

Executive Summary from the Report: Analysis of Adverse Reactions to Monosodium Glutamate (MSG)

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Life Sciences Research Office Report

Executive Summary from the Report: Analysis of Adverse Reactions to Monosodium Glutamate (MSG)¹⁻³

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FOREWORD

The Life Sciences Research Office (LSRO)⁴, Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments on 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. The Federation recognizes that the safety of monosodium glutamate (MSG) as a food ingredient is a recurring question of widespread interest and that FASEB's resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in this reexamination of scientific information on possible adverse reactions to monosodium glutamate.

This report was developed for the Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) in accordance with the provisions of Task Order #1 and Task Order #7 of Contract No. 223-92-2185. It was edited by Daniel J. Raiten, Ph.D., Senior Staff Scientist, with the assistance of John M. Talbot, M.D., Senior Medical Consultant, Kenneth D. Fisher, Ph.D., Senior Scientific Consultant, and the LSRO staff. The report is based on discussions of, and materials evaluated by, an ad hoc Expert Panel convened by LSRO. The members of the Expert Panel were chosen for their qualifications, experience, and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Expert Panel and others who assisted in preparation of the report are identified in Chapter XII.

This study was initiated in September, 1992. In a notice in the *Federal Register* of December 4, 1992, the FDA announced that, as a component of Task Order #1, FASEB was inviting data, information, and views bearing on the topic under study (Food and Drug Administration, 1992). Accordingly, FASEB provided an opportunity for public oral presentations in an Open Meeting held on April 7 and 8, 1993, and for written submissions. Twenty-eight (28) individuals

made oral presentations at the Open Meeting. Two hundred eighty-four (284) individuals and organizations have provided written submissions for consideration by the Expert Panel (FDA Docket No. 92N-0391). These individuals and organizations are listed in Chapter XIII. The LSRO wishes to express its appreciation to all individuals and organizations who have contributed materials for this study.

Task Order #1 was divided into two phases. In Phase I, an Expert Panel of three scientists reviewed the adequacy of the available literature and reports of adverse effects of MSG to address 18 questions posed by the FDA (1992). Phase I culminated in a Tentative Report, made available for public review and comment on February 23, 1993. The release of the Tentative Report was followed by the Open Meeting on April 7-8, 1993, at which time interested parties submitted additional information and comments on the content of the Tentative Report as noted above.

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²The full report from which this Executive Summary is derived is available from the American Institute of Nutrition, 9650 Rockville Pike, Bethesda, MD 20814 for \$65.00 plus \$6.00 shipping and handling (\$9.00 shipping and handling for orders outside the U.S.).

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⁴Abbreviations used: ACTH, adrenocorticotrophic hormone; ADI, acceptable daily intake; ARMS, FDA's Adverse Reactions Monitoring System; CNS, central nervous system; DBPCFC, double-blind, placebo-controlled food challenges; FAO/WHO, Food and Agricultural Organization/World Health Organization; FDA, Food and Drug Administration; GRAS, generally recognized as safe; HP, hydrolyzed protein; HVP, hydrolyzed vegetable protein; IFT, Institute of Food Technologists; i.p., intraperitoneal; i.v., intravenous; LH, luteinizing hormone; LSRO, Life Sciences Research Office; MSG, monosodium glutamate; NMDA, N-methyl-D-aspartate; s.c., subcutaneous; SCOGS, Select Committee on GRAS Substances; TSH, thyrotropin.

Phase II of Task Order #1, initiated following the Open Meeting, involved an expansion of the Phase I ad hoc Expert Panel to eight members. The Phase II Panel was charged with evaluation of the available scientific literature and the materials received at the Open Meeting. The Panel met four times to assess and evaluate the available data on exposure and reports on adverse effects of MSG and hydrolyzed proteins. The Expert Panel members reviewed report drafts and provided additional documentation and evaluation of scientific information for incorporation into the draft report.

In September, 1994, LSRO submitted a draft report of the Expert Panel to FDA. Based on its review of that draft, FDA requested an expansion of the discussions as well as further clarification and additional information concerning the conclusions on the 18 questions. In addition, FDA indicated that the draft report raised several issues that needed to be addressed. To accomplish these additional assignments, FDA issued Task Order #7 which supplemented the Scope of Work in Task Order #1. Accordingly, the Expert Panel met a fifth time to add additional information to the draft report and to expand on and clarify the conclusions and recommendations contained in that report. The results of that meeting were incorporated by LSRO staff into the final report of Task Order #7. The deliberations of the Expert Panel, in response to Task Order #7, did not lead to any change in either the conclusions or the recommendations of the Task Order #1 draft report.

Throughout the course of the study, the Expert Panel members reviewed each draft and provided additional documentation and viewpoints for incorporation into the final report. However, the listing of these individuals in Chapter XII does not imply that the individual Panel members specifically endorse all statements in the report. The LSRO accepts responsibility for the study conclusions and accuracy of the report.

The final 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 FASEB 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 opinions of the individual members of the FASEB constituent Societies. *Marvin Snyder, Ph.D., Director, Life Sciences Research Office, July 31, 1995.*

EXECUTIVE SUMMARY

The following paragraphs contain the responses of an ad hoc Expert Panel to 18 questions posed by FDA in regard to the possible role of MSG in eliciting or mediating (1) the symptom complex often referred to as the "Chinese Restaurant Syndrome"; (2) more severe reactions such as dyspnea, asthma, or cardiac arrhythmias that could be life-threatening; (3) brain lesions or neurotoxicity; and (4) release of certain hormones from the pituitary glands of subhuman primates. The body of the report contains additional material that documents the scientific basis of the conclusions contained in this Executive Summary. Because it was not feasible to include all conclusions and data in the responses to each question, citations are noted that identify additional material in the body of the report.

1.a. What are the symptoms and signs of acute, temporary, and "self-limited" adverse reactions that have been reported to occur with oral ingestion of MSG?

Based on testimonial reports received by the FDA Adverse Reaction Monitoring System (ARMS) and the Life Sciences Research Office (LSRO) and a review of the literature addressing adverse effects in humans, the following manifestations are considered representative of the acute, temporary, and self-limited reactions to oral ingestion of MSG which the Expert Panel would include in the "MSG Symptom Complex"⁵:

- burning sensation back of neck, forearms, chest
- facial pressure/tightness
- chest pain
- headache
- nausea
- palpitation
- numbness in back of neck radiating to arms and back
- tingling, warmth, weakness in face, temples, upper back, neck and arms
- bronchospasm (observed in asthmatics only)
- drowsiness
- weakness

(See full report², Chapter VII, A for additional information.)

⁵Because the Expert Panel considered the term "Chinese Restaurant Syndrome" to be pejorative and not reflective of the extent or nature of the symptoms that have been associated with the myriad of potential exposure possibilities, the term "MSG symptom complex" will be used in connection with those symptoms that have been verified to occur with oral exposure to MSG.

b. Do these reports provide a basis for establishing causality by MSG?

The testimonial reports submitted to the ARMS and LSRO suggest, but do not establish, causality by MSG. However, the overall impression of the Expert Panel is that causality has been demonstrated. Based on scientifically verifiable evidence, there is a subgroup of presumably healthy individuals within the general population that responds, generally within one hour of exposure, with manifestations of the MSG Symptom Complex to an oral bolus of MSG ≥ 3 g in the absence of food. (See full report², Chapter IX for conclusions.)

c. Do these reports indicate a dose-related response or a requirement for accessory factors such as predisposing medical or dietary conditions, in the occurrence or relative severity of the adverse reactions?

In some individuals, there is evidence of a dose-related response to an oral MSG challenge of 3 g or more given without food. To date, asthma is the only documented predisposing medical condition associated with adverse effects from ingestion of MSG. Ingestion of MSG on an empty stomach is more often associated with occurrence of adverse reactions than is ingestion with food. Changes in vitamin B-6 status, either deficiency or excess, may be another factor that can influence the response to MSG; however, no studies have been performed to test this possibility in humans (see full report², Chapter VII, in particular VII-D-2).

While there is a body of evidence linking anomalies in endogenous glutamate metabolism with such chronic and debilitating diseases as Alzheimer's disease, Huntington's chorea, and amyotrophic lateral sclerosis, *no evidence exists to support a role of ingested glutamate in the etiology or exacerbation of these or any other long-term or chronic illnesses.* (For detailed information, see full report², Chapter V, section B.)

2.a. What serious (life-threatening) reactions have been reported to occur with oral ingestion of MSG?

The FDA received no reports of unconsciousness, coma, or death related to ingestion of MSG. Of the 439 complaints of adverse reactions to MSG received by the FDA-ARMS as of February 8, 1993⁶, 36 (8.2%) were judged by FDA staff to be severe (e.g., difficulty breathing, changes in heart rate and/or blood pressure, chest pain).

A total of 154 anecdotal reports (letters) were received by LSRO as of July 1, 1994. These included 20 potentially life-threatening reactions including: anaphylaxis (1); seizures (3); dysrhythmias (6); "con-

stricted throat" (1); dyspnea with head or neck edema (5); hypovolemic shock (1); and, syncope (3) all self-reported to be associated with consumption of MSG. While no cases of death have been directly attributable to MSG, the Expert Panel noted that at least 40% of anaphylaxis cases are wrongly reported (Sørensen et al., 1989).

With few exceptions, reports of adverse reactions to MSG in the medical and scientific literature are case reports rather than experimental studies with appropriate controls. The majority of these reported symptoms are transient and not life-threatening.

The exception to the above are two case studies that report cardiac arrhythmia following ingestion of wonton soup (Gann, 1977; Goldberg, 1982). While the subjects were reported to be otherwise normal adults (one male, one female), no data were provided on periods between meals and onset of symptoms or MSG content of the ingested foods. In addition to the arrhythmias, both authors referenced the similarity of symptoms with the "Chinese Restaurant Syndrome," i.e., tingling and burning sensation in the head, chest, and arms, as reported by Kwok (1968).

The two cases of cardiac arrhythmias suggest that certain individuals may have serious adverse reactions to consumption of foods presumed to have a high MSG content, e.g., wonton soup. It must be noted that the evidence linking these symptoms in these studies with MSG is presumptive as neither the glutamate content of the individual food or foods consumed nor the blood glutamate levels or any other corroborative evidence was presented. No case reports of cardiac arrhythmias have been reported in the literature since these reports in 1977 and 1982. However, the absence of such case studies is not necessarily evidence of the absence of such cases in the general population.

The studies of Allen et al. (1987) provide scientific evidence for a role of MSG in the onset of severe asthma in selected asthmatic patients. (See below and full report², Chapter VII, A. for additional discussion and explanation.)

b. What is the quantity and quality of these reports?

The number of letters and reports received by the FDA-ARMS and submitted to LSRO is substantial. The 20 potentially life-threatening reactions listed above were unsubstantiated anecdotes in letters to LSRO and the quality of these reports was highly variable in terms of informational content.

⁶This represents the last date for which LSRO received data from the FDA-ARMS reporting system.

The Expert Panel had no basis to question the veracity of the reports; however, these accounts are essentially descriptive and are not verifiable without follow-up clinical investigations. Further, because the FDA-ARMS and LSRO submissions were voluntary, it is difficult to predict, generalize, or make inferences about the incidence of such adverse reactions in the general population.

Case reports by Asnes (1980), Gann (1977), and Goldberg (1982) described potentially serious reactions. However, these reports can generally be characterized by an inconsistent reporting of patient medical history, nutritional status (i.e., fed versus fasted state), condition of exposure (i.e., with or without other foods), and a lack of confirmatory evidence definitively linking the reactions to MSG.

The Expert Panel reviewed 11 available reports of the possible role of MSG ingestion on precipitation or exacerbation of severe asthma in known asthmatic patients (full report², Appendix Table 9). All of the studies reviewed contained design flaws or presented insufficient evidence to characterize the patient sample adequately. The most consistent problem was related to either the continuation or discontinuation of medications. The continuation of drugs could potentially prevent the precipitation of a MSG-induced asthmatic attack, while the discontinuation of drugs could be responsible for increased susceptibility to attacks irrespective of cause. In those cases where the latter scenario was involved, e.g., several cases noted by Allen et al. (1987) in which drugs had been discontinued, the investigators reproduced the MSG effects on separate occasions under controlled circumstances. Delayed responses were also documented by Moneret-Vautrin et al. (1987) in patients who had been off asthma-related medication for three days.

Out of a total of 321 asthmatic subjects across all studies reviewed, 28 could be described as responders to MSG. The Expert Panel concluded that the report of Allen et al. (1987) was a reasonably well-designed scientific oral challenge study in asthmatic subjects that provided evidence to support the existence of a subgroup of asthmatic responders to MSG. (See full report², Chapter VII, D, 1 for discussion of MSG and asthma.)

c. How do dose and time relationships compare with "self-limited" adverse reactions?

No studies have been performed in which dose and time have been associated. For example, no attempt was made to correlate the size of the doses eliciting responses in either Allen et al. (1987) or Moneret-Vautrin et al. (1987) and the time of onset of symptoms.

The range of dosages producing an effect in the report of Allen et al. (1987) was 0.5 g MSG (n=1) to

2.5 g MSG (n=12). Moneret-Vautrin et al. (1987) reported bronchospasm (n=2) after doses of 2.5 g MSG. Both Allen et al. (1987) and Moneret-Vautrin et al. (1987) used capsules as the challenge vehicle and challenged subjects after an overnight fast.

Temporal data from the report of Allen et al. (1987) indicated an interval of 1-2 hours before onset of asthma and/or the MSG symptom complex in 7 of 32 subjects orally challenged with MSG. Six other subjects did not have the symptom complex but exhibited asthma 6-12 hours post-challenge. The interval before onset of symptoms in these subjects is longer than that of the self-limited adverse reactions usually described for the symptom complex (15-30 minutes).

The Expert Panel, in reviewing the study by Allen et al. (1987), noted that data on patient compliance while on the elimination diet were not reported. Although all subjects reportedly were continued on corticosteroid medication and inhaled β -adrenergic agonist bronchodilators during the challenge protocol, questions about the chronic medication status of the responders prevent any definitive conclusions about the timing of symptom onset as some of the six patients with delayed onset could conceivably have experienced a reaction following the removal of their theophylline medication. Although they presented data for only one patient, Allen et al. (1987) noted a "reproducibility of the delay after challenge with MSG... observed in all our patients." Similar delayed responses were also documented by Moneret-Vautrin et al. (1987) in patients who had been off medication for three days. The Expert Panel concluded that while the protocol of Allen et al. (1987) was reasonable, these results require independent replication in order to rule out the possibility of an "off-drug" phenomenon. (See full report², Chapter VII, D, 1 for more information on MSG and asthma.)

d. Are there predisposing medical conditions associated in the specific reactions?

MSG-induced bronchospasm has been demonstrated in some asthmatic patients, but an accurate estimate of the prevalence of asthmatics at risk for MSG-induced asthmatic attacks cannot be ascertained from available data.

With the possible exception of abnormal vitamin B-6 status, predisposing conditions other than asthma have not been identified.

3. Assuming that reproducible associations with MSG ingestion can be demonstrated, what is a reasonable classification scheme for the various types of adverse reactions to MSG that have been reported? Expand discussions of the proposed schema to include how the classification

scheme might be useful in designing future studies.

The Expert Panel concluded that in the absence of reliable and valid epidemiological data and, given the limited current state of knowledge, the creation of a classification scheme would be premature at this time.

Several schemes are plausible based on the current state of knowledge about glutamate. Such schemes or combinations thereof could be based on conditions of use (i.e., specific types of foods consumed under defined circumstances), the nature of the physiological response (e.g., MSG symptom complex only, respiratory problems, or gastrointestinal problems), and/or predisposing factors (e.g., genetic predisposition, physiological condition, nutritional status, or concurrent drug use). However, insufficient epidemiology data exist which might be used to construct such schemes. Conceivably, a multivariate analysis such as cluster analysis might be applied to a large enough sample of verifiable responders to allow for an identification of specific subgroups of the population who might have a unique group of characterizing features.

Another classification scheme could be based on central versus peripheral effects of ingested MSG. The distinguishing characteristic of central effects would be an elevation in blood glutamate concentrations, perhaps coupled with observable neuroendocrinological changes, e.g., fluctuations in prolactin and cortisol levels. However, such biochemical measures cannot be taken in isolation and must be correlated with symptoms of central effects such as mood changes, dizziness and balance, pain, altered vision, difficulty breathing, and pulse rates. Admittedly, these symptoms are nonspecific, but efforts to correlate signs and symptoms of central effects under double-blind controlled experimental situations are needed. Similarly, additional experimentation is needed to establish any strong correlations among symptoms and signs of peripheral effects such as gastrointestinal discomfort, fatigue, muscle weakness, chest pain, altered activity levels, blood pressure, pulse rate, and body temperature. *The Expert Panel strongly suggested that the reliability and validity of any classification scheme must be established through vigorous research and statistical corroboration.*

(See Response to Question 5, below, and full report², Chapter IV, F and Table 5, Chapter V, and Chapter VII, D and Appendix Table 10; Challenge Studies.)

4. Is it possible to classify adverse reactions based upon:

a. The length of time after MSG administration to the onset of the reactions?

No. Valid data are very limited; the typical reported interval for the MSG symptom complex is

between 15 and 60 minutes; but, in some asthmatic patients (Allen et al., 1987; Moneret-Vautrin, 1987), it can be up to 6 to 12 hours post-challenge. *(See response to Question 3 above and full report², Chapter VII, D.)*

b. Dose responsiveness?

No. There are some data from a single-blind challenge of asthmatic subjects (Allen et al., 1987) that support the concept of dose responsiveness. *See response to Question 3 above.* Additional discussion of dose responsiveness in terms of central and peripheral effects is provided in the full report² Chapter VII and in Chapter IX.

c. Type of adverse reaction elicited?

No. These are identified in Question 2 above and in the full report², Chapter VII, Tables 10 and 11 and Appendix Tables 9 and 10. *See also response to Question 3 above.*

d. Predisposing factors?

No. As noted in Question 2, the only predisposing factor that has been documented is unstable asthma. *See response to Question 3 above.*

5. Is it possible to determine the mechanism whereby any glutamate-based adverse reaction might occur? Additional discussion and documentation of mechanisms that are testable experimentally would be helpful.

Not at the present time. However, a number of plausible mechanisms could be identified to explain reported adverse effects from MSG ingestion. The majority of potential mechanisms would be mediated through interaction at the level of either central or peripheral glutamate receptors. Among the potential mechanisms are excitotoxicity, stimulation of CNS glutamate receptors that activate neuroendocrine systems, mediate pain, inflammation, blood pressure regulation and respiration, stimulation of peripheral glutamate receptors associated with gastrointestinal motility, respiration, and the endocrine system (e.g., the adrenal glands and the anterior pituitary gland). *To date, no scientifically valid studies have been performed to confirm these hypothesized mechanisms. An expanded discussion of these topics, including suggestions on mechanisms that might be tested experimentally, can be found in the full report², Chapters V and IX.*

The Expert Panel found that a major constraint in identifying mechanisms has been the inability to make connections between studies of adverse effects and those of metabolic response to oral MSG challenges. The former lacked data on objective measures of response, in particular blood glutamate concentrations, while the latter focused on blood glutamate data without evaluation of adverse ef-

fects. The animal studies employing both parenteral and enteral challenges that have been used to support the possibility of adverse effects have, in general, lacked data on blood glutamate levels. It is difficult to draw conclusions about the relationship between potential adverse effects of enteral MSG challenge in nonhuman primates given the fact that blood data have been rarely reported and none of the relevant reports contains any measure of a neuroendocrine effect. The bulk of the enteral challenge studies employing animal models have focused on either supporting or refuting the contention that neonatal exposure to MSG causes hypothalamic lesions. The vast majority of animal studies using parenteral challenges have used MSG as a probe to explore the function of the arcuate nucleus and other structures close to and within circumventricular areas.

With the exception of the studies on severe asthma and a single attempt to examine the possible role of ingested MSG in esophageal pain (Kenney, 1979), no studies in humans have been designed to explore potential mechanisms of either the MSG symptom complex *in toto*, individual aspects therein (e.g., headache, warmth, burning etc.), or other problems that have been reported to occur consequent to ingestion of MSG. Because of the dearth of appropriately designed studies, the Expert Panel could only speculate about potential mechanisms based on disparate sources of information on the physiology of glutamate.

6. What have other authoritative organizations concluded regarding the potential of MSG to elicit adverse clinical reactions? What is the basis for their conclusions?

Between 1978 and 1992 five authoritative scientific organizations have published statements on the potential of MSG to elicit adverse reactions. These include the Select Committee on GRAS Substances (1978a,b; 1980a,b); the Joint FAO/WHO Expert Committee on Food Additives (1987); the Commission of the European Communities (1991); the American Medical Association, Council on Scientific Affairs (1992); and the Institute of Food Technologists, Office of Public Affairs (1992). The conclusions of these authoritative organizations are summarized in the full report², Appendix Table 1.

While the five organizations are recognized as prestigious and preeminent entities within their respective disciplinary areas, the published statements are not equally authoritative scientifically.

The Select Committee on GRAS Substances (SCOGS) of the Federation of American Societies for Experimental Biology published four monographs (1978a,b; 1980a,b) that evaluated the then extant literature supporting or questioning the con-

tinuation of generally recognized as safe (GRAS) food ingredient status of MSG and protein hydrolysates. The four SCOGS reviews are the only ones that include documentation of the scientific literature on which the conclusions were based. In regard to MSG, in 1978 SCOGS concluded that continued GRAS usage was acceptable for individuals beyond infancy, but that uncertainties required additional studies. In 1982, SCOGS concluded that, at the then-current levels of use, MSG posed no hazard, but noted that the Committee could not determine without additional data if increased consumption would be hazardous.

With regard to protein hydrolysates, SCOGS concluded in 1978 that, at the estimated use levels, soy sauces were safe; however, if consumption increased, additional data would be needed to confirm this conclusion. With regard to acid and enzymatically hydrolyzed protein and yeast autolysates, use at then-current levels as a GRAS substance was acceptable for individuals beyond infancy, but some uncertainties required additional study. Based on evaluation of additional data, in 1982 SCOGS concluded that protein hydrolysates could be continued as GRAS substances.

The Joint FAO/WHO Expert Committee on Food Additives published a report based on an extensive review of scientific literature on MSG in 1991. As with most reports of Joint FAO/WHO Expert Committees, the scope and extent of scientific studies examined are not fully documented. The Committee did not set an acceptable daily intake (ADI), but stated that several glutamate salts including MSG were "of low toxicity" and did not constitute a human health hazard as a result of their use to achieve technical effects (flavoring agents). The absence of additional statements on MSG or on protein hydrolysates since 1991 is puzzling in view of the ongoing controversy concerning adverse reactions.

In 1991 the Commission of the European Communities concluded that no specific toxic effects were evident in various animal models except for varying vulnerability of neonatal rodent central nervous systems where "massive doses" were administered. The Commission also noted reports of adverse reactions in humans who ingested doses of over 3 g but stated that such reactions occurred with foods not containing glutamates and that no objective clinical measurements were associated with reported symptoms. The Commission review was based on selective reviews and evaluations of scientific literature submitted to or commissioned by the group. These sources are not fully documented.

In 1992 the Institute of Food Technologists (IFT), Office of Scientific Public Affairs, published a position paper based on an internal selective

review of scientific literature from 1987 to 1992. The IFT did not identify the scientific literature cited in reaching its conclusions. The IFT paper stated that, for the vast majority of persons, MSG is safe, that adverse reactions do occur but these are exceptions rather than the rule, that sensitive persons should seek medical advice and controlled challenge tests, and that foods to which MSG is added should be so labeled. The IFT also recommended additional research (i.e., double-blinded challenge tests under controlled conditions) to clarify the association of MSG with adverse reactions.

In 1992 the Council on Scientific Affairs of the American Medical Association stated that L-glutamate in any form had not been shown to be a "significant health hazard" and supported the exclusion of labeling glutamate derived from protein hydrolysate products. This publication was an historical review of regulatory status and position papers prepared by WHO, the IFT, and a literature review by the International Glutamate Technical Committee (1991). This position paper does not provide evidence of an independent reevaluation of the scientific literature by the American Medical Association Council on Scientific Affairs.

In summary, only the four evaluative reviews of the SCOGS provide complete documentation of the scientific literature used in reaching the "authoritative" position. The other four authoritative organizations have published position statements that, in general, reach analogous positions; however, in retrospect, documentation of the scope and extent of scientific literature evaluated is lacking.

7.a. What are the free glutamate levels in food containing hydrolyzed vegetable protein (HVP) as used in the range of products manufactured for consumption by American consumers?

The acid hydrolysis process produces a mixture of amino acids that reflects the composition of the intact protein except that tryptophan is destroyed while cysteine and methionine concentrations are markedly reduced. The glutamate content of commercial products, on a dry weight basis, expressed as glutamic acid, ranges from 5.6% to 14.17%. The International Hydrolyzed Protein Council specified an upper limit for glutamic acid of 25% for acid hydrolyzed protein (Select Committee on GRAS Substances, 1978b).

More recent analyses (Krukar, 1993; Patti, 1993) demonstrated that, during the period 1989-1991, the average free glutamic acid content was 8.2% for acid hydrolyzed protein manufactured in the United States and 5.2% for autolyzed yeast extracts. (See also full report², Chapter III, B, 2.)

Hydrolyzed vegetable protein typically comprises 0.6% or less of finished food products that incorpo-

rate hydrolyzed protein. The associated free glutamate level in the finished foods contributed by HVP is 0.05% or 0.11 g per 8 ounce (224 g) serving. The estimated annual free glutamate consumption from autolyzed yeast extracts and HVP is 8 g per person annually or 0.022 g per person per day which is approximately 2% of the lowest dose demonstrated to cause adverse effects in humans. (See full report², Chapter III, B, 2.)

b. What is the evidence that HVP ingestion is associated with adverse reactions similar to those reported to occur after MSG ingestion?

Only two reports were found that addressed the potential adverse effects of glutamate contained in protein hydrolysates; however, only the study by Olney et al. (1973) specifically evaluated the adverse effects of glutamate contained in hydrolyzed proteins. The study by Stegink et al. (1974) made extrapolations based on comparisons between blood glutamate concentrations obtained in their own feeding study and the blood glutamate and histological findings of Olney et al. (1973). Olney et al. (1973) reported lesions in the hypothalamus of 10-day-old mice given enzymatic casein hydrolysate subcutaneously at doses ranging from 1 to 5 g per kg body weight. These experiments used enzymatically hydrolyzed casein. Assuming that the free glutamic acid content of casein hydrolysates is 25 g per 100 g of amino acids (the upper level specified by the International Hydrolyzed Protein Council [Select Committee on GRAS Substances, 1978b]), then lesions occurred in neonatal mice receiving total free glutamate doses of 1.5 to 7.5 mg (sample calculation: a dose of 5 mg per g body weight \times 6 g body weight/mouse \times 25% = 7.5 mg).

No such effects have been reported from studies of other animal species; no adverse effects have been reported in studies employing enteral challenge. No comparable human data are available.

While parenteral feedings in humans may involve the use of hydrolyzed proteins, the Expert Panel was unaware of any studies that have been performed to assess the potential for adverse effects specifically attributable to the glutamate contained in these mixtures. Moreover, the relevance of these findings to potential adverse effects in humans under normal conditions of ingestion is unclear.

The Expert Panel found no scientific reports of glutamic acid-related adverse effects of ingesting either protein hydrolysates of microbial, vegetable, or animal origin.

Of the 154 testimonial letters received by LSRO as of July 1, 1994, only one correspondent mentioned hydrolyzed vegetable protein (HVP) as a likely cause of symptoms, and this was HVP contained in a skin moisturizing preparation (Moore,

1993). FDA-ARMS noted, "We still have no documented evidence that hydrolyzed vegetable protein (HVP) causes reactions similar to MSG. Unconfirmed reports from consumers state that adverse effects are experienced from both MSG and HVP although none report reactions to HVP alone." (See also full report², Chapter III, B, 2 and Chapter VII, A.)

c. Have life-threatening adverse reactions been verified to occur with the levels of glutamate reported to be used in this range of products?

The Expert Panel found no studies that reported glutamate-related life-threatening adverse reactions to various forms of protein hydrolysates.

Per unit of body weight, the greatest human consumption of protein hydrolysates occurs in infants fed protein hydrolysate-based formulas. The intakes of glutamates by such infants (perhaps 0.26 g/kg/d or 0.04 g/kg/feeding) are similar to those (3 to 5 g MSG/dose or 0.04 to 0.07 g MSG/kg/dose) associated in some reports with adverse reactions. The Expert Panel found no reports of glutamate-related adverse effects associated with the use of these foods in infants.

In view of these calculations and the lack of reports of adverse reactions, it is unlikely that life-threatening reactions would result from normal patterns of consumption of products containing HVP. (See full report², Chapter III, B, 2 and Chapter VII, A.)

d. Explain more fully the relevance of data on subcutaneous administration of HP to mice to the oral administration of HP and MSG. Can a dose relationship or comparison be made between the quantity of MSG in foods containing HP and glutamate per se be made?

Other than the study of Olney et al. (1973) cited above, there are no relevant data that establish a relationship between subcutaneous administration of HP to mice and oral ingestion of HP and MSG by humans. Consequently, a dose relationship cannot be determined in humans. See full report², Appendix Table 6 for a summary of Olney et al. (1973).

8. Are there any defined human subgroups that are more susceptible to glutamate than the general population? Expand the discussion of the extent and possible bases of similarities and differences among subjects ingesting MSG or placebos in regard to reported adverse reactions.

There is limited evidence that some asthmatic patients are more likely to suffer adverse effects than members of the general population. As mentioned previously, the Expert Panel's review of the literature revealed several possible situations in

which subgroups of the general population might be identified who may be more susceptible to the effects of MSG. These groups include individuals with either vitamin B-6 malnutrition, infants (*in utero* and newborns), women taking oral contraceptives, and individuals with affective disorders. Each of these possibilities has been discussed in Chapter V and Chapter VII, in addition to questions involving the predisposing conditions addressed above. Again, the Expert Panel emphasized that, in the face of a complete lack of studies addressing these contingencies, any statements about the potential increase in susceptibility in these subgroups to adverse effects from the ingestion of MSG are speculative at this time.

In order to be comprehensive, the Expert Panel recognized that there exists in the medical literature on idiosyncratic reactions and "food allergy" anecdotal reports of manifestations frequently identified as being typical of MSG sensitivity. For example, idiosyncratic responses are well known in persons with non-immunologic food intolerance and subjects in food challenge trials who react to placebos. Moreover, the reported symptoms resemble those that FDA has observed since 1983 in its tracking system on symptoms and signs allegedly resulting from consumption of aspartame. The symptoms also resemble those observed in military subjects when the nature of the macronutrient content of the diet is precipitously changed as in military testing of new field rations (Schnackenberg et al., 1986). Thus, it is reasonable to conclude that subgroups do exist who are more likely to experience adverse reactions to foods and food ingredients, including glutamate, than is the general population of consumers. However, the physiological, biochemical, immunological, psychological, or behavioral bases of these experiences are neither known nor are they common across defined subgroups. (See also full report², Chapter VII, A and D, and Chapter VIII, A.)

9.a. Are there clinical adverse reaction reports of physiological mechanisms that would explain why a glutamate-sensitive individual might respond adversely to "synthetic" or added MSG but not to comparable levels of free glutamates that occur naturally in such food products as tomato juice and Parmesan cheese?

No. Without the use of experimental techniques such as radioactive tracers, it is not possible analytically to distinguish between naturally occurring and added glutamates because the analytical method for identification of MSG is based on identification of L-glutamate. (See full report², Chapter II.)

b. Is there evidence that adverse reactions similar to those reported for MSG occur when foods naturally high in glutamates are consumed?

No; even anecdotal observations are difficult to interpret in this regard as those who report reactions to MSG rarely provide information on all foods consumed during the previous 24 hours.

10.a. During testing for MSG mediation of adverse reactions, what is a reasonable range of doses to be administered to assure that potentially MSG-sensitive individuals would be detected for each class of adverse reaction while assuring patient safety? Provide additional details on rationale for the suggested dosage levels recommended for future experimental studies.

Available data suggest strongly that precipitation of adverse reactions is most likely to occur when the dose is given in the fasting state as a liquid or capsule without food. An adverse reaction has been reported in one subject who received a single dose of 0.5 g of MSG, and it is therefore suggested that double-blind, placebo-controlled testing begin with this dose. In subjects with no reaction to 0.5 g, an additional test with 3 g should be carried out. Testing at greater doses is probably not needed because it is unlikely that subjects who fail to react to a dose of 3 g given under fasting conditions will react to the quantities of glutamates consumed with food under "real-life" circumstances.

b. What study designs are appropriate for testing MSG mediation of different types of reported adverse reactions?

The most appropriate study design for challenge tests is a double-blind placebo-controlled protocol as outlined by Bock et al. (1988) and the Workshop on Adverse Reactions to Food and Food Additives (Metcalf and Sampson, 1990) or a more rigorously controlled alternative thereof. For confirmation of the symptom complex, double-blind placebo-controlled challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with the placebo. For confirmation of an objective response, e.g., bronchoconstriction in asthmatic patients, a single, double-blind, placebo-controlled challenge with response to MSG and nonresponse to placebo would be sufficient.

All of the above challenge tests should be conducted in appropriately uniform settings with standardized procedures. Emergency medical service capabilities should be available immediately adjacent to the setting.

In addition to the challenge tests, objective physiological and psychometric tests should also be applied. For example, tests could include complete neurological examination, blood tests (for amino acid levels and standard parameters, e.g., glucose, insulin, vitamin B-6 status indices, etc.) and psychometric assessments including mood scales, etc. In addition, consideration should be given to inclusion of functional imaging techniques (e.g., PET scan) and/or recording of visual or auditory evoked potentials, and measures of physiological stress, e.g., circulating cortisol levels and skin conductivity, should be considered.

11.a. During testing for MSG mediation of each class of adverse reactions, what is the best manner to control for various possible disease triggers?

All subjects involved in any double-blind placebo-controlled challenge testing should have a complete medical history and examination prior to testing. Subjects should be segregated into population samples on the basis of these screening criteria, e.g., chronic asthma, diagnosed food allergies, abnormal vitamin B-6 status, etc.

b. What are the appropriate subject selection criteria?

To determine the prevalence of adverse reactions to glutamates in the general population, the frequency of adverse reactions should be determined in patients with asthma and in randomly chosen individuals without asthma. Vitamin B-6 status should be determined in both groups. In addition, it may be useful to determine the prevalence of adverse reactions to glutamates in individuals with self-reported history of adverse reactions to glutamates. These individuals should also be classified with regard to the presence or absence of asthma and vitamin B-6 status should be determined. (See additional discussion in full report², Chapter VIII.)

c. Can the test solution be adequately blinded?

Liquid or capsule forms can be blinded adequately. As noted in the discussion in Chapter VIII, the placebo must be indistinguishable from the active agent (MSG-containing vehicle), but not necessarily perceived as identical. Investigators must validate the placebo by demonstrating that an independent panel was unable to distinguish the "active" from "placebo" agent in a pilot testing procedure prior to initiation of the actual protocol.

d. When is it appropriate to use MSG in capsules rather than in solution or in food matrices?

The Expert Panel recognized that the use of capsules ensures the greatest control over dose and blinding; however, the Expert Panel also noted that the use of capsules obviates the potential role of the oral cavity and esophagus in the precipitation of potential adverse effects. The Expert Panel suggested that the use of capsules versus liquids would depend on the goal of the study. For example, if the goal is to study the potential for adverse effects of MSG ingestion under conditions of normal use, a liquid vehicle would be most appropriate. The Expert Panel also noted the report by Stegink et al. (1979) in which marked differences in peak plasma glutamate concentrations were found when MSG was delivered in capsules rather than liquid vehicles. (Administration in capsules resulted in a 3- to 4-fold attenuation of peak glutamate response.)

e. What sample size is needed to assure that adequate sensitivity is present to detect an effect or the absence of an effect?

The double-blind placebo-controlled protocols outlined above are sufficiently rigorous to preclude the possibility that one laboratory, at one time, could identify sufficient subjects who would be willing to participate in such challenge tests. In a practical sense, such experiments will need to be conducted at several locations over a period of several years in a collaborative effort. Thus, it seems that actual sample size is less of a factor than the number of subjects and number of challenges at several locations over an extended period. Multivariate analyses of data will be required to confirm statistical significance of challenge test results. At a minimum, the absence of reaction of any parameter in 40 subjects with suggestive history would provide a 95% confidence level. This estimate is based on a power analysis designed to compute the number of subjects in a study employing a nominal (e.g., yes/no, +/-) response paradigm utilizing a binomial distribution.

f. Given the possibly high incidence of subjective symptoms in adverse reactions, additional discussion of study parameters such as statistical aspects of sample size is warranted.

As noted by Rosenzweig et al. (1993) in a review of controlled trials involving over 1200 subjects, adverse events were reported by about 20% of the subjects when placebos were administered. Consequently, multiple double-blind placebo-controlled food challenges (DBPCFC) will be necessary to confirm subjective symptoms. Based on the following mathematical relationships, five DBPCFC may be necessary to conclude that subjective symptoms (e.g., headache, chest tightness, numbness, etc.) are secondary to MSG in a highly suggestible individual.

This assumes a binomial distribution of a nominal response. Therefore, with a one-in-two chance of a positive response with each challenge, 5 positive responses to MSG with all negative responses to placebo could occur in 1 of 32 chances, or $p=0.03$.

In subjects not considered highly suggestible, one could assume a false positive rate of 20% to 25% as suggested by Rosenzweig et al. (1993). In such cases, three DBPCFC would be necessary to confirm the association of subjective symptoms and MSG (i.e., one in four chance cubed [$1/4^3$] or $p < 0.02$).

In patients with objective findings following MSG challenge (e.g., marked bronchospasm, anaphylaxis, vomiting, etc.), a single DBPCFC can be regarded as definitive. (See full report², Chapter VIII for further discussion of issues in experimental design.)

12. What are the relative sensitivities of rodents and nonhuman primates to the acute central nervous system (CNS) effects of MSG?

The Expert Panel found no scientific studies that carefully assessed the relative sensitivities of both rodents and nonhuman primates to the central nervous system effects of MSG. However, numerous studies have shown that doses of 0.5 to 4.0 g MSG/kg body weight produce hypothalamic lesions in infant mice. For enteral administration, the minimum effective dose is 0.5 to 0.7 g MSG/kg body weight (Daabees et al., 1985; O'Hara and Takasaki, 1979; Olney and Ho, 1970). Similarly, Olney et al. (1972) described "small focal lesions" in the brains of infant rhesus monkeys given 1 to 2 g MSG/kg body weight enterally (by gavage) in a 50/50 solution of water and skim milk. Based on these few studies, the Expert Panel concluded that the relative sensitivities of rodents and nonhuman primates to enteral MSG-induced brain lesions are likely to be of the same order of magnitude.

The Expert Panel noted that pharmacokinetic comparisons between species assume a similar inherent sensitivity of brain to fluctuations in concentrations of either plasma glutamate or brain extracellular glutamate consequent to MSG exposure. The Expert Panel was unaware of any data to support that contention. It is conceivable that the inherent susceptibility of brain may differ across species, regardless of peripheral pharmacokinetic or blood-brain barrier (BBB) effects. The Expert Panel referred to the study of McDonald and Johnston (1990) that reported that the susceptibility to extracellular glutamate varies markedly in rat brain slices during development. Consequently, it may have no meaning to compare doses in different species that give a certain peak plasma concentration until the inherent sensitivity of the brain has been determined for multiple species and across varying developmental periods. Additional work is required with

both adult and immature animals to more precisely define threshold levels of MSG neurotoxicity.

13. Are there any studies conducted *in vivo* during the 1980's or 1990's that provide additional insight concerning the capacity of orally-administered MSG to mediate acute damage (lesion) of the arcuate nucleus of the anterior hypothalamus or of other circumventricular structures in the CNS of nonhuman primates?

No. The Expert Panel was unaware of any studies performed within the last 15 years that have directly addressed the ability of orally ingested MSG to produce lesions in nonhuman primates. Several studies have documented the impact of parenterally administered MSG on the hypothalamic morphology in nonhuman primates. (See also full report², Chapter VI, B, 2.)

14.a. What evidence is available concerning the ability of exogenously administered MSG to mediate changes in pituitary function following acute oral or parenteral dosing?

The evidence linking glutamate challenge with changes in pituitary function was found in the extensive literature on parenteral exposure of animal models, primarily rodents, but also in monkeys (see full report², Appendix Table 7). Two classes of pituitary response to parenteral glutamate have been observed: chronic changes following neonatal glutamate-induced lesions of the hypothalamus, and acute effects following glutamate challenge later in development. The former have been studied only in rodents. With regard to the latter, which do not appear to involve the neurotoxic actions of glutamate, numerous studies have demonstrated discrete elevations in gonadotropin, prolactin, ACTH, and growth hormone in rodents and nonhuman primates consequent to s.c., i.p., or i.v. exposure to glutamate. Good evidence exists to indicate that the ability of glutamate to elicit pituitary hormone secretion is mediated largely by an indirect action on the hypothalamus where the amino acid stimulates hypophysiotropic neurons to release their release/release-inhibiting hormones into the hypophysial portal circulation.

The Expert Panel found no studies in which levels of pituitary hormones (or hormones from the target glands) were assessed in enterally challenged rodents or nonhuman primates (See full report², Appendix Tables 4 and 5). However, in rodents, enteral challenge has been associated with behavioral changes such as decreased activity levels, cognitive deficits, neurochemical changes, convulsions, changes in appetite regulation, and increased pituitary gland weights. While several of these findings would presumably involve neuroendocrine

changes, no studies have been found that have specifically documented anomalies in neuroendocrine function, e.g., changes in circulating hormone levels, in enterally challenged rodents.

Carlson et al. (1989) examined the potential of several amino acids including 10 g of glutamic acid and 10 g aspartic acid (aspartate and glutamate challenges given on separate days) to influence pituitary function in humans (see summary in full report², Appendix Table 10). In addition to groups receiving glutamate and aspartate (n=11 and 9, respectively), subjects received taurine capsules, and two doses of cysteine (5 and 10 g) also in gelatin capsules. Subjects were challenged with these amino acids on separate days. As the intention was to assess the impact on prolactin, which normally peaks at midday, no attempt was made to maintain an overnight fast prior to the challenges (Carlson, 1993).

Carlson et al. (1989) reported significant increases in both serum prolactin and cortisol after glutamate challenge. They observed that the time of peak levels relative to challenge coincided with peak plasma glutamate concentrations. Mean baseline values of prolactin (6.6 ng/ml) and cortisol (6.6 µmol/dL) increased to peaks of 12.9 ng/ml and 12.6 µmol/dL, respectively, 1 hour post-challenge with glutamate. Carlson et al. (1989) observed no changes in serum levels of growth hormone, TSH, or LH following either glutamate or aspartate challenge. Similarly, no changes in either cortisol or prolactin were noted after aspartate.

The Expert Panel was aware that the study by Carlson et al. (1989) had been preceded by a study in which similar results, i.e., elevations in serum prolactin and cortisol, had been elicited by dietary protein (Carlson et al., 1983). While it would be a simple matter to attribute the rise in cortisol and prolactin to protein or generically to amino acids, the Expert Panel noted that no such rise occurred following aspartic acid or any of the other amino acids tested by Carlson et al. (1989). Consequently, while it is possible that the effect on cortisol and prolactin could be a result of protein consumption, it is also possible that the effect seen by Carlson et al. (1983) was due to the glutamate content of the protein meal. As noted by Carlson (1994), "It is difficult to reach a definite conclusion, since in no study was there a direct comparison of the cortisol responses to glutamate and to mixed or protein meals in the same subjects." Carlson (1994) also acknowledged that similar responses in both serum cortisol and prolactin have been documented following physical and mental stress.

The Expert Panel concluded that the report by Carlson et al. (1989), while not definitive proof of a direct neuroendocrinological response to ingested

MSG, does offer evidence for the potential for such a reaction. Consequently, this possibility must be considered plausible in the absence of contradictory evidence, particularly in light of the irrefutable evidence supplied by the animal studies of an effect of parenterally administered MSG on these hormones. The Expert Panel strongly recommends that future studies be designed to replicate and further explore this effect in humans.

b. What controls were used to demonstrate that this effect was specific to MSG and not related to nonspecific changes in such factors as plasma pH or osmolarity?

The Expert Panel was convinced that MSG given parenterally to neonatal animals at sufficient doses (between 2 and 4 g MSG/kg body weight in rodents and > 6 g MSG/kg body weight in hamsters, in single repeated daily doses) will cause long-term changes in the neuroendocrine axes governing pituitary hormone secretion. In addition, equally convincing evidence is available demonstrating that parenteral glutamate administration to adult animals (monkeys and rodents) stimulates the secretion of many pituitary hormones. The majority of studies have used isomolar concentrations of saline to control for the potential effects of sodium in the MSG challenge and have clearly established that the effects are due to the glutamate and not the sodium or changes in osmolarity or pH (see full report², Appendix Tables 6 and 7). Also, acute pituitary hormone release in response to glutamate and related amino acid analogs may be blocked by concomitant administration of specific glutamate receptor antagonists (see response to question 14c, below; full report², Chapter V and discussion of glutamate receptor antagonists in Chapter VI, C).

c. What evidence is provided that specific excitatory neurotransmitter receptors are involved in any effect observed?

Numerous studies in rodents and nonhuman primates have made the link between release of hormones, including luteinizing hormone, prolactin, hypothalamic gonadotropin-releasing hormone, follicle-stimulating hormone, and specific excitatory neurotransmitter receptors, particularly the NMDA receptor (Abbud and Smith, 1991; Arslan et al., 1988; Gay and Plant, 1987; Gay and Plant, 1988; Plant et al., 1989; Wilson and Knobil, 1982). The Expert Panel found this evidence convincing and conclusive.

15.a. What are the comparative blood levels of glutamate and aspartate that are produced from large orally-administered doses of MSG from solutions (such as in clear soups) and the blood

levels inducing the release of luteinizing hormone in nonhuman primates?

Following large orally administered doses of MSG in humans, elevations in blood glutamate levels with maximal concentrations of approximately 600 μM have been reported (Carlson et al., 1989). In the monkey, intravenous glutamate injections of 48 mg MSG/kg body weight, and greater, have been reported to elicit luteinizing hormone release. Although plasma glutamate levels achieved following the threshold dose of 48 mg glutamate/kg body weight were not measured, an intravenous injection of 150 mg glutamate/kg body weight in this species produced circulating levels of glutamate between 4,000 and 6,000 μM . Therefore, if intravenous glutamate dose and circulating glutamate concentrations are linearly related, it may be suggested that an estimate of threshold circulating glutamate concentration for luteinizing hormone release in the monkey is 1,000 to 2,000 μM .

b. What is the probability of MSG ingestion with foods influencing the release of pituitary hormones?

The Expert Panel concluded that it is unlikely, but possible, that ingestion of MSG with foods could cause the release of pituitary hormones. Studies have been performed in both animals and humans that support the contention that glutamate given in a liquid medium, i.e., water or clear broth, to a fasted subject will result in higher circulating concentrations of glutamate than when glutamate is given with a mixed meal or food matrix, e.g., liquid formula (see full report², Chapter IV, Table 5). No studies have been performed that have attempted to link blood levels to effects other than hypothalamic lesions in neonatal animals. Few of the parenteral challenge studies have linked the lesions or neuroendocrinological effects observed to circulating levels of glutamate. Moreover, no studies have been found that have measured both blood levels of glutamate and related amino acids and either luteinizing hormone or any other neuroendocrine parameter in nonhuman primates orally exposed to MSG.

Any conclusions expressed by the Expert Panel about the relationship between ingestion of MSG with food and alterations in the release of pituitary hormones in nonhuman primates would be speculation. The data available to the Expert Panel were insufficient to support the contention that elevations in plasma glutamate concentrations per se are the *sine qua non* of adverse effects from glutamate.

16.a. What are the relative effects of treatment conditions, or circumstances of oral ingestion, on the plasma concentrations of MSG, e.g., does

MSG given in water produce a different plasma level of glutamate than the same dose given in a more complex food matrix containing carbohydrates?

Evidence summarized in the full report², Chapter IV, Table 5 and Appendix Tables 2 and 3, clearly demonstrates that the composition of the challenge vehicle and the conditions of challenge, e.g., fed versus fasted, significantly impact on changes in circulating glutamate in response to an oral challenge. The extent of the rise in plasma concentrations of glutamate and related amino acids is affected by a number of factors including the size of the dose (increase with increasing dose); the nature of the challenge vehicle (e.g., water causes greater rise than mixed meal); the temporal proximity of food consumption (fasted subjects have greater response than those challenged with a meal); and macronutrient composition of concurrent food (carbohydrate and mixed meals have an attenuating effect compared with fasting or protein). The Expert Panel noted that no data are available on the impact of a 15- to 20-minute delay between challenge in a liquid broth as would be consumed in the beginning of a meal and consumption of a mixed meal on blood glutamate concentrations or manifestation of adverse effects.

As summarized in the full report², Chapter IV, Table 5, available data do support an incremental increase in plasma glutamate concentrations consequent to increasing doses of MSG in water in adult humans. A total of five studies were identified in which adults received MSG in water only. Doses in these studies ranged from 60 to 150 mg MSG/kg body weight and responses in terms of peak glutamate concentrations ranged from 155 μM (at 60 mg dose) to 718 μM (at 150 mg/kg).

b. What influence does strength of MSG concentration and mode of administration (human sipping versus animal gavage) have on plasma levels of glutamate?

The Expert Panel was unaware of any studies examining potential adverse effects of MSG in humans that have addressed the impact of the mode of administration (e.g., sipping) on circulating glutamate concentrations. Similarly, no studies have been performed that compare relative impact of sipping in humans versus gavage in animals. However, it should be noted that the majority of the human studies reviewed by the Expert Panel endeavored to ensure that subjects consumed the challenge vehicle within a prescribed time limit. In animals, the vast majority of studies of enteral MSG challenge used the gavage method as opposed to self-selection. No studies were found that com-

pared different routes of administration of MSG either within or between animal species.

17. What evidence is available concerning the relative rates of MSG metabolism in infants, children, and adults? What is the evidence for altered sensitivity of the CNS to circulating levels of glutamates?

Based on the limited data set, particularly in humans, the Expert Panel has concluded that insufficient evidence exists to answer this question at this time. Moreover, since blood glutamate levels may not be the only factor in predicting some responses to ingested glutamate, future efforts should be focused on identifying additional and appropriate parameters for the study of glutamate metabolism and response in infants and children.

Only two published reports evaluated the metabolic response to ingested glutamate in human infants (Stegink et al., 1986; Tung and Tung, 1980). As the report by Tung and Tung (1980) contained highly variable data sets in a sample of infants that included two premature infants, the Expert Panel concluded that the study by Stegink et al. (1986) contained more useful information. Stegink et al. (1986) randomly assigned 8 infants (mean age 10 months) to receive consommé (with 56 mg MSG/8 oz or 4.1 mg/kg when 160 ml is fed to a 9.1 kg infant) containing either 0, 25, or 50 mg MSG/kg at 1-week intervals. All challenges occurred at 0800 hours after an overnight fast.

Infants were randomly assigned to one of two blood collection schedules 0, 30, 60, and 120 minutes and 0, 15, 45, and 90 minutes; each group had four infants. Infant data were compared with the adult data from Stegink et al. (1985). Whereas in the previous study with adults given 15 minutes to consume the challenge soup (mean time of consumption was 7 minutes), infants in this study took a mean of 18 minutes to consume the soup.

Infants had significantly higher baseline levels of both aspartate and glutamate and demonstrated a different pharmacokinetic response to challenge with both 25 and 50 mg MSG/kg when compared with previously studied adults. Baseline glutamate and aspartate levels were significantly lower in adults at all levels of challenge (glutamate: 36.9, 39.3, and 37.7 $\mu\text{mol/L}$ versus 62.4, 72.2, and 67.1 $\mu\text{mol/L}$; aspartate 7.0, 6.6, 4.3 $\mu\text{mol/L}$ versus 12.5, 15.0, and 15.9 $\mu\text{mol/L}$ at 0, 25, and 50 mg MSG/kg, respectively). Peak infant glutamate levels at 25 mg/kg dose occurred at 15 minutes (106 $\mu\text{mol/L}$) versus at 30 minutes in adults (102 $\mu\text{mol/L}$). Peak aspartate levels occurred at 45 minutes in infants (21.1 $\mu\text{mol/L}$) and 30 minutes in adults (11.2 $\mu\text{mol/L}$). Similarly, at 50 mg/kg dose peak infant glutamate levels occurred at 15 minutes

(120 $\mu\text{mol/L}$) versus at 30 minutes in adults (170 $\mu\text{mol/L}$). Peak aspartate levels occurred at 45 minutes in infants (22.9 $\mu\text{mol/L}$) and 30 minutes in adults (14.0 $\mu\text{mol/L}$). No changes in erythrocyte glutamate or aspartate levels relative to baseline levels were noted in the infants at any dose level.

No data were provided with regard to method of infant feeding, i.e., breast- versus bottle-fed. Differences in the timing of consumption of the soup and blood sampling between the infants and adults could have been reflected in the pharmacokinetic differences in this report, i.e., glutamate levels peaked sooner and aspartate levels peaked higher and later in infants than in adults. There were no reported adverse effects.

Results of animal studies indicate that sensitivity to CNS effects of exogenous MSG decreases following the neonatal period; however, large doses given parenterally can induce CNS damage in juvenile and adult animals.

18. What have other authoritative organizations concluded regarding the potential of MSG to elicit neurotoxic reactions? What are the bases for their conclusions?

None of the previous reports by other authoritative organizations has made the distinction between adverse effects associated with peripheral and/or CNS effects of MSG and those resulting specifically from neurotoxicity, i.e., effects associated with lesions. The conclusions of these organizations, as outlined in the response to Question 6, imply an absence of data to support a neurotoxic effect from MSG at levels required to produce a flavor-enhancing effect. The response to Question 6 includes a discussion of the basis of the conclusions of these organizations.

With regard to a role of MSG in producing adverse effects in humans, the Expert Panel concluded that there is sufficient evidence to support the existence of a subgroup of the general population of otherwise healthy individuals who may respond to large doses (≥ 3 g) under specific conditions of use (see Questions 1 and 2). In addition, there may be a small subgroup of previously diagnosed unstable asthmatics who also may respond to large doses of MSG under specific conditions of use (see Questions 1, 2, and 3). The mechanisms of these reactions are unknown at this time; however, no evidence exists to support the ability of orally ingested glutamate to produce neurotoxic or lesioning effects in humans.

The Expert Panel noted that any differences in its conclusions from those reached by other authoritative organizations are based on the documented exhaustive nature of its literature review (see full report², Literature Cited). As opposed to organiza-

tions other than the SCOGS Committee, who performed a similarly thorough review of the existing literature, the Expert Panel relied solely on its own interpretations of the extant data. Differences between the conclusions of the SCOGS and the Expert Panel are due to the publication of literature since 1980 that is related to the evolving knowledge about glutamate neurobiology and neurophysiology.

LITERATURE CITED

Ed. Note: this section contains a list of literature cited in the Executive Summary of the report "Analysis of Adverse Reactions to Monosodium Glutamate (MSG)." The text of the full report includes a complete list of literature cited in all sections and tables of the full report.²

- Abbud, R. & Smith, M.S. (1991) Differences in the luteinizing hormone and prolactin responses to multiple injections of kainate, as compared to N-methyl-D,L-aspartate, in cycling rats. *Endocrinology* 129:3254-3258.
- Allen, D.H.; Delohery, J. & Baker, G. (1987) Monosodium L-glutamate-induced asthma. *J. Allergy Clin. Immunol.* 80:530-537.
- American Medical Association Council on Scientific Affairs. (1992) Report regarding the inclusion of added L-glutamic acid content on food labels. Report D (A-92). p.1-6.
- Arslan, M.; Pohl, C.R. & Plant, T.M. (1988) DL-2-amino-5-phosphopentanoic acid, a specific N-methyl-D-aspartic acid receptor antagonist, suppresses pulsatile LH release in the rat. *Neuroendocrinology* 47:465-468.
- Asnes, R.S. (1980) Chinese restaurant syndrome in an infant. *Clin. Pediatr.* 19: 705-706.
- Bock, S.A.; Sampson, H.A.; Atkins, F.M.; Zeiger, R.S.; Lehrer, S.; Sachs, M.; Bush, R.K. & Metcalfe, D.D. (1988) Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J. Allergy Clin. Immunol.* 82:986-997.
- Carlson, H.E. (1993) Personal communication on January 14 with D. Raiten, Life Sciences Research Office, Federation of American Societies for Experimental Biology.
- Carlson, H.E. (1994) Personal communication on October 14 with D. Raiten, Life Sciences Research Office, Federation of American Societies for Experimental Biology.
- Carlson, H.E.; Miglietta, J.T.; Roginsky, M.S. & Stegink, L.D. (1989) Stimulation of pituitary hormone secretion by neurotransmitter amino acids in humans. *Metabolism* 38:1179-1182.
- Carlson, H.E.; Wasser, H.L.; Levin, S.R. & Wilkins, J.N. (1983) Prolactin stimulation by meals is related to protein content. *J. Clin. Endocrinol. Metab.* 57:334-338.
- Commission of the European Communities. (1991) Food - science and techniques. Reports of the Scientific Committee for Food. Twenty-fifth series. EUR 13416 EN. Luxembourg: Office for Official Publications of the European Communities.
- Daabeas, T.T.; Finkelstein, M.W.; Stegink, L.D. & Applebaum, A.E. (1985) Correlation of glutamate plus aspartate dose, plasma amino acid concentration and neuronal necrosis in infant mice. *Food Chem. Toxicol.* 23:887-893.
- Food and Drug Administration (1992) Analysis of adverse reactions to monosodium glutamate (MSG); announcement of study; request for scientific data and information; announcement of open meeting. *Fed. Reg.* 57:57467-57469.
- Gann, D. (1977) Ventricular tachycardia in a patient with the "Chinese restaurant syndrome". *South. Med. J.* 70:879-881.
- Gay, V.L. & Plant, T.M. (1987) N-methyl-D,L-aspartate elicits hypothalamic gonadotropin-releasing hormone release in pre-

- pubertal male rhesus monkeys (*Macaca mulatta*). *Endocrinology* 120:2289-2296.
- Gay, V.L. & Plant, T.M. (1988) Sustained intermittent release of gonadotropin-releasing hormone in the prepubertal male rhesus monkey induced by N-methyl-DL-aspartic acid. *Neuroendocrinology* 48:147-152.
- Goldberg, L.H. (1982) Supraventricular tachyarrhythmia in association with the Chinese restaurant syndrome. *Ann. Emerg. Med.* 11:333.
- Institute of Food Technologists, Office of Scientific Public Affairs. (1992) Monosodium glutamate: an Institute of Food Technologists scientific perspective. *Food Technol.* 46:34.
- International Glutamate Technical Committee. (1991) Scientific literature review on glutamates. Atlanta, GA: The Glutamate Association.
- Joint FAO/WHO Expert Committee on Food Additives. (1987) L-glutamic acid and its ammonium, calcium, monosodium and potassium salts. In: *Toxicological evaluation of certain food additives and contaminants*. New York: Cambridge University Press. p.97-161.
- Kennedy, R.A. (1979) Placebo-controlled studies of human reaction to oral monosodium L-glutamate. In: Filer, L.J., Jr.; Garattini, S.; Kare, M.R.; Reynolds, W.A.; Wurtman, R.J., eds. *Glutamic acid: advances in biochemistry and physiology*. New York: Raven Press. p.363-373.
- Krukar, R.J. (1993) Champlain Industries, Inc. Clifton, NJ. Letter submitting data on the glutamate content of hydrolyzed protein.
- Kwok, R.H.M. (1968) Chinese-restaurant syndrome. *N. Engl. J. Med.* 278:796.
- McDonald, J.W. & Johnston, M.V. (1990) Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res. Rev.* 15:41-70.
- Metcalf, D.D. & Sampson, H.A. (1990) Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J. Allergy Clin. Immunol.* 86:421-442.
- Moneret-Vautrin, D.A. (1987) Monosodium glutamate-induced asthma: study of the potential risk in 30 asthmatics and review of the literature. *Allerg. Immunol.* 19:9-35.
- Moore, C.A. (1993) Letter and submission, May 12, to Life Sciences Research Office.
- O'Hara, Y. & Takasaki, Y. (1979) Relationship between plasma glutamate levels and hypothalamic lesions in rodents. *Toxicol. Lett.* 4:499-505.
- Olney, J.W. & Ho, O.L. (1970) Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine. *Nature* 227:609-611.
- Olney, J.W.; Ho, O.L. & Rhee, V. (1973) Brain-damaging potential of protein hydrolysates. *N. Engl. J. Med.* 289:391-395.
- Olney, J.W.; Sharpe, L.G.; & Feigin, R.D. (1972) Glutamate-induced brain damage in infant primates. *J. Neuropathol. Exp. Neurol.* 31:464-488.
- Patti, R.A. (1993) International Hydrolyzed Protein Council. Letter submitting data to the Life Sciences Research Office, Federation of American Societies for Experimental Biology.
- Plant, T.M.; Gay, V.L.; Marshall, G.R. & Arslan, M. (1989) Puberty in monkeys is triggered by chemical stimulation of the hypothalamus. *Proc. Natl. Acad. Sci. USA* 86:2506-2510.
- Rosenzweig, P.; Brohier, S. & Zipfel, A. (1993) The placebo effect in healthy volunteers: influence of experimental conditions on the adverse events profile during phase I studies. *Clin. Pharmacol. Ther.* 54:578-583.
- Schnackenberg, D.D.; Carlson, D.; Vogel, J.A.; Johnson, R.; Szlyk, P.C.; Francesconi, R.P. & Hubbard, R.W. (1986) Combat field feeding system - Force development test and experimentation test report. U.S. Army Combat Developments Experimentation Center, Ft. Ord, CA and U.S. Army Research Institute of Environmental Medicine, Natick, MA. Report No. CDEC-TR-85-006a.
- Select Committee on GRAS Substances. (1978a) Evaluation of the health aspects of certain glutamates as food ingredients. SCOGS-37a. Prepared for the Food and Drug Administration under contract No. FDA 223-75-2004 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology. Available from: Special Publications Office, FASEB, Bethesda, MD.
- Select Committee on GRAS Substances. (1978b) Evaluation of the health aspects of protein hydrolyzates as food ingredients. SCOGS-37b. Prepared for the Food and Drug Administration under contract No. FDA 223-75-2004 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology. Available from: Special Publications Office, FASEB, Bethesda, MD.
- Select Committee on GRAS Substances. (1989a) Evaluation of the health aspects of certain glutamates as food ingredients. SCOGS-37a-supplement. Prepared for the Food and Drug Administration under contract No. FDA 223-75-2004 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology. Available from: Special Publications Office, FASEB, Bethesda, MD.
- Select Committee on GRAS Substances. (1980b) Evaluation of the health aspects of protein hydrolyzates as food ingredients. Supplemental review and evaluation. SCOGS-37b-supplement. Prepared for the Food and Drug Administration under contract No. FDA 223-75-2004 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology. Available from: Special Publications Office, FASEB, Bethesda, MD.
- Sørensen, H.T.; Nielsen, B. & Nielsen, J. (1989) Anaphylactic shock occurring outside hospitals. *Allergy* 44:288-290.
- Stegink, L.D.; Filer, L.J., Jr. & Baker, G.L. (1985) Plasma glutamate concentrations in adult subjects ingesting monosodium L-glutamate in consommé. *Am. J. Clin. Nutr.* 42:220-225.
- Stegink, L.D.; Filer, L.J., Jr.; Baker, G.L. & Bell, E.F. (1986) Plasma glutamate concentrations in 1-year-old infants and adults ingesting monosodium L-glutamate in consommé. *Pediatr. Res.* 20:53-58.
- Stegink, L.D.; Filer, L.J., Jr.; Baker, G.L.; Mueller, S.M. & Wu-Rideout, M.Y.-C. (1979) Factors affecting plasma glutamate levels in normal adult subjects. In: Filer, L.J., Jr.; Garattini, S.; Kare, M.R.; Reynolds, W.A.; Wurtman, R.J., eds. *Glutamic acid: advances in biochemistry and physiology*. New York: Raven Press. p.333-351.
- Stegink, L.D.; Shepherd, J.A.; Brummel, M.C. & Murray, L.M. (1974) Toxicity of protein hydrolysate solutions: correlation of glutamate dose and neuronal necrosis to plasma amino acid levels in young mice. *Toxicology* 2:285-299.
- Tung, T.-C. & Tung, K.-S. (1980) Serum free amino acid levels after oral glutamate intake in infant and adult humans. *Nutr. Rep. Int.* 22:431-443.
- Wilson, R.C. & Knobil, E. (1982) Acute effects of N-methyl-DL-aspartate on the release of pituitary gonadotropins and prolactin in the adult female rhesus monkey. *Brain Res.* 248:177-179.