The Safety Evaluation of Monosodium Glutamate[1]

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ABSTRACT L-Glutamic acid and its ammonium, calcium, monosodium and potassium salts were evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1988. The Committee noted that intestinal and hepatic metabolism results in elevation of levels in systemic circulation only after extremely high doses given by gavage (>30mg/kg body weight). Ingestion of monosodium glutamate (MSG) was not associated with elevated levels in maternal milk, and glutamate did not readily pass the placental barrier. Human infants metabolized glutamate similarly to adults. Conventional toxicity studies using dietary administration of MSG in several species did not reveal any specific toxic or carcinogenic effects nor were there any adverse outcomes in reproduction and teratology studies. Attention was paid to central nervous system lesions produced in several species after parenteral administration of MSG or as a consequence of very high doses by gavage. Comparative studies indicated that the neonatal mouse was most sensitive to neuronal injury; older animals and other species (including primates) were less so. Blood levels of glutamate associated with lesions of the hypothalamus in the neonatal mouse were not approached in humans even after bolus doses of 10 g MSG in drinking water. Because human studies failed to confirm an involvement of MSG in "Chinese Restaurant Syndrome" or other idiosyncratic intolerance, the JECFA allocated an "acceptable daily intake (ADI) not specified" to glutamic acid and its salts. No additional risk to infants was indicated. The Scientific Committee for Food (SCF) of the European Commission reached a similar evaluation in 1991. The conclusions of a subsequent review by the Federation of American Societies for Experimental Biology (FASEB) and the Federal Drug Administration (FDA) did not discount the existence of a sensitive subpopulation but otherwise concurred with the safety evaluation of JECFA and the SCF. J. Nutr. 130: 1049S–1052S, 2000.

KEY WORDS: • *humans* • *safety* • *food safety* • *food additives* • *monosodium glutamate* • *toxicity*

The Joint FAO/WHO Expert Committee on Food Additives (JECFA)[3] was established in the mid-1950s by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to assess the safety of chemical additives in food on an international basis. Its brief has been broadened subsequently to include contaminants and veterinary drug residues. In the early 1960s, the Codex Alimentarius Commission (CAC), an international intergovernmental body that sets food standards, was established; its primary aims were to protect the health of the consumer and facilitate international trade in food. It was decided that JECFA would provide expert advice to Codex on matters relating to food additives. Additionally, JECFA provides advice directly to FAO and WHO member states, and requests for assessment may come directly from them.

Members of JECFA are independent scientists, drawn mainly from government or academic research institutes, who serve in their individual expert capacity and not as representatives of their governments or institutions. Members are assisted by Temporary Advisers (WHO) or Consultants (FAO), also appointed in their personal capacity. In relation to food additives, the goals are to establish safe levels of intake and to develop specifications for identity and purity.

Through mid-1998, 51 meetings of JECFA have been held. The reports are published in the WHO Technical Report Series and the toxicological evaluations, which form the basis of the safety assessment, are published in the WHO Food Additives Series; specifications are published in the FAO Food and Nutrition Paper Series.

The safety evaluation of monosodium glutamate (MSG) by JECFA was conducted along with the group of related compounds, i.e., L-glutamic acid and its ammonium, calcium, monosodium and monopotassium salts. These substances were first evaluated at the fourteenth and seventeenth meetings in

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[3] Abbreviations used: ADI, acceptable daily intake; CAC, Codex Alimentarius Commission; CNS, central nervous system; FASEB, Federation of American Societies for Experimental Biology; FDA, Food and Drug Administration; JECFA, Joint FAO/WHO Expert Committee on Food Additives; LD_{50}, dose that is lethal to 50% of subjects; MSG, monosodium glutamate; SCF, Scientific Committee for Food.

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1971 and 1974, respectively (FAO/WHO 1971 and1974). At that time, an Acceptable Daily Intake (ADI) of 0–120 mg/kg body weight was allocated, encompassing the L-glutamic acid equivalents of the salts; this was considered additional to the intake from all nonadditive dietary sources. In the absence of human infant data at that time, and in view of the observation that neonatal rodents appeared to be more sensitive than adults to the neurologic effects of high blood levels of glutamate, it was stated that the ADI did not apply to infants <12 wk of age. A more recent and comprehensive safety evaluation was conducted in 1987 (Joint FAO/WHO Expert Committee on Food Additives 1988); the basis of that evaluation will be discussed below. The Scientific Committee for Food of the Commission of the European Communities (SCF) also reviewed the data in 1991 and reached conclusions similar to those of the JECFA (SCF 1991). Subsequently, the Federation of American Societies for Experimental Biology (FASEB) conducted a review of reported adverse reactions to MSG and reported in 1995 (FASEB 1995). This report and the response of U.S. Food and Drug Administration (FDA) will also be mentioned briefly.

The safety evaluation of the JECFA

The JECFA reviewed the then available data on metabolism and pharmacokinetics of MSG, together with relevant experimental toxicologic data and results of studies in humans. The Committee noted that, after ingestion, transamination to alanine occurs during intestinal absorption, leading to the formation of α-ketoglutarate; glutamine, γ-aminobutyrate and glutathione are other quantitatively minor but physiologically important metabolites. Excess glutamate, after deamination, may be utilized in gluconeogenesis. The available data indicated that, under normal conditions, mammals have the metabolic capacity to handle large oral doses although the more readily available nature of free MSG compared with the slow release during protein digestion must be borne in mind. As a consequence of the ready metabolism, concentrations of glutamate in portal blood show only a small rise after administration of MSG unless very large bolus doses are administered by gavage. Further metabolism occurs in the liver, and systemic blood levels rise only when such large bolus doses are given as to overwhelm this hepatic metabolism or if MSG is given by irrelevant parenteral routes. Gavage doses in excess of ~30 mg/kg body weight are required to produce detectable elevations of blood levels, and the same dose of MSG administered in food produces lower peak plasma levels than if administered in aqueous solution. Foods rich in available carbohydrate were most effective in blunting the peak plasma levels. In fact, only slight rises in plasma glutamate were observed after a dose of 150 mg MSG/kg body weight in human adults. Infants, including premature babies, could also metabolize similar doses given in infant formulae (Tung and Tung 1980).

The conventional toxicologic database available for review by the JECFA was very extensive, including acute, subchronic and chronic toxicity studies in rats, mice and dogs, together with studies on reproductive toxicity and teratology.

Glutamate has a very low acute toxicity under normal circumstances; the oral dose that is lethal to 50% of subjects (LD_{50}) in rats and mice is ~15,000–18,000 mg/kg body weight, respectively. Subchronic and chronic toxicity studies of up to 2 y duration in mice and rats, including a reproductive phase, did not reveal any specific adverse effects at dietary levels of up to 4%. A 2-y study in dogs at dietary levels of 10% also did not reveal any effects on weight gain, organ weights, clinical indices, mortality or general behavior. Reproduction and teratology studies using the oral route of administration have been uneventful even when the dams were fed glutamate at high doses, indicating that the fetus and suckling neonate was not exposed to toxic levels from the maternal diet through transplacental transfer. This latter observation is in accord with reports that glutamate levels in fetal blood do not rise in parallel with maternal levels. For example, in rats, although single oral doses of 8000 mg/kg given to pregnant females late in gestation caused plasma levels to rise from 100 to 1650 nmol/mL, no significant increases were observed in plasma levels of the fetuses. Similarly, in pregnant rhesus monkeys, the infusion of 1 g MSG/h led to a 10- to 20-fold increase in maternal plasma levels but no changes in fetal plasma levels. In rats and monkeys, oral ingestion of these large doses of MSG did not lead to detectable increases in glutamic acid levels in maternal milk.

The toxicologic picture arising from conventional studies therefore seemed quite reassuring. Nevertheless, two other major issues had to be addressed in relation to high intakes of MSG, namely, *1*) potential neurotoxicity, especially to the infant, and *2*) the putative role of MSG in "Chinese Restaurant Syndrome" (e.g., flushing, tightness of the chest or difficulty in breathing) after consumption of Chinese foods.

In relation to the neurotoxicity, the Committee considered reports of 59 studies conducted in mice (40), rats (12), hamsters, guinea pigs, chicks, ducks, rabbits, dogs and primates (21). Lesions (focal necrosis) in the arcuate nucleus of the hypothalamus were observed reproducibly in rodents and rabbits after parenteral administration of glutamate (intravenously or subcutaneously) or after very high bolus doses by gavage. These neural lesions were observable within hours of administration. The mouse appeared to be the most sensitive species, and there were significant differences with age and maturity; the neonate was particularly sensitive. Notably, most of the studies in primates were negative with regard to hypothalamic lesions; these were reported in only 2 of 21 studies, both conducted in the same laboratory (Olney and Sharpe 1969, Olney et al. 1972)

The oral gavage doses required to produce the lesions were on the order of 1000 mg/kg body weight as a bolus dose, and in only one study were lesions seen after "voluntary" ingestion of MSG. In that case, weanling mice were deprived of food and water overnight, then given solutions containing 5 or 10% MSG as the sole drinking fluid. No such lesions were seen when MSG was given at 10% of the diet even though plasma glutamate levels were doubled, nor after administration at high concentrations in drinking water ad libitum.

In relation to the question of the relevance of this neurotoxicity for humans receiving MSG in the diet, biochemical and human studies have been crucial. The transport rate of glutamate from blood to brain in mature animals is much lower than that for neutral or basic amino acids, and normal plasma levels of glutamate are nearly four times the Michaelis-Menten constant (Km) of the transport system to the brain i.e. the concentration associated with half maximal velocity. This implies that this transport system is virtually saturated under physiologic conditions. However, the blood-brain barrier may be less effective in the neonatal mouse, which raises the possibility that this is the reason for the exquisite sensitivity of this model. However, the question of the comparability of the mouse and the human infant remains an issue, in that the level of brain development in the two species is quite dissimilar at parturition.

The threshold blood levels associated with neuronal damage in the mouse (the most sensitive species) are 100–130

μmol/dL in neonates rising to 380 μmol/dL in weanlings and >630 μmol/dL in adult mice. In humans, plasma levels of this magnitude have not been recorded even after bolus doses of 150 mg/kg body weight (~10 g for an adult). Additionally, the studies in infants previously mentioned have confirmed that the human infant can metabolize glutamate as effectively as adults. It is thus concluded that blood levels of glutamate + aspartate do not rise significantly even after abuse doses of up to 10 g, and infants are no more at risk than adults. Similarly, the comparisons of maternal and fetal blood levels after high doses indicate that the fetus is not at greater risk. Intake levels associated with the use of MSG as a food additive and natural levels of glutamic acid in foods, therefore, do not raise toxicologic concerns even at high peak levels of intake because the mechanism of toxicity appears to be related to the peak plasma level achieved rather than the area under the curve. A putative mechanism for the neuronal damage is that high levels of glutamate at the target site lead to continuous excitation of the glutaminergic neurons, depleting ATP and leading to cell death. Such a situation is difficult to achieve with oral administration in food. Furthermore, the JECFA noted that the oral ED_{50} for production of hypothalamic lesions in the neonatal mouse is ~500 mg MSG/kg body weight by gavage, whereas the largest palatable dose for humans is ~60 mg/kg body weight with higher doses causing nausea; thus, voluntary ingestion would not exceed this level.

Idiosyncratic intolerance (Chinese Restaurant Syndrome)

With regard to the second issue, reports of the so-called "Chinese Restaurant Syndrome" were linked to the use of MSG in Chinese cuisine and suggested that there may be idiosyncratic intolerance in some individuals. Most of the reports of these subjective symptoms were anecdotal, although in some investigative studies, MSG was also claimed to provoke these symptoms. However, more extensive studies in human volunteers were reviewed, and these failed to demonstrate that MSG was the causal agent in provoking the full range of symptoms. Properly conducted and controlled double-blind crossover studies have failed to establish a relationship between Chinese Restaurant Syndrome and ingestion of MSG, even in individuals claiming to suffer from the syndrome. Some food symptom surveys were considered technically flawed because of inappropriate questionnaire design.

In its conclusion on this matter, the JECFA stated "controlled double-blind crossover trials have failed to demonstrate an unequivocal relationship between 'Chinese Restaurant Syndrome' and consumption of MSG. MSG has not been shown to provoke bronchoconstriction in asthmatics."

JECFA safety evaluation

The overall safety evaluation led the JECFA to conclude that the total dietary intake of glutamates arising from their use at levels necessary to achieve the desired technological effect and from their acceptable background in food do not represent a hazard to health. For that reason, the establishment of an ADI expressed in numerical form was not deemed necessary and an "ADI not specified" was allocated to L-glutamic acid and the monosodium, potassium, calcium and ammonium salts.

The JECFA also noted the evidence that it was not necessary to treat pregnant women and infants as special cases; however, they did retain the previously expressed position that food additives, in general, should not be used in infant foods to be consumed before 12 wk of age.

The Scientific Committee for Food of the Commission of the European Communities

The SCF (1991) conducted a safety evaluation similar to that of the JECFA and reached the same conclusion, i.e., that MSG could be allocated an "ADI not specified," and this is the current situation in the European Union.

FASEB and the FDA

Because of the FDA's concern over continuing reports of adverse reactions to MSG and other glutamate-containing ingredients, and in light of the expanding knowledge on the role of glutamate in brain function, the FDA contracted with FASEB to conduct a review with the following objectives:

1. To determine whether MSG and hydrolyzed protein products, as used in the American food supply, contribute to the presentation of a complex of symptoms (initially described as Chinese Restaurant syndrome) after oral ingestion of levels up to or beyond 5 g per eating occasion . . . and or the elicitation of other reactions, including more serious adverse reactions . . . reported to occur following ingestion of 25–100 mg per eating occasion.
2. To determine whether MSG and hydrolyzed protein products . . . have the potential to contribute to brain lesions in neonatal or adult nonhuman primates and whether there is any risk to humans ingesting dietary MSG.
3. To assess whether hormones are released from the pituitary of nonhuman primates following ingestion of MSG or hydrolyzed protein products and whether any comparable risk to humans ingesting these substances exists.
4. To define the metabolic basis that might underlie any adverse reactions to MSG and hydrolyzed protein products.

The FASEB report was submitted to the FDA in July 1995 (FASEB 1995). In this report, the term "MSG symptom complex" is used instead of "Chinese Restaurant Syndrome" because the latter was considered pejorative and characterized the symptoms as an acute, temporary and self-limiting complex including the following: *1*) a burning sensation of the back of the neck, forearms and chest; *2*) facial pressure or tightness; *3*) chest pain; *4*) headache; 5) nausea; 6) upper body tingling and weakness; *7*) palpitation; 8) numbness in the back of the neck, arms and back; 9) bronchospasm (in asthmatics only); and *10*) drowsiness.

In passing, it is interesting to note the term "MSG symptom complex" was used when the terms of reference clearly included protein hydrolysates and other natural sources of glutamic acid.

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 documentation to indicate that there is a subgroup of presumably healthy individuals that responds, generally within 1 h of exposure, with manifestations of the MSG symptom complex when exposed to an oral (bolus) dose of MSG of 3 g *in the absence of food*. Although the FDA appears to have accepted this conclusion of the existence of the MSG symptom complex (Hattan, 1996), it was pointed out that the key data relate to single-dose challenges in capsules or simple solutions and are limited in their ability to predict adverse reactions resulting from the use of MSG in food. This is an important caveat because available carbohydrate in foods appears to modulate

the pharmacokinetics. The Hattan memorandum also indicates that the FDA did not consider the evidence regarding sensitivity of asthmatics to MSG compelling and questioned the inclusion of bronchoconstriction in the MSG symptom complex in the absence of confirmatory data in a well-controlled study. The reasons are outlined and relate to limitations in the key study (Allen et al. 1987), and a call was made for further work in this area.

The FASEB report concludes that there is no evidence to support a role for dietary MSG or other forms of free glutamate in causing or exacerbating serious, long-term medical problems resulting from degenerative nerve cell damage. The FDA accepted the conclusion that serious neurotoxicologic effects from MSG are limited to animals given very large doses by parenteral, pharmacologic or other nondietary conditions of use or administration.

With regard to the potential disruption of the neuroendocrine axis, the FASEB Expert Panel gave particular consideration to the potential of dietary MSG to affect adversely the structure and function of areas of the brain not protected by the blood-brain barrier. The Panel focused their evaluation on a study conducted by Carlson et al. (1989) of the stimulation of pituitary hormone secretion by neurotransmitter amino acids, which showed that a dose of 10 g glutamic acid in saline caused a twofold increase in peak serum concentrations of prolactin and cortisol over baseline values. However, a subsequent study (Fernstrom et al. 1996) using equivalent (pharmacologic) doses of MSG rather than the free acid failed to demonstrate any effect on plasma prolactin, luteinizing hormone, follicle-stimulating hormone, testosterone, growth hormone, cortisol, thyroid-stimulating hormone or thyroid hormones despite an 11-fold increase in plasma glutamate levels (cf. Carlson et al. 1989). The FDA concurred with the conclusion (from animal studies) that large doses of glutamate can influence hormonal function but concluded further that it did not believe that there was evidence to indicate that MSG as ordinarily consumed in foods disrupts the neuroendocrine axis in humans.

It has been contended in some quarters that glutamate in commercial products such as MSG or hydrolyzed protein, is different in some way from naturally occurring glutamate. The FASEB Panel rejected this contention.

Finally, the FDA interpreted the findings of the FASEB Report to be generally consistent with the safety assessments of other authoritative organizations (presumably including the JECFA and SCF) that have affirmed the safety of MSG at levels normally consumed by the general population, and concurred with the conclusion that there is no evidence linking current MSG food use to any serious, long-term medical problems in the general population.

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