Fact or Fiction? The MSG Controversy

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FACT OR FICTION?
The MSG Controversy

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Abstract

Monosodium glutamate (“MSG”) has become one of the most well-known and controversial food ingredients in recent history. Linked to the “Chinese Restaurant Syndrome,” the use of MSG has caused an outpouring of anecdotal evidence alleging adverse effects caused by ingestion of the food ingredient. These claims have been fueled by the popular press which has devoted considerable coverage to the debate surrounding the food additive. Yet, scientific studies have repeatedly indicated that MSG is safe at ordinary levels of consumption for the general population. In response to the controversy, in 1995, the Food and Drug Administration commissioned the FASEB Report to provide a comprehensive review of the monosodium glutamate scientific literature. This paper will examine the history of the MSG debate, including the scientific evidence, the role of the media, the positions of both sides and the response of the FDA.

Introduction

“Why doesn’t everyone in China have a headache?” Jeffrey Steingarten, a Harvard Law School graduate turned renowned food critic, poses this question in an essay investigating the controversy surrounding monosodium glutamate.\(^1\) While Steingarten’s question may come across as flippant, even insolent, to some, it does in effect encapsulate the long-drawn-out and enduring debate regarding the safety and potential health effects of monosodium glutamate, or MSG. A simple Internet search reflects the extraordinary degree to which the MSG question has taken hold in the United States, with numerous advocates and opponents on both sides.\(^2\) MSG is the quintessential “hot topic,” with those speaking out on the issue including not only everyday consumers, but scientists, physicians and government officials. From the “NO MSG” signs

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\(^2\) A Google search using the terms “MSG” and “monosodium glutamate” yields 53,200 hits.
plastered all over Asian restaurants to the constantly-referenced and peculiarly-titled “Chinese Restaurant Syndrome,” the American public has been made exceptionally aware of this particular flavor enhancer that has been used extensively for almost a century. MSG has even been implicated in Presidential scandal. And yet despite its heightened exposure in the popular press, the scientific reality of MSG remains obscure to most laypeople. While it is likely that a survey of the general population would reflect a widely held belief that MSG is a “bad chemical,” it is much less likely that these same individuals would be aware that glutamate, the group of chemicals that includes MSG, is found in many of the foods they consume on a daily basis.

Has MSG been unfairly vilified in the United States by over-zealous researchers and influential media forces? Or is the concern justified – is MSG in fact a harmful food ingredient that needs to be taken more seriously by regulating agencies like the Food and Drug Administration (“FDA”? In the past half-decade, the FDA has been repeatedly subject to requests for additional studies and for stricter regulations regarding the use of monosodium glutamate in the food industry. Despite its strapped resources, FDA has managed to address some aspects of the MSG controversy, launching a comprehensive examination and follow-up report on the safety of MSG in 1995. This paper will examine the complicated history of MSG, including the role of the media and various well-known activists, the results of previous scientific studies and the response by the FDA, in an effort to determine what is reality and what is myth in the debate on MSG?

**Glutamate: Its Role in Food and in the Body**

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3 Adrienne Samuels, a well-known anti-MSG activist, wrote a letter to Barbara Bush attributing the collapse of Former President George Bush during his visit to Japan to MSG. Samuels wrote, “Please for [President Bush’s] sake, for [the First Lady’s] sake, and for the welfare of our country, consider the possibility that the President is sensitive to MSG.” *MSG Role in Bush Collapse Suggested to First Lady,* Food Chemical News, Inc., Vol.33, No.48, Jan. 27,1992 available at 1992 WL 2211350.
Monosodium glutamate belongs to the larger group of chemicals that are labeled “glutamate.” Glutamate is one of many different amino acids, which are considered to be the building blocks of proteins. Glutamate itself is regarded as one of the most important components in proteins. In fact, it is found naturally in many protein-containing foods, including cheese, milk, meat, fish and a number of different vegetables. The levels of MSG are particularly high in foods like tomatoes, mushrooms and Parmesan cheese. Glutamate is a key component in determining the flavor of these foods, however it only functions as an enhancer when it is in its “free” form, not when it is bound with other amino acids in proteins.

More specifically, MSG is the sodium salt of the amino acid, glutamic acid, and a form of glutamate. When MSG is added to a food, it serves as a flavor enhancer, similar to the flavoring function provided by glutamate which occurs naturally in some foods. MSG itself is simply comprised of water, sodium and glutamate. MSG has no texture or smell of its own, and therefore serves to emphasize the natural flavor of the food itself, rather than adding an independent flavor. The flavor-enhancing properties of MSG were first discovered in 1908 by Professor Kikunae Ikeda, a Japanese chemist at Tokyo Imperial University, who had been working to isolate the ingredient that gave a particular taste in kombu (a Japanese seaweed). According to Ikeda, this taste was also “common to asparagus, tomatoes, cheese and meat but . . . not one of the four well-known tastes of sweet, sour, bitter and salty.” Ikeda labeled this distinct taste “umami.”

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5 *Id.*
6 *Id.* There is 0.339 mg of glutamate in 3 slices of tomato; 0.094 mg in ¼ cup of mushrooms; 0.047 mg in 2 Tbsp of parmesan cheese.
8 *Id.* at 1.
9 *Everything You Need to Know About Glutamate and Monosodium Glutamate, supra* note 4.
11 International Glutamate Information Service, Discovery, at [http://www.glutamate.org/media/glutamate.html](http://www.glutamate.org/media/glutamate.html).
which best translates into the word “savory” for purposes of the English language.\textsuperscript{12} Using a kombu broth, Ikeda was able to extract crystals of glutamate. To make glutamate viable as a seasoning, Ikeda realized that it would need to be easily soluble in water, but not solidify or absorb humidity (like salt or sugar).\textsuperscript{13} He found that monosodium glutamate possessed these ideal “storage properties” and provided a potent umami taste.\textsuperscript{14} In fact, recent “taste” research has further defined this fifth taste and offered confirmed identification of glutamate receptors on the tongue.\textsuperscript{15}

Today, MSG is generally derived from starch, corn sugar, molasses, sugar cane or sugar beets.\textsuperscript{16} MSG is produced through a natural fermentation process, like that which is used to produce yogurt and beer.\textsuperscript{17} MSG is currently found in thousands of different processed foods, including soups, salad dressings, mayonnaise, canned vegetables and frozen dishes. It is also sold alone as a white crystal substance, similar in texture and appearance to salt or sugar.\textsuperscript{18} On average, an individual in the United States consumes approximately 11 grams of glutamate each day from natural protein sources, and less than 1 gram of glutamate per day from MSG.\textsuperscript{19} According to one source, “this amount of added MSG is the same as adding 1 to 1.5 ounces of parmesan cheese.”\textsuperscript{20} Compare this to figures outside of the United States, like Taiwan, where daily MSG

\textsuperscript{12} Id. One writer has defined the taste of umami as the “full-mouthed, savoury, meaty sensation one gets from a well-concentrated broth or a hunk of aged beef.” Mireille Silcoff, \textit{The ascent of the 5\textsuperscript{th} taste: Umami conquers America, finally}, National Post, Nov. 20, 2004.\textsuperscript{13} International Glutamate Information Service, Discovery, supra note 11.\textsuperscript{14} Id. This site also suggests that fish sauce may have been the original “umami” seasoning, dating back to the seventh century BC. Fish sauce, which was full of glutamate, was among the most important trade commodities in ancient Greek and Roman civilization. http://www.glutamate.org/media/ginfoods.html.\textsuperscript{15} New Science Provides New Insights into Health of Glutamate, Food Insight Newsletter (International Food and Information Council Foundation, Washington D.C.), March/April 2000, available at http://www.ific.org/foodinsight/2000/ma/gluamatefi200.cfm See also Glutamate and Monosodium Glutamate: Examining the Myths, IFIC Review (International Food Information Council Foundation), January 1997, at 1.\textsuperscript{16} Everything You Need to Know About Glutamate and Monosodium Glutamate, supra note 4.\textsuperscript{17} Id.\textsuperscript{18} FDA Backgrounder, supra note 7, at 1.\textsuperscript{19} Everything You Need to Know About Glutamate and Monosodium Glutamate, supra note 4. See also MSG does not cause headaches, Gloucestershire Echo, April 29, 2004, available at 2004 WL 74129106.\textsuperscript{20} Everything You Need to Know About Glutamate and Monosodium Glutamate, supra note 4.
intake averages 3 grams per day. In addition, it is important to note that most researchers believe that once ingested, the human body treats glutamate that is added to foods via MSG the same as glutamate which is found naturally in foods, like tomatoes or cheese.

However, glutamate is not used simply to enhance the flavor of foods; it has important biological functions within the body as well. As one researcher maintained, “few biological molecules have the importance to such a wide range of body functions as glutamate.” This is an important consideration given that the role of glutamate in the body has been implicated in the MSG controversy, with concerns that the flavor enhancer may negatively affect certain critical physiological processes, like the functioning of the nervous system. In terms of nutrition, glutamate is considered a non-essential amino acid, meaning that the body can produce glutamate on its own from various other protein sources. In fact, the body itself generates approximately 50 grams of free glutamate per day for use as a component of metabolization. In addition, approximately two kilograms of naturally occurring glutamate can be found in the body's organs and tissues, including the brain, the kidneys, the liver and various muscles. The glutamate that is actually produced by the brain assists in the organ's normal functions and also serves as a neurotransmitter. Dietary glutamate, derived naturally from foods and from MSG, plays an important role in the digestive system, serving as a primary source of energy for the intestine. In fact, one study has emphasized the demands of the intestine.

21 Examining the Myths, supra note 15, at 2.
22 New Science Provides New Insights into Health of Glutamate, supra note 15. See also Everything You Need to Know About Glutamate and Monosodium Glutamate, supra note 4.
23 John D. Fernstrom, PhD, conference co-chair and Professor of psychiatry, pharmacology, and neuroscience at the University of Pittsburgh School of Medicine, as cited in New Science Provides New Insights into Health of Glutamate New Science, supra note 15.
25 Id.
26 Id.
28 Id.
indicating that of all the dietary glutamate consumed, approximately only four percent escapes into other parts of the body. Therefore glutamate provides important benefits to human health, well beyond its role as a food component. Some have argued that even as a food enhancer, glutamate can provide significant nutritional benefits by increasing food intake, particularly for the elderly for whom losses in taste and smell contribute to poor nutritional status. In addition, the use of MSG as a food ingredient may promote lower sodium intake, since it contains only one third the amount of sodium as table salt and has been shown to produce the same “good taste” as its “high-sodium” counterpart when added to a low-sodium food product.

History of MSG from a Public Health Perspective

Monosodium glutamate was originally designated as a Generally Recognized as Safe (“GRAS”) ingredient by the FDA in 1958, along with other commonly used food ingredients like salt and baking powder. Specifically, the relevant portion of the United States Code of Federal Regulations states, “It is impracticable to list all substances that are generally recognized as safe for their intended use. However, by way of illustration, the Commissioner regards such common food ingredients as salt, pepper, vinegar, baking powder and monosodium glutamate as safe for their intended use.” The safety of MSG has been repeatedly reaffirmed by a number of different sources within the scientific community, including the FDA, since that

29The Glutamate and Nutrition Fact Sheet, supra note 27. Dietary glutamate, together with cysteine and glycine, is also used for the production of glutathione, an antioxidant that assists in the body’s defense mechanism.
30Schiffman, SS. Taste and smell losses in normal aging and disease, J. Am. Med. Assoc., 278:1357-1362, 1997, as cited in Examining the Myths, supra note 15, at 1-2. Studies show “that moderate levels of added MSG in certain foods, such as mushroom soup and mashed potatoes, can increase food intake in an institutionalized older population, thus increasing intake of necessary vitamins, minerals and protein from food.”
32Examining the Myths, supra note 15, at 2.
3321 C.F.R. § 182.11(a) (italics added).
time. In 1987, the Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organization and the World Health Organization placed MSG in the safest category of food ingredient.\footnote{34}{FDA Backgrounder, supra note 7, at 2. See also International Glutamate Information Service, Approvals, http://www.glutamate.org/media/approvals.html} In addition, a report done in 1991 by the European Communities’ Scientific Committee for Foods confirmed this finding, classifying the “acceptable daily intake” of MSG as “not specified,” which is the most favorable categorization for a food ingredient.\footnote{35}{Id.} The Council on Scientific Affairs of the American Medical Association also weighed in on the issue, stating that glutamate as not been shown to pose a “significant health hazard” in any form.\footnote{36}{AMA Report done in 1992. Id. In addition, please note the following findings: In 1980, the FASEB Select Committee on GRAS Substances found that MSG was safe at current levels of use. In 1986, the FDA’s Advisory Committee on Hypersensitivity to Food Constituents found that MSG poses no threat to most individuals, but “reactions of brief duration” may occur in some. FDA Backgrounder, supra note 7, at 2.} And yet despite the seemingly general scientific consensus that MSG is safe, the food ingredient has nonetheless been subject to overwhelming controversy in the past several decades.

Moreover, the FDA’s position on MSG labeling has remained relatively static for sometime, and yet has become a key component in the larger MSG controversy. The FDA requires labeling of all ingredients in processed and packaged foods. Therefore, whenever MSG is added to a food product, it must be listed on the ingredient list under its common name, “monosodium glutamate.” However, when glutamate-containing ingredients, such as Parmesan cheese, soy sauce and hydrolyzed proteins, are included in a food, they are to be listed by their common name.\footnote{37}{Examining the Myths, supra note 15, at 2.} The FDA, in 1993, proposed adding the phrase “contains glutamate” to certain protein hydrolysates that contain substantial amounts of glutamate, however this initiative was never finalized.

The MSG Controversy
For a food ingredient that has received so many safety approvals and for which there is virtually no confirmed, scientific evidence of deaths or serious illness, MSG has nevertheless created what can essentially be termed “mass hysteria” in the general population. MSG has been faulted for a whole host of medical conditions, from headaches to cardiac arrhythmia; it has even been blamed for murder. One of the most contested issues that arises in the MSG debate is the question of whether to base findings of MSG safety solely on double-blind scientific studies or to take into consideration the anecdotal evidence. A great deal of the outcry against MSG based on potential adverse health effects relies on these personal accounts of MSG intolerance. These types of reports, though not inherently invalid, do raise scientific concerns in that these episodes cannot be directly linked to the ingestion of MSG, and could in fact be attributed to a variety of other factors. Some of the most common allegations made against MSG are investigated below.

**General Adverse Affects and Chinese Restaurant Syndrome**

The name is peculiar. Medical conditions generally have names that the majority of the general population cannot even pronounce, let alone identify. And yet, Chinese Restaurant Syndrome (“CRS”), the condition linked to the adverse affects of MSG, is well-known by the layman. A medical dictionary blurb defines CRS as follows:

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MSG Was Blamed, Food Chemical News CRC Press, Inc., Vol.35, No.21, July 19, 1993. A San Francisco gunman who killed eight people and himself blamed MSG for his actions. A document was found on the gunman’s body which blamed the FDA and the Surgeon General for allowing the food ingredient to be marketed.

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The syndrome refers to a group of symptoms that can occur after eating Chinese food. The symptoms can include headache, sweating, facial pressure or swelling, nausea, numbness or burning around the mouth, chest pains and heart palpitations. Typically, the symptoms are temporary and not life-threatening, said William Geimeirer, a Wilmington-based allergist. The food additive monosodium glutamate, or MSG, which is commonly used as a food preservative, flavor enhancer or meat tenderizer, has been implicated but never proven to be the cause, according to the National Institutes of Health. The condition was first reported in 1968, the Institute said. Treatment depends on the symptoms. Most people recover on their own.

The term “CRS” was first coined in 1968 by Dr. Robert Ho Man Kwok to describe the above-noted collection of symptoms he experienced after eating Chinese food. Anecdotal reports of MSG inducing CRS have been repeatedly subject to scientific examination. The vast majority of these studies have been relatively unfavorable, or at best inconclusive, towards these anti-MSG claims. A study by two Italian scientists, P.L. Morselli and S. Garatini of the Institute of Pharmacologic Research in Milan, indicated that CRS may ultimately be a result of “autosuggestion.” In a double-blind crossover study, the two scientists examined 17 males and seven females, between the ages of 18 and 34. The two administered 3 gram doses of MSG via 150ml of beef broth and evaluated the participants every 20 minutes for a three hour period. There were two groups of subjects, one group that received broth with MSG and one group that received broth without MSG. An examination of the test results revealed that the group that had received the broth without MSG reported a number of CRS symptoms, including headache, flushing and tightness in the chest, whereas the group that received the actual MSG broth reported no such symptoms.

Other researchers have reached similar conclusions with regard to the scientific link between MSG and CRS. Richard Kenney, MD, of George Washington University has done a number of different studies to examine whether there is in fact any scientifically credible evidence indicating a food intolerance to MSG. In one

40 A double-blind study is considered to be the “gold standard” for testing adverse reactions to any particular substance. In a double-blind study, neither the subject nor the researcher/tester knows whether a placebo or the actual substance has been administered. This type of study eliminates all possibility of bias, freeing the results from both the opinions of the test subject and from the expectations of the researcher. See Examining the Myths, supra note 15, at 6.

41 Bendarde, supra note 10, at 131-32 and Examining the Myths, supra note 15, at 5.
study, Kenney fed 60 subjects a variety of liquids, including orange juice, black coffee, flavored milk, spiced tomato juice and a two percent MSG solution. Kenney’s results indicated that six subjects reacted to coffee, six to spiced tomato juice and only two subjects responded to the MSG, indicating that “MSG was not unique in producing symptoms typical of CRS.”

Kenney did a follow-up double-blind study using subjects who claimed that they suffered adverse reactions after ingesting foods with MSG. The test participants drank a “soft drink” solution for four days, on two of which the solution contained 6 grams of MSG. Once again, Kenney’s results proved unfavorable to the anti-MSG camp. Two of the six participants reacted to both of the solutions (with and without MSG), and the other subjects reacted to neither of the solutions. Indeed, there are number of other studies that have produced similar results, failing to produce the adverse reactions that many individuals associate with dietary intake of MSG. One researcher has attempted to explain the existence of these “CRS-like” symptoms even without exposure to MSG, attributing some of these postprandial adverse reactions to high histamine levels in some foods.

Of course, these studies and their accompanying results are not without critics. One of the most outspoken opponents of MSG, Dr. Adrienne Samuels, has publicly disapproved of many of these studies on grounds that they have been industry-sponsored, “sloppy in . . . design and execution; focus[ing] on areas which were irrelevant to an understanding of the toxic effects of MSG; and . . . even . . . involved in clear-cut scientific

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42 Examining the Myth, supra note 15, at 5.
43 Id.
44 Dr. Jonathan Wilkin of the Medical College of Virginia conducted a study using 24 subjects, 18 of whom described a history of CRS symptoms, in particular, flushing of the skin. After feeding the subjects both 3 gram and 5 gram doses of MSG, Wilkin found no MSG-provoked flushing. Scientists, Tarasoff and Kelly, also conducted a study to test the sensory side effects potentially caused by MSG. Using a double-blind study with 71 participants, Tarasoff and Kelly administered five different treatments, which included two placebos and three different doses of MSG. Two hours after intake, the subjects were interviewed and half reported more than one CRS symptom regardless of MSG content. One of the largest studies was conducted in 1998 using 130 subjects who declared to have an MSG intolerance. Using double-blind placebo-controlled testing, the researchers once again found that no adverse reactions were produced with MSG or the placebo when taken with food. Any reactions that were observed were “mild, transient and non life-threatening.” Examining the Myth, supra note 15, at 6.
Specifically, Samuels suggests that some of the placebo studies were inappropriate since the placebos themselves contained glutamate resulting from manufacture. Samuels and her husband, Jack Samuels, who claims to suffer life-threatening symptoms following ingestion of MSG are by far the most vocal of the anti-MSG activists. Their claims seem to center primarily on the fact that these studies are funded by industry and that the FDA has been bought by these very same industry players. However, there is evidence of studies conducted independent of industry that have resulted in the same dubious conclusions regarding the claim that MSG causes CRS; moreover, there is indication that these anti-MSG activists may sometimes attribute industry ties to those who do not hold them.

While the plurality of results repeatedly call into question MSG’s causative role in food hypersensitivity, the number of anecdotal reports continues to grow. As one group of scientists reflected, “…a vast array of materials are present in all foods, and the range of pharmacological and allergic effects that foods can elicit in individuals with idiosyncratic sensitivities makes causative agents difficult to pinpoint. Readily recognizable, but poorly understood, acronyms such as MSG and CRS may have served as scapegoats since they were coined in the late ‘60s. This statement begs the question – to what degree are CRS and its associated symptoms simply a product of the human mind and the power of the popular press? Researchers studying this phenomenon of “pseudo-food allergy” found that almost 30 percent of adults in the United

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47 Id.
48 Dr. Roland Auer, one of the independent scientists who served on the Federation of American Societies for Experimental Biology’s Expert Panel for the report on MSG has accused Jack Samuels of making false statements about his industry connections and discrediting scientific results without basis. In a letter to Samuels, Auer stated, “Let me reemphasize that I am an independent scientist, receive no money from the food industry, and do not march to the tune of the food industry . . . I would request that you, in your speaking and writing, not denigrate our efforts. Instead, appreciate the seriousness and honesty of the massive effort that has gone into independent scientists addressing this problem in which we have no vested interest.” MSG Sensitivity Requires Double-Blind Tests: Auer, Food Chemical News CRC Press, Inc., Vol.37, No.32, October 2, 1995.
50 MSG Safety Allegations Based on Errors, Food Chemical News CRC Press, Inc., Vol.35, No.23, August 2, 1993. This term “pseudo-food allergy” has been used to describe the “false conviction that one suffers from a food allergy.”
States believe that they suffer from a food allergy, when in actuality less than two percent of the adult population has a true sensitivity to certain foods or food additives. After conducting an MSG study, Dr. Daryl Altman, a medical consultant for Allerx Incorporated and the Food Allergy Center, commented that she found it disturbing that even after participants were shown that they had consumed large amounts of MSG without experiencing any sort of reaction, “that didn’t stop them from believing that MSG was a problem.” Dr. Altman summarized her findings by stating, “there’s a high prevalence of belief, and a low prevalence of reality.” These psychological factors are nonetheless having a major impact, as the purchase and consumption decisions of this group of people are being influenced by mistaken concern of food allergies, a phenomenon that one researcher has labeled “a national epidemic.”

In the case of MSG, it seems that the popular news media may also contribute to the large numbers of unconfirmed reactions to foods and, more generally, to the misattribution of causation. The public confusion surrounding MSG has become increasingly aggravated by the overexposure of the food additive in the popular press. Arthur T. Schramm, in his capacity as Chairman of the National Academy of Sciences’ Industry Liaison Committee, weighed in strongly on this issue, stating:

51 Examining the Myth, supra note 15. See also Mild Reactions Triggered in IGTC-Backed MSG Challenge Study, Food Chemical News CRC Press, Vol.36, No.21, July 18, 1994. In a 1993 study funded by Allerx Inc., it was reported that 14% of U.S. households believed one or more individuals in their household suffered from a food allergy. Based on these figures, the study estimated that 16 million people, 7% of the population, believed they had a food allergy, a figure which is two to three times the number of people that experts say are actually food allergic.

52 Mild Reactions Triggered, supra note 51. Dr. Altman conducted a double-blind, placebo-controlled study, administered to 16 individuals who claimed to have an MSG sensitivity. Dr. Altman reported mild, self-limiting reactions in only three subjects who had been given MSG only, ingested on an empty stomach.

53 Id.

54 Id. Allerx’s Vice-President of Operations, Betty Rauch, found this misperception of food allergy to be a deeply disturbing phenomenon.
The communications media, particularly TV, have given considerable publicity to experimental data actually having little or no bearing on safety, but presented in such manner as to dispose a large majority of the lay public to draw dire conclusions. I am referring, of course, to TV reports on chick embryo studies involving cyclamates and subcutaneous injection studies involving sodium glutamate [MSG]. Both reports were inconclusive with respect to the safety of their use in food, but this type of psychological pressure has already taken its toll in the defensive action recently employed by the baby food manufacturers. The entire atmosphere growing out of such TV programming, coupled with politically oriented Congressional hearings and careless statements by apparently qualified publicity seeking individuals, is one of economic terrorism.

Schramm’s reference to the actions of “baby food manufacturers” stems from their decision to remove MSG from baby food after charges that it was unnecessary, deceptive and potentially harmful to infant’s nervous systems. This move by manufacturers was done before any response by the FDA, who had the same information as the researchers and yet chose to take no action. And while generally it is alleged that industry is the one putting forth biased information for its own economic benefit, Schramm’s pointed words seem to indicate that in the case of food additives, MSG in particular, industry point of view has not received the same “press time” as that of the anti-MSG activists. This effect of the media on the economic choices of consumers may be due, in part, to a loss of confidence in the FDA and the food supply. Some have alleged that in the wake of the disclosure of the “filth guidelines,” the existence of PCBs in chickens and high levels of mercury in fish, some consumers have decided to take government assurance or inactions with a grain of salt. Regardless of the reasons, it is clear that the media has an extraordinary influence on the actions and beliefs of the average consumer. The FDA has also recognized the effect of the popular press, with one FDA official emphasizing the need for consumer education, but maintaining that currently “too much [of this education] is carried by the public media in sound bites.”

56 Id. at 88.
57 Id. at 97-98.
Neurological Effects

Though Chinese Restaurant Syndrome is undoubtedly the most well-known of the alleged MSG effects, other more serious accusations have also been made with respect to a possible link between the food additive and neurological disorders. As mentioned previously, in addition to serving more generally in protein and energy metabolism, glutamate also plays a key role in the neurological system, acting as a nerve impulse transmitter to the brain. The malfunction of glutamate receptors in the brain has been associated with a variety of different neurological diseases, including Alzheimer’s disease and Huntington’s Chorea. Approximately, 2.3 grams of free glutamate is naturally found in the human brain.\(^{59}\) Glutamate is found to have high intracellular concentrations, and low extracellular concentrations. Certain conditions, like strokes, may damage the blood-brain barrier, which would in turn affect the level of glutamate concentration.\(^{60}\) Whether dietary intake of high doses of glutamate can also cause the same type of shift in glutamate concentration and therefore adversely affect brain function has been the subject of great debate.

Perhaps one of the most influential players in the MSG – neurological disorders debate has been John Olney, a psychiatrist at Washington University. Dr. Olney has been hyper-critical of a number of different food additives, but has focused a great deal of time on aspartame and MSG. With regards to the latter, Dr. Olney conducted numerous studies in which MSG was injected or force-fed to rodents to examine whether MSG could cause neurotoxicity among these animals. In one study, Olney used neonatal mice and varying doses of


\(^{60}\) International Glutamate Information Service, News, available at http://www.glutamate.org/media/news.html Other researches that have noted that in some abnormal circumstances, excess glutamate can be released which causes a flooding of cells with calcium, which has been implicated in a number of different diseases. However, there is no evidence that dietary glutamate has this effect. *MSG Critic Alleges Relevant Data Suppressed*, Food Chemical News CRC Press, Inc., Vol.36, No.24, August 8, 1994.
MSG, as large as 4 grams per kilogram of the animal’s body weight. The injections seemed to induce brain lesions. Olney has also reported that MSG can trigger obesity, neuroendocrine disturbances, behavioral disturbances, and fetal brain damage in mice whose mothers were fed MSG when pregnant. Studies by other researchers also claim that MSG fed to infant mice damaged nerve cells in the hypothalamus of the brain. More generally, Olney has attacked the FDA on grounds that it had succumbed to “an industry-arranged whitewash,” selectively choosing favorable studies to support in order to maintain MSG’s “GRAS” standing. In addition, Olney suggested that many of these FDA-backed studies employed researchers with intimate industry connections.

Though Olney, by making himself and his studies very public in the MSG arena, has been quite influential, he has also been subject to an enormous amount of very pointed and aggressive criticism. One critic ranked him as one of the top ten individuals who has “led to mass confusion and distrust of our food supply” by “misusing scientific design of toxicological experiments to cause millions of mothers to worry about brain damage to their children from MSG.” More specifically, a review by the International Food Information Council Foundation criticized the methodology of Olney’s studies, stating,

...the dosages of MSG used in these studies were extremely high and the methods of injection, as well as force-feeding, do not accurately represent the way humans consume MSG ... Olney’s results could not be duplicated when large amounts of MSG were added to the diet ... studies evaluating the normal dietary ingestion of MSG in food, including amounts exceeding 40g/kg body weight (5,000 times higher than normal amount ingested), found no harmful effects on the brain.

Follow-up studies similarly contradict Olney’s findings. A study in which large
amounts of glutamate were fed to both adult humans and adult gerbils found no sign of any adverse reactions, in particular no neurological changes.  

Moreover, an increasing understanding of the role of glutamate in the brain has further called into question Olney’s previous findings. Research done by Dr. John Fernstrom, Professor of psychiatry, pharmacology and neuroscience at the University of Pittsburgh School of Medicine, has shown that the glutamate receptors found in the brain are different from those that have been discovered on the tongue.  

The brain generates its own glutamate through glucose and other amino acids, and has an intricate transport system to protect the brain cells. As Fernstrom states, “while it was earlier thought that circulating glutamate in the body might enter the brain and cause damage, it is now clearer than ever that circulating glutamate is kept strictly separate from the glutamate inside the brain that is used for normal neural function.”  

Other scientists have confirmed Fernstrom’s findings by showing that the levels of glutamate in the brain do not vary based on changes in the glutamate levels of the plasma. The research regarding the issue of MSG linkage to neurotoxicity thus overwhelmingly indicates that glutamate-containing food, even in extremely high concentrations, will not have a detrimental affect on the functioning of the brain as was previously speculated.

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68 Study by Bazzano, D’Elia and Olson involving 11 human adult males who consumed diets containing MSG dosages of up to 147 grams/day for a maximum of 42 days. Id. Olney has responded to some of these claims, maintaining that the reasons that other laboratories have not been able to replicate his glutamate-induced neurotoxic effects is due to the use of phencyclidine hydrochloride (PCP) by other researchers. PCP, an animal tranquilizer which is used for sequential animal testing, is known to protect neurons from glutamate testing. However, researchers like Dr. Lewis Stegink of the University of Iowa College of Medicine defends that Olney also uses PCP in his primate studies and therefore use of PCP by other groups was an effort to replicate Olney’s original results. Testimony on Reported Adverse MSG Effects Disputed, Food Chemical News, Vol.35, No.52, February 21, 1994.  


70 Id.  

71 William Pardridge, M.D., illustrated that dietary glutamate cannot pass through the blood-brain barrier. Brian Meldrum, M.D., also concluded that “dietary consumption of glutamate has not been shown to cause neuropathology in man.” Quentin Smith, Ph.D., reaffirmed these findings in his study of neural glutamate concentration. Examining the Myths, supra note 15, at 4.
Pregnant/Lactating Women

In addition, Olney’s studies indicating that administration of MSG to pregnant mice would result in lesions of the fetal brain has also been discredited by subsequent research. A study in which large amounts of MSG were intravenously injected into the blood stream of pregnant monkeys reveals no increase in the fetal glutamate levels.\(^\text{72}\) Thus, while most amino acids are transferred across the placenta in order to ensure fetal development, researchers have found that the placenta is “virtually impermeable to glutamate, even at high levels.”\(^\text{73}\) This research has also extended to women who are breast-feeding, with research indicating that increased levels of MSG in the lactating woman did not increase the level of glutamate in the breast milk.\(^\text{74}\)

Asthma

Finally, some have alleged that the ingestion of MSG may cause another serious health consequence by triggering or aggravating asthma in certain individuals. Once again, the weight of scientific evidence tends to contradict this claim. Dr. Donald Stevenson of the Division of Allergy, Asthma and Immunology at the Scripps Clinic and Research Foundation in La Jolla, California, summarized the current research, stating “we now know from numerous well-designed clinical studies that MSG or glutamate cannot trigger or exacerbate asthma, even among individuals who believe their asthma is caused by MSG.”\(^\text{75}\) The National Institute of Health’s Institute of Allergy and Infectious Diseases conducted two studies in 1991 and 1993 to examine


\(^{73}\)Id.

\(^{74}\)Examining the Myths, supra note 15, at 3. Moreover, free glutamate is 10 times more plentiful in human breast milk than in cow’s milk, and therefore a newborn infant who is being breastfed will ingest more free glutamate per kg of body weight than during any other period in his life.

\(^{75}\)New Science Provides New Insights, supra note 15.
the possible link between MSG and asthma. In a single-blind oral study using 13 non-asthmatics and 30 asthmatics, a dose of 7.6 grams of MSG was administered over a period of two hours. None of the non-asthmatics reported any change in pulmonary reactions, and only one asthmatic subject reported an adverse effect. When this same asthmatic subject was tested using a double-blind placebo-controlled challenge, no effect was reported. Researchers have generally concluded that MSG does not affect asthma, and it is safe for asthmatics to ingest glutamate-containing foods.

FDA Response

Given the limited understanding of the average consumers when it comes to chemistry, toxicity and nutrition, many individuals rely on regulatory agencies like the FDA or the United States Department of Agriculture (USDA) to make the critical decisions as to which food ingredients are safe for general consumption by the public and which are not. It is interesting to examine the response of the FDA to MSG in light of this reality and the overwhelmingly negative publicity surrounding this particular food additive. The FDA has been repeatedly criticized for not proactively addressing the MSG controversy, for not implementing more stringent regulations and more generally for siding with industry executives. Some have even paralleled FDA’s handling of the MSG issue to its management of silicone breast implants on the grounds that, as with implants, the FDA is exhibiting a preference for “erroneous and in some cases deliberately falsified or

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76 Examining the Myths, supra note 15, at 7.
77 Id.
78 Id.
79 See Verrett, supra note 55, at 87-93. See also letter from anti-MSG activist, Jack Samuels, to FDA Commissioner David Kessler, alleging that the FDA used devious means to “assure the GRAS status of [certain] substances and to continue the poisoning of America” and that the American people “with the help of the FDA and the glutamate industry organizations . . . have been kept from knowing the truth about neurotoxic sensitivity and where MSG is hidden in food.” Amino Acid Report Seen As Posing Dilemma for FDA, Food Chemical News, Vol.34, No.32, October 5, 1992 available at 1992 WL 2212017.
However, the FDA has defended its handling of the MSG issue on the grounds that it has appropriately engaged in a process of reassessment and evaluation. Dr. Fred Shank, as the director of the FDA's Center for Food Safety and Applied Nutrition, commented on the MSG controversy, stating, “the public wants a quick fix: Ban it, remove it, or put a warning label on it.”

Though FDA has not taken such definitive actions, it does require that when MSG is added to a food, it be included on the ingredient list using its full name, “monosodium glutamate.” Moreover, the FDA considers it misleading for a product to advertise “No MSG” if it includes other forms of free glutamate, given that the average consumer generally associates the term “MSG” with all free glutamate.

In addition, the FDA has repeatedly commissioned studies to reaffirm the safety of MSG. The Select Committee on GRAS Substances (“SCOGS”) of the Life Sciences Research Office (“LSRO”) and the Federation of American Societies for Experimental Biology (“FASEB”) reviewed the health aspects of MSG in two independent studies in 1978 and 1980 as part of FDA’s update of GRAS safety assessments. The Committee concluded that MSG was generally safe at ordinary levels of consumption. The 1980 report did indicate that additional research was necessary to determine whether significantly higher levels of glutamate consumption would produce adverse effects.

Taking into account the new studies and the development of additional information regarding the physiological effects of glutamic acid, the FDA has defended its handling of the MSG issue on the grounds that it has appropriately engaged in a process of reassessment and evaluation. Dr. Fred Shank, as the director of the FDA’s Center for Food Safety and Applied Nutrition, commented on the MSG controversy, stating, “the public wants a quick fix: Ban it, remove it, or put a warning label on it.”

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acid that has accumulated since the publication of the SCOGS reports, combined with the ongoing public concern surrounding this food ingredient, the FDA announced in 1992 that it was contracting with FASEB to review the available scientific data on MSG and to prepare a comprehensive evaluation of glutamate safety.\footnote{Department of HHS Notice, \textit{supra} note 83.}

\section*{FASEB Report}

The FDA specified that this scientific review of MSG was to have five primary objectives: 1) to determine whether MSG can induce a complex set of symptoms known as Chinese Restaurant Syndrome, or other serious adverse reactions, after oral ingestion of MSG at levels ranging up to or beyond 5 grams per meal; 2) to determine whether MSG as used in the American food supply (including as used in hydrolyzed protein products) has the potential to contribute to brain lesions in neonatal or adult nonhuman primates and whether there is any risk to humans from dietary MSG; 3) to determine whether hormones are released from the pituitary of nonhuman primates following ingestion of MSG and whether there exists any comparable risk to humans; 4) to define the metabolic basis that might underlie these types of adverse reactions; and 5) to compile a report on the findings of the review and evaluation.\footnote{Dept. of Health and Human Services Notice. Analysis of Adverse Reactions to Monosodium Glutamate; Announcement of Study, Request for Scientific Data and Information; Announcement of Open Meeting. 57 FR 57467.}

The review was to be conducted in two separate phases – the first being an exhaustive review of the existing scientific literature and the second being a comprehensive evaluation of the safety of MSG using the Phase I results as the focus for the Phase II analysis. The FDA put forth 18 detailed questions regarding MSG that
FASEB was to focus on in preparing its report. The questions generally dealt with the possible role of MSG in eliciting MSG symptom complex, the possible role of dietary glutamate in causing brain lesions in humans, any underlying conditions that may predispose an individual to adverse effects from MSG, whether levels of consumption or other factors may affect an individual’s response to MSG and the quality of previous scientific data and safety reviews. The FASEB Report deemed the symptoms associated with MSG as “MSG symptom complex,” a term the Expert Panel preferred over the more popularized CRS which the panel felt was “pejorative” and “not reflective of the extent or nature of the symptoms that have been associated with the myriad of potential exposure possibilities.”

The FASEB final report is detailed and complex, over 350 pages long. The general consensus has been that the report reaffirms the safety of MSG for the general population at normally consumed levels, finding no evidence connecting MSG to any serious, long-term medical problems. Specifically, the report stated that though endogenous glutamate metabolism has been linked to certain neurological diseases, such as Alzheimer’s disease or Huntington’s Chorea, there is no evidence indicating that dietary or circulating MSG or glutamate contributes to changes in brain neurochemistry and therefore chronic consumption of MSG cannot be deemed to contribute to or exacerbate any of these glutamate-mediated neurodegenerative diseases. Moreover, while the Expert Panel indicated that some studies have documented the impact of parenterally administered MSG on the hypothalamus of nonhuman primates, the Panel maintained that no studies performed in the prior fifteen years had indicated the ability of orally ingested MSG to produce

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88The list of these 18 questions is attached as Appendix A.
89FDA Backgrounder, supra note 7, at 3.
lesions or damage nerve cells in nonhuman primates. The report did, however, indicate possible short-term effects following MSG ingestion in two particular subgroups of the general population: 1) otherwise healthy individuals who, within one hour of exposure to a dosage of MSG greater than 3 grams in the absence of food, experience manifestations of the MSG Symptom Complex and 2) individuals with severe and unstable asthma who may experience MSG Symptom Complex when given MSG in the absence of a meal containing protein and carbohydrate. With regard to this latter subgroup, the Expert Panel reviewed 11 available reports regarding the link between MSG and asthma, and found that all of the studies were flawed in some capacity or presented insufficient evidence with which to characterize the patient sample. With respect to this “asthma effect,” the FASEB report recommends additional research.

The Expert Panel maintains that reports of adverse reactions to MSG in the scientific and medical literature are case reports as opposed to experimental studies, and the “majority of these reported symptoms are transient and not life-threatening.” The Expert panel did note two exceptions in the case studies that reported cardiac arrhythmia following ingestion of wonton soup. However, in response to these reports, the Panel notes that “the evidence linking these symptoms in these studies with MSG is presumptive, as neither

92 Id. at Ch. VII, Sec.B (2) (p. 52-56). Moreover, the Expert Panel states, “The relative paucity of studies, particularly those employing oral (rather than intragastric) challenges with MSG, the lack of relevant biochemical date, and the lack of assessment of functional changes (e.g., behavioral or endocrinological) in challenged infants preclude the possibility of extrapolating available data from nonhuman primates to conditions of human exposure.”

93 A reaction is most likely if the MSG is consumed in large quantities or in a liquid. FASEB Report, supra note 90, at xv. The Expert Panel maintains that the testimonial reports suggest, but do not establish, causality by MSG. However, they write, “the overall impression of the Expert Panel is that causality has been demonstrated.” FASEB Report, supra note 90, at v.

94 The Expert Panel indicated that evidence to support any other predisposing factor, aside from asthma, would be conjunctural, but studies to test for such potential conditional are “research avenues worth pursuing.”

95 In particular, the issues of continuation and discontinuation of asthma medication proved problematic to these studies.

96 Though the FASEB Report lists unstable asthma as the only potential predisposing factor, they maintain that the literature indicates the following situations in which subgroups may be effected by MSG: individuals with vitamin B-6 deficiency, infants, women taking oral contraceptives, and individuals with affective disorders. It goes on to state 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.” FASEB Report, supra note 90, at Ch.IX,Sec.B(5), p.105.

97 FASEB Report, supra note 90, a vi.
the glutamate content of the individual food or foods consumed nor the blood glutamate levels or any other corroborative evidence was presented.\textsuperscript{98} Moreover, even with these potential subgroups, the Expert Panel maintains that, with the exception of one study, there is no evidence in humans of response when an MSG challenge is given with a mixed meal.\textsuperscript{99}

The Expert Panel declined FDA’s request to determine a reasonable classification scheme for the different types of adverse reactions to MSG, declaring that given the limited state of knowledge and the absence of valid epidemiological data, such a scheme would be premature. The Panel recommended “vigorous research and statistical corroboration” before a valid classification scheme could be designed. The Panel did indicate that adverse reactions were more likely to occur when MSG was ingested in capsule or liquid form on an empty stomach or without food. For purposes of determining an appropriate range of doses and methodology to administer during MSG testing, the Expert Panel recommended a double-blind, placebo-controlled test using.5 g and 3 g doses of MSG.\textsuperscript{100}

In summary, given that adverse effects were only seen after ingesting 3 grams or more of MSG on an empty stomach, and that the typical serving of glutamate-treated food contains less than.5 grams of MSG, the FASEB Report essentially reaffirms the safety of MSG at normal consumption levels for the general population. The Report does however call for further, more extensive research in certain areas of MSG study, in particular the effect of glutamates on asthmatics.\textsuperscript{101}

\textsuperscript{98} In addition, the Expert Panel notes that no case reports of cardiac arrhythmias have been presented since these reports in 1977 and 1982. FASEB Report, supra note 90, at vii.

\textsuperscript{99} As compared to MSG being given without food and on an empty stomach. FASEB Report, supra note 90, at Ch.IX, Sec.B(5), p.103. The exception was a study in which 5 g of MSG was given with a small meal.

\textsuperscript{100} The Expert Panel states that a dose greater than 3 grams is probably not needed since a subject who failed to react to a dose of 3 gram given under fasting conditions will not likely react to the quantities of glutamates found in foods under “real-life” circumstances.

\textsuperscript{101} Though not the focus of this paper, the FASEB Report did offer two other primary findings: 1) The level of vitamin B6
Conclusion

Despite the FDA’s objective to provide a complete and exhaustive study of MSG, the FASEB report was nonetheless subject to criticism from both sides of the debate. Given the report’s conclusion that MSG was safe for the general population, the anti-MSG activists felt that the FASEB report missed important studies and was, once again, overly favorable to industry. More surprisingly, however, was the criticism launched by the International Glutamate Technical Committee (IGTC). Though the IGTC showed appreciation for “the clean bill of health” given to glutamate by the Expert Panel, it nonetheless felt that there were “instances of serious misunderstanding . . . that led the expert panel to a few unjustifiable conclusions.” Specifically, the IGTC called into question the findings with regard to asthmatics, stating that the panel overlooked the “no asthma” findings of one clinic and noted that another study cited by the FASEB Report had been criticized in the literature for its methodological and design flaws.

Nevertheless, the findings of the FASEB study remain relatively unaffected, even ten years later. MSG is still “generally recognized as safe” by the FDA, and despite numerous attempts to implement more stringent labeling standards for the food additive, the FDA’s long-standing labeling policy remains intact. And, even in spite of the enormous amount of time, resources and research that have been devoted to the investigation of MSG, the controversy has not subsided. The anti-MSG activists remain dogged in their attempts to reverse the FDA’s current position on the food additive, despite the realities of the past which indicate that their calls will be answered. In addition, the exposure devoted to MSG by the public press remains virtually

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104 Id. The Scripps Clinic had no findings of asthma after MSG exposure. In addition, the IGTC reported “misinterpretations” of the MSG data on the grounds that the panel assumed equal toxic sensitivities across animal species, when in fact, there is a great deal of data indicating that “neonatal rodents are far more sensitive [to MSG] than non-rodent species.”
unparalleled in the world of food additives. As one scholar reflected on this general media phenomenon, “if public paranoia continues, it is only a matter of time before apple pie itself comes under the toxicologist’s scrutiny.” And yet, despite the numerous scientific attempts to separate myth from reality, the body of anecdotal evidence targeting MSG continues to grow, as do the passionate responses from both sides of the debate, making only one thing clear – the controversy surrounding MSG is far from over.

APPENDIX A

1. What are the symptoms and signs of acute, temporary, and “self limited” adverse reactions that have been reported to occur w/ oral ingestion of MSG? Do these reports provide a basis for establishing causality by MSG? Do these reports indicate a dose-related response or requirement for accessory factors, such as predisposing medical or dietary conditions, in the occurrence or relative severity of the adverse reactions?

2. What, if any, serious (life-threatening) reactions have been reported to occur w/ oral ingestion of MSG? What is the quantity and quality of these reports? How do dose and time relationships compare w/ “self-limited” adverse reactions? Are there predisposing medical conditions associated w/ specific reactions?

3. Assuming that reproducible associations w/ MSG ingestions can be demonstrated, what is a reasonable classification scheme for the various types of adverse reactions to MSG that have been reported?

105 Benarde, supra note 10, at 14.
4. Is it possible to classify adverse reactions based upon: (1) The length of time following MSG administration to onset of the reaction, (2) dose-responsiveness, (3) type of adverse reactions elicited, or (4) predisposing factors?

5. Is it possible to determine the mechanism whereby any glutamate-based adverse reaction might occur?

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

7. 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? What is the evidence that HVP ingestion is associated with adverse reactions similar to those reported to occur after MSG ingestion? Have life-threatening adverse reactions been verified to occur with the levels of glutamate reported to be used in this range of products?

8. Are there any defined human subgroups that are more susceptible to glutamate than the general population?

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

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

11.
During testing for MSG-mediation of each class of adverse reactions, what is the best manner to control for various possible disease triggers? What are the appropriate subject selection criteria? Can the test solution be adequately blinded? When is it appropriate to use MSG in capsules rather than in solution or in food matrices? What sample size is needed to assure that adequate sensitivity is present to detect an effect or the absence of an effect?

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

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

14. What evidence is available concerning the ability of exogenously administered MSG to mediate changes in pituitary function following acute oral or parenteral dosing? 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? What evidence is provided that specific excitatory neurotransmitter receptors are involved in any effect observed?

15. 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? What is the probability of MSG ingestion w/ foods influencing the release of pituitary hormones?

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

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