The report reflects the opinions expressed by participants in two ad hoc study groups that met in the Lee Building, FASEB, on June 4-5, 1979, and October 15-16, 1979. The report also reflects information and data obtained from a comprehensive literature review that was based on topics discussed at the two ad hoc group meetings. In accordance with the policy guidelines of the LSRO Advisory Committee, literature compilations are open for inspection and use by members of the scientific community and the general public for a period of two years beyond the date of report publication.

An attempt has been made to incorporate the various viewpoints and opinions expressed by meeting participants and other consultants. The listing in Section VII of consultants who have reviewed this report does not imply that they endorse the study. LSRO accepts responsibility for the contents of this report. The 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.

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

This report presents guidelines for evaluating potential adverse effects of ingesting high levels of nutrients as part of a comprehensive system for assessing safety. The recognition of nutrient toxicities may be obscured by the fact that nutrients are required for normal growth and development. In the absence of toxicological testing, nutrients cannot be assumed to be free of adverse effects even at levels of intake that may be possible from normal diets. Because essential nutrients cannot be excluded from the diet, research efforts directed toward delineating the potential adverse effects of nutrients would be a significant contribution to public health.

Comprehensive systems that have been developed for assessing the safety of environmental and food chemicals are examined for useful criteria of safety and for guidance in selecting appropriate test systems. Currently available protocols that may be selectively applied to the evaluation of potential adverse effects of nutrients are discussed. Problems unique to the testing of nutrients are outlined, including nutrient interactions and metabolic comparability of experimental animal models. The report concludes that a nutrient-by-nutrient approach would be most efficient in evaluating existing data. For most nutrients, identifying and quantitating the probability of potential adverse effects will require additional research. The extent to which the components of a complete protocol should be specified will be dependent on the degree of assurance of safety sought. Data from short-term in vivo and in vitro tests, animal feeding studies, and human experimental reports would be complementary and would provide insight into potential adverse effects as part of a complete protocol for testing nutrients. Where possible, consideration should be given to conducting studies to identify predictive indicators rather than diagnostic endpoints of toxicity in human beings. Based on effects observed in experimental animals, a working knowledge of the comparative metabolism and mechanisms of nutrient toxicity will aid in the assessment of risk to human health. Such assessments could be used as criteria for judging the safety of acute as well as chronic ingestion of nutrients in excess of normal or optimal dietary levels.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>iii</td>
</tr>
<tr>
<td>Summary</td>
<td>v</td>
</tr>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>A. Background</td>
<td>1</td>
</tr>
<tr>
<td>B. Scope of the study</td>
<td>1</td>
</tr>
<tr>
<td>II. Rationale for Evaluation of Nutrient Safety</td>
<td>5</td>
</tr>
<tr>
<td>A. General considerations</td>
<td>5</td>
</tr>
<tr>
<td>1. Current status of available methodology</td>
<td>5</td>
</tr>
<tr>
<td>2. Prospective human studies</td>
<td>7</td>
</tr>
<tr>
<td>B. Nutrient toxicities</td>
<td>7</td>
</tr>
<tr>
<td>1. Lesion permanence</td>
<td>8</td>
</tr>
<tr>
<td>2. Indicators of toxicity</td>
<td>10</td>
</tr>
<tr>
<td>III. Components of Evaluation Programs</td>
<td>11</td>
</tr>
<tr>
<td>A. Information and toxicity tests</td>
<td>11</td>
</tr>
<tr>
<td>B. Priority for nutrient evaluation</td>
<td>11</td>
</tr>
<tr>
<td>IV. Proposed System for Nutrient Safety Assessment</td>
<td>13</td>
</tr>
<tr>
<td>A. Evaluation of information</td>
<td>13</td>
</tr>
<tr>
<td>1. Animal studies</td>
<td>13</td>
</tr>
<tr>
<td>a. Diets</td>
<td>15</td>
</tr>
<tr>
<td>b. Evidence of adverse effects</td>
<td>16</td>
</tr>
<tr>
<td>2. Human studies</td>
<td>17</td>
</tr>
<tr>
<td>3. Physiological effects</td>
<td>19</td>
</tr>
<tr>
<td>4. Short-term tests</td>
<td>19</td>
</tr>
<tr>
<td>B. Final evaluation</td>
<td>20</td>
</tr>
<tr>
<td>V. Conclusions</td>
<td>23</td>
</tr>
<tr>
<td>VI. Literature Cited</td>
<td>25</td>
</tr>
<tr>
<td>VII. Study Participants</td>
<td>31</td>
</tr>
</tbody>
</table>

vii
I. INTRODUCTION

A. BACKGROUND

The Food and Drug Administration (FDA) is responsible for evaluating and monitoring the safety of foods, establishing regulations, and providing nutrition information to consumers. During the past several decades, comprehensive systems for evaluation of the safety or absence of adverse health effects have been developed for food additives, flavoring agents, colors, and ingredients that are Generally Recognized as Safe (Food Safety Council, 1978; Hall and Oser, 1968; Life Sciences Research Office, 1976; National Academy of Sciences, 1975; National Research Council, 1970; Siu et al., 1977). These systems utilize a variety of criteria for evaluating substances for possible adverse health effects. Recognizing that the broad issue of food safety assessment is currently under intensive scrutiny in the scientific, legislative, and public sectors, FDA requested the LSRO to develop, if possible, objective guidelines useful in evaluating possible adverse health effects of nutrients.

Current and proposed testing and evaluation systems have some limitations for applicability to decisions on safety of nutrients. For example, an option in existing systems is the elimination from the food supply of substances presenting a health hazard to the public. However, essential nutrients cannot be eliminated from the diet, even though some are known to be harmful at high doses. Furthermore, the margin of safety between current levels of ingestion and toxic levels may be narrow for some nutrients. The highest "no-adverse-effect" level of ingestion is poorly defined for most nutrients (National Nutrition Consortium, Inc., 1978; National Research Council, 1980). The FDA is concerned that consuming conventional foods and dietary supplements, in some instances, may provide harmful levels of nutrients. Determining total nutrient intake for any population segment is complex, especially when subsets of the population alternately adopt and discard "fad" diets (Herbert, 1979). In addition to level-of-exposure data, accurate descriptors of the potential adverse health effects of high intakes of nutrients, particularly long-term and/or irreversible effects, are essential in any system of safety evaluation. In practice, such a system should evaluate and compare data on toxicity and essentiality of nutrients at various levels of intake.

B. SCOPE OF THE STUDY

The overall physiological and biochemical functions of most nutrients are known. Similarly, ranges of nutritional requirements have been estimated although there are some gaps in this information (National Research Council, 1980). Based on
• How can evidence of adverse effects demonstrated in animal studies be extrapolated to potential adverse effects in man?

• Are prospective human studies a necessary part of a comprehensive system for establishing nutrient safety?

While these questions served to focus the discussions of the ad hoc group participants on the current status of knowledge on nutrient toxicities, no attempt was made to develop a comprehensive answer for each. However, many of the issues identified in the discussions of these questions are highlighted in this report as guidelines that may be useful for evaluating data concerning potential adverse effects of nutrients.
II. RATIONALE FOR EVALUATION OF NUTRIENT SAFETY

A. GENERAL CONSIDERATIONS

1. Current status of available methodology

Current and proposed systems used for assessing safety of added chemicals have yet to be used in the evaluation of nutrient safety. Many nutrients were among the food ingredients whose health aspects were evaluated by the Select Committee on GRAS Substances (SCOGS). The SCOGS cautioned that it relied primarily on the absence of substantive evidence of a significant risk to the public health when addressing the addition of essential nutrients to foods by commercial food processors. The SCOGS "... accepted the burden of proof of the lack of safety ..." in consonance with the spirit of then current legal constraints (Siu et al., 1977). Thus, although the data in most cases might not be regarded as constituting "proof of safety", the SCOGS considered it sufficient to provide a deliberate scientific judgment regarding the absence of potential adverse health effects. Additionally, the SCOGS outlined those toxicological tests that it considered important for obtaining convincing evidence of general acceptance of safety in cases where there were questionable toxicological observations (Siu et al., 1977).

Although no data were reviewed to support this conclusion, the Food Protection Committee (National Research Council, 1970) equated the assurance of safe use with "... virtual certainty that no injury will result." More recently, the Food Safety Council (1978), in its comprehensive system directed at evaluating food additives, proposed that a food additive be regarded "... as safe if it presents a socially acceptable risk of an unfavorable effect at levels of consumption that are experienced by high consumers of foods in which the substance occurs." Thus, it may be useful to assess nutrient safety at various levels of intake in terms of the acceptability of risks, a process Lowrance (1976) says is normative and political. Comprehensive systems for safety evaluation are used to measure risk in a stepwise fashion, either rejecting a substance as unsafe based on a set of data or proceeding through additional testing and decision points. Such systems aid only in making a qualitative decision; that is, a substance is safe or unsafe. However, a quantitative evaluation is necessary for nutrients because the range of nutritional adequacy is interposed between deficiency and possible toxicity (Campbell et al., 1980).

The Select Committee on Flavor Evaluation Criteria (Life Sciences Research Office, 1976) proposed that the minimal acceptable basic information for safety assessment includes absorption, transport, distribution, and excretion data, knowledge of metabolic biotransformations, biochemical actions, and interactions with drugs, nutrients, and food additives. The Food Safety
incorporate, in most instances, a panel of experts who interpret test results and maintain a flexible system by adopting new, appropriate tests as they become available.

Participants in the LSRO ad hoc meetings envisioned a flexible test and evaluation program designed to assess the safety of nutrients on an individual basis. Recognizing that an essential nutrient cannot be excluded from the diet, the criteria for experimental analysis of adverse health effects would be those for any food ingredient. An estimation of the maximum amount that can be consumed without increasing the probability of potential adverse health effects over a long period of time could then be determined. Thus, the system proposed must be based on animal toxicity tests that are acceptable and useful in the estimation of a quantitative risk assessment for man.

2. Prospective human studies

Contemporary ethical principles influence the conduct of prospective human studies that may be incorporated into a nutrient safety evaluation system (McMahon, 1978; U.S. Department of Health, Education, and Welfare, 1980). However, innovative experimental designs and methodologies for clinical research investigations and drug trials can yield valuable information within contemporary ethical guidelines and evolving Federal regulations (Food and Drug Administration, 1979; Tukey, 1977).

The fact that nutrients, by their very nature, have been and continue to be consumed by millions of people, often in high doses, might provide human toxicological data. Unfortunately, many variables are uncontrolled in these reports (Saegert and Saegert, 1976). For this reason, such data are difficult, if not impossible, to interpret with confidence. Nevertheless, the fact that man has consumed these nutrients in high doses for long periods adds a dimension not often found in safety evaluation studies on nonnutrient chemicals. A thorough understanding of the kinetics of metabolic and physiological responses to essential nutrients in man will be an important factor in assessing the relevance of adverse effects observed in animal studies with relatively higher dosage than judged appropriate for human studies.

B. NUTRIENT TOXICITIES

The Food Protection Committee of the Food and Nutrition Board (National Research Council, 1970), when considering the safety of food chemicals, defined toxicity as the capacity of the substance to produce injury. In evaluating the toxicity of any substance through the use of experimental animal studies, the evidence of toxicity includes widely accepted endpoints such as teratogenic, mutagenic, and carcinogenic effects. Additionally, toxicity may be ascribed to more subtle effects that have less
type are classic and include cancer, mutations, and certain birth deformities. These lesions are generally thought to be initiated by chemically reactive compounds usually generated in situ and reacting nonenzymatically to form covalent adducts. Examples of the second type may include myelin sheath degeneration similarly initiated as above, blindness through loss of optic tissues, and possibly, the initiation of certain atherosclerotic plaques. An example of the third type might include the chronic suppression of certain steroid hormone syntheses followed by a continued dependence on an exogenous supply of hormone(s) after withdrawal of the responsible suppressant. What is striking about irreversible lesions, insofar as excess stimulating chemical is concerned, is the critical need for chemically reactive compounds usually produced in situ.

To generalize whether or not nutrient toxicities are, in fact, reversible first demands a clear definition of reversibility in terms of biological mechanisms. An outstanding example of reversibility can be observed with vitamin A toxicity in humans. Jenkins (1978) has documented that in virtually all cases of hyper-vitaminosis A reported in the literature, symptoms were reversed when vitamin A supplements were withdrawn. Data concerning the potential of certain essential nutrients to cause irreversible effects such as teratogenicity or carcinogenicity have not been confirmed (Gass and Allaben, 1977; Geelen, 1979). Nutrients, when ingested, are neither known to possess the property of forming irreversible bonds nor known to be metabolized to products having this property.

On the other hand, many nutrients may enhance or depress the development of irreversible lesions initiated by other compounds. Examples include nutrients which result in greater caloric intake (Tannenbaum, 1945), modify carcinogen metabolism (Campbell, 1979), depress immunosurveillance mechanisms, or perhaps modify critical concentrations of free radicals. Nutrient deficiencies may also modify toxic lesions. Examples of these include the enhancement of certain carcinogenic effects associated with deficiencies of vitamin A, vitamin C, and possibly vitamin E and/or selenium. It may be difficult, if not impossible, because of continuity of the dose-response relationship, to differentiate between levels of intake which positively modify an initiated lesion from levels that do not. When interpreting results of toxicological testing, a search should be made within a range of nutrient intakes meeting nutrient requirements for a level that minimizes the potential for lesion promotion. Higher or lower levels may increase lesion development or increase the probability of other adverse effects. However, these same levels may be associated with desirable and beneficial health responses. For example, the dietary level of a nutrient that provides for maximal growth may be associated with greater than minimal risk of an adverse effect such as reduced life span or positive modification of irreversible lesions.
III. COMPONENTS OF EVALUATION PROGRAMS

The discussions in this section are based on the reports of expert committees that have considered the problems associated with establishing comprehensive evaluation systems for assessing the safety of food and environmental chemicals as a guide for regulatory decisions by government agencies (Food Safety Council, 1978; Life Sciences Research Office, 1976; National Academy of Sciences, 1975; National Research Council, 1970; Siu et al., 1977). Several common procedural elements can be identified in these evaluation systems: the selection of qualified experts to evaluate scientific data; the collection of extant, relevant data on each substance to be evaluated; the deliberative evaluation of existing data; the rendering of an opinion or recommendation as to the completeness and significance of the toxicity data; and implementation of those findings. No decision of safety is considered final. A periodic reevaluation is expected as new tests provide relevant information on the risks associated with the use of a substance.

A. INFORMATION AND TOXICITY TESTS

Assessment of the probability of man experiencing adverse effects from excessive ingestion of nutrients depends on data from many test systems. The basic information and types of toxicity tests requested in existing safety evaluation programs would be no different for nutrients than for other substances. These would include data on chemical and physical properties, human experiential data, short-term in vivo and in vitro tests (metabolic and mutagenicity studies), estimates of human exposure to nutrients, animal tests with appropriate pathological examinations of at least two mammalian species, and physiological effects in animals and man after oral administration. The intent should be to select tests judiciously rather than to perform tests that may provide data of little utility for safety evaluation.

B. PRIORITY FOR NUTRIENT EVALUATION

Numerous attempts have been made to establish priorities by which chemicals in the environment might be nominated for the expensive and time consuming protocols necessary for a toxicity evaluation. Scientists who have addressed the problem of priority were considering food additives, environmental contaminants, natural toxicants, indirect food additives from packaging, and similar substances rather than nutrients. Bearing this in mind, two questions are important. First, should the toxicity testing of nutrients have a higher priority than the testing of other chemicals? Second, which nutrients should be assigned highest priority
IV. PROPOSED SYSTEM FOR NUTRIENT SAFETY ASSESSMENT

The FDA has previously conducted extensive literature reviews on many essential nutrients as part of its review of the health aspects of GRAS substances. An estimation of the amount of GRAS substances produced and used in foods is also available (Subcommittee on Review of the GRAS List--Phase II, 1972). Based on the available data, an evaluation of these individual substances has been made by the Select Committee on GRAS Substances (Siu et al., 1977). These critical evaluative reports based on the often incomplete information available provide an assessment of the potential hazards to be expected from the consumption of these substances. It is proposed that toxicological assessments already reported, such as those prepared on GRAS substances, could provide the database for protocol design for animal and human studies on nutrients. Databases available for many of the essential nutrients have been recently evaluated by several expert committees and their evaluations provide an excellent point of departure for protocol design (National Nutrition Consortium, Inc., 1978; National Research Council, 1980; Siu et al., 1977).

A. EVALUATION OF INFORMATION

Details of testing rationale such as statistical procedures and control of experimental conditions through protocol design affect the general utility of data from toxicity tests (Food Safety Council, 1978; National Academy of Sciences, 1975). Additionally, the purpose for which a study was designed may restrict the usefulness of data derived from reports published in the scientific literature. For example, Gori (1980) has pointed out that in the bioassay of carcinogens, test findings have restricted meanings within the specific experiments but cannot be translated into quantitative assessment of human risk. Few experimental animal feeding studies have been undertaken specifically with the intent of evaluating the safety of high doses of essential nutrients. Reports of feeding trials conducted for purposes other than to test nutrient safety may be misleading, and factors such as insufficient numbers of animals, inappropriate dose levels, too short feeding periods, or poor animal survival may be cause for omitting data from review. In addition to these problems, the application of various toxicity tests to nutrients may present some unique problems and limitations.

1. Animal studies

The commonality of the physiological function of nutrients across species and strains offers numerous opportunities to study differences in pharmacokinetic handling of the same nutrient. If, for example, the available data suggest additional
never imply absolute safety. Still awaiting development are criteria for the adequacy of the design and conduct of the experiments so that the possibility of false negative results is reduced. As experiments of increasing methodological and protocol sophistication are conducted, a greater confidence is acquired in the determination of intake levels associated with adverse effects. This is also true for the extrapolation of animal testing results to man (Rall, 1979).

a. Diets

A major problem in testing nutrients for toxicity in animals is the diet. For example, the high protein commercial diets commonly used for rodents are intended for rapid growth and reproduction and not necessarily for maintenance or long life. It may be advisable to conduct experiments with a variety of human diets rather than animal diets, perhaps using omnivorous pigs as experimental animals. The Committee on Laboratory Animal Diets (National Research Council, 1978) underscored the need to carefully select and control the diet of experimental animals in order to conduct reproducible experiments.

The dosage of the test nutrient poses a difficult problem of establishing cause-and-effect relationships in animal feeding studies. It should be possible to select a dosage schedule (perhaps four doses) to give dose-response curves that are meaningful (Mercer et al., 1978). However, caution must be exercised in selecting dosage levels which represent the spectrum from no observed adverse effect to one producing an adverse but nonlethal response. Very large doses of some nutrients may result in a diet deficient or unbalanced with respect to specific vitamins or essential minerals either because of concomitant dilution or because of nutrient-nutrient interactions. These nutrient imbalances may be crucial for understanding the potential for nutrient interactions in the human situation. In addition, if energy content or palatability is changed to such a degree that the animals will not consume adequate quantities of diet, then the intake of a specific nutrient will be difficult to interpret. For these reasons, it is vital to measure individual food consumption frequently during the entire test period to express correctly the dosage.

Feeding studies generally include weanling rodents; therefore, consideration should be given to their higher metabolic activity, rapid growth rate, and greater consumption of food (on a body-weight basis) than that of fully grown adults. For these reasons, the dietary concentration of many substances is often adjusted weekly to compensate for the rapidly changing rate of food intake; however, this may be inappropriate when testing nutrients. For example, for human beings the nutrient composition of the diet of children is usually similar to that of adults. On the other hand, dietary supplements that are administered on a body-weight basis may represent an exception requiring a protocol that adjusts for this phenomenon.
Particular attention should be given to the use of non-invasive techniques to monitor changes in normal physiology and nervous system response. For example, ophthalmoscopic examination is one way to assess untoward effects. Biomicroscopy using the slit lamp permits examination of living tissues for induced changes (Saunders, 1969). Changes in the cornea, iris, lens, and vitreous humor can be detected in this manner. Retinal function also may be investigated by means of an electroretinogram (ERG). Abnormal ERGs can be detected by this means and reflect retino-choroidal atrophies or degeneration. In addition, early rod or cone abnormalities can be detected by the recordings of the ERG.

2. Human studies

Some untoward effects observed in human beings are not often found in experimental animals. The ability of certain foods to precipitate hypersensitivity reactions in certain individuals is well recognized but equivalent animal models are often lacking. There are relatively few accurate figures on the prevalence of hypersensitivity to various food ingredients. In part, this is a reflection of the difficulty in defining a true hypersensitive reaction and ascribing a cause-and-effect relationship. The issues confronted in attempting to determine the degree of hazard associated with hypersensitivity to a food are illustrated indirectly by hypersensitive reactions alleged to occur in patients consuming corn syrup (Fisher and Carr, 1974) and peanut products in their diet (Fisher, 1979). Interactions inevitably influence observed untoward effects and obscure identification of a specific causal substance for hypersensitive reactions. By repeated challenges with the suspected agent, a few individuals have been able to identify correctly the cause of their response.

The use of human volunteers is always a matter of concern requiring appropriate safeguards and the study of nutrients is no exception. With proper medical supervision, the conduct of studies similar to those of Phase I for clinical drug investigations would appear appropriate (Campbell et al., 1980; Food and Drug Administration, 1977; U.S. Department of Health, Education, and Welfare, 1980). It has been suggested that short-term human tests might be conducted on those nutrients for which studies have not demonstrated undesirable effects on tumor formation, mutagenicity, or other serious toxicity (Food Safety Council, 1978). The history of ingestion of large doses of vitamins, minerals, protein supplements, and other nutrients by many people has provided a basis for careful epidemiologic and toxicologic studies in man. Retrospective case-control studies are one method for identifying adverse health effects of nutrients that might represent a public health problem (Campbell et al., 1980; MacMahon and Pugh, 1970). From this background of human experience, appropriate protocols might be designed for studying human volunteers if and when such studies are warranted.
3. **Physiological effects**

Extensive metabolic data are required for interpreting chronic feeding studies in the case of nutrients. The pharmacokinetics of absorption, distribution, excretion, interconversions, and metabolic fate require careful quantitative analyses. It is the nature of nutrients to interact with various enzymes, subcellular organelles, cells, tissues, organs, and organ systems. An understanding of the metabolic capacities of those pathways associated with nutritive function is necessary to interpret pharmacological or adverse effects which may become more significant at higher dosage. The Food Protection Committee (National Research Council, 1970) cautioned against attributing undue importance to adverse effects from relatively high dosage levels although an adjustment in metabolism may be a mechanism to cope with high dosage. Ultimately, a pathologist's finding of a tissue lesion relates to a mechanism of toxicity that must be interpreted in terms of tissue saturation, altered organ function, or other metabolic data if the most appropriate levels of nutrient intake are to be defined.

Measurements of tissue nutrient levels provide important supplementary data and may be useful if properly interpreted (Hamilton, 1979; Morrison, 1979). On the other hand, decisions on safety will ultimately depend on those tests which detect tissue dysfunction or damage. These procedures include many of the classical methods used for the assessment of other types of chemical toxicities. Specific organ function tests are available and should be selected based on existing knowledge for the nutrient under study. However, with proper validation, the measurement of secondary effects with somewhat more general tests requiring cautious interpretation can give useful insight. An assessment of hormonal status or behavioral characteristics may reflect the evolution of a stress syndrome after progressive deterioration of the organism. Such data, an important part of nutrient evaluation, often require additional validation of the biological relationship between the primary event of nutrient intake and adverse health outcome. For example, virtually every drug is disposed of through its metabolism to more polar metabolites, and the responsible enzyme activities have been shown to be readily modified with alterations in nutrient intake (Campbell, 1977; Campbell and Hayes, 1974). Understanding less obvious associations between excessive nutrient intake and toxicity symptoms will require thorough knowledge of fundamental effects of nutrient excess in animal models particularly at the cellular and subcellular levels.

4. **Short-term tests**

Over 100 short-term in vivo and in vitro test systems have been developed for carcinogens and mutagens in the hope that they might reliably predict biological effects in less time and at less expense than is required for animal feeding.
undertaken only on the basis of the best available estimate of the level of human exposure to the specific nutrients and on the results of animal toxicity studies.

The central issue in evaluating nutrient toxicity data is the quantifying of probable adverse health effects at various intake levels. Essential to such quantitation are appropriate and definitive criteria of abnormal and potentially toxic reactions. This is somewhat analogous to the sensitivity of method approach currently proposed by the FDA for use in the regulation of drug residues, where an arbitrary probability of risk factor is employed to estimate the maximum level of permissible intake. Perhaps similar probabilities would be useful for each type of "toxic" response. The final evaluation might provide some quantitative scaling in the absence of definitive data, or apply one or more of the numerous available techniques of mathematical interpretation. However, these techniques cannot substitute at present for the considered judgment of qualified experts who must emphasize empirical assessment procedures rather than mathematical algorithms in interpreting the available data.
V. CONCLUSIONS

- In the absence of toxicological testing, nutrients cannot be assumed to be free of adverse effects even at levels of intake possible from normal diets. The fact that certain minimum levels of nutrients are required for growth and development has tended to obscure the recognition of potential nutrient toxicities that may occur with higher levels of intake.

- Research efforts directed toward delineating the potential adverse effects of nutrients would represent a significant contribution to public health. A review of data available on individual nutrients by qualified experts would be useful for designing test protocols and identifying those nutrients that might have priority for further research.

- Currently available procedures for the evaluation of food and environmental chemicals may be selectively applied to the evaluation of possible adverse effects of nutrients. These procedures provide for periodic review of safety as new information becomes available. It would be helpful in the assessment of nutrient safety to have data from a toxicologic testing protocol that includes chronic feeding studies in selected animal species. Short-term in vivo and in vitro studies, behavioral studies in animals, and other indirect methods may provide valuable insight into adverse effects. Consideration should also be given to conducting, where possible, limited prospective human studies.

- Based on the adverse effects observed in experimental animals, a quantitative and qualitative assessment of risk to human health should be made. These assessments should rely on a working knowledge of the metabolism and mechanism of nutrient toxicity. Such assessments could be used as criteria for judging the safety of acute as well as chronic ingestion of nutrients in excess of normal dietary levels.
VI. LITERATURE CITED


VII. STUDY PARTICIPANTS

A. AD HOC GROUP PARTICIPANTS, OCTOBER 15-16, 1979

CO-CHAIRMEN

Frederic R. Senti, Ph.D.
Associate Director
Life Sciences Research Office

Herman I. Chinn, Ph.D.
Senior Staff Scientist
Life Sciences Research Office

CONSULTANTS

John G. Bieri, Ph.D.
Chief, Nutrition and Biochemistry Section
National Institute of Arthritis, Metabolism, and Digestive Diseases
National Institutes of Health
Bethesda, Maryland 20205

Lucille S. Hurley, Ph.D.
Professor of Nutrition
Department of Nutrition
University of California, Davis
Davis, California 95616

T. Colin Campbell, Ph.D.
Professor of Nutritional Biochemistry Division of Nutritional Sciences
Cornell University
Ithaca, New York 14853

Albert C. Kolbye, M.D.
Associate Bureau Director for Toxicology
Bureau of Foods
Food and Drug Administration
Washington, D.C. 20204

C. Jelleff Carr, Ph.D.
Executive Director
Food Safety Council
1725 K Street, N.W.
Washington, D.C. 20006

Joyce McCann, Ph.D.
Department of Biochemistry
University of California, Berkeley
Berkeley, California 94720

Richard A. Griesemer, D.V.M., Ph.D.
Associate Director for Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Donald B. McCormick, Ph.D.
Fuller E. Callaway Professor and Chairman, Department of Nutrition
Emory University School of Medicine
Atlanta, Georgia 30322

Johnnie R. Hayes, Ph.D.
Assistant Professor of Pharmacology Division of Toxicology
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia 23288

Howerde E. Sauberlich, Ph.D.1
Chief, Department of Nutrition Letterman Army Institute of Research Presidio of San Francisco, California 94129

1Dr. Sauberlich's current address: Western Nutrition Research Center, Science and Education Administration, U.S. Department of Agriculture, Presidio of San Francisco, California 94129

31
C. SPECIAL CONSULTANTS

Robert B. Bennett, M.B.A.
7413 Grace Street
Springfield, Virginia 22150

C. Wayne Callaway, M.D.
Nutrition Consulting Services
Division of Endocrinology and Metabolism
Mayo Clinic
Rochester, Minnesota 55901

Tyron E. Huber, M.D.
6002 Roosevelt Street
Bethesda, Maryland 20014

D. OTHER CONTRIBUTING LSRO STAFF

Elizabeth M. DeWitt
Administrative Aide

Beverly Keder
Literature Retrieval/
Technical Report Specialist

C. Grace Gurtowski
Bibliographer, Librarian

Mary Monahan
Secretary