A Review of the Alleged Health Hazards of Monosodium Glutamate

Anca Zanfirescu, Anca Ungurianu, Aristides M. Tsatsakis, George M. Nitulescu, Demetrios Veskoukis, Dimitrios Tsoukalas, Ayse B. Engin, Michael Aschner, and Denisa Margină

Abstract: Monosodium glutamate (MSG) is an umami substance widely used as flavor enhancer. Although it is generally recognized as being safe by food safety regulatory agencies, several studies have questioned its long-term safety. The purpose of this review was to survey the available literature on preclinical studies and clinical trials regarding the alleged adverse effects of MSG. Here, we aim to provide a comprehensive overview of the reported possible risks that may potentially arise following chronic exposure. Preclinical studies have associated MSG administration with cardiotoxicity, hepatotoxicity, neurotoxicity, low-grade inflammation, metabolic disarray, and premalignant alterations, along with behavioral changes. However, in reviewing the available literature, we detected several methodological flaws, which led us to conclude that these studies have limited relevance for extrapolation to dietary human intake of MSG risk exposure. Clinical trials have focused mainly on MSG effects on food intake and energy expenditure. Besides its well-known impact on food palatability, MSG enhances salivary secretion and interferes with carbohydrate metabolism, while the impact on satiety and post-meal recovery of hunger varied in relation to meal composition. Reports on MSG hypersensitivity or links of its use to increased pain sensitivity and atopic dermatitis were found to have little supporting evidence. Many of the reported negative health effects of MSG have little relevance for chronic human exposure and are poorly informative as they are based on excessive dosing that does not meet with levels normally consumed in food products. We conclude that further clinical and epidemiological studies are needed, with an appropriate design, accounting for both added and naturally occurring dietary MSG.

Keywords: flavor enhancer, food palatability, monosodium glutamate, toxicity, umami

Introduction

Monosodium glutamate (MSG) is a widely used flavor enhancer derived from L-glutamic acid, a naturally occurring amino acid in a variety of food products (Stanska & Krzeski, 2016; Wifall, Faes, Taylor-Burds, Mitzelfelt, & Delay, 2007). MSG possesses a specific taste—umami, which was first considered a predominant taste in Asia and much later in Western cultures (Kurihara, 2015; Stanska & Krzeski, 2016). This molecule was identified about 100 years ago by Kikunae Ikeda as the fifth basic taste, in addition to sweet, sour, salty, and bitter. MSG is found in high-protein food products, such as meat or fish, and also in certain types of cheese (Roquefort and Parmesan) or vegetables (tomatoes, mushrooms, broccoli) (Kochem & Breslin, 2017; Shigemura, Shirosaki, Sanematsu, Yoshida, & Ninomiya, 2009; Stanska & Krzeski, 2016; Wifall et al., 2007; Yamaguchi & Ninomiya, 2000). In addition to its basic specificity, the umami taste can enhance overall flavor intensity and improve food palatability. This effect is dependent on a variety of factors, the most important being the concentration of umami molecule and the food matrix (Masic & Yeomans, 2013).

In addition to MSG, other well-established umami substances are inosine 5'-monophosphate (IMP) and guanosine 5'-monophosphate (GMP). They can be found in a variety of natural sources and also as additives in certain food products, such as processed meat, canned vegetables, soups, sauces, dried bouillon cubes, and salty flavored snacks (Conn, 1992; Scopp, 1991). Moreover, IMP is also used as a flavor enhancer to accentuate the umami taste of MSG (Shigemura et al., 2009; Wifall et al., 2007; Yamaguchi & Ninomiya, 2000).

Interestingly, L-glutamic acid itself and its disodium salt analog have mild umami properties, when compared to MSG. The umami taste is diminished by other chemical alterations, such as esterification or amide formation. Only acidic analogs of glutamic acid, such as γ-aspartic acid, γ-homocysteine acid, and succinic acid, were reported to have some umami effects (Kawai, Okiyama, & Ueda, 2002). The free carboxylic group...
hypothesis regarding structure–taste relationship, is confirmed by t-γ-glutamylethylamide, also known as theanine, a natural constituent of green tea, which exhibits umami properties (Sharma, Joshi, & Gulati, 2018; Turkozu & Sanlier, 2017; Williams et al., 2019; Zhang, Venkitasamy, Pan, Liu, & Zhao, 2016). Also, various cyclic derivatives of glutamic acid have umami properties, provided they contain a free carboxylic group, this being the case for pyroglutamic or ibotenic acid (Zhang et al., 2016).

MSG is supplemented in many processed foods (Conn, 1992; Scopp, 1991), with an estimated average daily human intake of around 0.3–1.0 g in European industrialized countries (Beyreuther et al., 2007). Although food safety regulatory agencies consider MSG consumption to be safe, some preclinical and clinical studies have challenged its safety, especially following chronic exposure. The controversy is likely fueled from the knowledge that endogenous glutamate plays a role in physiological as well as pathological processes. Glutamate has various physiological functions: it is a major substrate for energy production in enterocytes, an intermediary substance in protein metabolism, precursor of significant metabolites such as glutathione (GSH, oxidative stress modulator) or N-acetylglutamate (metabolic regulator), and also a central nervous system (CNS) excitatory neurotransmitter (Meldrum, 2000; Newsholme, 2001). An increase in CNS glutamate concentration is associated with brain damage, similar to status epilepticus, cerebral ischemia, or traumatic injuries, as well as with chronic neurodegeneration analogous to Huntington’s chorea (Meldrum, 2000).

Following oral administration, glutamate undergoes oxidation within enterocytes, in the small intestine (Blachier, Boutery, Bos, & Tome, 2009). Only a very small quantity is subsequently found in the portal blood and, most likely, this originates from glutamine catabolism as a result of intestinal glutaminase activity, rather than from the absorption of dietary glutamate (Battezzati, Brillon, & Matthews, 1995). In healthy human volunteers, nearly all of the enterally delivered glutamate is removed by the splanchic bed on the first pass (Matthews, Marano, & Campbell, 1993). Following oxidation, glutamate is further converted to other amino acids or used as a precursor for the synthesis of different bioactive compounds (Reeds et al., 1997; Wakabayashi, Iwashima, Yamada, & Yamada, 1991; Wu, 2009).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), the U.S. Food and Drug Administration (FDA), and the European Food Safety Association (EFSA) considered MSG to be a substance generally recognized as safe (GRAS). A food additive can be included on the GRAS list if widely used in food prior to 1958 (approval based on experience) or when its safety is confirmed by scientific toxicological reports based on its estimated dietary intake. However, some authors now argue that GRAS inclusion criteria, either for scientific-based or for experience-based procedures require updating, based on the developments made in toxicity testing (Barraj, Murphy, Tran, & Petersen, 2016; Burdock, Carabin, & Griffiths, 2006; Hartung, 2018). As a consequence, in 2006, EFSA established an acceptable daily intake (ADI) for several food additives taking into account their no-observed-adverse-effect level (NOAEL) (Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment, 2006). The considered additives were quinoline yellow (E104), sunset yellow (E110), carmoisine (E122), Ponceau 4R (E124), indigo carmine (E132), brilliant blue (E133), sodium benzoate (E211), sulfur dioxide (E220), monosodium glutamate (E621), acesulfame K (E950), aspartame (E951), and saccharin (E954). A similar review was undertaken in June 2017, when EFSA reassessed the safety of glutamic acid and glutamates and found a group ADI of 30 mg/kg/day, expressed as glutamic acid. All data are presented in Table 1 (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2006; EFSA Panel on Food Additives and Nutrient Sources Added to Food, 2017).

Furthermore, EFSA’s scientific panel has also concluded this ADI exceeded levels for all population groups. This is worrisome since results from rodent studies associated its consumption with neurotoxicity, cardiotoxicity, hepatic, and renal disturbances, as well as metabolic disorders. However, as mentioned, in our analysis of preclinical studies, we identified several issues regarding the employed protocols, and consequently, we question the relevance and merit of these data, as they fail to provide an estimate of safety parameters, such as margin of exposure. These reports led to multiple analyses (Geha et al., 2000b; Henry–Uñaee, 2017; Husarova & Ostatnikova, 2013; Obayashi & Nagamura, 2016; Sanska & Krzéski, 2016; Tarasoff & Kelly, 1993; Williams & Woessner, 2009) regarding the effects of MSG consumption on human health, as highlighted in Table 2.

Taking all of the above into account, we surveyed the available data from preclinical studies and clinical trials regarding the adverse health effects of MSG administration, analyzing study design and methodology, and evaluating the relevance of these data for chronic dietary human exposure.

### Methods

A systematic review of the literature for all relevant articles was performed using PUBMED. Articles were limited to those published in the English language, focusing on most recent work, between 2010 and 2018 (50% of the cited material), but not neglecting any older relevant studies. As such, 32.35% of articles were published between 2000 and 2010 and 13.52% in the 1990 to 2000 period, with 4.11% before 1990. For preclinical studies, the search strategy used the keywords and MeSH terms: “monosodium glutamate,” “flavor enhancer,” “umami substance,” “umami molecule,” and “preclinical studies,” “mice,” “rats,” and “toxicity,” “effects,” “obesity,” “insulin resistance,” “metabolism,” “pain,” “heart toxicity,” “liver toxicity,” “neurotoxicity,” and “oxidative balance.” A total of 76 papers were selected post eligibility analysis and cross-checking, following the rules of systematic review—PRISMA (Transparent reporting of systematic reviews and meta-analyses, http://www.prisma-statement.org/). For clinical trials, the search strategy used the keywords and MeSH terms: “monosodium glutamate,” “flavor enhancer,” “umami substance,” “umami molecule,” and “clinical studies” and “toxicity,” “health impact,” “effects.” A total of 40 papers were selected after eligibility analysis and cross-checking, as described above. For the effects of other umami molecules, the search strategy used the keywords

<table>
<thead>
<tr>
<th>Food additive</th>
<th>NOAEL</th>
<th>ADI</th>
</tr>
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<tbody>
<tr>
<td>Quinoline yellow</td>
<td>1000 mg/kg bw/day</td>
<td>0 to 10 mg/kg bw/day</td>
</tr>
<tr>
<td>Sunset yellow</td>
<td>500 mg/kg bw</td>
<td>0 to 2.5 mg/kg bw</td>
</tr>
<tr>
<td>Carmoisine</td>
<td>400 mg/kg bw/day</td>
<td>0 to 4 mg/kg bw/day</td>
</tr>
<tr>
<td>Ponceau 4R</td>
<td>375 mg/kg</td>
<td>0 to 4 mg/kg bw/day</td>
</tr>
<tr>
<td>Indigo carmine</td>
<td>500 mg/kg bw/day</td>
<td>0 to 5 mg/kg bw/day</td>
</tr>
<tr>
<td>Brilliant blue</td>
<td>2500 mg/kg bw/day</td>
<td>0 to 12.5 mg/kg bw/day</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>500 mg/kg bw/day</td>
<td>0 to 0.7 mg/kg</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>70 mg/kg bw</td>
<td>0 to 0.7 mg/kg</td>
</tr>
<tr>
<td>MSG</td>
<td>3200 mg/kg</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Acesulfame K</td>
<td>900 mg/kg bw/day</td>
<td>0 to 9 mg/kg bw/day</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Not specified</td>
<td>0 to 40 mg/kg bw/day</td>
</tr>
<tr>
<td>Saccharin</td>
<td>500 mg/kg bw</td>
<td>0 to 5 mg/kg bw</td>
</tr>
</tbody>
</table>
Table 2–Reviews regarding the impact of MSG on human health.

<table>
<thead>
<tr>
<th>Objective Content</th>
<th>Conclusions</th>
<th>Observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence-based safety review</td>
<td>MSG is safe for all life-cycle stages. No alterations of nervous system function or of blood concentrations of pituitary hormones were found.</td>
<td>The human body does not discriminate between naturally occurring glutamate in foods and added glutamate. Added MSG is much lower than daily dietary glutamate intake from natural sources. Thus, it is hard to attribute causal role in major central and endocrine pathologies only to MSG used as a flavor enhancer.</td>
<td>Henry-Unaeze, 2017</td>
</tr>
<tr>
<td>Systematic review assessing the incidence of headache after an oral administration of MSG. Studies were analyzed taking into consideration MSG administration in relation to meals, due to the significant differences in kinetics when taken with or without food.</td>
<td>Five papers of MSG administered with food were analyzed and none showed a significant difference in the incidence of headache except for the female group in one study (dose: 3 g in 150 mL beef bouillon). Of seven studies without food, four studies showed a significant increase in the frequency of headaches.</td>
<td>MSG was administered, being dissolved in beverages or soup at relatively high concentrations. Authors emphasize that most of the studies involved administration of MSG in high concentrations (~2%), and it could easily be identified, due to its unpleasant taste at concentrations over 1.3%, and, as such, these studies were not properly blinded.</td>
<td>Obayashi &amp; Nagamura, 2016</td>
</tr>
<tr>
<td>Assessment of the effects of MSG consumption on human health</td>
<td>No effects of MSG administration on postprandial glycaemia and insulinemia were found. No correlation between MSG consumption and obesity was found. Large doses of MSG (&gt;3 g) ingested on an empty stomach without concomitant food ingestion may elicit some of the symptoms associated to CRS. It is unlikely that MSG consumption plays a role in the provocation of asthma. Dietary ingestion of MSG may be a rare cause for urticaria (accounting for under 3% of cases) and angioedema. Doses of 5 g of MSG given without food may determine symptoms (general weakness, muscle tightness, flushing, sweating, headache, numbness or tingling) in individuals who are self-proclaimed “MSG sensitive”.</td>
<td>Results regarding the association of MSG intake with CRS and asthma were contradictory. Clinical trials with better design are needed for a conclusion. There is no evidence that dietary MSG of a typical western diet induces symptoms of the CRS. There are not enough data to associate MSG consumption with rhinitis. The overall quality of the evidence supporting a relationship between MSG consumption and for urticaria and angioedema is low.</td>
<td>Husarova &amp; Ostatnikova, 2013</td>
</tr>
<tr>
<td>Assessment of the possible role of MSG in the so-called Chinese restaurant syndrome and in eliciting asthmatic bronchospasm, urticaria, angioedema, and rhinitis</td>
<td>No evidence linking the CRS associated symptoms to MSG consumption was found.</td>
<td>The frequency of the responses was low and the responses were inconsistent and not reproducible. The results were not observed when MSG was given with food.</td>
<td>Williams &amp; Woessner, 2009</td>
</tr>
<tr>
<td>Assessment of correlation between MSG consumption and Chinese restaurant syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literature review and original study of link between MSG consumption and Chinese restaurant syndrome</td>
<td>No evidence linking the CRS associated symptoms to MSG consumption was found.</td>
<td>MSG was administered in doses of 1.5, 3.0 and 3.15 g/person in capsules and specially formulated drinks, before breakfast.</td>
<td>Tarasoff &amp; Kelly, 1993</td>
</tr>
</tbody>
</table>

and MeSH terms: “umami substance,” “umami molecule,” “flavor enhancer,” and “toxicity,” “effects,” “health impact,” “effects.” A total of 16 studies were found eligible, as described above, and further analyzed.

Preclinical studies assessing MSG effects

As for the preclinical data, we included in our search studies employing a single dose or chronic administration of MSG, in order to analyze its effects on biochemical parameters (total plasma protein, HDL, LDL, glucose, triglycerides, oxidative stress biomarkers, insulin, leptin), as well as on the histology and morphology of several organs (heart, brain, ovaries, liver), and also behavioral test-based studies evaluating the effects on CNS, withorphensively (i.p.), intragastrically, or subcutaneously (s.c.).

MSG administration was associated with biochemical and morphological alterations of the heart tissue, as well as changes in cardiac rhythm (Kumar & Bhandari, 2013; Liu et al., 2013; Baky, Mohamed, & Faddah, 2009), and hepatotoxic effects, with fibrosis and neoplastic changes (Collison et al., 2011; Eweka, Igbigbi, & Uchefia, 2011), metabolic alterations and obesity (Diniz et al., 2005, Hirata, Andrade, Vaskevicius, & Dolnikoff, 1997), neurotoxicity (Izumi et al., 2009; Rivera-Cervantes et al., 2014; Swamy et al., 2014; Weil, Norman, De-Vries, & Nelson, 2008), modified behavioral and physiological alterations, such as increased aggressivity, decreased locomotor activity, and loss of muscle strength (Campos-Sepulveda et al., 2009). Significant changes in the neuronal redox homeostasis (increased levels of lipid peroxidation, nitrite concentration, decreased levels of antioxidants), and in the neuronal histology of the hippocampus, along with an increase of brain and serum cholinesterase (ChE) levels, were also reported (Onaolapo, Onaolapo, Akannu, & Gbola, 2016; Sadek, Abouzed, & Nasr, 2016).

Effects on the cardiovascular system

Four studies regarding MSG cardiovascular toxicity were identified and their results are summarized in Table 3. These indicated that MSG administration increased cardiac tissue oxidative stress and also determined biochemical changes, namely increasing some heart disease biomarkers, such as lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) (Kumar & Bhandari, 2013). Doses between 0.5 and 1.5 g/kg induced changes of cardiac rhythm, as well as lethal tachyarrhythmia in myocardially infarcted rats (Liu et al., 2013).

However, when analyzing whether these studies could indicate a threat to human health one must consider the high doses and routes of administration used. The subcutaneous, intraperitoneal, or intravenous administrations of doses that are a few-folds higher...
Significantly increasing lipid peroxidation significantly increases serum glucose, bradycardia (1.5 g/kg); increases malondialdehyde levels and decreases serum lactate dehydrogenase.

Comprehensive Reviews in Food Science and Food Safety Vol. 18, 2019 but there was only one control group study, which comprised doses of 0.04 and 0.08 g/kg, as they were extremely low, restricted dietary regimens have a profound impact on glycemic control. Since restricted dietary regimens have a profound impact on glycemic control, we consider this to be a noteworthy issue.

Evaluation of hepatotoxicity Several studies reported hepatotoxic effects following MSG administration, their key findings being summarized in Table 4. Dilatations of the central hepatic vein, with lysed erythrocytes and distorted hepatocytes, possibly due to impaired membrane permeability, were reported in adult Wistar rats, following controlled feeding with a mixture of food containing 0.04 and 0.08 g/kg MSG, on a daily basis for 42 days. Furthermore, similar results were reported in an adult male Rattus norvegicus study, when MSG was given with food, but in a much higher daily dose of 6 g/kg. We carefully reviewed the hepatotoxic effects reported for the 0.04 and 0.08 g/kg doses, as they were extremely low, and found that the authors justified the employed dosages based on previous work. However, the quoted study comprised doses of 1.46 g/kg and, respectively, 2.92 g/kg (Eweka & Om’iniabohs, 2007).

We consider studies in which MSG was given with food to be important, as their design is relevant to chronic human intake. However, before considering their results, we must emphasize that the actual quantity of MSG per day ingested by each individual animal was somewhat difficult to quantify.

Furthermore, one study (Fujimoto et al., 2014) had an inadequate control group. The authors administered 2 g/kg of MSG (n = 36) associated with unrestricted (n = 18), or restricted dietary regimens (n = 18), but there was only one control group (distilled water s.c. 0.1 mL/10 g), which received only a restricted dietary regimen. Obesity, increased adiposity, hyperinsulinemia, increase in triglycerides, and LDL-cholesterol were reported for the MSG-treated groups, with unrestricted dietary regimen. Since restricted dietary regimens have a profound impact on glycemic control, we consider this to be a noteworthy issue.

MSG administration was associated with increased hepatic lipid peroxidation, reduced GSH levels, and decreased catalase (CAT) and superoxide dismutase (SOD) activity. Reports of diabetes and obesity, accompanied by steatosis, inflammation, and infiltration of lymphocytes, monocytes, and macrophages, with fibrosis and neoplastic alterations, nodular lesions, and deterioration of bile ducts, were also found. Moreover, it was reported that orally administered MSG determined an increase of liver oxidative stress at a dose that extrapolated for humans would be 0.6 mg/kg (El-Meghawry El-Kenawy, Osman, & Daghistani, 2012; Eweka et al., 2011; Nakaniishi et al., 2008; Onyema, Farombi, Emerole, Ukoha, & Onyeze, 2006; Paul, Abhilash, Varghese, Alex, & Nair, 2012).

The seven studies included in this analysis indicated alterations in hepatic morphology and antioxidant defense, observed for different doses and routes of administration. Only one report (Onyema et al., 2006) of increased oxidative stress, following oral administration of doses that approach human dietary intake, seems substantial. The high dosing and routes of administration that fail to mimic the normal metabolic pathway of orally ingested glutamate make it difficult to extrapolate to plausible hepatotoxic effects associated with chronic dietary intake of MSG.
Table 4—Summary of preclinical studies associating MSG exposure with hepatic toxicity.

<table>
<thead>
<tr>
<th>Mode of administration</th>
<th>Species</th>
<th>MSG dosage/day</th>
<th>Duration of administration (days)</th>
<th>MSG effect (compared with control)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed with diet</td>
<td>Wistar rats</td>
<td>0.04 mg/kg (n = 8)</td>
<td>42</td>
<td>➢ Morphological changes: dilated central veins, cyto-architectural distortions of the hepatocytes, centrallobular hemorrhagic necrosis; ➢ Biochemical changes: increase in total protein, albumin, aspartate transaminase, and alanine transaminase activities; ➢ Changes were dose-dependent.</td>
<td>Eweka et al., 2011</td>
</tr>
<tr>
<td>Mixed with diet</td>
<td>Adult male <em>Rattus norvegicus</em></td>
<td>6 g/kg</td>
<td>45</td>
<td>➢ Central veins dilations, severe cyto-architectural distortions of the hepatocytes, vacuolated cytoplasm, swollen mitochondria and vesiculated rough endoplasmic reticulum with picknotic nuclei; ➢ Collagen deposition and connective tissue fiber impairment in the hepatocytes, together with severe reduction of mucopolysaccharide content; ➢ Increase of the expression of ki-67 and p53 pro-apoptotic proteins in hepatocytes. El-Meghawry El-Kenawy et al., 2012</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Male Wistar Rats</td>
<td>8 g/kg (n = 6)</td>
<td>20</td>
<td>➢ Increased lipid peroxides in liver, kidney, and serum; ➢ Diminished reduced glutathione in serum, liver, and kidney; ➢ Increased triglycerides, total cholesterol, urea; ➢ Morphological changes in liver (central venous congestion, diffuse degeneration, necrosis of hepatocytes) and kidney (cortical tubular degeneration).</td>
<td>Paul et al., 2012</td>
</tr>
<tr>
<td>Oral</td>
<td>Male Wistar Rats</td>
<td>0.6 g/kg (n = 6)</td>
<td>10</td>
<td>➢ Increased lipid peroxidation and the activities of glutathione-S-transferase, catalase, superoxide dismutase in the liver; ➢ Decreased reduced glutathione level in the hepatocytes; ➢ Increased activities of aspartate transaminase, alanine transaminase and gamma glutamyl transferase. Onyema et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Newborn C57BL/6J male mice</td>
<td>4 g/kg (n = 6)</td>
<td>Single dose administration within 5 days of their birth</td>
<td>Characteristic liver histopathology of nonalcoholic steatohepatitis. Metabolic syndrome-like features: ➢ Increase in serum levels of insulin and cholesterol; ➢ Microvesicular steatosis and inflammatory cell infiltration in the liver; ➢ Enlarged adipocytes and crown-like structures in the epididymal fat; ➢ Increased frequencies of monocytes and M1 macrophages in the liver and epididymal fat tissue;</td>
<td>Takai et al., 2014</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>ICR male mice</td>
<td>2 g/kg (n = 36) associated with unrestricted (n = 18) or restricted dietary regimens (n = 18)</td>
<td>From birth to day 5 of life</td>
<td>➢ Obesity, increased adiposity in the absence of hyperphagia, hyperinsulinemia; ➢ Increase in triglycerides, LDL-cholesterol and alanine transaminase activity after 6 months for both groups. Reversible at month 12 for group receiving MSG and restricted dietary regimen; ➢ After 6 months, major liver steatosis, but no fibrosis, for both MSG groups. ➢ At 12 months of age, the MSG-unrestricted mice, but not those with restricted diet, had mild fibrosis with steatohepatitis and liver nodules. Fujimoto et al., 2014</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Male albino Wistar-Norwegian brown hybrid rats</td>
<td>4 g/kg</td>
<td>10</td>
<td>➢ Significant increase of lipid peroxidation and of glutathione-S-transferase activity in liver, kidney, brain of rats; ➢ Decrease of glutathione level in the liver, kidney and brain; ➢ Increased catalase and superoxide dismutase activities in liver, decreased their activities in kidney and brain; ➢ Increased activity of aspartate transaminase, alanine transaminase and gamma glutamyl transferase. Farombi &amp; Onyema, 2006</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 5—Summary of preclinical studies investigating MSG neurotoxicity.

<table>
<thead>
<tr>
<th>Mode of administration</th>
<th>Species</th>
<th>MSG dosage/day</th>
<th>Duration of administration (days)</th>
<th>MSG effect (compared with control)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Mice</td>
<td>10 mg/kg ((n = 10))</td>
<td>28</td>
<td>The doses of 40 and 80 mg/kg MSG determined: ➢ Neuronal damage in the cerebrum, hippocampus and cerebellum; ➢ Increase in plasma glutamate and glutamine, but not in brain tissue; ➢ Superoxide dismutase and catalase decrease and nitric oxide increased in brain tissue.</td>
<td>Onaolapo et al., 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg/kg ((n = 10))</td>
<td></td>
<td>➢ Induces neuronal death; ➢ Alters the expression of hippocampal NMDA receptor subunit NR1, of the AMPA receptor subunits GluR1/GluR2; ➢ Increases the expression of the NRSF gene silencing factor via p38-MAPK pathway.</td>
<td>Rivera-Cervantes et al., 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg/kg ((n = 10))</td>
<td></td>
<td>➢ Elevation in lipid peroxidation markers; ➢ Increase of glutathione-s-transferase, superoxide dismutase and catalase activities and gene expression; ➢ Decrease in glutathione content; ➢ Increased levels of brain and serum cholinesterase, creatin phosphokinase and lactate dehydrogenase; ➢ Upregulation of pro-apoptotic Bax in neuronal cells.</td>
<td>Sadek et al., 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg/kg ((n = 10))</td>
<td></td>
<td>➢ Significant decrease in spontaneous locomotor activity; ➢ Impairment of oxidative defense in brain tissue (raised levels of lipid peroxides, nitrite concentration, reduced activities of glutathione-s-transferase and catalase, depletion of glutathione); ➢ Alteration of hippocampal neuronal histology; ➢ Behavioral and physiological alterations (precipitation of aggressiveness, decreased locomotor activity and loss of muscle strength); ➢ Loss in the hippocampal region, marked cerebral edema, neuronal eosinophilia; ➢ Decreased glutathione and reduced the superoxide dismutase and catalase activities in brain tissue.</td>
<td>Shivasharan, Nagakannan, Thippeswamy, &amp; Veerapur, 2014</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Newborn Wistar rats</td>
<td>4 g/kg ((n = 8))</td>
<td>4 (postnatal days 1, 3, 5, and 7)</td>
<td>➢ Induces neuronal death; ➢ Alters the expression of hippocampal NMDA receptor subunit NR1, of the AMPA receptor subunits GluR1/GluR2; ➢ Increases the expression of the NRSF gene silencing factor via p38-MAPK pathway.</td>
<td>Rivera-Cervantes et al., 2014</td>
</tr>
<tr>
<td></td>
<td>Male Wistar rats</td>
<td>5 mg/kg ((n = 8))</td>
<td>30</td>
<td>➢ Elevation in lipid peroxidation markers; ➢ Increase of glutathione-s-transferase, superoxide dismutase and catalase activities and gene expression; ➢ Decrease in glutathione content; ➢ Increased levels of brain and serum cholinesterase, creatin phosphokinase and lactate dehydrogenase; ➢ Upregulation of pro-apoptotic Bax in neuronal cells.</td>
<td>Sadek et al., 2016</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>CFW strain mice</td>
<td>2 g/kg on the 2nd and 4th postnatal days</td>
<td>5</td>
<td>MSG postnatal treatment led to adult mice with: ➢ Increased susceptibility of the depressor effect of aminoxyacetic acid; ➢ Other effects: obesity (not due to hyperphagia) body and tail length shortening, cryptorchidism.</td>
<td>Campos-Sepulveda et al., 2009</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Adult female Wistar rats</td>
<td>2 g/kg</td>
<td>7</td>
<td>➢ Significant decrease in spontaneous locomotor activity; ➢ Impairment of oxidative defense in brain tissue (raised levels of lipid peroxides, nitrite concentration, reduced activities of glutathione-s-transferase and catalase, depletion of glutathione); ➢ Alteration of hippocampal neuronal histology; ➢ Behavioral and physiological alterations (precipitation of aggressiveness, decreased locomotor activity and loss of muscle strength); ➢ Loss in the hippocampal region, marked cerebral edema, neuronal eosinophilia; ➢ Decreased glutathione and reduced the superoxide dismutase and catalase activities in brain tissue.</td>
<td>Shivasharan, Nagakannan, Thippeswamy, &amp; Veerapur, 2014</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Wistar albino rats of both sexes</td>
<td>2 g/kg</td>
<td>7</td>
<td>➢ Significant decrease in spontaneous locomotor activity; ➢ Impairment of oxidative defense in brain tissue (raised levels of lipid peroxides, nitrite concentration, reduced activities of glutathione-s-transferase and catalase, depletion of glutathione); ➢ Alteration of hippocampal neuronal histology; ➢ Behavioral and physiological alterations (precipitation of aggressiveness, decreased locomotor activity and loss of muscle strength); ➢ Loss in the hippocampal region, marked cerebral edema, neuronal eosinophilia; ➢ Decreased glutathione and reduced the superoxide dismutase and catalase activities in brain tissue.</td>
<td>Swamy et al., 2014</td>
</tr>
</tbody>
</table>

**Impact on CNS function and morphology**

The main findings of the preclinical studies, which reported behavioral and physiological alterations following MSG administration, are presented in Table 5.

As for CNS function, increased aggressiveness, possibly due to overactivation of glutamate pathways, associated with decreased γ-aminobutyric acid (GABA) levels (Campos-Sepulveda et al., 2009; Swamy et al., 2014) and lower locomotor activity, possibly on account of free radical-induced dopaminergic neurodegeneration (Swamy et al., 2014), were reported. Administration of MSG was also correlated with alteration in antioxidant defense homeostasis, secondary to loss of integrity and functionality of neuronal
membranes, with increased nonspecific permeability to several ions, and pathological changes of intracellular metabolic processes (Swamy et al., 2014).

Oral and subcutaneous administration of MSG was associated with changes in the hippocampus, such as a lower cyclic AMP-activated protein kinase (AMPK) activity and increased levels of apoptosis mediator Fas ligand (Dief, Kamha, Baraka, & Elshorbagy, 2014). Also, the upregulation of pro-apoptotic Bax (Bcl-2-associated X) protein (Sadek, Abouzed, & Nasr, 2016) was reported. Morphological changes, such as alterations of hippocampal neuronal histology or neuronal damage in the cerebrum and cerebellum, were reported following parenteral or oral MSG treatment in rodents (Onaolapo et al., 2016; Swamy et al., 2014).

Although a significant increase in plasma glutamate and glutamine were reported following oral administration in mice, no significant differences in total brain glutamate or glutamine levels were found (Onaolapo et al., 2016). Moreover, mammals have the ability to metabolize very large oral doses, and plasma glutamate concentrations fluctuate during the day as a result of changes in diet, metabolism, and protein turnover (Henry-Unaeze, 2017). Therefore, it seems unlikely that the use of lower and orally administered doses could induce histopathological alterations in the brain.

From the located six studies, five employed parenteral routes of administration and, in some, newborn rats/mice were used. In pups, the blood–brain barrier (BBB) is just forming and they are substantially more vulnerable to MSG effects, than dogs or primates (Walker & Lupien, 2000). Also, it was highlighted that infant mice are not equipped with enzymes necessary to metabolize MSG and that doses of 2 mg/g, administered to infant mice, were comparable to about 6 g in human infants (Blood, 1969). In adult rodents, brain regions with an intact BBB were not affected by changes in plasma glutamate (Price et al., 1984; Price, Olney, Lowry, & Buschbaum, 1981). Only the nervous structures not protected by the BBB, such as the circumventricular organs, the dorsal root ganglia, and autonomic ganglia, could be vulnerable to acute fluctuations of large magnitude (Smith, 2000).

Taking all of the above into consideration, it remains to be proven that diet-added MSG could induce behavioral, biochemical, and morphological changes in structures such as cerebrum, hippocampus, and cerebellum of adult mammals.

Effects on fertility and fetal development

An important safety issue raised by preclinical studies is the effects of MSG chronic exposure on fertility and fetal development. Results of the preclinical studies found researching these matters are summarized in Tables 6 and 7.

In adult male rats, morphological changes in testes, as well as sperm abnormalities, were reported following intraperitoneal MSG administration. The changes were reversible, as improvements were observed after cessation of treatment (Nosseir, Ali, & Elbaid, 2012). Dietary exposure of adult female Wistar rats to 0.04 to 0.08 mg/kg MSG, determined pathological alterations of oocytes (Eweka & Om’iniabohs, 2011) and of the fallopian tubes (Eweka, Eweka, & Om’iniabohs, 2010), in a dose-dependent manner. Once again, we point out that there are some inconsistencies regarding these studies, one issue being the dosage employed. The authors have justified the dosages based on previous work done with this food additive. However, the previous study was comprised of doses of 1.46 g/kg and, respectively, 2.92 g/kg (Eweka & Om’iniabohs, 2007). Furthermore, the studies did not include a report of the employed statistics and the exact number of pathological changes per group was not specified. Therefore, the relevance of these results to human health risk is questionable.

MSG intake was associated with an increased number of primary follicles and of primary spermatocytes in the pachytene stage, in two different studies, both of which employed newborn mice (Das & Ghosh, 2011a, 2011b). However, the control group of Das and Ghosh (2011a) included only five mice. We believe that using a slightly higher number of animals could have offered higher reliability, from a statistical point of view. The same studies investigated the effects of MSG administration during the perinatal period, reporting pathological alterations (Das & Ghosh, 2011a, 2011b).

Taking into consideration the high doses used, and the mode and duration of administration, as highlighted in Table 6, we consider them to have little impact on human toxicology following dietary intake.

Another important issue related to MSG is exposure during pregnancy. Negative health effects on offspring after MSG administration during gestation, such as decreased convulsion threshold, impaired Y-maze discrimination learning, increased body weight, and lower serum levels of growth hormone and insulin growth factor 1 (IGF-1) were reported (Yu et al., 2006; Yu, Zhao, Shi, Ma, & Yu, 1997). The offspring in utero-exposed to MSG exhibited functional and morphological cerebral alterations, with increased expression of apoptosis-related genes and genetic toxicity (Yu et al., 2006).

With respect to MSG’s effects on fertility and fetal development, six of the eight studies included in the analysis used exceedingly high doses, with little relevance for human dietary intake, and/or parenteral routes of administration. We consider further investigations, using appropriate dosages and routes of administration, are necessary to assess the toxicity of chronic MSG exposure on the reproductive system and fetal development.

Promotion of tumor development in MSG-induced obesity

Various non-neuronal cells, including lymphocytes and thymocytes, have been shown to express glutamate receptor (Pavlovic, Cekic, Sokolovic, & Djindjic, 2006). Obesity models in mice can be established via treatment of newborn pups with MSG (2 mg/kg body weight for 4 days, followed by 4 mg/kg body weight for the next 6 days). A low-grade chronic inflammatory state, accompanied by pro-inflammatory cytokine increments and adiponectin gene expression reduction were observed (Figure 1) (Hernandez-Bautista et al., 2014; Tchkonia et al., 2010). Serum biochemical profile of MSG-treated mice showed hyperinsulinemia, hypercholesterolemia, and hyperglycemia (Hata et al., 2012). Indeed, neonatal administration of MSG in mice provides a model of obesity with impaired glycemic control and increased serum levels of resistin and leptin (Roman-Ramos et al., 2011). An increase in mRNA expression of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), resistin, and leptin was observed, also with the activation of both peroxisome proliferator-activated receptor α (PPARα) and γ (PPARγ), reflecting the MSG-induced pro-inflammatory profile (Figure 1; Roman-Ramos et al., 2011). MSG-treated obese mice showed metabolic alterations, with differential gender susceptibility throughout a lifespan and during the aging process, as at 8 months male mice had a 13% higher body weight, while at 12 months females had significantly higher body weight than males (Hernandez-Bautista et al., 2014). In this context, obesity promoted-hepatic steatosis and
Inflammation were closely associated with liver carcinogenesis (Park et al., 2010; Siegel & Zhu, 2009). Additionally, MSG-induced obesity and diabetes, with steatosis and steatohepatitis, resemble human nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), with pre-neoplastic lesions (Figure 1) (Nakanishi et al., 2008). In fact, cellular hyperexcitability, via stimulation of mineral sodium voltage-gated channels and ligand excitatory glutamate, and non-neuronal excitatory receptors, could be a significant causative and pathogenic factor of cancer (Hoang, Levine, Pham, & Shaw, 2007). Increased levels of oxidative stress and aberrant hepatic lipogenesis, both of which are significantly linked to obesity and metabolic syndrome, were also dominantly observed during liver carcinogenesis and hepatocellular carcinoma progression (Ratziu et al., 2002; Siegel & Zhu, 2009). Elevated activities of drug-metabolizing enzymes, NAD(P)H:quinone oxidoreductase 1 and UDP-glucuronosyltransferases 1A, caused alterations in drug pharmacokinetics, in an MSG-mouse model of obesity (4 mg/g/day, s.c., MSG to newborn mice, in the first 6 days of life, followed by 10 mg/g day in days 7 and 8, and 20 mg/g in days 9 and 10). Moreover, decreased capacity of glutathione S-transferases, in obese animals, indicated a potentially reduced antioxidant defense and diminished chemoprotection (Dluzen & Lazarus, 2013; Matouskova et al., 2015). These enzymes can either inactivate carcinogens or, in some cases, generate reactive species with higher reactivity compared to the original compound. Data on the relation between the cytochrome P450, glutathione S-transferase, and UDP-glucuronosyltransferase activities and

### Table 6—Summary of preclinical studies investigating MSG administration effect on fertility.

<table>
<thead>
<tr>
<th>Mode of administration</th>
<th>Species</th>
<th>MSG dosage/day</th>
<th>Duration of administration</th>
<th>MSG effect (compared with control)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed with diet</td>
<td>Adult female Wistar rats</td>
<td>0.04 mg/kg ($n = 8$) 0.08 mg/kg ($n = 8$)</td>
<td>14</td>
<td>➢ Morphological changes of the fallopian tubes (cellular hypertrophy of the columnar epithelium, distortion of the basement membrane separating the endosalpinx from the myosalpinx); ➢ Changes were more pronounced with the higher doses of MSG.</td>
<td>Eweka &amp; Om’iniabohs, 2011</td>
</tr>
<tr>
<td>Mixed with diet</td>
<td>Adult female Wistar rats</td>
<td>0.04 mg/kg ($n = 8$) 0.08 mg/kg ($n = 8$)</td>
<td>14</td>
<td>➢ Morphological changes of the ovaries (cellular hypertrophy of the theca folliculi, distortion of the basement membrane separating the theca folliculi from the zona granulosa). Degenerative and atrophic changes in the oocyte; ➢ More severe changes were reported for MSG 0.08mg/kg.</td>
<td>Eweka et al., 2010</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Wistar male rats</td>
<td>4 g/kg ($n = 24$)</td>
<td>14</td>
<td>➢ Loss of spermatogenic cells; ➢ Spermatic cells showed abnormalities in the shape; ➢ Atrophy of the seminiferous tubules intercellular vacuolation in the stroma and peritubular fibrosis; ➢ Decrease in testicular weight, tubular diameter, germin epithelium height.</td>
<td>Nosseir et al., 2012</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Female Swiss Albino mice newborns</td>
<td>2 g/kg ($n = 8$)</td>
<td>5 (2nd, 4th, 6th, 8th and 10th day of life)</td>
<td>After 75 days of recovery, the following results were reported for MSG groups: ➢ Increase in number of primary follicles; ➢ Follicle-stimulating hormone level similar to control; ➢ Increase in serum prolactin and growth hormone; ➢ Decrease in the serum estradiol.</td>
<td>Das &amp; Ghosh, 2011a</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Male Swiss Albino mice newborns</td>
<td>2 g/kg ($n = 7$)</td>
<td>5: 2nd, 4th, 6th, 8th and 10th day of life.</td>
<td>After 75 days of recovery, the following results were reported for MSG groups: ➢ Similar mean weight and volume of the testes as control; ➢ Increase in the number of the pachytene stage of primary spermatocytes.</td>
<td>Das &amp; Ghosh, 2011b</td>
</tr>
</tbody>
</table>
### Table 7—Summary of preclinical studies investigating the effect of MSG administration on fetal development.

<table>
<thead>
<tr>
<th>Mode of administration</th>
<th>Species</th>
<th>MSG dosage/day</th>
<th>Duration of administration</th>
<th>MSG effect (compared with control)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intragastric</td>
<td>Swiss Albino mice</td>
<td>Maternal mice were given 1.0, 2.0, 4.0 g/kg MSG</td>
<td>Maternal mice received MSG for 17–19 days of pregnancy. Offspring were assessed.</td>
<td>MSG administration alters behavior, histopathology, genetic toxicity, and expression of apoptosis-related gene.</td>
<td>Yu et al., 2006</td>
</tr>
<tr>
<td>Oral</td>
<td>Kunming mice</td>
<td>Maternal mice were given 2.5 g/kg or 4.0 g/kg MSG</td>
<td>Maternal mice received MSG for 17–19 days of pregnancy. Offspring were assessed.</td>
<td>➢ Decreased threshold of convulsion; ➢ Impaired discrimination learning; ➢ Increased rate of weight gain; ➢ No significant difference in spatial learning or pain thresholds assessed by tail flick latency; ➢ No impact on the reproductive capacity of the offspring.</td>
<td>Yu et al., 1997</td>
</tr>
<tr>
<td>Mixed with diet</td>
<td>Wistar rats male and female offspring</td>
<td>(a) 2.5 g MSG /day representing 10% of dry weight of the average daily food ration (b) 5 g MSG /day representing 20% of dry weight of the average daily food ration (in mother and offspring)</td>
<td>In utero life + 90 days after</td>
<td>Maternal feeding with 5 g MSG per day results in: ➢ Severe birth weight reduction of the offspring and of the weaned pup; ➢ Lower growth hormone and insulin-like growth factor 1 serum levels, which are maintained low in mice fed with high MSG diet (5 g MSG per day). Animals kept on medium MSG diet (2.5 g MSG per day) showed low serum growth hormone levels at day 30 of life but partially recover before day 90; ➢ Dose-dependent voracity. The animals fed 5 g MSG per day increased water uptake by threefold (P &lt; 0.01), and food uptake by almost twofold (P &lt; 0.01).</td>
<td>Hermanussen et al., 2006</td>
</tr>
</tbody>
</table>

It was shown that diethylnitrosamine (DEN)-induced liver tumorigenesis, in MSG-treated mice, reflected steatosis-related liver carcinogenesis in human (Figure 1; Miyazaki et al., 2016). In a model that aimed to investigate the involvement of obesity-related factors in colorectal cancer, newborn mice were administered MSG, 2 mg/g, s.c., for 4 days and azoxymethane (AOM), 15 mg/kg, i.p, a potent carcinogen that induces precancerous lesions in the colon. Hyperinsulinemia, hypercholesteremia, and hyperglycemia were observed in MSG-treated mice, with or without AOM administration. The mRNA expression of IGF-1 receptor (IGF-1R) was increased in the MSG-AOM mice, when compared to the mice given AOM alone (Hata et al., 2012). The findings suggested that MSG-treated mice are highly susceptible to AOM-induced colorectal carcinogenesis.

As a result of the metabolic reprogramming of many types of cancer cells, glucose is mainly catabolized by aerobic glycolysis in tumors, while glutamine is converted to glutamate by glutaminase, which is further converted to α-ketoglutarate through the Krebs cycle. This reprogrammed pathway plays a major role in ATP synthesis, maintains redox balance, and regulates energy consumption in cancer cells (Scalise, Pochini, Galluccio, Console, & Indiveri, 2017).

Treatment of newborn rats with repeated doses of MSG resulted in altered morphology and functionality of alveolar macrophages. Intracellularly, numerous lipid vacuoles and lamellar structures were observed, in addition to an approximately 50% increase in total cellular lipid content. As a result, a decreased intracellular killing ability and inhibitory function on the growth and progression of tumor cells was reported (Liu, Wong, & Mak, 1989). Prior to the implanting of Walker-256 tumor cells, newborn male Wistar rats were subcutaneously injected with 400 mg/kg MSG. The development of the tumor was higher in obese-MSG tumor rats compared to control tumor rats. Activation of the insulin-IR-ERK1/2 pathway and an anti-apoptotic effect might be the mechanisms involved in the higher development of tumors in obesity (de Queiroz, Akamine, de Carvalho, Sampaio, & Fortes, 2015; Fonseca et al., 2011).

Thus, MSG was shown to contribute to tumor progression in a preclinical setting. However, these experimental conditions do not mimic human dietary consumption of MSG and have little relevance for human tumorigenesis.

### Effects on the immune system

The effect of MSG on the immune system was directly assessed in experiments employing cell cultures. MSG (250 to 8000 µg/mL) significantly, and dose-dependently, increased the frequencies of chromosome aberrations and sister-chromatid exchanges in human lymphocytes. However, replication and nuclear division indices were not affected. These results indicate that, at a cellular level, MSG may exert genotoxic effects on human peripheral blood lymphocytes (Figure 1; Ataseven, Yuzbasioglu, Keskin, & Unal, 2016). Exposure to increasing MSG concentrations (1 to 100 mM) showed a dose-dependent effect on B cell viability.

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Glutamate-induced apoptosis in both memory and naive B cell populations and this effect is most likely mediated through metabotropic glutamate receptor (mGluR) 7 receptors (Jovic et al., 2009). Likewise, naive and memory lymphocytes express different glutamate receptors. Differential expression profiles of glutamate receptors contribute to the induction of oxidative stress and apoptosis in immune cells (Jovic et al., 2009).

Neonatal administration of MSG (4 mg/g, s.c., days 2, 4, 6, 8, and 10 of life) to rats, led to elevated serum concentrations of interleukin (IL)-1β and IL-12, with a lowering of IL-4, IL-10, and tumor growth factor (TGF)-β levels (Falalyeyeva et al., 2017). During the acute phase response of inflammatory stress, in newborn MSG-treated (4 mg/g, i.p., day 2 of life) rats, the corticotropic–adrenal response, leptin, insulin, and triglyceride levels were higher, pro-inflammatory cytokine response was impaired, and anti-inflammatory cytokine response remained normal. These results indicate that metabolic and neuroendocrine-immune functions were altered in MSG-exposed rats (Castrogiovanni, Gaillard, Giovanbattista, & Spinedi, 2008). Further, altered lipid absorption due to MSG (2% solution, intraduodenally) may be related to inflammatory responses and damage to the lining of the small intestine (Kohan, Yang, Xu, Lee, & Tso, 2016). The detrimental effects of postnatal MSG administration (2 mg/g, s.c., days 1, 2, 4, 6, 8, and 10 of life) may lead to impairment of defense mechanisms against pathogenic microorganisms (Nakade, Motojima, Hirakawa, & Tanaka-Nakade, 2016).

Glutamate-induced apoptosis in both memory and naive B cell populations and this effect is most likely mediated through metabotropic glutamate receptor (mGluR) 7 receptors (Jovic et al., 2009). Likewise, naive and memory lymphocytes express different glutamate receptors. Differential expression profiles of glutamate receptors contribute to the induction of oxidative stress and apoptosis in immune cells (Jovic et al., 2009).

A decline in the percentage of blood lymphocytes, but without influencing the basal phagocytic activity of the neutrophils, was reported (Hriscu, Saulea, Vidrascu, & Baciu, 1997). In contrast, a neonatal MSG study (4 mg/g, s.c., day 4 of life) showed an increase in the number of macrophages, and their phagocytic activity as well (Pelaez, Blazquez, Pastor, Sanchez, & Amat, 1999).

MSG treatment (4 mg/g, i.p., 6 consecutive days) influenced thymocyte proliferation by enhancing apoptosis rate (Pavlovic et al., 2006), and it was also related to the increase of oxidative stress (Farombi & Onyema, 2006; Pavlovic et al., 2007). In addition to higher apoptotic rates, malondialdehyde (MDA) levels and xanthine oxidase (XO) activity increased, while CAT activity decreased (Pavlovic et al., 2007). Also, more MSG-induced thymocyte apoptosis can be ameliorated with high doses (250 µM) of ascorbic acid (Campbell, Cole, Bunditrutavorn, & Vella, 1999; Maelaro, Bello, & Comporti, 1996; Pavlovic, Cekic, Bojanic, Stojiljkovic, & Rankovic, 2005).

Analysis of the delayed-type hypersensitivity (DTH) depression in MSG-treated (2 mg/g, s.c., days 2 to 7 of life) mice, by the use of the macrophage migration inhibition assay, showed dysfunction of DTH effector T cells (Kato et al., 1986). A correlation between natural killer (NK) cell cytotoxicity depression and decreased numbers of large granular lymphocytes was also noted, in the MSG-treated mice (Belluardo, Mudo, & Bindoni, 1990).
Although we do not contest the results of the studies presented above, we cannot conclude that MSG exerts detrimental effects on the immune system in humans, as their design is inappropriate for extrapolation to human dietary exposure.

Other effects associated with MSG

Preferential consumption of water containing various concentrations of MSG, compared with plain water, was reported in mice. The higher the concentration, the greater the preference (71% consumption difference in favor of 3% MSG solution). However, the total liquid consumption was unaffected by MSG addition, the control group and the tested groups consumed approximately 150 mL liquid/group (Buzescu, Cristea, Avram, & Chiriță, 2013). Similar results were also seen in human volunteers, as described in the following section referring to clinical trials.

The addition of 100 g/kg MSG to standard diet increased food consumption. Aside from food overconsumption, the MSG group presented a metabolic dysfunction with increased levels of glucose, triacylglycerols, insulin, leptin, and homeostasis model assessment index (Diniz et al., 2005). However, this study used a mega-dose of the food additive (more than 25 times higher than the regular dietary intake), which could not be reached in real life.

An existing relation between neural taste processing and working memory networks was hypothesized (Meyer-Gerspach et al., 2016). Administration of 1 g MSG as a 30 mM solution, via a nasogastric tube, significantly altered brain activation patterns in the primary gustatory cortex, as well as in subcortical structures, previously reported to be involved in emotional learning and memory. Nevertheless, working memory performance was unaffected (Meyer-Gerspach et al., 2016). This aspect is important in establishing whether flavor enhancers have some bearing on affective responses and possibly behavior, thereby causing food overconsumption (Meyer-Gerspach et al., 2016).

Studies based on animal models have been inconsistent regarding a relationship between MSG consumption and body weight: while some reported a negative correlation (Kondoh & Torii, 2008), others suggested a direct link, associating MSG intake with higher energy intake and weight gain (Hirata et al., 1997). The observed differences might be a consequence of the different macronutrient composition of the preloads used in the different studies.

MSG administration seemed to have an impact on glucose metabolism. When given to healthy (Bertrand, Puch, Loubatières-Mariani, & Bockaert, 1995) and, respectively, type 2 diabetic rats (Bertrand, Ravier, Puch, Loubatières Mariani, & Bockaert, 1997), during an oral glucose tolerance test, insulin secretion was increased and glucose tolerance was improved. MSG seemed to interfere with hepatic gene expression. In a feline model (MSG diet: 30% protein and 1,125% MSG, with an average MSG intake of 201.4 ± 18.65 mg/kg), MSG exposure in vivo in the first months of life led to obesity, steatosis, insulin secretion impairment, and alterations in the expression of genes involved in lipid metabolism (Collison et al., 2011; Tomankova et al., 2015).

Systemic administration of MSG (10 and 50 mg/kg) led to a two- to threefold elevation in interstitial glutamate levels, in the rat maser muscle, and a decrease in afferent mechanical threshold. These results indicate that even small elevations of interstitial glutamate concentration can induce afferent mechanical sensitization and alter musculoskeletal pain sensitivity (Cairns et al., 2007).

Our research group investigated the effects of oral administration of various doses of MSG on the nociceptive threshold. Our results indicated that a 300 mg/kg MSG dose, but not a 150 mg/kg dose, administered orally for 21 days, reduced significantly the thermal nociceptive threshold, the effect also being correlated with an increase in brain nitrates concentration (Zanfirescu, Cristea, Nitulescu, Velescu, & Gradinaru, 2017). However, these effects were observed for high doses, unattainable in normal human diets. We believe that an interesting future direction of research could represent the assessment of chronic low-dose MSG exposure on nociceptive threshold.

A synopsis of the in vivo studies mentioned above is summarized in Table 8. The five studies included in this section indicate that the use of MSG might be associated with different types of pain, but at very high doses, and also that it could influence metabolism and weight.

Clinical trials on MSG exposure

Effects on food consumption and energy intake

MSG increases food palatability, when added in low concentrations, with an expected effect of reducing satiety. However, most studies reported the opposite effect: a satiety enhancement, which could be partially sensory-specific (Masic & Yeomans, 2014b). Sensory-specific satiety consists in the decline of palatability for a specific taste after exposure to a food product (Wilkinson & Brunstrom, 2016).

Data on MSG effects on energy intake are contradictory. Some clinical studies showed no significant differences in hunger ratings or subsequent energy intake. Other studies, undertaken in nursing homes and institutions for the elderly, reported a similar dietary intake of foods with and without MSG. However, it should be taken into consideration that the chemosensory perception diminishes with age, and that the heterogeneity of the study population could have masked small differences between the treatment and control group (Essed et al., 2009; Essed, Kleikers, van Staveren, Kok, & de Graaf, 2009; Essed, van Staveren, Kok, & de Graaf, 2007; Rogers & Blundell, 1990).

The addition of 0.6% MSG to foods of medium palatability increased their spontaneous intake, without affecting overall energy intake, due to a reduction of non-MSG-enriched foods consumption, in both healthy and diabetic elderly groups (Carter, Msoni-vais, Perrigue, & Drenowski, 2011). Similar results were found when supplementing chicken broth with MSG, with an increase in subjective ratings for satiety, but no alteration of energy intake at the next meal, in young adult normal-weight women, aged 20 to 40 years old (Luscombe-Marshal, Smeets, & Westerterp-Plantenga, 2008).

However, these results contradict those in other studies, which reported an increased energy intake for the MSG–supplemented soup group, compared with a control broth (Imada, Hao, Torii, & Kimura, 2014; Luscombe-Marsh, Smeets, & Westerterp-Plantenga, 2009). The time between MSG presentation and the test meal were similar in both studies study (45 min). These contradictory results suggest that the influence of MSG on appetite is directly linked to the macronutrient content of meals to which it is added: a low level of protein (3 g) in the first study compared with a high amount of protein in the second one (30 g). Similar results were observed regarding MSG effects on satiety, which appear to be dependent upon nutrient content, as an increase in satiety was reported only for MSG–enriched protein meals, and not for carbohydrate meals (Kochem & Breslin, 2017). Interestingly, individuals who preferred higher concentrations of MSG solution had a lower nutritional/protein status than those who preferred lower concentrations, suggesting the taste detection threshold for this food enhancer, when choosing a food product, may be correlated with a preference for protein and with habitual protein intake.
Increased the nitrite concentration
Increase in voluntary food intake
Increased adiposity, induction of
Afferent mechanical sensitization
Metabolic dysfunction character-
Imbalance between the oxidant
Impaired glucose tolerance;
Insulin resistance to peripheral glu-
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2- to 3-fold elevation in interstitial
Increase in fasting insulin and

Yeomans, 2017). Magerowski et al. examined the neurocognitive
tractions of MSG (Luscombe-Marsh et al., 2008, 2009; Masic &
with lower nutritional/protein status preferred higher concen-
tein meals, but not carbohydrate meals, increase satiety . The nu-
non-MSG-enriched food products was concomitantly observed.
MSG increases food palatability and enhances satiety , partially
chose food product might be impacting satiety—for example, there is evidence suggesting leucine could suppress food intake by increasing satiety (Casperson, Sheffield-Moore, Hewlings, & Paddon-Jones, 2012; Laeger et al., 2014).
Administration of a 2 g MSG-supplemented meal for 6 days determined a significant increased antral distension for the 2-h post-ingestion, compared to sodium chloride, and led to significantly increased levels of circulating leucine, isoleucine, valine, lysine, cysteine, alanine, tyrosine, and tryptophan (Boutry et al., 2010).
The clinical studies assessing MSG consumption impact on food consumption and energy intake are summarized in Table 9. The 11 clinical trials we identified investigating the effect of MSG on food consumption and energy intake, indicate that adding MSG increases food palatability and enhances satiety, partially due to a sensory-specific mechanism. While consumption of MSG-enriched meals may increase food intake, a reduction of non-MSG-enriched food products was concomitantly observed. However, the macronutrient composition is a key regulator of MSG’s effect on satiety and energy intake, as MSG-enriched protein meals, but not carbohydrate meals, increase satiety. The nutritional status of the individual is also important, as individuals with lower nutritional/protein status preferred higher concentrations of MSG (Luscombe-Marsh et al., 2008, 2009; Masic & Yeomans, 2017). Magerowski et al. examined the neurocognitive mechanisms underlying this effect. The most striking observation was that adding MSG to soups increased the engagement of a brain region associated with successful self-control during dietary decisions in a group of healthy women, suggesting that glutamate might play a significant role in cognitive executive processes regulating eating behaviors and food choices (Magerowski et al., 2018).
The epidemiological studies assessing the correlation between MSG consumption and food intake, satiety, and body weight are presented in Table 10. The INTERMAP cross-sectional study positively associated MSG consumption with increased body mass, in Chinese population (He et al., 2008). A prospective open-cohort, nationwide health and nutrition survey, China Health and Nutrition Survey (CHNS), seem to confirm these results (He et al., 2011). MSG intake was associated with increased BMI and prevalence of metabolic syndrome, in a dose-dependent manner, independent of the total energy intake and level of physical activity (Insawang et al., 2012). However, analysis of other subgroups included in the CHNS, as well as studies in other regions of Asia, found no association between MSG intake and weight gain (Shi et al., 2010; Thu Hien, Thi Lam, Cong Khan, Wakita, & Yamamoto, 2012).
One of the reasons underlying the different results observed could be that the studies used different methods, especially regarding MSG and food records. The method of measurement seems highly imprecise. In the INTERMAP study, participants were asked to demonstrate the amount of MSG shaken out during preparation of a meal, this being weighed by trained interviewers. If participants went to a restaurant, interviewers asked chefs to estimate the amount of MSG added to the served dish. In the CHNS, although the number of subjects was large, the MSG intake was estimated based on the proportion of each individual’s food

Table 8—Summary of preclinical studies investigating other effects of MSG administration.

<table>
<thead>
<tr>
<th>Mode of administration</th>
<th>Species</th>
<th>MSG dosage/day</th>
<th>Duration of administration</th>
<th>MSG effect (compared with control)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed with diet</td>
<td>Male Wistar rats</td>
<td>(a) 100 g/kg in standard diet (b) 100 g/kg in high-fiber diet</td>
<td>45 days</td>
<td>Increase in voluntary food intake and decrease of feed efficiency; Metabolic dysfunction characterized by increased levels of glucose, triacylglycerol, insulin, leptin; Imbalance between the oxidant and antioxidant systems.</td>
<td>Diniz et al., 2005</td>
</tr>
<tr>
<td>Mixed with diet</td>
<td>Cats</td>
<td>Average intake 201.4 ± 18.65 mg/kg</td>
<td>In utero exposure and 9 months after birth</td>
<td>Increased adiposity, induction of hepatic steatosis and the expression of genes involved in cholesterol and steroid metabolism; Increase in fasting insulin and HOMA-IR values.</td>
<td>Collison et al., 2011</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Newborn male Wistar rats</td>
<td>4 g/kg (n = 10)</td>
<td>First 10 days of life (injection 5 times, every other day)</td>
<td>Impaired glucose tolerance; Insulin resistance to peripheral glucose uptake.</td>
<td>Hirata et al., 1997</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Sprague-Dawley rats of either sex (n = 16)</td>
<td>10 mg/kg 50 mg/kg</td>
<td>Single dose administration</td>
<td>MSG, 50 mg/kg, determined: 2- to 3-fold elevation in interstitial glutamate levels in the masseter muscle; Affenter mechanical sensitization through NMDA receptor activation.</td>
<td>Cairns et al., 2007</td>
</tr>
<tr>
<td>Oral</td>
<td>Male NMRI mice</td>
<td>150 mg/kg 300 mg/kg</td>
<td>21 days</td>
<td>MSG, 300 mg/kg, determined: Reduced thermal nociceptive threshold and increased nociceptive behavior; Increased the nitrite concentration in brain tissue.</td>
<td>Zanfirescu et al., 2017</td>
</tr>
</tbody>
</table>
Table 9—Summary of clinical studies on MSG impact on food consumption and energy intake.

<table>
<thead>
<tr>
<th>Number of participants (characteristics)</th>
<th>Vehicle for MSG</th>
<th>Study protocol</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 volunteers (age 18–34 years old; mean BMI 22.7 kg/m²)</td>
<td>Spiced carrot soup</td>
<td>3 hr after standardized breakfast, volunteers received 450 g of (a) low energy or (b) high-energy, high-carbohydrate and protein soup preload with added MSG/IMP (0.6% MSG [w/w] and 0.25% [w/w] IMP) or without MSG/IMP. Changes in appetite during soup intake and at a subsequent (after 45 min) ad libitum lunch were recorded.</td>
<td>Increase flavor and immediate appetite but reduced subsequent ad libitum test meal intake regardless of the protein content of the soup.</td>
<td>Masic &amp; Yeomans, 2014b</td>
</tr>
<tr>
<td>35 volunteers (age: 18–28 years old; mean BMI: 22 kg/m²)</td>
<td>Spiced carrot soup</td>
<td>3 hr after standardized breakfast, volunteers received 450 g of (a) low energy, (b) high-energy high-carbohydrate or (c) high-energy high-protein soup preload with added MSG [1 % (w/w) MSG] or without MSG. Changes in appetite during soup intake and at a subsequent (after 45 min) ad libitum lunch were recorded.</td>
<td>MSG addition enhances significantly compensation for energy added as protein. There were no differences between MSG or specific macronutrient conditions in rated satiety over the course of testing after preload intake.</td>
<td>Masic &amp; Yeomans, 2014a</td>
</tr>
<tr>
<td>30 infants (age: 1.0–3.7 months; Weight-for-length percentile at study entry: 63.9 ± 4.9)</td>
<td>Milk formula</td>
<td>Infants received iso-caloric formulas: (a) CMF (cow milk formula)—low in free amino acids and small peptides (b) ePHF (extensive protein hydrolysate formula)—abundant in free amino acids and small peptides or (c) cow milk formula with added free glutamate 84 mg/100 mL A second meal of CMF was given when hunger was signaled again.</td>
<td>Infants consumed less of formulas higher in free glutamate than of an iso-caloric formula lower in free glutamate, yet showed equivalent levels of satiation and greater levels of satiety.</td>
<td>Ventura, Beauchamp, &amp; Mennella, 2012</td>
</tr>
<tr>
<td>33 elderly individuals (age: 74.6-87 years old; BMI: 21.3 ± 2 kg/m²) and 29 young subjects (age: 19.1-23.5; BMI: 27.4 ± 4.9 kg/m²)</td>
<td>Mashed potatoes, spinach and ground beef</td>
<td>Volunteers rated pleasantness (10 point scale) of the 3 foods each with 0 g, 0.5 g, 0.8 g, 1.3 g and 2.0 g of MSG/100 g.</td>
<td>0.5% MSG (P &lt; 0.05) was preferred in mash potatoes. No optimal concentration was found for the other courses.</td>
<td>Essed et al., 2009</td>
</tr>
<tr>
<td>53 elderly (age: 74.6-87 years old; BMI: 26.5 ± 4.2 kg/m²)</td>
<td>Cooked meal</td>
<td>The participants were randomly assigned to the control group (placebo 1 g maltodextrine; n = 25), the MSG group (300 mg MSG + 700 mg maltodextrine; n = 24), the flavor group (700 mg flavor + 300 mg maltodextrine; n = 24) or to the flavor plus MSG group ((700 mg flavor + 300 mg MSG; n = 25) for 16 weeks. Anthropometry data (body weight, body composition), dietary intake of the cooked meal, pleasantness and appetite data were assessed.</td>
<td>➢ Body fat, total body water, and extra cellular water did not change within any of the four groups; ➢ No differences were found in changes in energy intake between groups.</td>
<td>Essed et al., 2007</td>
</tr>
<tr>
<td>83 elderly individuals institutionalized in a nursing home (age: 79.2 to 94.1 years old)</td>
<td>Tomato soup</td>
<td>Participants received (a) 1,200 mg/L MSG (0.12% MSG) + 3 g/L celery powder compared with (b) non-enhanced soup. The effect on intake and pleasantness was assessed.</td>
<td>➢ No difference in intake, liking, and strength between the soups was found; ➢ No difference was reported within the low olfactory/low gustatory group (elderly compared with young).</td>
<td>Essed et al., 2009</td>
</tr>
<tr>
<td>Number of participants (characteristics)</td>
<td>Vehicle for MSG</td>
<td>Study protocol</td>
<td>Results</td>
<td>Reference</td>
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</tbody>
</table>
| 35 women (age: 20 to 40 years old; BMI: 18.5-24.9 kg/m²) | Chicken broth | Participants received:  
- Preload 1 (given at 9:00 a.m.): 240 mL broth  
- Preload 2 (given at 11:00 a.m.): 240 mL broth  
- Ad libitum test lunch (12:30 a.m.)  
Four sessions were conducted each using one of the following broths (preloads): (a) base chicken broth (base broth), (b) chicken broth with MSG and nucleotides (MSG 1.2 g/serving), (c) chicken broth with MSG (MSG 1.2 g/serving), and (d) chicken with added fat. |  
➢ Hunger and desire to snack between the second preload exposure and the test meal were significantly reduced in the MSG condition relative to the base broth condition (both, \( P < 0.03 \));  
➢ The addition of MSG to chicken broth did not increase energy intakes at lunch or affect motivational ratings over the entire testing session. | Carter et al., 2011 |
| 60 volunteers (age: 19 to 63; BMI: 20–30 kg/m²) | Soup stock | On two separate experimental sessions, each subject determined (using a single blinded design) the lowest detected concentration of (a) MSG or (b) MSG + IMP. MSG was added in concentrations of 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8% (w/w) and IMP 0.25% (w/w). On each day, subjects assessed the sensory properties of the soup and their 'liking' and 'eating frequency' of high carbohydrate, fat and protein food items. |  
➢ The taste threshold (and therefore sensitivity) of MSG was lowered from 0.33 ± 0.24% to 0.26 ± 0.22% when 0.25% (w/w) of IMP was added;  
➢ 'Liking' and 'preference' scores for protein were found to be related to the threshold of MSG ± 0.25% IMP. | Luscombe-Marsh et al., 2008 |
| 22 volunteers (age: 19 to 63; BMI: 20 to 30 kg/m²) | Vegetable soup and rolls filled with minced meat | On five experimental sessions (single-blinded, randomized cross-over design), subjects consumed:  
- preloads consisting in (a) control (water); (b) a high-protein meal + 0.6% MSG w/w + 0.25% IMP-5 w/w; (c) high-protein meal with no additives; (d) a high-protein meal + MSG 0.6% w/w; (e) sham-fed meal 2 (sham high-protein + MSG + IMP).  
- ad libitum meal (after 30 min) |  
➢ The addition of MSG to a high protein meal does not influence the perceptions of appetite or satiety. It increases significantly the energy intake at a second course compared with high-protein meal with no MSG;  
➢ There was no significantly difference in the insulin and blood glucose responses between any of the high-protein conditions (with or without additives) (though GLP-1 values were higher for high-protein meal + MSG 0.6% compared with high-protein meal with no additives). | Luscombe-Marsh et al., 2009 |
| 86 women (age: 30 to 45; BMI: 20 to 26 kg/m²) | Chicken flavor broth | Volunteers received  
- preload: (a) a low-energy chicken flavor broth (200 mL); (b) broth + MSG (0.5 g/100 mL) (c) broth + MSG + IMP (0.05 g/100 mL)  
- ad libitum testing meal (snacks varying in taste and fat content) |  
➢ MSG and MSG + enhanced savory taste and broth properties;  
➢ MSG preload resulted in less consumption of total energy, as well as energy from sweet and high-fat snacks compared with control and reduced added sugar intake;  
➢ These findings were not observed after MSG + IMP preload;  
➢ Appetite ratings were not different across the three preloads. | Imada et al., 2014 |
| 13 volunteers (age: 30 to 50 years; BMI: 23 to 28 kg/m²) | Capsule Dietary adaptation for 2 × 7 days (cross-over, single-blinded design) | Volunteers received with food (a) MSG 2 g/day or (b) NaCl 0.87 g. On test day they received a test meal (38 g milk protein, 27 g fat, 99 g carbohydrate final volume of 600 mL) + (1) MSG 2g or (2) NaCl 0.87 g. |  
➢ MSG addition to the meal determines antral distension significant between 30 and 90 min compared with control. It elicited a significant increase in the area under the curve of plasma concentrations of glutamate, serine, cysteine, isoleucine, leucine, tyrosine, and ornithine at 60 or 120 min post-meal;  
➢ MSG favors the interaction between time and treatment on hunger sensation, but the effect is not significant, nor the effect on fullness;  
➢ No change in body weight, urea concentration, glycemia, plasma insulin, glucagon like peptide-1, and ghrelin compared with control. | Boutry et al., 2010 |
Table 10–Summary of epidemiological studies regarding the correlation between MSG consumption and obesity.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Number of volunteers</th>
<th>Protocol</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>China Health and Nutrition Survey</td>
<td>10,095 healthy Chinese adults (age 18 to 65 years old)</td>
<td>Diet, including MSG and other condiments, was assessed with a weighed food inventory in combination with three 24-hr recalls. The cumulative mean (±SD) MSG intake was 2.2 ± 1.6 g/day. MSG consumption was positively associated with BMI, in a dose-dependent manner, after adjustment for age, physical activity, total energy intake, and other major lifestyle factors. The adjusted hazard ratio of overweight was 1.33 (95% CI: 1.01, 1.75; P for trend &lt; 0.01).</td>
<td>He et al., 2011</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional study INTERMAP</td>
<td>752 healthy Chinese adults (age 40–59 years old)</td>
<td>Diet was assessed with four in-depth multipass 24 hr recalls. Average intake was 0.33 ± 0.40 g/day. MSG consumption was positively associated with BMI, in a dose-dependent manner, after adjustment for age, physical activity, total energy intake, and other major lifestyle factors. The multivariable-adjusted odds ratios of overweight (BMI ≥ 25.0 and ≥ 30.0) were 2.10 (P = 0.03) and 2.75 (P = 0.04).</td>
<td>He et al., 2008</td>
<td></td>
</tr>
<tr>
<td>Epidemiological survey (2009–2010)</td>
<td>349 healthy Thai adults (age 33 to 55 years old)</td>
<td>MSG was given as the sole source for the use in meal preparation for 10 days. Average MSG intake was 4.0 ± 2.2 g/day. The prevalence of overweight and obesity (BMI &gt; 25 kg/m²), insulin resistance (HOMA-IR &gt; 3), and the metabolic syndrome (ATP III criteria) were assessed. MSG intake increases the prevalence of the metabolic syndrome or of BMI in a dose-dependent manner, independent of the total energy intake and the level of physical activity.</td>
<td>Insawang et al., 2012</td>
<td></td>
</tr>
<tr>
<td>Jiangsu Nutrition Study</td>
<td>1,277 healthy Chinese adults (average age 49.3 years old)</td>
<td>Dietary intake patterns during the previous year were investigated by a series of detailed questions about the usual frequency and quantity of intake of thirty-three food groups and beverages. Average intake was 3.80 ± 4.30 g/day. MSG intake was not associated with significant weight gain, after adjusting for age, sex, multiple lifestyle factors and energy intake.</td>
<td>Shi et al., 2010</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional survey (2008)</td>
<td>1,528 Vietnamese adults (age ≥ 20 years old)</td>
<td>Dietary intake was assessed by the 24 hr recall method for 3 days. MSG intake was evaluated by the weighing method on three consecutive days. Average intake was 2.2 ± 1.8 g/day. MSG intake was not associated with significant weight gain, after adjusting for age, sex, multiple lifestyle factors and energy intake.</td>
<td>Thu Thu Hien et al., 2012</td>
<td></td>
</tr>
</tbody>
</table>

MSG consumption and it is not clear how many times it was assessed. Another issue of these studies involved extremely large differences in the mean MSG intakes (0.33 ± 4 g/day in the INTERMAP compared with 2.2 ± 1.6 g/day in the CHNS). The mean intake of the INTERMAP was similar to the lowest group in the CHNS study.

The Jiangsu Nutrition Study (JNS), showing a negative association between MSG consumption and body weight, also used an imprecise method for assessing MSG consumption: Members of each household were interviewed about their monthly consumption of MSG and other seasonings (Shi et al., 2010). These subjects were surveyed in 2002 and then followed for 5 years. In 2007, interviewers did not query the amount of MSG consumed in a month as in 2002, but estimated it based on a food frequency questionnaire.

The Thai epidemiological study is the only one in which participants were provided with a fixed amount of MSG (250 g) as the sole source of MSG for food preparation for 10 days. The amount used was determined on day 10, based on the remaining quantity. The MSG consumption was calculated by dividing the number of subjects over 10 years of age, in order to estimate grams/person/day.

Therefore, large clinical trials are needed to assess the effects of the long-term exposure to this food additive on satiety and food consumption, in relation to body weight and BMI, in which the daily MSG intake is closely monitored.

**MSG sensitivity**

The “Chinese restaurant syndrome” (CRS), later described as the “MSG symptom complex” (MSC), as MSG was incriminated as the main culprit (Freeman, 2006), consists of a series of symptoms such as weakness, flushing, dizziness, headache, difficulty in breathing, numbness, muscle tightness, and even syncope (Freeman, 2006; Niaz, Zaplatic, & Spoor, 2018; Walker, 1999; Williams & Woessner, 2009; Yang, Drouin, Herbert, Mao, & Karsh, 1997). MSG sensitivity is estimated to be less than 1% in the general population (Yang et al., 1997). In individuals that had a history of CRS or were MSG-sensitive, the administration of this flavor enhancer has been shown to cause mild to severe late onset (1 to 2 hr post ingestion) of asthmatic symptoms (Freeman, 2006). However, MSG sensitivity is usually self-assessed and placebo response is thought to play an important part in these reports (Freeman, 2006; Yang et al., 1997). Also, the cumulative effects that two or more additives can exert, must be taken into account, even if they are found at lower concentrations than their NOAEL (Kostoff, Goumenou, & Tsatsakis, 2018).

The first studies linking MSG to CRS had flawed designs and a low number of subjects. When the study population was increased in subsequent double-blind studies, no differences were detected between study and placebo groups (Freeman, 2006; Geha et al., 2000a; Tarasoff & Kelly, 1993; Williams & Woessner, 2009).

The administration of high doses (5 g) of MSG on an empty stomach to individuals with self-assessed MSG sensitivity induced
CRS-associated symptoms (Freeman, 2006; Yang et al., 1997), and intake of a high dose of MSG in the absence of solid food was linked to a higher incidence of several CRS symptoms (Bawaskar, Bawaskar, & Bawaskar, 2017).

Some case reports have linked MSG consumption to urticaria and angioedema (Williams & Woessner, 2009). In patients with chronic urticaria, a high MSG dose caused no changes, even in those who reported a previous exacerbation believed to be MSG-related (Simon, 2000). Other contradictory studies had design shortcomings, such as discontinuing chronic medication and failure to disguise the taste associated with MSG (Williams & Woessner, 2009), which must be taken into account since high-dose MSG solutions have an unpleasant taste and may cause gastrointestinal discomfort, affecting a “blind” study design (Obayashi & Nagamura, 2016).

Similarly, studies linking MSG consumption to asthma exacerbation had a small sample size and questionable study design, which involved the withholding of asthma medication (Freeman, 2006; Niaz et al., 2018; Williams & Woessner, 2009). A study enrolling a large number of Chinese adults found no association between MSG consumption and asthma (Shi et al., 2012). In addition, other smaller clinical studies found no link between MSG (1 g or 5 g each) and asthmatic symptoms (Woods, Weiner, Thien, Abramson, & Walters, 1998). Other studies have noted an association between MSG and rhinitis, rhinorrhea, sneezing, and nasal itching, with improvement of symptoms following an additive-free diet and relapse when MSG was administered (Williams & Woessner, 2009). However, due to lack of reliable clinical studies, no conclusions may be drawn as to the link between MSG and rhinitis symptoms.

**Impact on atopic dermatitis**

Intake of MSG was alleged to aggravate atopic dermatitis, a chronic remittent skin disease common in infancy and early childhood. The undesirable effects of MSG and other food additives on atopic dermatitis were previously highlighted (Van Bever, Dox, & Stevens, 1989; Worm, Ehlers, Sterry, & Zuberbier, 2000). Adult patients with atopic dermatitis, who consumed a diet low in pseudoallergens, including MSG, showed a significant improvement of their symptoms (Worm et al., 2000). Also, when breast-feeding mothers of children with atopic dermatitis avoided certain nut-related products and fermented foods such as soy sauce, 73% of children had significantly reduced symptoms (Uenishi, Sugiura, Tanaka, & Uehara, 2011).

Since atopic dermatitis is a complex disease, with inflammatory and immune-mediated pathogenesis, with a variety of environmental factors, contact allergens, and food additives that can act as trigger molecules (Kim, 2015; Overgaard et al., 2017). It seems plausible that food additives may worsen symptomatology, while an individualized, closely monitored additive-free diet might greatly benefit these patients. However, a direct link between MSG consumption and atopic dermatitis has yet to be established.

### Influence of MSG on pain-associated conditions

Several claims have been made as to the potentiating effect of MSG regarding headaches and migraines, although strong clinical evidence in support of such claims is lacking (Freeman, 2006). In studies with MSG administration with food, no significant differences were observed at doses of 1.5 to 3 g (Obayashi & Nagamura, 2016).

Oral administration of MSG in doses of 75 or 150 mg/kg to healthy subjects brought about a significant increase in the frequency of headache reports and subjectively reported pericranial muscle tenderness. The results of this double-blinded, placebo-controlled crossover study also showed an elevation of systolic blood pressure for the higher dose. No muscle pain or robust changes in mechanical sensitivity were reported (Baa-Hansen, Cairns, Ernberg, & Svensson, 2009). Other studies using MSG could not demonstrate a significant increase in the incidence of headache or the frequency of headache. It seems plausible that food additives may worsen symptomatology, while an individualized, closely monitored additive-free diet might greatly benefit these patients. However, a direct link between MSG consumption and atopic dermatitis has yet to be established.

### Table 11–Clinical studies regarding the impact of MSG consumption on headache.

<table>
<thead>
<tr>
<th>Study design</th>
<th>MSG vehicle</th>
<th>Number of participants</th>
<th>Protocol</th>
<th>Results</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blinded, placebo-controlled, crossover study</td>
<td>400 mL sugar-free soda</td>
<td>14 healthy participants</td>
<td>Volunteers received (a) MSG (75 or 150 mg/kg) or (b) NaCl (24 mg/kg, placebo) in three separate sessions</td>
<td>Significant increase in the incidence of headache (P &lt; 0.05) for MSG group 75 mg/kg, but not for MSG 150 mg/kg. Systolic BP was elevated in the high MSG session. Significant increase in the frequency of headache (P &lt; 0.05) for MSG group compared with placebo.</td>
<td>Baad-Hansen et al., 2009</td>
</tr>
<tr>
<td>Double-blinded, placebo-controlled, crossover study</td>
<td>400 mL sugar-free lemon soda</td>
<td>14 healthy participants</td>
<td>Volunteers received (a) MSG 5g or (b) NaCl (24 mg/kg), in two distinct 5-days sessions. Volunteers received (a) MSG 5 g one day or (b) no MSG (placebo) the following day</td>
<td></td>
<td>Shimada et al., 2016</td>
</tr>
<tr>
<td>Multicenter, multiphase, double-blind, placebo-controlled crossover study</td>
<td>200 mL citrus soda</td>
<td>130 self-reported MSG-reactive participants</td>
<td>Volunteers received (a) MSG 1.25 g, (b) MSG 2.5 g, (c) MSG 5 g or (d) placebo (no MSG), in four distinct 1-day sessions.</td>
<td>Significant increase in the incidence of headache for MSG 2.5 g and 5 g compared with placebo (P &lt; 0.05), not for MSG 1.25 g.</td>
<td>Geha et al., 2000b</td>
</tr>
<tr>
<td>Double-blinded, placebo-controlled, crossover study</td>
<td>200 mL citrus-tasting soda</td>
<td>36 participants</td>
<td>Volunteers received (a) MSG 1.5 g, (b) 3 g MSG or (c) placebo (gelatin powder) immediately followed by breakfast. The following 2 days, 300 mL soda containing (1) a 3.15 g MSG or (b) placebo.</td>
<td>No correlation between MSG consumption and headache.</td>
<td>Yang et al., 1997</td>
</tr>
<tr>
<td>Randomized double-blind, placebo controlled crossover study</td>
<td>Capsule</td>
<td>71 participants</td>
<td>On first 3 days, capsules containing (a) 1.5 g MSG, (b) 3 g MSG or (c) placebo (gelatin powder) immediately followed by breakfast.</td>
<td>No correlation between MSG consumption and headache.</td>
<td>Tarassoff &amp; Kelly, 1993</td>
</tr>
<tr>
<td>Soft drink</td>
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</tbody>
</table>
quantities ranging between 2.5 and 5 g also reported an increase in the incidence of headache (four out of five clinical studies; Geha et al., 2000b; Shimada et al., 2016; Tarasoff & Kelly, 1993; Yang et al., 1997). These studies are summarized in Table 1. Nevertheless, given the small sample size, it is difficult to extrapolate these results to the general population (Baad-Hansen et al., 2009; Shimada et al., 2016) and to determine a dose that exceeded the taste threshold, thus affecting the “blind” study design (Geha et al., 2000b). Taken together, there seems to be some evidence in support of the hypothesis that MSG might trigger headaches, but again, so may other food-derived molecules (Finocchi & Sivori, 2012; Taheri, 2017).

The results of a randomized, double-blinded, placebo-controlled study, showed that a single MSG administration (oral administration, 150 mg/kg) in myofacial temporomandibular disorder (TMD) patients, led to increased interstitial glutamate concentration in the masseter muscle, significantly increasing the intensity of spontaneous pain (Kitamura, Sato, Uneyama, Torii, & Nijjima, 2010).

MSG administration may also impact patients suffering from fibromyalgia. One study reported that the administration of 5 g of MSG, over 3 consecutive days, led to a worsening of fibromyalgia severity, as determined by the revised fibromyalgia impact questionnaire, and a nonsignificant trend toward worsening fibromyalgia pain, as based on a visual analog scale (Vellisca & Latorre, 2013). However, the administration of MSG and aspartame-free meals, did not improve symptoms of fibromyalgia in a trial enrolling 72 female patients suffering from this disease (Holton, Taren, Thomson, Bennett, & Jones, 2012). The results of the above-mentioned studies suggest a plausible link between MSG use and pain-associated conditions.

Implications for other umami molecules

The best-known umami molecule is MSG. Nonetheless, 5′-mononucleotides, such as IMP and GMP, can also be included in this category and, to some extent, other L-amino acids (Kitamura et al., 2010; Kochem & Breslin, 2017; Staniska & Krzeski, 2016; Wifall et al., 2007).

It is well established that IMP and GMP have umami effects on their own, yielding responses similar to MSG (Wifall et al., 2007). However, the pathway triggered by IMP ingestion, and central nervous integration of signals, is still only partially known (Tsurgizawa, Uematsu, Uneyama, & Torii, 2011). G-protein-coupled taste receptors TIR1/TIR3 and glutamate receptor 1, found mainly in the oral cavity and the gastrointestinal tract, but also in the pancreas, liver, adipose tissue, skeletal muscles, and hypothalamus, were shown to be activated, besides l-glutamate, by 5′-ribonucleotides (Blonde & Spector, 2017; Kitamura et al., 2010; Kochem & Breslin, 2017; Tsurgizawa et al., 2011).

The 5′-monophosphate nucleotides were found to augment glutamate effects in taste receptor cells and cortex (Festring & Hofmann, 2011; Nakamura et al., 2011; Narukawa et al., 2011; Tsurgizawa et al., 2011; Wifall et al., 2007), as the presence of IMP and GMP increases TIR1/TIR3 activation by glutamate (Blonde & Spector, 2017; Kinnamon & Vandenbeuch, 2009; Kochem & Breslin, 2017). GMP was found to be 2.3 times more effective than IMP in enhancing MSG stimulation, due to its ability to undergo Maillard-type reactions, yielding molecules with umami properties about six times higher than IMP (Festring & Hofmann, 2011). In addition to the MSG umami sensitivity enhancement, 5′-ribonucleotides increased sensations of sweetness and saltiness, while decreasing sourness and bitterness (Shim et al., 2015).

When testing IMP and GMP effects in rats, the two nucleotides were shown to possess similar detection thresholds and taste/hedonic qualities, with no capacity of discriminating between them (Wifall et al., 2007). However, although yielding analogous responses to MSG, the experimental animals were able to discriminate between 5′-mononucleotides and glutamate, as the nucleotides exhibited a lower detection threshold than MSG (Wifall et al., 2007).

Studies on taste receptors in solitary tract cells of rats showed that some receptors are activated by both MSG and GMP while others responded to either MSG or 5′-ribonucleotides (Kinnamon & Vandenbeuch, 2009; Wifall et al., 2007). Receptors for IMP and MSG are present in the oral cavity. Gastric administration of IMP and MSG has been shown to stimulate distinct brain areas, indicating the existence of some differences in their signaling pathways (Tsurgizawa et al., 2011). Effects on the activity of the celiac vagus nerve and on the adrenal splanchic nerve were analogous to those of glutamate, and blocking the vagal gastric innervation resulted in blockade of IMP and glutamate signaling. Thus, 5′-ribonucleotides are implicated in controlling intestinal motility and secretory activity in the gastric phase of digestion (Kitamura et al., 2010). Moreover, it was found that gastrically administrated IMP can interfere, in a dose-dependent manner, with the activity of the vagal gastric afferent nerve, resulting in triggering vago-vagal and vago-sympathetic reflexes, while glucose, sucrose, and sodium chloride administration failed to do so (Kitamura et al., 2010).

Another molecule that potentiates MSG effect on palatability is sodium chloride. Dietary use of sodium chloride (NaCl) was associated with noticeable odor and flavor enhancement effects (Ventanas, Mustonen, Puolanne, & Tuorila, 2010). However, it is well known that high dietary sodium (Na⁺) intake is linked to an increase of blood pressure, and more than 85% of Na⁺ is being consumed as table salt (McCullam, Lip, & Padmanabhan, 2015). MSG can be used to substitute NaCl as a flavor enhancer in low-sodium products, as it does not substantially increase the total Na⁺ content, while the pleasantness of reduced-salt foods was reported to increase upon its addition (Roiminen, Lahteenmaki, & Tuorila, 1996).

Both sodium and glutamate contribute to the flavor-enhancement effect in an independent manner (Oikyama & Beauchamp, 1998). It was reported that when NaCl levels were reduced from their optimal concentration of 0.92%, the palatability score decreased dramatically. However, a concentration of 0.38% MSG and 0.41% NaCl caused the recovery of the initial 0.92% NaCl-yielded palatability rating. Moreover, a 32.5% reduction in sodium levels was possible by adding 0.7% MSG to the spicy soups (Jinap et al., 2016; Yamaguchi & Takahashi, 1984). As such, a reduction in total sodium intake is possible by partly substituting dietary NaCl with MSG, while maintaining of food palatability.

MSG administration had no influence on the postprandial glucose, insulin, glucagon-like peptide (GLP)-1, and ghrelin when compared to NaCl-supplemented meals. Subjective assessments of hunger and fullness were neither affected by MSG supplementation. It seems that MSG supplementation promoted greater postprandial elevations of several indispensable amino acids in plasma suggesting a sparing effect on the uptake of some amino acids (Di Sebastiano et al., 2013).

Addition of MSG, alone or in combination with IMP, to a high-protein meal did not lead to changes in appetite and in GLP-1, glucose, or insulin levels (Imada et al., 2014).
In addition to MSG, analogous molecules also possess noteworthy umami properties and can be used for enhancing MSG effects, or for reducing the quantity of MSG/NaCl added in food products for the improvement of palatability, thereby diminishing any possible undesired effects.

Discussion

MSG was originally defined by the FDA as a GRAS substance and its safety has been repeatedly reaffirmed by various sources within the scientific community, including the JECFA and EFSA. However, in June 2017, EFSA reassessed the safety of dietary glutamates and found a group ADI of 30 mg/kg/day (expressed as glutamic acid), highlighting that this is frequently exceeded in all age groups.

The numerous negative effects reported by preclinical studies (Figure 2) are a matter of debate, as several shortcomings of these studies (Figure 3) are apparent, namely: lack of adequate control groups, small sample size, methodological flaws, lack of dosage accuracy, or usage of extremely high doses far exceeding those unattained in normal diets. The route of administration is another important issue that must be addressed, with effects varying accordingly, as presented in Figures 4, 5, and 6. Subcutaneous or intraperitoneal administration of high doses in preclinical studies has little, if any, relevance to dietary human exposure, as they bypass the normal metabolic pathway of orally ingested MSG. Another issue that would benefit from further studies is the impact of dietary MSG on fetal development. Preclinical studies indicated behavioral changes in the rats born from mothers exposed to MSG, but due to the design of these studies, it is hard to establish their relevance for human prenatal exposure.

Most clinical trials have focused on food consumption and energy intake effects (Figure 7). In addition to its impact on food palatability, MSG exhibited the ability to enhance salivary secretion and to interfere with carbohydrate metabolism, while its impact on satiety and post-meal recovery of hunger varied in relation to meal composition.

Reports on MSG hypersensitivity or links of its use to atopic dermatitis were found to have little supporting evidence. Furthermore, MSG was considered a possible trigger agent for some types of pain, including headache and fibromyalgia-associated pain, although strong clinical evidence supporting these claims is lacking. We consider that the influence of chronic exposure to low doses of this flavoring agent on nociception is still not fully understood and that further investigations could help clarify this matter. Moreover, this is also intriguing from the pharmacological point of view: could MSG consumption interfere with the pharmacodynamic effect of analgesics?
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Figure 5—Subchronic exposure in adult rodents—oral administration. NOAEL, no-observed-effects level; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase.

Figure 6—Acute exposure in adult rodents—parenteral administration. NOAEL, no-observed-effects level.

Conclusions

Based on a critical analysis of existing literature, we posit that many of the reported negative health effects of MSG have little relevance for chronic human exposure to low doses. In order for preclinical studies to be significant for human dietary intake, they must mimic the real context of exposure to flavor enhancers (adequate species, dosage, route of administration). Moreover, clinical and epidemiological studies need to have an optimal design, accounting for both added and natural originating MSG, thereby reporting accurate and significant data that truly impart relevant information on its health effects. Furthermore, we consider that the assessment of MSG impact on nociception and on fetal neurodevelopment, following chronic exposure to dietary doses, represent valid research directions that should be considered.

Author Contributions

Anca Zanfirescu has contributed to: Introduction; Effects on cardiovascular system; Impact on CNS function and morphology; Effects on food consumption and energy intake; Figure 4, 5, and 6; Anca Ungurianu has contributed to: Introduction; Methods; Evaluation of hepatotoxicity; MSG sensitivity; Implications of other umami molecules; Figure 4, 5, and 6; Paper editing and preparation; Aristides M. Tsatsakis has contributed to critical review of the manuscript; George M. Nitulesscu has contributed to: Effects on fertility and fetal development; Other effects associated with MSG administration; Demetrios Kouretas and Aris Veskoukis have contributed to Figure 2, 3, and 7; Dimitrios Tsoukalas contributed to: Impact on pain-associated conditions; Conclusions; and critical review of the manuscript.

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Conflict of Interest

The authors have no affiliation with entities/organizations with any interest in the subject matter addressed in this paper and have no conflict of interest to declare.

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