

Statement of Grounds relevant to the Citizen Petitions filed with the FDA by Adrienne Samuels, Ph.D., on January 4, 2021 to request that MSG and MfG be stripped of their GRAS status

Every Citizen Petition has a Statement of Grounds which gives the rationale behind submission of the petition. This one begins by noting violations of the Federal Food, Drug, and Cosmetic Act in declaring MSG and its toxic component, manufactured free glutamate (MfG) to be generally recognized as safe (GRAS). Subsequently discussed in detail are the topics of L-glutamate, monosodium glutamate, evidence of MSG toxicity, metabolism, the alleged safety of MSG: the animal studies, L-glutamate and MSG-induced brain damage, alleged safety of MSG: the human studies, and how the FDA has turned a blind eye to relevant research.

Violations of Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act).

Under sections 201(s) and 409 of the Act, and FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food under 21 CFR 170.30(b). Under 21 CFR 170.30(c) and 170.3(f), general recognition of safety through experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers.

The L-glutamate used in MSG, and thus MSG itself, were reformulated by Ajinomoto in 1957. Prior to that change, there had been no accounts of brain damage or adverse reactions caused by MSG or the L-glutamate in it. The L-glutamate component of MSG in use since 1957 (Modern MSG) is made using genetically modified bacteria that excrete glutamate through their cell walls. The L-glutamate component of MSG was previously made through extraction of glutamate from a protein source. Consequently, when 21 CFR 170.30(c) and 170.3(f), general recognition of safety through experience were written in 1958, Modern MSG had existed for less than a year, and there would have been no time for Modern MSG to have produced a substantial history of consumption by a significant number of consumers.

It could be argued that the products of extraction and bacterial fermentation are identical, but there are no data to demonstrate that. Suggesting that there is a difference comes, in part, from the observation that prior to the change in manufacturing process, there had been no reports of either MSG-induced brain damage or adverse reactions.

According to 21CFR170.30 eligibility for classification as GRAS (c)(1), "General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive. General recognition of safety through

experience based on common use in food prior to January 1, 1958, shall be based solely on food use of the substance prior to January 1, 1958, and shall ordinarily be based upon generally available data and information. An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.”

Both MSG and L-glutamate are such ingredients. Modern MSG was not in common use in food prior to January 1, 1958.

“General recognition of safety through scientific procedures” is based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

In the case of L-glutamate and MSG, the evidence in published studies that demonstrates that the L-glutamate and the MSG in which L-glutamate is found are toxic, does not support the thesis of MSG safety (1). Neither does a review of the badly flawed industry-sponsored studies that allege to have found that MSG is “safe” (2). Review of studies that affirm the safety of MSG and L-glutamate, demonstrate that glutamate-industry-sponsored studies allegedly demonstrating the safety of MSG are badly flawed.

According to 21CFR182.1045, Glutamic acid is GRAS when used as a salt substitute in accordance with good manufacturing practices.

L-glutamate

L-glutamate is the L enantiomer of glutamic acid (glutamate), an acidic amino acid which when present in protein or released from protein in a regulated fashion (through routine digestion) is vital for normal body function. It is the principal neurotransmitter in humans, carrying nerve impulses from glutamate stimuli to glutamate receptors throughout the body. Yet, when present outside of protein in amounts that exceed what the healthy human body was designed to accommodate (which can vary widely from person to person), glutamate becomes an excitotoxic neurotransmitter, firing repeatedly, damaging targeted glutamate-receptors and/or causing neuronal and non-neuronal death by over exciting those glutamate receptors until their host cells die (3,4).

Glutamate is the name given by scientists to the sodium salt of glutamic acid. It is found in most unadulterated foods that contain protein. It is also found in monosodium glutamate (MSG) and all other ingredients where protein content is fermented, hydrolyzed, autolyzed, or otherwise converted to free amino acids.

L-Glutamate occurs naturally in unadulterated fruits, grains, and vegetables, where it is a constituent of the protein in those fruits, grains, and vegetables. In **ingredients** such

as hydrolyzed proteins, autolyzed yeast, hydrolyzed yeast, yeast extract, soy extracts, and protein isolates, glutamate is created when those ingredients are manufactured. The brain-damaging potential of those ingredients has been demonstrated (5). Glutamate is an essential and unavoidable part of each of those ingredients.

Monosodium glutamate

Monosodium glutamate (MSG) is a man-made product composed of L-glutamic acid (L-glutamate), sodium, moisture, D-glutamic acid (D-glutamate), pyroglutamic acid, and other impurities (unwanted and unavoidable by-products of the manufacture of L-glutamate). MSG is manufactured in plants throughout the world. In the United States, MSG is produced in Ajinomoto's factory in Eddyville, Iowa. Its principal ingredient is its excitotoxic – brain damaging -- L-glutamate.

For purposes of labeling, monosodium glutamate is the common or usual name of the flavor enhancer that contains nothing but glutamate, sodium, moisture and unwanted (but unavoidable) by-products of production.

All flavor-enhancers contain L-glutamate. The difference between MSG and other flavor-enhancers lies in the fact that MSG has no taste of its own. The flavor-enhancing properties of MSG stem from the fact that the L-glutamate in MSG triggers glutamate receptors in the mouth and on the tongue, producing the perception of a more robust taste than there would otherwise be. Other flavoring constituents are derived from spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products that start out with their own flavors, and are processed to the point that protein will be broken down into its constituent amino acids with toxic properties identical to those present in the L-glutamate component of MSG.

Evidence of MSG toxicity

There are three lines of evidence pointing to the toxic potential of monosodium glutamate.

I. The first study to address the possibility that glutamate from exogenous sources (eating for example) might cause brain damage followed by obesity and reproductive dysfunction was published in 1969. At the time, researchers were administering glutamate to laboratory animals subcutaneously using Accent brand MSG because it had been observed that MSG was as effective for inflicting brain damage as more expensive pharmaceutical grade L-glutamate (6).

In the decade that followed, research confirmed that glutamate induces hypothalamic damage when given to immature animals after either subcutaneous or oral doses (1).

II. In the 1980s, researchers focused on identifying and understanding abnormalities associated with glutamate, often for the purpose of finding drugs that would mitigate glutamate's adverse effects. Researchers had found that glutamate was an excitotoxic amino acid. When consumed in controlled quantities, it is essential to normal body function as neurotransmitters and building blocks of protein. But when accumulated in interstitial tissue in quantities greater than needed for normal body function (in excess) it becomes excitotoxic, firing repeatedly and killing brain cells.

It is well documented that L-glutamate is implicated in kidney and liver disorders, neurodegenerative disease, and more. By 1980, glutamate-associated disorders such as headaches, asthma, diabetes, muscle pain, atrial fibrillation, ischemia, trauma, seizures, stroke, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, depression, multiple sclerosis, schizophrenia, obsessive-compulsive disorder (OCD), epilepsy, addiction, attention-deficit/hyperactivity disorder (ADHD), frontotemporal dementia and autism were on the rise, and evidence of the toxic effects of glutamate were generally accepted by the scientific community. A November 15, 2020 search of the National Library of Medicine using PubMed.gov returned 3872 citations for "glutamate-induced."

By and large, the glutamate in question here was, and still is, glutamate from endogenous sources. The possible toxicity of glutamate from exogenous sources such as glutamate-containing flavor enhancers has generally not been considered. Only Olney and a few others have suggested that ingestion of free glutamate might play a role in producing the excess amounts of glutamate needed for endogenous glutamate to become excitotoxic.

III. The third line of evidence comes from studies undertaken by the producer of MSG to convince the public that MSG is a harmless food additive.

It would appear that to counter data that demonstrated that L-glutamate and MSG cause brain damage, researchers pretended to replicate toxicity studies but did not do so.

There is a certain sameness to these studies. They are generally methodologically inadequate, statistically unsound, and/or irrelevant to the safety/toxicity of MSG. Researchers have gone so far as to use aspartame and/or excitotoxic manufactured free glutamate (MfG) in placebos to cause subjects to respond to placebos just as they would respond to monosodium glutamate test material (2).

Metabolism

Although the claim is made by the FDA and the producers of MSG and other flavor-enhancers that the human body utilizes and metabolizes glutamate in the same way whether it comes from MSG or other dietary sources of glutamate, there are no studies to back that claim.

Alleged safety of MSG: the animal studies

The FDA maintains that MSG is a safe ingredient. But they offer no evidence. It would appear that they base their declarations of safety, in part, on **alleged** replications of animal studies of MSG-induced brain damage done for Ajinomoto by Filer, Stegink, Lemkey-Johnston, Boaz, Brummel, Reynolds, Pitkin, and Butler. When Olney and others demonstrated that both L-glutamate and MSG causes brain lesions and causes neuroendocrine disorders in maturing animals fed L-glutamate-containing MSG as neonates and infants, glutamate industry researchers produced studies that they claimed were failed attempted replications -- but their procedures were different enough to guarantee that toxic doses had not been administered, or that all evidence that nerve cells had died would be obscured. Industry-sponsored researchers said they were replicating studies but did not do so. Instead, discussion was phrased to suggest that studies were "replications," and the conclusions were based on what was said, not on what was done.

When it became undeniable that L-glutamate was toxic — when L-glutamate was being used by researchers to kill brain cells in laboratory animals in order to identify interventions for treating glutamate-related abnormalities — Ajinomoto decreed that animal studies did not represent the human condition and were therefore meaningless. The FDA did not comment.

L-glutamate and MSG-induced brain damage

In the 1960s and 1970s it was repeatedly demonstrated that animals fed L-glutamate as fetuses, or in the first 12 days of life suffered brain damage and neuroendocrine disturbances including obesity, stunting, abnormalities of the reproductive system, and underdevelopment of certain endocrine glands. In addition, researchers observed pathological changes in several brain regions associated with endocrine function in maturing mice that had been given L-glutamate as neonates. In those studies, Accent brand monosodium glutamate was used as the source of L-glutamate, because the L-glutamate in Accent brand monosodium glutamate had been found to be comparable to pharmaceutical-grade L-glutamate in its ability to cause brain damage, but less expensive (1).

While much of the investigation into the toxicity of L-glutamate focused on MSG-induced toxicity, it was found that hydrolyzed proteins produced brain damage as well (5).

Alleged safety of MSG: the human studies

Glutamate-industry agents made no attempt to examine MSG-induced brain damage in humans. Rather, in the 1980s human studies of adverse reactions as opposed to brain damage were offered to the FDA as evidence that MSG was a harmless food additive.

These weren't alleged replications like the brain-damage studies were, but were creatively designed, each apparently calculated to produce negative results (i.e., no harm done by MSG). Negative results were ensured when researchers considered the effects of glutamate on irrelevant variables, i.e., variables such as blood pressure and weight loss that have never been shown to be associated with glutamate-induced toxicity. Or if females exhibited MSG-induced reproductive disorders and males did not, males would be studied. A variation used was to study the effects of ingestion of glutamate on plasma glutamate levels. Elevated plasma glutamate is associated with production of brain lesions but has never been shown to be relevant to glutamate-induced adverse reactions. The logical fallacy in these studies comes when it is concluded that finding nothing while studying irrelevant variables proves that glutamate is safe.

Negative results were also reliably produced by a series of double-blind studies conducted by a variety of researchers from various universities and medical schools who were given study protocols that would guarantee negative results, all supervised by Andrew G. Ebert, Ph.D., Ajinomoto's agent in charge of research at the time (without the involvement of Ajinomoto being disclosed). Although these studies had common elements, no two studies were identical. There was, however, one feature that was shared by all – use of placebos that contained excitotoxic amino acids that would trigger reactions identical to those caused by the MSG test material. According to a letter from Ebert to Sue Ann Anderson, Senior Staff Scientist with the Life Sciences Research Office at FASEB, this practice began in 1978 (7).

In a double-blind study, test material is given to a subject on one occasion, and on another occasion the subject is given a placebo. The placebo, if it's a true placebo, looks, tastes and smells like the test material, but it will not cause a reaction. If the subject reacts to the inert placebo, the researchers could conclude that the subject is not reacting to the test material, but is responding to the **thought** of consuming MSG. In other words, the subject would be portrayed as some kind of nut case who might react to anything, and reactions to MSG test material would be discounted.

To make sure that it appeared to be appropriate for researchers to conclude that MSG is harmless, glutamate-industry researchers guaranteed that subjects would react to placebos by using aspartame in their placebos, for the aspartic acid in aspartame and the glutamic acid in MSG cause virtually identical reactions as well as identical brain damage (8,9). Having set that up, glutamate-industry researchers (and those who quote them) will say "These people aren't sensitive to MSG, they reacted to the 'placebo' too" (2).

Conclusions drawn from these industry-sponsored studies were based on negative results. The inferential statistics used ask the question of whether a difference between two groups of subjects or two sets of measurements could have occurred by chance. If statistical analysis determines that observed differences rarely would have occurred by chance, an investigator would describe those differences as statistically significant and would specify the probability with which differences of that magnitude would be

expected to be reproduced if the experiment were replicated at another time. In statistical parlance, the investigator had tested the hypothesis that there would be no difference between two groups — the null hypothesis — and had rejected that hypothesis when he found that there was indeed a significant difference. The statistical model on which these statistics are based allows the investigator to conclude that it is highly likely — the probability used usually being 95 percent or 99 percent — that differences found were not due to chance. The statistical model does not allow the investigator to conclude that no difference **exists** between the two groups when a statistically significant difference is not found. The industry-sponsored studies invariably violated the assumptions of the statistics used.

The FDA has reviewed studies of the safety of MSG on multiple occasions, but has never done reviews of MSG toxicity.

The FDA has built and then reinforced its case for the "safety" of MSG on misleading and deceptive studies sponsored by the glutamate industry.

FDA regulations require that those who manufacture food additives must provide evidence demonstrating that they are "safe." The glutamate industry has, indeed, presented evidence, but they have falsified data -- not by changing test scores or research results, but by rigging the procedures used in conducting their studies so that only after careful scrutiny would one discern that their studies were flawed to the point of being fraudulent. In addition, industry's researchers have been known to draw conclusions that did not follow from the results of their studies.

What is known about the toxicity of MSG is also true of all other free-glutamate-containing ingredients (5).

Turning a blind eye to relevant research

Over the course of the last 50 years, the FDA has summarily dismissed much of the research that clearly demonstrates that MSG places humans at risk. They don't counter it, they simply ignore it. Reports of adverse reactions to MSG collected by its own Adverse Reactions Monitoring System (8,9) have been dismissed because "they could have been caused by something else."

The FDA has suppressed results of studies that might suggest that use of MSG places humans at risk. The FDA suppressed results of its own study that suggested that use of free glutamic acid in supplements is unsafe. In a July, 1992 report to the FDA, the Federation of American Societies for Experimental Biology (FASEB) had concluded, in part, that: "...it is prudent to avoid the use of dietary supplements of L-glutamic acid by pregnant women, infants, and children.... and...by women of childbearing age and individuals with affective disorders." (MSG is called L-glutamic acid when used in supplements.) Mention has not been made of those recommendations – not to the medical community or anywhere else.

Persons who have identified themselves as representing The Glutamate Association, an organization created and maintained by Ajinomoto, declared that both the FDA and regulators around the world have found monosodium glutamate to be safe. However, neither independent scientists nor independent regulators have deemed monosodium glutamate safe. FDA studies, which were actually reviews, have always been staffed by persons with ties to the glutamate industry. And the regulators and/or authoritative bodies referred to here did no research of their own; they were given copies of FDA opinions on MSG safety or were provided review information by Ajinomoto, its not-for-profit corporations, and/or its agents — the International Food Information Council (IFIC) and the International Life Sciences Institute (ILSI), for example.

Glutamic acid is one of a class of excitotoxic – brain damaging -- amino acids. When consumed in controlled quantities, it is essential to normal body function as neurotransmitters and building blocks of protein. But when consumed in quantities greater than needed for normal body function it becomes excitotoxic, firing repeatedly and killing their targeted glutamate receptors. In 1969 John Olney described the actions of glutamic acid and MSG (6) and coined the term “excitotoxin.”

At one time it would have been meaningful to note that the amount of excitotoxic material in a particular ingredient would not be sufficient to cause brain damage or adverse reactions. But since the 1957 change in method of MSG production, there are so many products that contain excitotoxins that it is easy for a consumer to ingest an excess of excitotoxic material during the course of a day (10-14).

Prior to 1957, the amount of free glutamate or other excitotoxic additives in the average U.S. diet had been unremarkable. During that year, however, the method of producing the free glutamate that makes up the excitotoxic portion of MSG changed from extraction of glutamate from a protein source, a slow and costly method, to a process of bacterial fermentation (15). This allowed virtually unlimited production of free glutamate and MSG.

It didn't take long for industry to add dozens more excitotoxic food additives to the American diet. Following MSG's surge in production and aggressive advertising, it was realized that profits could be significantly increased if companies produced their own flavor-enhancing additives. Since that time, the market has been flooded with flavor enhancers and protein substitutes that contain manufactured free glutamate (MfG) such as hydrolyzed proteins, yeast extracts, maltodextrin and soy protein isolate, as well as MSG. To that has been added the toxic load contributed by excitotoxic aspartic acid, approved by the FDA for use in aspartame, equal, and related products starting in 1974.

Soon after use of genetically modified bacteria in the production of MSG began, availability of MSG and other MfG-containing products increased to the point where there was more than sufficient MfG to become excitotoxic if a number of processed and ultra-processed foods were consumed during the course of a day.

Information known to the petitioner which representatives of industry will claim are unfavorable to the petition.

For more than 50 years, Ajinomoto has maintained that monosodium glutamate is a harmless, even beneficial, product. Illustrations of their deceptive and misleading activities including detail of the ways in which they rigged the research from which they concluded that MSG is a harmless food additive are included the Statement of Grounds. Additional detail can be found in a 1999 peer reviewed published study, The Toxicity/Safety of Processed Free Glutamic Acid (MSG): A Study in Suppression of Information (16). Ajinomoto's single most clearly documented unethical activity has been the use of excitotoxic aspartic acid (in aspartame) in placebos used in double-blind studies proclaiming the safety of MSG.

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