

# MONOSODIUM GLUTAMATE

## A Safety Assessment

TECHNICAL REPORT SERIES NO. 20

**FOOD STANDARDS AUSTRALIA NEW ZEALAND**  
**June 2003**

© Food Standards Australia New Zealand 2003  
ISBN 0 642 34520 1  
ISSN 1448-3017  
Published June 2003

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## SUMMARY

Monosodium glutamate (MSG) is the sodium salt of the non-essential amino acid glutamic acid, one of the most abundant amino acids found in nature. Glutamate is thus found in a wide variety of foods, and in its free form has been shown to have a flavour enhancing effect. Because of its flavour enhancing properties, glutamate is often deliberately added to foods – either as the purified monosodium salt (MSG) or as hydrolysed protein.

Since the late 1960s MSG has been claimed to be the cause of a range of adverse reactions in people who had eaten foods containing the additive. In particular, MSG has been implicated as the causative agent in the symptom complex known as Chinese restaurant syndrome and also as a trigger for bronchoconstriction in some asthmatic individuals.

The purpose of this report is to examine the evidence for a relationship between MSG exposure and (i) the Chinese restaurant syndrome and (ii) the induction of an asthmatic reaction in susceptible individuals. This assessment has considered the conclusions of previous significant safety evaluations as well as the results of more recent studies.

### **Adverse reactions attributed to MSG**

In the late 1960s numerous case reports appeared in the scientific literature describing a complex of symptoms which came to be known as the *Chinese restaurant syndrome* (CRS) because they typically followed ingestion of a Chinese meal. Investigations have mainly focussed on MSG as the causative agent in CRS. An increasing number and variety of symptoms have been classified as CRS, however the most frequently reported symptoms are headache, numbness/tingling, flushing, muscle tightness, and generalised weakness. More recently, the term *MSG symptom complex* has been used instead of CRS. The reports of MSG-triggered CRS were followed in the early 1980s by reports of a possible association between MSG and the triggering of bronchospasm/bronchoconstriction in small numbers of asthmatics.

The prevalence of CRS is not really known but is suggested to be between 1 and 2% of the general population. While a number of mechanisms have been proposed to explain how MSG might trigger the various reported reactions, none have been proven and very little follow-up research has been conducted to further investigate any of the proposed mechanisms.

### **Physical and chemical properties of MSG**

MSG (MW: 187.13) is typically produced as a white crystalline powder from fermentation processes using molasses from sugar cane or sugar beet, as well as starch hydrolysates. MSG has a characteristic taste called *umami* (“savoury deliciousness”), which is considered distinct from the four other basic tastes (sweet, sour, salty, and bitter). The optimal palatability concentration for MSG is between 0.2 – 0.8% with the largest palatable dose for humans being about 60mg/kg body weight.

### **Sources of MSG**

Glutamate occurs naturally in virtually all foods, including meat, fish, poultry, breast milk and vegetables, with vegetables tending to contain proportionally higher levels of free

glutamate. Various processed and prepared foods, such as traditional seasonings, sauces and certain restaurant foods can also contain significant levels of free glutamate, both from natural sources and from added MSG.

No data is available on the average consumption of MSG for Australian or New Zealand consumers however data from the United Kingdom indicates an average intake of 590mg/day, with extreme users consuming as much as 2330mg/day. In a highly seasoned restaurant meal, however, intakes as high as 5000mg or more may be possible.

### **Kinetics and metabolism of MSG**

Glutamate occupies a central position in human metabolism. It comprises between 10 – 40% by weight of most proteins, and can be synthesised *in vivo*. Glutamate supplies the amino group for the biosynthesis of all other amino acids, is a substrate for glutamine and glutathione synthesis, is an key neurotransmitter in the brain and is also an important energy source for certain tissues.

Humans are exposed to dietary glutamate from two main sources – either from ingested dietary protein, or ingestion of foods containing significant amounts of free glutamate (either naturally present, or added in the form of MSG/hydrolysed protein). Dietary glutamate is absorbed from the gut by an active transport system into mucosal cells where it is metabolised as a significant energy source. Very little dietary glutamate actually reaches the portal blood supply. The net effect of this is that plasma glutamate levels are only moderately affected by the ingestion of MSG and other dietary glutamates. Its only when very large doses (>5g MSG as a bolus dose) are ingested, that significant increases will occur in plasma glutamate concentration, however, even then the concentration typically returns to normal within 2 hours. In general, foods providing metabolisable carbohydrate significantly attenuate peak plasma glutamate levels at doses up to 150mg/kg body weight.

Breast milk concentrations of glutamate are only modestly influenced by the ingestion of MSG and the placenta is virtually impermeable to glutamate. Although glutamate is an important neurotransmitter in the brain, the blood brain barrier effectively excludes passive influx of plasma glutamate.

### **Review of the safety of MSG**

Two major evaluations of the safety of MSG have been undertaken in recent history. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) undertook an evaluation of MSG in 1987, and the Federation of American Societies for Experimental Biology (FASEB) undertook a review in 1995.

The JECFA and FASEB reviews both concluded that MSG does not represent a hazard to health for the general population. In relation to MSG being a cause of adverse effects in a subset of the population the two expert bodies reached slightly differing conclusions.

JECFA noted that controlled double-blind crossover trials have failed to demonstrate an unequivocal relationship between CRS and consumption of MSG and also that MSG has not been shown to provoke bronchoconstriction in asthmatics. The FASEB evaluation concluded that sufficient evidence exists to indicate some individuals may experience manifestations of CRS when exposed to a  $\geq 3$ g bolus dose of MSG in the absence of food. In addition, they concluded there may be a small number of unstable asthmatics who respond to doses of 1.5 – 2.5g of MSG in the absence of food.

In reviewing the individual studies considered by both the JECFA and FASEB evaluations as well as more recent studies it is clear that many of the earlier studies have suffered from numerous methodological flaws and have produced conflicting and inconclusive results, which are difficult to reconcile. The more recent studies – those conducted following the FASEB review – have largely addressed many of the earlier study design problems and their results may thus be considered more reliable.

In relation to more serious adverse effects, the bulk of the clinical and scientific investigation has focussed on the triggering of asthmatic attacks. The evidence for MSG as a cause of such reactions however is inconclusive. The more recently conducted studies, which were undertaken with asthmatic individuals who believed themselves to be sensitive to MSG, would suggest that MSG is not a significant trigger factor. Follow up studies would be helpful to confirm this finding.

In relation to CRS, the evidence from recent studies supports the conclusions reached in the FASEB review. Namely, that ingestion of large amounts ( $\geq 3$ g) of MSG in the absence of food may be responsible for provoking symptoms similar to CRS in a small subset of individuals. These symptoms, although unpleasant, are neither persistent nor serious. As MSG would always be consumed in the presence of food, an important question that remains unanswered by the scientific literature is what effect consumption with food would have on the incidence and severity of symptoms. The pharmacokinetic evidence suggests food, particularly carbohydrate, would have an attenuating affect.

Although the prevalence of CRS has been estimated to be about 1 –2% of the general population it is not clear what proportion of the reactions, if any, can be attributed to MSG. The vast majority of reports of CRS are anecdotal, and are not linked to the actual glutamate content of the food consumed. Furthermore, when individuals with a suspected sensitivity to MSG are tested in double-blind challenges the majority do not react to MSG under the conditions of the study (or react equally to placebo). Many individuals may therefore incorrectly be ascribing various symptoms to MSG, when in fact some other food component may be the cause. This highlights the need for individuals with suspected MSG sensitivity to undergo appropriate clinical testing.

While many of the more recently conducted studies have addressed the design flaws of earlier studies, one of the difficulties remaining is that the CRS symptoms are highly subjective in nature and are rarely associated with any objective clinical signs (e.g. vomiting, increased pulse rate, etc). The placebo response therefore plays a significant role in many of the reactions observed, making it difficult to interpret the significance of any responses to MSG. The elucidation of a possible mechanism of CRS, plus associated objective clinical measures, would greatly aid in the further study of this symptom complex.

## **Conclusion**

There is no convincing evidence that MSG is a significant factor in causing systemic reactions resulting in severe illness or mortality. The studies conducted to date on CRS have largely failed to demonstrate a causal association with MSG. Symptoms resembling those of CRS may be provoked in a clinical setting in small numbers of individuals by the administration of large doses of MSG without food. However, such affects are neither persistent nor serious and are likely to be attenuated when MSG is consumed with food. In terms of more serious adverse effects such as the triggering of bronchospasm in asthmatic individuals, the evidence does not indicate that MSG is a significant trigger factor.

## 1. INTRODUCTION

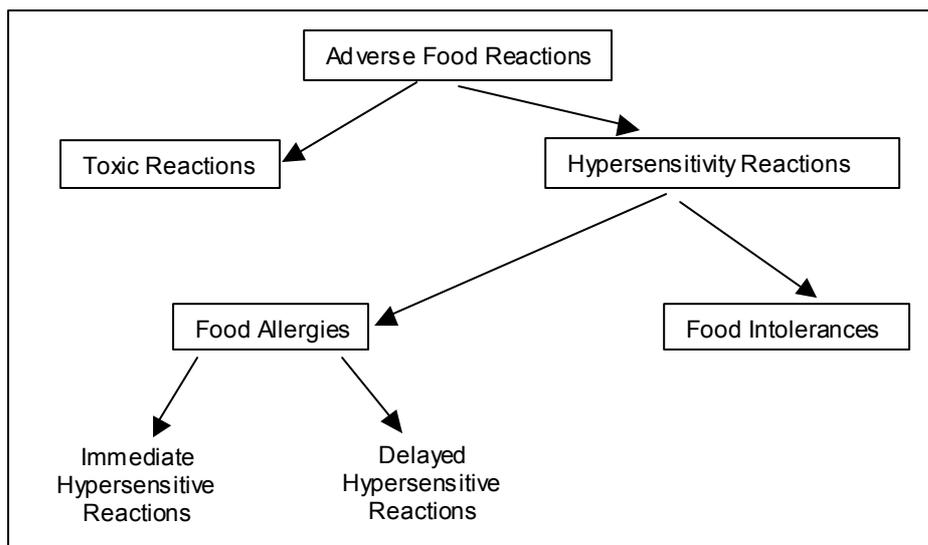
Monosodium glutamate (MSG) is the sodium salt of the non-essential amino acid glutamic acid. Glutamic acid is one of the most abundant amino acids found in nature and exists both as free glutamate and bound with other amino acids into protein. Animal proteins may contain about 11 to 22% by weight of glutamic acid, with plant proteins containing as much as 40% glutamate (Giacometti 1979). Glutamate is thus found in a wide variety of foods, and in its free form, where it has been shown to have a flavour enhancing effect, is also present in relatively high concentrations in some foods such as tomatoes, mushrooms, peas and certain cheeses. As a result of its flavour enhancing effects, glutamate is often deliberately added to foods – either as the purified monosodium salt (MSG) or as a component of a mix of amino acids and small peptides resulting from the acid or enzymatic hydrolysis of proteins (e.g. hydrolysed vegetable protein or HVP). Other substances, such as sodium caseinate and “natural flavourings”, are also added to many savoury foods and these can also contain considerable amounts of free glutamate.

The use of added MSG became controversial in the late 1960s when it was claimed to be the cause of a range of adverse reactions in people who had eaten foods containing the additive. An ongoing debate exists as to whether MSG in fact causes any of these symptoms and, if so, the prevalence of reactions to MSG.

The purpose of this assessment is to review previous considerations of the safety of MSG, as well as any more recent scientific publications, to determine if MSG has the potential to cause severe adverse reactions when ingested with food.

## 2. ADVERSE REACTIONS TO FOODS

Adverse reactions to food can be defined as any abnormal physiological response to a particular food (Taylor 2000) and can be classified into a number of different categories of reaction (Wüthrich 1996), as illustrated below.



Toxic reactions will occur in virtually all individuals in a dose-dependent manner, whereas hypersensitivity reactions are usually idiosyncratic reactions that only occur in a small subset

of individuals. Hypersensitivity reactions can be further divided into two major subcategories – food allergies and food intolerances. Food allergies are immune system-mediated and can be classified as either immediate or delayed hypersensitivity reactions whereas food intolerances are non-immune system-mediated.

## 2.1 Food allergies

Food allergies are an abnormal response by the body's immune system to certain components of foods, usually specific proteins. True food allergies may involve several types of immunological responses (Sampson and Burks 1996). The most common food allergy reactions are the immediate hypersensitivity reactions, which are mediated by allergen-specific immunoglobulin E (IgE) antibodies. Symptoms of IgE-mediated allergic reactions, such as acute urticaria or anaphylaxis, can occur immediately after ingestion of the offending food, depending on the dose ingested but they may be delayed by several hours in other cases, such as atopic dermatitis.

Although all humans have low levels of circulating IgE antibodies, only individuals predisposed to the development of allergies produce IgE antibodies that are specific for and recognise allergens. The IgE-mediated response is divided into two stages: (i) sensitisation; and (ii) the allergic reaction. Exposure to a food allergen elicits the formation of specific IgE antibodies by the B-lymphocytes. The IgE antibodies attach with exceptionally high affinity to receptors on the surface of tissue mast cells and blood basophils (immature red blood cells). At this point the individual is sensitised to the allergenic substance but has yet to experience an allergic reaction. Subsequent exposure to the allergen will result in the cross-linking of the allergen to the IgE molecules on the mast/basophil cell surface. The cross-linking triggers the mast/basophil cells to release various chemical mediators, such as histamine and cytokines. The release of these mediators results in various inflammatory reactions that may occur in the skin, gastrointestinal tract or the respiratory tract. In extreme cases, food allergens can cause anaphylactic shock resulting in the rapid and potentially life threatening collapse of the cardio-respiratory system.

IgE-mediated food allergies affect between 1 and 2% of the population (Metcalf *et al* 1996, Niestijl-Jansen *et al* 1994), however, infants and young children are more commonly affected with the prevalence in children under three years of age being between 5 and 8% (Bock 1987, Sampson 1990a, Taylor *et al* 1989).

True food allergies also include delayed hypersensitivity reactions, the mechanisms of which are less clear. Such reactions include cell-mediated mechanisms involving sensitised lymphocytes in tissues, rather than antibodies (Sampson 1990b). In cell-mediated reactions, the onset of symptoms occurs more than 8 hours after ingestion of the offending food. The prevalence of food-induced, cell-mediated reactions is not known (Burks and Sampson 1993) but the reactions are well documented in infants and typically occur following exposure to milk and soybeans. The most common cell-mediated hypersensitivity reaction affecting all age groups is coeliac disease, also known as gluten-sensitive enteropathy. Coeliac disease results from an abnormal response of the T lymphocytes in the small intestine to the gluten proteins in cereals and affects genetically predisposed individuals. The T cells have specific markers on their surface that recognise the allergen deposited at a local site such as the gastrointestinal mucous membrane, resulting in an inflammatory reaction affecting the epithelium of the small intestine.

## 2.2 Food intolerances

Food intolerances can be described as any form of food sensitivity that does not involve an immunological mechanism. They can be classified according to their mechanism e.g., enzymatic, pharmacological or undefined (Wüthrich 1996, Anderson 1996), or alternatively can be defined in terms of the reactions they elicit e.g., metabolic food disorders, anaphylactoid reactions or idiosyncratic reactions (Taylor 2000). Food intolerances usually produce less severe symptoms than food allergies, and affected individuals can usually tolerate some of the offending food in their diets.

The best-known examples of metabolic food disorders are lactose intolerance and favism both of which involve the inherited deficiency of an enzyme. In the case of lactose intolerance the reaction is due to an inherited deficiency of the enzyme lactase in the gut of the affected persons. Favism is intolerance to consumption of faba beans or inhalation of pollen from the *Vicia faba* plant. Reactions are due to an inherited deficiency of the enzyme, erythrocyte glucose-6-phosphate dehydrogenase. Most metabolic food disorders are genetically acquired and both lactose intolerance and favism occur at much higher frequencies in certain ethnic groups (Taylor 2000).

Anaphylactoid reactions have symptoms similar to those of anaphylaxis, but are triggered instead by non-immunological mechanisms, which directly lead to the release of chemical mediators from mast cells. To date, no specific substances in foods causing this response have been identified, with the majority of cases being associated with the administration of certain drugs or the radio-contrast dyes used for X-ray studies.

Idiosyncratic reactions refer to adverse reactions where the mechanism is undefined. One example is sulphite-induced asthma, which has been estimated to affect 1 – 2% of all asthmatics.

## 2.3 Adverse reactions to food additives

Sensitivity to most food additives is believed to occur in only a small minority of the population (ANZFA 1997, MAFF 1987), with most adverse effects due to various pharmacological and other non-immunological mechanisms (Hannuksela and Haahtela 1987), rather than being true allergic reactions.

Exacerbation of asthma is one of the adverse effects most typically reported as being associated with food additives. Although 23 to 67% of people with asthma perceive that food additives exacerbate their asthma (Dawson *et al* 1990, Abramson *et al* 1995), various double blind, placebo-controlled trials report a prevalence rate of less than 5% (Bock and Aitkins 1990, Onorato *et al* 1986).

# 3. ADVERSE REACTIONS ATTRIBUTED TO MSG

## 3.1 Reported reactions

In 1968, a letter was published in the *New England Journal of Medicine* describing a syndrome, which began 15 to 30 minutes after eating in certain Chinese restaurants, and lasted about 2 hours with no lasting effects. The symptoms were described as “numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and

palpitation” (Kwok 1968). The author noted that the symptoms simulated those he has had from hypersensitivity to acetylsalicylic acid, but were milder. The author suggested numerous possible causes for the symptoms, including alcohol, salt and MSG used in cooking. The term “Chinese Restaurant Syndrome (CRS)” was coined to describe the symptom complex.

Since that time numerous other case reports have appeared in the literature, with the focus mainly on MSG as the causative agent in CRS. An increasing number and variety of symptoms have also subsequently been added to the list of manifestations of CRS. In 1995, the Federation of American Societies for Experimental Biology (FASEB), who had been commissioned by the United States Food and Drug Administration (FDA) to undertake a review of reported adverse reactions to MSG, reported that the following symptoms are considered representative of the acute, temporary, and self-limited reactions to oral ingestion of MSG (FASEB 1995):

- burning sensations in the back of the 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.

In its report, FASEB noted that this catalogue of symptoms is based on testimonial reports received by the FDA Adverse Reaction Monitoring System as well as a review of the literature and is therefore based on accounts that are anecdotal and not verifiable. The FASEB report indicated that while the testimonial reports do not establish causality by MSG, the overall impression of the Expert Panel was that causality had been demonstrated.

Reports of more serious symptoms, such as atrial fibrillation, ventricular tachycardia and arrhythmias were not given any credence by the FASEB, as they were single case reports that lacked confirmatory evidence linking the reactions to MSG content of foods (Raiten *et al* 1995).

In the FASEB report, the term *Chinese restaurant syndrome* was abandoned as pejorative, and instead the term *MSG symptom complex* was used to describe the range of symptoms experienced by affected individuals.

An interesting feature of the CRS is that the presentation of symptoms often varies, with affected individuals usually only reporting one or a few of the characterising symptoms at any one time. In some recently conducted studies, the most frequently reported symptoms were headache, numbness/tingling, flushing, muscle tightness, and generalised weakness (Yang *et al* 1997, Geha *et al* 2000a).

### 3.2 Prevalence of reactions

A small number of studies have been conducted to try and determine the true prevalence of CRS and these have produced conflicting results. While one survey has classified CRS as very common, putting its prevalence at 25% (Reif-Lehrer 1977), another survey has estimated its prevalence to be much lower, at between 1 to 2% of the general population (Kerr *et al* 1979a). The conflicting results appear in part to be due to the way the studies have been conducted and also the way various symptoms have been characterised by the different investigators.

The Reif-Lehrer (1977) survey, which estimated the prevalence of reactions to be 25%, has been criticised as having several inherent biases and therefore is considered to represent an exaggerated estimate of the true prevalence (Kerr *et al* 1979b, Pulce 1992, Geha *et al* 2000b). The main criticisms relate to methodological problems, such as demand bias in the questionnaire where leading questions such as “Do you think you get Chinese restaurant syndrome?” were asked, and population bias, where the surveyed population was not considered representative of the general population and had a higher than average awareness of CRS prior to the survey. Another major criticism is that the clinical criteria used for selecting reactors from non-reactors were quite broad and thus could have led to an overestimate of CRS prevalence in the population group studied.

A slightly later survey by Kerr *et al* (1979a), which reported an estimated prevalence for “possible CRS” of between 1 and 2%, attempted to redress some of the biases inherent in the first survey, and thus is considered a more reliable indicator of the true prevalence of reactions. This survey was conducted using the National Consumer Panel of the Market Research Corporation of America, and therefore should have avoided any population bias. Efforts were also made to avoid demand-biased questions in the questionnaires used. Kerr *et al* (1979b) noted however that many unresolved issues still remain in relation to the true prevalence of CRS. The most problematic of these is that numerous symptoms have been associated with CRS and many of these symptoms are ambiguous and imprecise. The various clinical presentations thus make it difficult to accurately diagnose CRS and this is likely an important confounding factor in questionnaire surveys.

### 3.3 Proposed mechanisms

Numerous mechanisms have been proposed for CRS. While some of the proposed mechanisms postulate an involvement for MSG, others do not.

It has been suggested that CRS resembles an immediate hypersensitivity reaction in that the symptoms typically occur within a few minutes to several hours after eating the offending food. However, no evidence for an IgE-mediated reaction exists (Pulce *et al* 1992), although the possibility of an anaphylactoid reaction cannot be discounted. Other non-allergenic mechanisms that have been suggested as the cause of CRS include acetylcholinosis, vitamin B<sub>6</sub> deficiency, reflux oesophagitis, and histamine toxicity.

Ghadimi *et al* (1971) suggested that CRS was the result of an increase in acetylcholine caused by the ingestion of MSG in large doses with the glutamate being converted to acetylcholine via the tricarboxylic acid (TCA) cycle. A similarity between the symptoms of CRS and those occurring after injection of acetylcholine (flushing, feeling of warmth, throbbing in the head, palpitations, and substernal constriction) was noted and it has also been

observed experimentally that in humans there is a 28% decrease in cholinesterase after MSG is ingested. The symptoms of CRS were also found to be capable of modulation using drugs affecting the cholinergic mechanisms.

Folkers *et al* (1984) have suggested that the reactions experienced by MSG-sensitive individuals are a result of vitamin B<sub>6</sub> deficiency. They found that when MSG responders received supplemental B<sub>6</sub>, CRS symptoms were prevented.

Kenney (1986) has suggested that the symptoms seen in CRS are caused by MSG but are not a neurological/physiological reaction. He has suggested that CRS is actually a case of reflux oesophagitis, with MSG acting as an oesophageal irritant. The symptoms and regions of the body affected by CRS were noted to be similar to those of pain referred from the upper oesophagus. Studies have shown that a variety of seemingly unrelated substances such as coffee, orange juice and tomato juice, ingested via oesophageal infusion, can cause similar types of symptoms (Price *et al* 1978). Adding weight to this hypothesis are the results of studies suggesting that individuals reacting to MSG may react to concentration rather than dose and that the same dose taken in capsules is associated with fewer reactions.

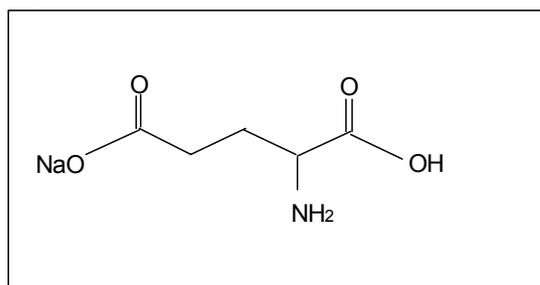
Chin *et al* (1989) suggested that there are similarities between CRS and scombroid poisoning, caused by naturally occurring histamine in foods and they therefore undertook assays of several common Chinese restaurant dishes and condiments for histamine content. It was concluded that while the histamine content of most of the foods assayed was not sufficient alone to cause histamine toxicity, in certain situations histamine intake over the course of an entire meal could approach toxic levels.

To date, very little research has been done to investigate any of these proposed mechanisms further. The FASEB report (1995) 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 lack data on any objective measures of response, in particular, blood glutamate concentrations, and the latter focus on blood glutamate data without evaluation of adverse effects.

#### **4. PHYSICAL AND CHEMICAL PROPERTIES OF MSG**

MSG (MW: 187.13) is typically marketed as a white crystalline powder and is readily soluble in water but sparingly soluble in ethanol. MSG is not hygroscopic and is considered quite stable in that it does not change in appearance or quality during prolonged storage at room temperature. MSG does not decompose during normal food processing or cooking but in acidic conditions (pH 2.2-2.4) and at high temperatures it is partially dehydrated and converted into 5-pyrrolidone-2-carboxylate (Yamaguchi and Ninomiya 1998). The chemical structure of MSG is shown in Figure 2 below.

**Figure 2: Chemical structure of MSG**



MSG is produced today through fermentation processes using molasses from sugar cane or sugar beet, as well as starch hydrolysates from corn, tapioca etc. Prior to the development of the fermentation process, MSG was produced by hydrolysis of natural proteins, such as wheat gluten and defatted soybean flakes.

MSG is a taste active chemical and is said to impart a unique taste. The characteristic taste of MSG is a function of its stereochemical structure with the D-isomer having no characteristic taste. The MSG taste is readily identified in Asian cultures as being distinct from the four basic tastes (sweet, sour, salty, bitter) and has been called *unami*. Roughly translated, unami means “savoury deliciousness”. Western cultures have had difficulty in describing this taste and thus have not identified it as unique. More recently however unami has gained widespread acceptance as a fifth basic taste (Yamaguchi and Ninomiya 2000).

The optimal palatability concentration for MSG is between 0.2 – 0.8% and its use tends to be self-limiting as over-use decreases palatability. The largest palatable dose for humans is about 60mg/kg body weight (Walker and Lupien 2000).

## 5. SOURCES

### 5.1 Occurrence

As an abundant amino acid, glutamate is found in a virtually all foods, including meat, fish, poultry, breast milk and vegetables. In general, protein-rich foods such as breast milk, cheese and meat, contain large amounts of bound glutamate, while most vegetables contain relatively low amounts. However, despite their lower protein contents, vegetables tend to contain proportionally higher levels of free glutamate, especially peas, tomatoes, and potatoes. The typical glutamate content of various foods is given in Table 1. The free glutamate content of other foods such as traditional seasonings, packaged foods and restaurant food is presented in Table 2.

### 5.2 Estimated intakes

There is no data available on the average consumption of MSG for Australian or New Zealand consumers. Data from the United Kingdom indicates an average intake of 590mg/day, with extreme users (97.5<sup>th</sup> percentile consumers) consuming 2330mg/day (Rhodes *et al* 1991). In a highly seasoned restaurant meal, however, intakes as high as 5000mg or more may be possible (Yang *et al* 1997).

**Table 1: Naturally occurring glutamate in various foods**

| <b>Food</b>          | <b>Bound glutamate<br/>(mg/100g)</b> | <b>Free glutamate<br/>(mg/100g)</b> |
|----------------------|--------------------------------------|-------------------------------------|
| Milk/dairy products: |                                      |                                     |
| Cow's milk           | 819                                  | 2                                   |
| Human milk           | 229                                  | 22                                  |
| Parmesan cheese      | 9847                                 | 1200                                |
| Poultry products:    |                                      |                                     |
| Eggs                 | 1583                                 | 23                                  |
| Chicken              | 3309                                 | 44                                  |
| Duck                 | 3636                                 | 69                                  |
| Meat:                |                                      |                                     |
| Beef                 | 2846                                 | 33                                  |
| Pork                 | 2325                                 | 23                                  |
| Fish:                |                                      |                                     |
| Cod                  | 2101                                 | 9                                   |
| Mackerel             | 2382                                 | 36                                  |
| Salmon               | 2216                                 | 20                                  |
| Vegetables:          |                                      |                                     |
| Peas                 | 5583                                 | 200                                 |
| Corn                 | 1765                                 | 130                                 |
| Carrots              | 218                                  | 33                                  |
| Spinach              | 289                                  | 39                                  |
| Tomatoes             | 238                                  | 140                                 |
| Potato               | 280                                  | 180                                 |

*Source:* Yamaguchi and Ninomiya 1998

**Table 2: Free glutamate content of traditional seasonings, various packaged foods and restaurant meals**

| <b>Food type</b>          | <b>Free glutamate content<br/>(mg/100g)</b> |
|---------------------------|---|
| Concentrated extracts:    |   |
| Vegemite                  | 1431  |
| Marmite                   | 1960  |
| Oyster sauce              | 900   |
| Soy sauce:                |   |
| China                     | 926   |
| Japan                     | 782   |
| Korea                     | 1264  |
| Phillippines              | 412   |
| Fish sauce:               |   |
| Nam-pla                   | 950   |
| Nuoc-mam                  | 950   |
| Ishiru                    | 1383  |
| Bakasang                  | 727   |
| Condensed soups           | 0 – 480                                     |
| Sauces, mixes, seasonings | 20 – 1900                                   |
| Chinese restaurant meals  | <10 – 1500                                  |
| Italian restaurant meals  | 10 – 230                                    |
| Western restaurant meals  | <10 – 710                                   |

*Source:* Nicholas and Jones (1991), Yoshida (1998)

## 6. KINETICS AND METABOLISM

### 6.1 The role of glutamate in metabolism

Glutamate performs a myriad of essential roles in intermediary metabolism and is present in large amounts in the organs and tissues of the body. The daily turnover of glutamate in the adult human has been estimated as 4800mg (Munro 1979). Some of the important metabolic roles of glutamate include:

- A substrate for protein synthesis – as one of the most abundant amino acids present in nature, comprising between 10 – 40% by weight of most proteins, L-glutamic acid is an essential substrate for protein synthesis. Glutamic acid possesses physical and chemical characteristics which make it a principal contributor to the secondary structure of proteins, namely the  $\alpha$ -helices (Young and Ajami 2000);
- A transamination partner with  $\alpha$ -ketoglutarate – L-glutamate is synthesised from ammonia and  $\alpha$ -ketoglutarate (an intermediate of the citric acid cycle) in a reaction catalysed by L-glutamate dehydrogenase. This reaction is of fundamental importance in the biosynthesis of all amino acids, since glutamate is the amino group donor in the biosynthesis of other amino acids through transamination reactions (Lehninger 1982);
- A precursor of glutamine – glutamine is formed from glutamate by the action of glutamine synthetase. This is also an important central reaction in amino acid metabolism since it is the main pathway for converting free ammonia into glutamine for transport in the blood. Glutamate and glutamine are thus key links between carbon and nitrogen metabolism in general and between the carbon metabolism of carbohydrate and protein in particular (Reeds *et al* 2000);
- A substrate for glutathione production – glutathione, a tripeptide composed of glutamic acid, cysteine and glycine, is present in all animal cells and serves as a reductant of toxic peroxides by the action of glutathione peroxidase. Glutathione is also postulated to function in the transport of amino acids across cell membranes (Lehninger 1982);
- A precursor of N-acetylglutamate – an essential allosteric activator of carbamyl phosphate synthetase I, a key regulatory enzyme in the urea cycle, ensuring that the rate of urea synthesis is in accord with rates of amino acid deamination (Brosnan 2000);
- An important neurotransmitter – glutamate is the major excitatory transmitter within the brain, mediating fast synaptic transmission and is active in perhaps one third of central nervous system synapses (Watkins and Evans 1981). Glutamate is also a precursor to another neurotransmitter GABA;
- An important energy source for some tissues (mucosa) – intestinal tissues are responsible for significant metabolism of dietary glutamate, where it serves as a significant energy yielding substrate (Young and Ajami 2000). A net effect of the extensive intestinal metabolism of dietary glutamate is a relatively stable plasma glutamate concentration throughout fasting and fed periods.

## 6.2 Kinetics and metabolism of dietary glutamate

Humans are exposed to dietary glutamate from two main sources – either from the digestion of ingested dietary protein, or from the ingestion of foods that contain significant amounts of free glutamate (either naturally present, or added in the form of MSG/hydrolysed protein).

Glutamate is absorbed from the gut by an active transport system specific for amino acids. This process is saturable, can be competitively inhibited and is dependent on sodium ion concentration (Schultz *et al* 1970). Glutamic acid in dietary protein is digested to free amino acids and small peptides, both of which are absorbed into mucosal cells where peptides are hydrolysed to free amino acids and some of the glutamate is metabolised. Excess glutamate appears in the portal blood, where it is metabolised by the liver.

A number of early studies with dogs (Neame and Wiseman 1958), and later, studies conducted in rats (Windmueller 1982, Windmueller & Spaeth 1974, 1975), demonstrated that the vast majority of dietary glutamate is metabolised by the gastrointestinal tract. In fact, very little dietary glutamate enters either the systemic or the portal blood supply (Young and Ajami *et al* 2000), indicating it is almost exclusively utilised by the intestinal tissues.

The process of dietary glutamate utilisation by the intestinal tract has recently been extensively studied using enteral infusions of [<sup>13</sup>C<sub>5</sub>] glutamate in rapidly growing piglets consuming diets based on whole-milk proteins (Reeds *et al* 1996, 1997, 2000). The results showed that 95% of dietary glutamate presented to the mucosa was metabolised in first pass and that of this, 50% appeared as portal CO<sub>2</sub>, with lesser amounts as lactate and alanine. This indicates that glutamate is the single largest contributor to intestinal energy generation. The studies also indicated that about 10% of dietary glutamate is incorporated into mucosal protein synthesis, with the remainder being used for the synthesis of proline, arginine and glutathione. In fact, all three substances – proline, arginine and glutathione – are derived almost exclusively from dietary glutamate, rather than the vast *in vivo* pool of glutamate.

As a consequence of the rapid metabolism of glutamate in intestinal mucosal cells, with any excess glutamate being metabolised by the liver, systemic plasma levels are typically low, even after ingestion of large amounts of dietary protein (Munro 1979, Meister 1979). Human plasma is reported to contain between 4.4 – 8.8 mg/L of free glutamate (Pulce *et al* 1992).

Studies on the effects of food on glutamate absorption and plasma levels have been done in mice, pigs and monkeys as well as humans. When infant mice were given MSG with infant formula or when adults were given MSG with consommé by gastric intubation, peak plasma glutamate levels were markedly lower than when the same dose was given in water, with the time to reach peak levels being longer (Ohara *et al* 1977). Similar effects of food on glutamate absorption and plasma levels have been observed in humans. Only slight rises in plasma glutamate have been observed following ingestion of a dose of 150 mg/kg bw to adults with a meal, with human infants, including premature babies, also demonstrating the same capacity to metabolise similar doses given in infant formula (Tung and Tung 1980). Human plasma glutamate levels were much lower when large doses of MSG were ingested with meals compared to ingestion in water. In general, foods providing metabolisable carbohydrate significantly attenuate peak plasma glutamate levels at doses up to 150mg/kg body weight (Bizzi *et al* 1977, Stegink *et al* 1979a, 1979b, 1982, 1983a, 1983b, 1983c, 1985, 1986).

In reviewing all the evidence in relation to the effect of MSG ingestion on plasma glutamate levels, the FASEB Expert Panel concluded that the composition of the dosing vehicle as well as the conditions of administration of the dose can significantly impact on changes in circulating glutamate in response to oral ingestion (Raiten *et al* 1995). Overall, the evidence indicates that the extent of the rise in plasma concentrations of glutamate is affected by a number of factors including the size of the dose (increases with increasing dose); the nature of the dosing vehicle (e.g. water causes greater rise than a mixed meal); the temporal proximity of food consumption (fasted subjects exhibit a greater response than those dosed with a meal); and macronutrient composition of the concurrent food (carbohydrate and mixed meals have an attenuating effect compared with fasting or protein).

Breast milk concentrations of glutamate are quite high and are also influenced only modestly by the ingestion of MSG (Pitkin *et al* 1979, Stegink *et al* 1972). Of the twenty free amino acids in human breast milk, glutamate is the most abundant, accounting for >50% of the total free amino acid content (Rassin *et al* 1978). Up to 540mg glutamate/L has been found in human milk, whereas cow's milk contains 10-20mg/L (Ninomiya 1998).

The placenta is considered virtually impermeable to glutamate (Battaglia 2000). Studies with both sheep and humans have shown the placenta removes glutamate from foetal circulation, while concurrently supplying glutamine into the foetal circulation in very large amounts (Lemons *et al* 1976, Hayashi *et al* 1978).

Although glutamate is an important neurotransmitter in the brain, the blood brain barrier effectively excludes passive influx of plasma glutamate. In guinea pigs, rats and mice, brain glutamate levels remained unchanged after administration of large oral doses of MSG which resulted in plasma levels increasing up to 18-fold (Peng *et al* 1973, Liebschultz *et al* 1977, Caccia *et al* 1982, Airoldi *et al* 1979, Bizzi *et al* 1977). Brain glutamate increased significantly only when plasma levels were about 20 times basal values following an oral dose of 2g MSG/kg body weight (Bizzi *et al* 1977). The majority of the glutamate used by the brain is derived from local synthesis from glutamine and TCA cycle intermediates and a considerable fraction is also derived from the recycling of brain protein (Smith 2000).

## **7. REVIEW OF THE SAFETY OF MSG**

### **7.1 Previous considerations**

#### *7.1.1 JECFA safety evaluations*

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has undertaken two evaluations of the safety of MSG. The first of these was conducted in 1971 – 1974, and the second was conducted in 1987. This review will consider only the most recent evaluation (JECFA 1988).

JECFA examined acute, subchronic, and chronic toxicity studies in rats, mice and dogs, together with studies on reproductive toxicity and teratology. Glutamate was found to have a very low acute oral toxicity. The LD<sub>50</sub> for rats and mice is about 15,000 and 18,000mg/kg body weight, respectively. Subchronic studies as well as chronic studies of up to two years duration in mice and rats, including a reproductive phase, did not reveal any specific adverse effects at dietary levels of up to 4%. A two-year study in dogs at dietary levels of 10% also did not reveal any effects on weight gain, organ weights, clinical indices, mortality or general

behaviour. Reproduction and teratology studies using the oral route of administration did not reveal any adverse effects, even at high doses.

The JECFA evaluation also addressed two other issues. These were (i) potential neurotoxicity, especially to the infant, and (ii) the putative role of MSG in CRS.

#### (i) Potential neurotoxicity

Examination of potential neurotoxicity was a major component of the safety evaluation, with reports from 59 separate studies in mice, rats, hamsters, dogs, rabbits, guinea pigs, duck and primates being considered. This issue was given a large amount of attention because of reports that lesions (focal necrosis) in the hypothalamus were observed reproducibly in rodents and rabbits after intravenous or subcutaneous administration of glutamate or after very high bolus doses by gavage. The neural lesions were observed within hours of administration and the mouse appeared to be the most sensitive species. Notably, most of the studies with primates were negative with regard to hypothalamic lesions.

The oral gavage doses required to produce the lesions were of the order of 1000mg/kg body weight as a bolus dose. The threshold blood levels associated with neuronal damage in the mouse are 100 – 300µmol/dL in neonates rising to 380µmol/dL in weanlings and > 630µmol/dL in adult mice. In humans, plasma levels of this magnitude have not been recorded even after bolus doses of 150mg/kg body weight (about 10g for an adult). The oral ED<sub>50</sub> for production of hypothalamic lesions in the neonatal mouse is about 500mg/kg body weight by gavage, whereas the largest palatable dose for humans is about 60mg/kg body weight with higher doses causing nausea. It was thus concluded that voluntary ingestion would not exceed this level.

#### (ii) Putative role of MSG in CRS

In consideration of idiosyncratic intolerance to MSG, most of the reports of reactions were found to be anecdotal, however a number of studies that had been undertaken with human volunteers were reviewed. Examination of these studies failed to demonstrate that MSG was the causal agent in provoking the full range of symptoms associated with CRS. It was therefore concluded that controlled double-blind crossover trials have failed to demonstrate an unequivocal relationship between CRS and consumption of MSG and also that MSG has not been shown to provoke bronchoconstriction in asthmatics.

It was concluded that the total dietary intake of glutamates arising from their use at levels necessary to achieve the desired technological effects and from their acceptable background in food do not represent a hazard to health. For that reason, the establishment of an Acceptable Daily Intake (ADI) was not considered necessary, and an “ADI not specified” was allocated to L-glutamic acid and the monosodium, potassium, calcium and ammonium salts.

It was also noted that the available evidence did not indicate that pregnant women and infants were at any greater risk in relation to exposure to glutamate than other members of the general population.

### 7.1.2 FASEB review

In response to continuing reports of adverse reactions to MSG and other glutamate-containing ingredients, the United States FDA contracted the FASEB to conduct a review of reported adverse reactions to MSG. The full report of the study was released in 1995 (FASEB 1995).

The report concluded that, although there was no scientifically verifiable evidence of adverse effects in most individuals exposed to high levels of MSG, there is sufficient documentary evidence to indicate there is a subgroup of presumably healthy individuals that responds, generally within 1 hour of exposure, with manifestations of the MSG symptom complex when exposed to an oral (bolus) dose of MSG of 3g in the absence of food. The report also stated available data suggest strongly that ingestion of MSG in capsule form on an empty stomach is more often associated with occurrence of adverse reactions, than is ingestion with food.

In relation to asthma, the report concluded that the only scientifically verified adverse effects of MSG in humans that have been reported are initiations of bronchospasms in a subgroup of people with severe unstable asthma. The report stated that there appears to be a small subset of people with severe unstable asthma who respond to doses of 1.5-2.5g of MSG given in a low energy challenge vehicle e.g. a capsule, in the absence of a meal containing protein and carbohydrate.

The report recommended that to confirm the MSG symptom complex, multiple double blind, placebo-controlled challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo. The Expert Panel suggested that five separated challenges would be necessary to conclude that subjective symptoms (e.g. headache, chest tightness, numbness, etc) are secondary to MSG in highly suggestible individuals, whereas only three would be necessary for those individuals not considered highly suggestible. In individuals with objective findings (e.g. bronchospasm, vomiting etc), a single double blind challenge was considered sufficient. The Expert Panel recognised that the use of capsules ensures the greatest control over dose and blinding, however, they also noted that the use of capsules obviates the potential role of the oral cavity and oesophagus 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 results of a study by Stegink *et al* (1979b) where administration of MSG in capsules resulted in a 3 to 4-fold attenuation of peak plasma glutamate levels.

## 7.2 Review of scientific literature

### 7.2.1 MSG as a trigger factor for asthmatic attacks

Asthma is a relatively common disorder that can have serious consequences for the sufferer, including death and therefore is a significant public health problem. In Australia, asthma affects between 22 – 24% of children and 13% of adults (Robertson *et al* 1991, Abramson *et al* 1992), although the prevalence of food-induced asthma is somewhat lower and has been estimated to affect 0.24% of adults and 11% of children (Woods 1997).

The causes of asthma are complicated and can vary from patient to patient, however inflammation of the bronchial airways is the characteristic finding in the majority of asthmatic patients (O'Byrne 1997). Multiple trigger factors can activate asthma attacks in asthmatic patients already afflicted with inflammation of the bronchial tree and these factors will vary from patient to patient but are important because identification and avoidance of such trigger factors can substantially improve the quality of life of asthmatic individuals (Stevenson 2000).

A possible association between MSG and the triggering of asthma attacks was first suggested in 1981 (Allen and Baker 1981). Since then a small number of studies have been conducted to investigate this association but have produced conflicting results. Five of these studies did not demonstrate MSG-induced asthma attacks (Schwartzstein *et al* 1987, Germano *et al* 1991, Altman *et al* 1994, Woods *et al* 1998, Woessner *et al* 1999), whereas three have concluded that some people with asthma do get MSG-induced attacks (Allen *et al* 1987, Moneret-Vautrin 1987, Hodge *et al* 1996).

The study by Allen *et al* (1987) recruited 32 subjects, including two subjects who were the subject of the original case report (Allen and Baker 1981). Of the 32 who were studied, 14 gave a history of asthmatic attacks after consuming a Chinese meal, with the other 18 having unstable asthma and a reported sensitivity to other chemicals (aspirin, benzoic acid, tartrazine, and sulphites). All subjects underwent single blind oral challenges with MSG (0.5, 1.5, and 2.5g in capsules) followed by peak expiratory flow (PEF) measurements for 12 hours after each challenge. PEF measures how fast a subject can blow air out of their lungs. A positive response was defined as a 20% decline in PEF. Some of the challenges were conducted in the morning and some in the afternoon. Subjects followed a specific exclusion diet (specific details not provided) beginning 5 days before challenges. Some asthma medications (theophylline) were ceased prior to the challenges. One subject was reported to react to all three doses, another to the 1.5g dose only and 12 to 2.5g only. Thirteen subjects were thus concluded to have experienced an MSG-induced asthma attack.

This study has been criticised for a variety of reasons, including: a lack of blinding of observers, that is, the study used a single blind, rather than a double blind protocol; inadequate procedures for establishing baseline and control data; the use of effort-dependent PEF, which can be influenced by subject bias; the cessation of anti-inflammatory and bronchodilator medications just prior to the challenge sequence making it hard to judge whether an asthmatic attack is due to the challenge substance, rather than simply a result of the withdrawal of therapy; and no measurements of immunologic inflammatory markers or changes in airway responsiveness were taken.

The study by Moneret-Vautrin (1987) used a single blind, placebo-controlled challenge protocol to study 30 asthmatic patients undergoing oral challenges with 2.5g MSG. The authors did not report the MSG history of the test subjects. No specific diet control was exercised during the course of the study. Declines in PEF were used as an indicator of a positive response, with PEF measurements being taken hourly for 12 hours after challenge. All treatment with corticoids was ceased 21 days prior to challenge, and treatment with theophylline was ceased three days prior to challenge. Two out of the 30 subjects were reported as having a positive reaction to MSG 6-10 hours after challenge.

This study has been criticised for the following reasons: the two positive reacting subjects were not rechallenged in a double blind protocol; both subjects exhibited wandering baseline

PEF values during their placebo challenges, therefore differences between placebo and MSG PEF measurements would have been difficult to detect; and bronchodilator therapy was discontinued three days before challenge, which could have led to airway instability, particularly as 7 of the 30 subjects tested were reportedly allergic to house dust.

Schwartzstein *et al* (1987) studied a total of 12 mildly asthmatic subjects using a double blind, placebo controlled protocol. The study was an outpatient study so the authors were not able to supervise diets with respect to MSG content. Six of the subjects did not require asthma medication and the other six were able to discontinue their medication for 12 hours without any change in lung function measurement. One subject had a positive history of asthmatic attacks following ingestion of a Chinese meal. Challenges were done with 1.5g MSG and used forced expiratory volume in one-second (FEV<sub>1</sub>) measurements plus the occurrence of asthma symptoms as indicators of whether an asthma attack had occurred. FEV<sub>1</sub> is an effort-independent measurement, which measures how much air can be blown out in one second of a forced manoeuvre. FEV<sub>1</sub> measurements were taken hourly for 4 hours after challenges with placebo or MSG. No subjects in the study were reported as having an MSG-induced asthma attack.

The criticisms of this study include: only one subject with a positive MSG history was recruited; the total study population was considered too small; the largest challenge dose used may have been too low (1.5g, compared to the 2.5g used in previous studies); lack of dietary supervision; and lung function measurements were only performed for up to 4 hours after challenge, compared to 12 hours for previous studies.

Germano *et al* (1991) studied 13 non-asthmatics and 30 asthmatics using a single blind oral challenge protocol with MSG administered in capsules containing increasing doses at 30-minute intervals for a total dose of 7.6g. Two of the subjects had a positive history of reacting to food containing MSG. Subjects were maintained on their asthma medications throughout the study. The study was an outpatient study and it is not known if any diet control was used. A positive reaction was defined as >20% fall in FEV<sub>1</sub> following MSG challenge. One of the subjects exhibited a significant drop in FEV<sub>1</sub> following MSG challenge. This subject was rechallenged using a double blind placebo controlled protocol with no change in FEV<sub>1</sub> being observed.

This study has been criticised for the following reasons: only 2 of the subjects used in the study had a history of bronchoconstriction after a Chinese restaurant meal; and the study was only reported in abstract form and therefore few experimental details are available.

Altman *et al* (1994) recruited 47 subjects for a study using a double blind placebo controlled protocol, although only eight of these were reported as having asthma. It is unknown whether the subjects were subject to any diet control during the course of the study or whether any changes were made to the asthma medications of any of the asthmatic subjects. The study was conducted in two phases. In phase I, three doses of MSG (1.5g, 3.0g, 6.0g) and three placebo doses in a liquid vehicle were administered after an overnight fast in random order on different days. The subject recorded symptoms in a 24-hour diet/symptom diary. Phase II repeated the challenge using self-administered capsules at home. Eleven out of the 26 people who completed Phase I reported symptoms after both MSG and placebo, and two after placebo only. Six reported no symptoms after any dose and seven after MSG only. In two of these cases, symptoms were reported at 3g but not at 6g. Ten out of the 16 subjects, who completed Phase II, reported no symptoms after any dose. Symptoms that were reported

were of short duration and did not affect daily activities. None of the subjects that had asthma were reported as having any asthmatic symptoms following MSG challenge.

This study has been criticised for the following reasons: the study was reported in abstract form only and therefore contains very little experimental detail; only a small number of asthmatic subjects were used and it is not known if any of these had a history of reacting to MSG; self-reported asthma symptoms were used rather than objective measures of asthma status; the study was funded in part by the International Glutamate Technical Committee and therefore has been considered by some to not be independent.

The Hodge *et al* (1996) study was designed to compare two different methods of testing for asthma reactions, however one of the substances used was MSG. A total of 11 asthmatic subjects were tested using a double blind placebo control challenge protocol. One of the two methods being tested required subjects to comply with a specific diet. All subjects continued to use their usual asthma medications. FEV<sub>1</sub> measurements were taken for two hours following each challenge. Graded doses from 1.2g up to 4.8g MSG were administered in capsule form. One of the subjects was reported as having an MSG-induced asthma attack.

The main criticism of this study is that its main aim was not to explore MSG-induced asthma therefore it is difficult to fully interpret the MSG results.

Woods *et al* (1998) undertook an outpatient study using 12 subjects with clinically documented asthma and a perception of MSG-induced asthma. Usual bronchodilator medications were continued and subjects complied with strict diet avoidance of MSG during the study. A randomised, double blind, placebo-controlled challenge protocol was used with subjects being administered with 1g and 5g MSG in capsule form (placebo used was 5g lactose). After challenge, subjects were monitored using FEV<sub>1</sub> measurements for 8 hours and then sent home for self-monitoring for the next 4 hours using a PEF monitor. The study also measured bronchial hyper responsiveness and soluble inflammatory markers. No immediate or late asthmatic reactions were apparent in any of the subjects after oral challenge with 5g MSG.

This study has been criticised for the following reasons: as an outpatient study, the reliability of the dietary program could not be supervised directly; during the last 4 hours of the post-challenge observation period, patients were at home performing unsupervised PEF measurements; and the study only looked at a small number of subjects.

Woessner *et al* (1999) recruited 100 subjects, 30 of whom had a history of Chinese restaurant asthma attacks and the remaining 70 subjects had suspected aspirin-sensitive asthma and did not have a perceived sensitivity to MSG. Subjects were admitted to an in-patient facility on the day prior to commencement of the challenges and remained in the facility for the duration of the study. The study used a single blind, placebo-controlled challenge protocol. Subjects followed a "low" MSG diet throughout the study. FEV<sub>1</sub> baseline measurements were taken prior to commencement of the study. Placebo challenges (2.5g sucrose capsules) were given in the morning and afternoon on the first day of the study followed by hourly FEV<sub>1</sub> measurements for a total of 12 hours. This was followed on the second day with MSG challenges (2.5g capsules) if during the placebo challenge, FEV<sub>1</sub> values varied by less than 10% over the course of observation. Again, hourly FEV<sub>1</sub> measurements were taken for a total of 12 hours. The criteria used for a presumptive MSG-induced asthma attack was a 20% decline in FEV<sub>1</sub> values from baseline with or without accompanying symptoms. If there was

a 20% drop in FEV<sub>1</sub> value, serum tryptase levels were determined and the subject underwent two double blind placebo-controlled MSG challenges on days 3 and 4. Only 1 of the 30 subjects with a history of asthma attacks following a Chinese restaurant meal experienced a 20% decline in FEV<sub>1</sub> values during the single blind screening challenge with MSG. The subject was without asthma symptoms throughout the MSG challenge and serum tryptase levels were normal. Subsequent double blind placebo-controlled MSG challenges in replicate were negative, with the post-MSG changes in FEV<sub>1</sub> values of less than 1%. No other subjects had a significant fall in FEV<sub>1</sub> value or the development of asthma symptoms during the MSG challenge. The mean change in FEV<sub>1</sub> with MSG challenge was no different from that of placebo challenge. For 15 of the 30 subjects who had previously perceived themselves to be MSG sensitive, causes other than MSG were identified as the trigger factor for their asthma attacks following a Chinese restaurant meal.

The criticisms of this study are that it was partly funded by the International Glutamate Technical Committee and that details of the “low” MSG diet were not reported.

### Discussion

Virtually all of the studies reviewed contained design flaws of some description. The most consistent problem with studies is the continuation versus discontinuation of asthma medication. While the continuation of medication could potentially prevent the triggering of an MSG-induced asthmatic attack, the discontinuation of the medication could result in the occurrence of a spontaneous asthmatic attack, which could incorrectly be attributed to MSG. Notwithstanding this, the FASEB review found 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” (Raiten *et al* 1995). The FASEB report therefore concluded that there appears to be a small subset of people with severe unstable asthma who respond to doses of 1.5 – 2.5g MSG given in capsule form without food. Others have suggested however that the selection of subjects with unstable asthma, combined with the discontinuation of their daily asthma medication, resulted in the subjects in both the Allen *et al* (1987) and Moneret-Vautrin (1987) study developing nothing other than spontaneous asthma as would be expected in patients deprived of their essential maintenance medications (Stevenson 2000).

It is difficult to reconcile the results of the Allen *et al* (1987) and Moneret-Vautrin (1987) studies with those of the Woods *et al* (1998) and Woessner *et al* (1999) studies, both of which failed to demonstrate MSG-induced asthma attacks and which were undertaken after the FASEB review. These two studies, particularly that of Woessner *et al* (1999), have addressed many of the design flaws of earlier studies and also clearly demonstrate the importance of double blind challenges in verifying a positive reaction. While both the Germano *et al* (1991) and Woessner *et al* (1999) studies identified individuals exhibiting a positive reaction to MSG on single blind challenge, subsequent double blind challenge protocols failed to reproduce the positive reactions. This type of follow-up was not done with the earlier studies of Allen *et al* (1987) and Moneret-Vautrin (1987).

### Conclusion

On balance, and taking into account the design and methodological flaws evident in many of the studies as well as the conflicting results that have been produced, the evidence for MSG-induced asthma attacks is inconclusive. More recent studies suggest MSG may not be a

significant trigger factor. Further challenge studies, conducted along the lines of the Woessner *et al* (1999) study, would be useful to help resolve the ongoing debate about whether MSG is a trigger factor for asthmatic attacks.

### 7.2.2 *MSG as the causative agent of CRS*

A number of published case reports, seemingly prompted by the appearance of the first case report of CRS (Kwok 1968), have suggested a causative role for MSG in CRS (Schaumburg 1968, Menken 1968, Beron 1968, Migden 1968, Rath 1968, Rose 1968). Since then a large number of clinical studies have been conducted but have produced conflicting results. Some studies have reported significant increases in symptoms after ingestion of MSG (e.g. Schaumburg *et al* 1969, Rosenblum *et al* 1971, Kenney and Tidball 1972, Gore and Salmon 1980, Yang *et al* 1997), whereas others have not or have been more equivocal (e.g. Zanda *et al* 1973, Kenney 1986, Wilkin 1986, Tarasoff and Kelly 1993, Geha *et al* 2000a).

The first clinical study was conducted by Schaumburg *et al* (1969) who administered MSG in a variety of vehicles such as soup, water, chicken broth and intravenously. Doses ranged from 1 – 12g, and a variety of double, single and unblinded tests were conducted. The study found that intravenous or oral administration of MSG could cause dose-dependent symptoms in nearly all six subjects tested.

Rosenblum *et al* (1971) conducted both single and double blind studies with 99 human volunteers using doses up to 12g MSG in water. Symptoms of light-headedness and tightness in the face appeared significantly more often in the MSG group than in the control but no subjects reported the characteristic triad of CRS symptoms. Measurements of blood pressure, pulse and serum chemistries were not significantly different between reactors and non-reactors.

Kenney and Tidball (1972) used an initial group of 77 subjects who they challenged with 5g MSG in tomato juice to identify MSG-sensitive individuals. Twenty-two of the 25 who reacted to this dose were then challenged with doses ranging from 1 – 4g MSG. A dose-response relationship in the symptoms of stiffness/tightness in the face and neck was observed and a less clearly defined dose-response in the symptoms of tingling, pressure and warmth was also observed. There was a threshold dose of 2 – 3g before any symptoms occurred but at the 1g dose level, a greater number of subjects reported adverse reactions to placebo than to MSG. Plasma glutamate levels were monitored in the subjects and while it was found that the rise in plasma glutamate was significant after ingestion of MSG, there was no significant difference in the level of plasma glutamate between reactors and non-reactors.

Zanda *et al* (1973) administered 3g MSG in a double blind study to 73 healthy subjects. All subjects were evaluated for subjective (e.g. burning sensation, nausea, headache) as well as objective (e.g. pulse rate, arterial blood pressure) changes. No differences in symptomology were observed between groups.

Gore and Salmon (1980) conducted a double-blind study with 55 subjects with no prior history of CRS. Subjects ingested three different doses of MSG (1.5, 3 and 6g) or a placebo in 150ml cold water after an overnight fast. Nine of the subjects reacted to MSG, two reacted to placebo and three reacted to both. Reactions to MSG (abdominal cramps, headache, nausea, and hypersalivation) were statistically more frequent but were not dose-related and were not typical of CRS.

Kenney (1986) used a double blind placebo controlled protocol to challenge six subjects who considered themselves to be MSG sensitive. The MSG was administered in a drink vehicle formulated to mask the taste of MSG. Challenges were done using 6g MSG. Four of the six subjects did not react to either MSG or placebo, and the remaining two reacted to both MSG and placebo. Of the subjects who reacted, one reported tingling of hands and warmth behind the ears after both MSG and placebo and the other subject experienced tightness of the face after ingesting either substance.

Wilkin (1986) undertook a study of flushing in 24 subjects, 18 of who had a history of flushing symptoms after eating Chinese foods. Subjects were challenged with 3 – 18.5g MSG and none of the subjects reported flushing symptoms.

Tarasoff and Kelly (1993) undertook a double blind study with 71 healthy subjects using doses of 1.5, 3.0 and 3.15g MSG. The MSG was administered in capsules as well as in specially formulated drinks that masked the taste of MSG. Most of the subjects tested reported no reactions to either placebo or MSG. Of the subjects that did react, the symptoms reported did not occur at a significantly higher rate than those elicited by placebo.

Yang *et al* (1997) conducted a double blind, placebo-controlled challenge study with 61 self-identified MSG-sensitive subjects. Subjects were enrolled in the study on the basis that they experienced, within 3 hours of a meal alleged to have contained MSG, two or more of the symptoms typically associated with CRS. Symptoms identified by subjects prior to the study were designated as index symptoms. All non-index symptoms noted after challenge were designated as other symptoms. All subjects underwent an initial challenge in which they ingested on an empty stomach 5g of MSG (dissolved in 200ml of a strongly citrus tasting beverage, containing sucrose as a sweetening agent) or placebo (same beverage without MSG) in random order on different days. Subjects who responded only to a single test agent then underwent rechallenge in random sequence in a double-blind fashion with placebo and 1.25, 2.5 and 5g MSG. A positive response was defined as the reproduction of  $\geq 2$  of the specific symptoms in a subject, ascertained on pre-challenge interview. Of the 61 subjects who entered the study, 18 responded to neither MSG nor placebo, 6 to both, 15 to placebo and 22 to MSG. The rates of reaction were not statistically significant with a greater than expected rate of reactivity to placebo. More symptoms were reported after ingestion of MSG (104 index, 105 other) than placebo (79 index, 76 other) however the differences were not statistically significant, although a feeling of flushing occurred at a statistically increased frequency after MSG ingestion compared with after placebo. The study demonstrated that the sequence of administration had introduced a bias into the study, with an unbalanced response to placebo being recorded. Fourteen of the 31 subjects who received placebo first responded positively compared with only 7 of 30 when placebo was administered second. In contrast, identical numbers responded to MSG administered either first or second. The rechallenge phase maintained the double-blind state. Of the original 37 uni-responders, only one declined rechallenge, which was done in random sequence with placebo and MSG at doses of 1.25, 2.5 and 5g. Analysis of rechallenge data revealed no effect of sequence of administration on the responses. Results showed that response to placebo was still a confounding part of the data, however analysis of the response found that frequency and severity of responses increased with increasing doses of MSG. Rechallenge also revealed an apparent threshold dose for reactivity of 2.5g MSG. Headache, muscle tightness, general weakness and flushing occurred more frequently after MSG than placebo ingestion. The authors concluded that these results support the conclusions of the FASEB review and

suggest that sensitivity to MSG exists, at least in the clinical setting described and is characterised by unpleasant reactions such as numbness, tingling, headache, muscle tightness, general weakness, and flushing.

Geha *et al* (2000a) conducted a multi-centre, double blind placebo-controlled challenge study of 130 subjects to analyse the response of subjects who report symptoms from ingesting MSG. This study was conducted according to the criteria established by FASEB for the confirmation of MSG symptom complex, that is, three double blind, placebo-controlled challenges on separate occasions must reproduce symptoms with the ingestion of MSG and produce no response with placebo (Raiten *et al* 1995). In 3 of the 4 protocols, MSG was administered without food in a 200ml citrus-flavoured beverage. A positive response was scored if the subject reported 2 or more symptoms from a list of 10 symptoms (general weakness, muscle tightness, muscle twitching, flushing, sweating, burning sensation, headache-migraine, chest pain, palpitations, numbness-tingling) reported to occur after ingestion of MSG-containing foods within 2 hours. In protocol A, 130 self-selected reportedly MSG-reactive volunteers were challenged with 5g of MSG and with placebo on separate days (days 1 and 2). Of the 86 subjects who reacted to MSG, placebo, or both in protocol A, 69 completed protocol B to determine whether the response was consistent and dose dependent. To further examine the consistency and reproducibility of reactions to MSG, 12 of the 19 subjects who responded to 5g of MSG but not to placebo in both protocols A and B were given, in protocol C, 2 challenges, each consisting of 5g of MSG versus placebo.

Of 130 subjects in protocol A, 50 (38.5%) responded to MSG only, 17 (13.1%) responded to placebo only, and 19 (14.6%) responded to both. Challenge with increasing doses of MSG in protocol B was associated with increased response rates. Only half ( $n = 19$ ) of 37 subjects who reacted to 5g of MSG but not to placebo in protocol A reacted similarly in protocol B, suggesting inconsistency in the response. Two of the 19 subjects responded in both challenges to MSG but not placebo in protocol C; however their symptoms were not reproducible in protocols A through C. These two subjects were challenged in protocol D 3 times with placebo and 3 times with 5g of MSG in the presence of food. Both responded to only one of the MSG challenges in protocol D and in neither case were the symptoms the same as those reported in the previous protocols.

The authors concluded that large doses of MSG given without food may elicit more symptoms than a placebo in individuals who believe they react adversely to MSG. However, they noted that neither persistent nor serious effects from MSG ingestion were observed, and frequency of responses was low. Moreover, the responses reported were inconsistent and were not reproducible, particularly when MSG was given with food.

## Discussion

One of the difficulties in studying adverse reactions to MSG is that the majority of reported symptoms (e.g. headache, numbness, tingling, muscle tightness) are subjective and there are no objective clinical measures associated with the wide variety of symptoms described. Because of this a placebo response would be expected to play a significant role in many of the reactions observed and this has made it hard to interpret the significance of any responses to MSG. Furthermore, many of the studies that have attempted to establish if a link exists between MSG and CRS have suffered from a number of methodological flaws (Tarasoff and Kelly 1993, Taliaferro 1995, Yang *et al* 1997, Samuels 1999, Geha *et al* 2000a). Many of the previous studies were unblinded or single blinded, or if they were double blinded did not take

any steps to disguise the taste of MSG. Often too few subjects were used and in many studies the results are confounded by symptom suggestion, where subjects have been notified of possible symptoms prior to testing. Other problems relate to the use of subjects that have no previous history of CRS or sensitivity to MSG, and use of inappropriate placebos.

While these studies have largely failed to demonstrate a causal association between MSG and CRS, what they have demonstrated is that symptoms resembling those of CRS may be provoked in a clinical setting in some individuals by the administration of large doses of MSG without food.

This was largely the conclusion drawn by the FASEB Expert Panel, who although considered that causality had not been established, did consider there was sufficient evidence to support the existence of a subgroup of the general population of otherwise healthy individuals who may respond to large doses ( $\geq 3$ g) of MSG under specific conditions (i.e., an oral bolus dose in the absence of food) (Raiten *et al* 1995). The reactions were categorised by the Expert Panel as “acute, temporary and self-limited” and the mechanism of these reactions are unknown.

Only two further studies (Yang *et al* 1997, Geha *et al* 2000a) have been conducted since the FASEB review. Both these studies have been arguably better conducted than many of the previous studies. Both studies were double-blinded, used a liquid rather than capsule vehicle and controlled for the taste of MSG, used subjects self-identified as MSG sensitive, used an appropriate placebo, and, in addition, the Geha *et al* (2000a) study used three separate double blind challenges as recommended by the FASEB Expert Panel. Both studies indicate that MSG, given in relatively large doses without food, will elicit a higher frequency of symptoms than placebo in certain individuals who consider themselves sensitive to MSG. These results appear to be consistent with the conclusions drawn by the FASEB review. The results of the Geha *et al* (2000a) study also suggest that in the presence of food the frequency of response will be reduced, as would be expected from pharmacokinetic studies with MSG.

An interesting observation that can be made from the various studies conducted to date is that it appears not all individuals who report as MSG-sensitive react to MSG in double blind challenges, suggesting that they may not be sensitive to MSG at all. This highlights the importance of having suspected sensitivities appropriately investigated as many individuals may be unnecessarily avoiding MSG in their diets.

Further studies would be helpful, firstly to ascertain the true prevalence of reactions to MSG in the general population, secondly to investigate how the ingestion of MSG with food is likely to affect any adverse response and thirdly to ascertain the mechanism(s) behind the reactions observed. The elucidation of a physiological mechanism behind CRS is likely to lead to the development of more objective clinical measures for the response and thus make challenge studies less open to residual confounding.

## Conclusion

The evidence suggests that ingestion of large amounts ( $\geq 3$ g) of MSG may be responsible for causing symptoms similar to CRS in a small subset of individuals. These symptoms, although unpleasant, are neither persistent nor serious and appear more likely to occur when MSG is ingested in the absence of food. As MSG would always be consumed in the presence of food, an important question that remains unanswered by the scientific literature is what

effect consumption with food would have on the incidence and severity of symptoms. The pharmacokinetic evidence suggests food, particularly carbohydrate, would have an attenuating affect.

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