

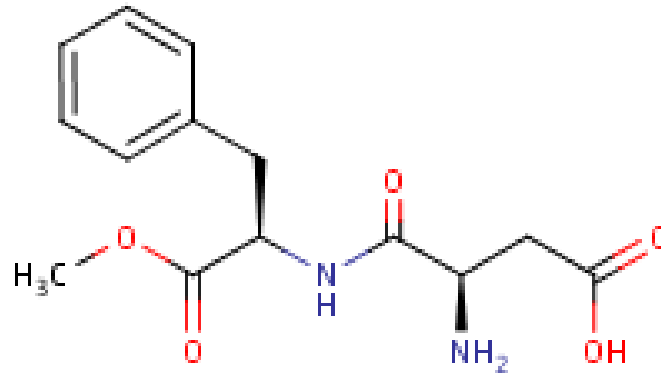
- Polypeptide (34 AA) produced by *Lactococcus lactis*
- Anti-microbial, affects cell membrane, gram positives
 - Puddings
 - Cheeses
 - Liquid egg
- ADI 0.13 mg/kg bw/d
- Ingested nisin inactivated by digestive enzymes, so no effect on gut flora

[EFSA 2004]

Case Study : Aspartame

Anne Constable
Nestle Research Centre
ILSI SA June 2014





- 200x sweeter than sucrose
- In 6000 products, consumed around the world
- Evaluated by US FDA, JECFA, SCF, EFSA:
1980, 1985, 1988, 1997, 2002, 2005, 2006, 2009, 2011, 2013

- Metabolised rapidly in the body to phenylalanine, aspartic acid, methanol.
- PKU individuals may need to avoid sources of phenylalanine (labelling)
- Extensive toxicological database
- ADI of 40 mg/kg bw/d .

- Consumer reports of adverse health effects post-launch
- Intake assessment by household menu survey (market research)
- Collection and evaluation of anecdotal reports by independent authority (CDC/FDA)
 - Intake confirmed to be within limits (up to 10.43 mg/kg bw/d)
 - Safety confirmed by additional targeted studies in humans and animals
 - No link between aspartame consumption and reported adverse events
 - Epidemiological studies do not support a consistent association with various types of cancers

Marinovich et al (2013) Aspartame, low calorie sweeteners and disease: Regulatory safety and epidemiological issues. Food and Chemical Toxicology , 60, 109 - 115



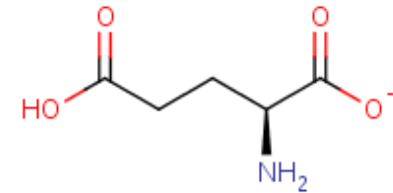
Case Study 2

Monosodium Glutamate

Anne Constable
Nestle Research Centre
ILSI SA
June 2014



- MSG is the sodium salt of the *non-essential* amino acid glutamic acid (glutamate)
- Glutamate naturally occurs in food incorporated into proteins, or in free form.
- Free form has flavour enhancing properties.
- Commercial MSG – 99% of L-glutamic acid.
- Flavour enhancer and food additive.
- Produced from fermentation processes (molasses), starch hydrolysates (corn, tapioca, ..)
- L-Glutamic acid and its ammonium, calcium, monosodium and potassium salts.



- MSG is one of the most extensively studied food ingredients in our food supply. Hundreds of studies and numerous scientific evaluations have concluded that monosodium glutamate provides a safe and useful taste enhancer for foods.
- Despite a small number of persons reporting sensitivity , scientific studies have not shown any direct link between MSG and adverse reactions from foods.
- <http://www.eufic.org/article/en/page/FTARCHIVE/artid/monosodium-glutamate/>

- **Group ADI of ‘not specified’ to L-glutamic acid and salts**
- Applied to substances of low toxicity for which the total dietary intake arising from its use as the levels necessary to achieve the desired technological effect and from its acceptable background in food is not considered to represent a hazard to health.
- Included particular consideration of
 - Neurotoxicity
 - Chinese Restaurant Syndrome

Incorporated into Proteins

- Animal 11 – 22g/100g protein
- Plant < 40g/100g protein



20% of ingested protein

- Breast milk 0.2g/100 g (free GLU = 22mg/100g)
- Vegetables 0.2 – 5 g/100g

As 'free' GLU

- Vegetables 0.33 – 0.2g/100g
- Soy sauce 0.4 – 1.2g/100g
- Sauces, mixes, seasonings 0.02 – 1.9g/100g
- Chinese restaurant meals < 0.01 – 1.5g/100g
- Western restaurant meals < 0.01 – 0.7g/100g

0.2 – 2g/100g

- From natural occurrence in food
 - **10 – 20g / day (170 – 330 mg/kg bw/d)**
- Breast fed infants
 - Total GLU **400 mg/kg bw/d (36 mg/kg bw/d free GLU)**
- From use as flavouring agent
 - **0.5 – 1- 5 g / d (8 – 25 mg/kg bw/d)**
- Use levels 0.2 – 0.8% in final food product
- Highest palatable dose 3.6g (60 mg/kg bw)
- Highly seasoned meal up to 5g in one serving (?)

- Same if ingested as free GLU or incorporated in proteins (released by digestion)
- Mainly absorbed and metabolised by intestinal mucosal cells
 - Energy source
 - Precursor for other amino acids
 - Precursor for glutathione
- Only enters circulation at very high oral doses (eg > 5g MSG).
- Uptake reduced in presence of other metabolisable substrates (carbohydrates, i.e food)

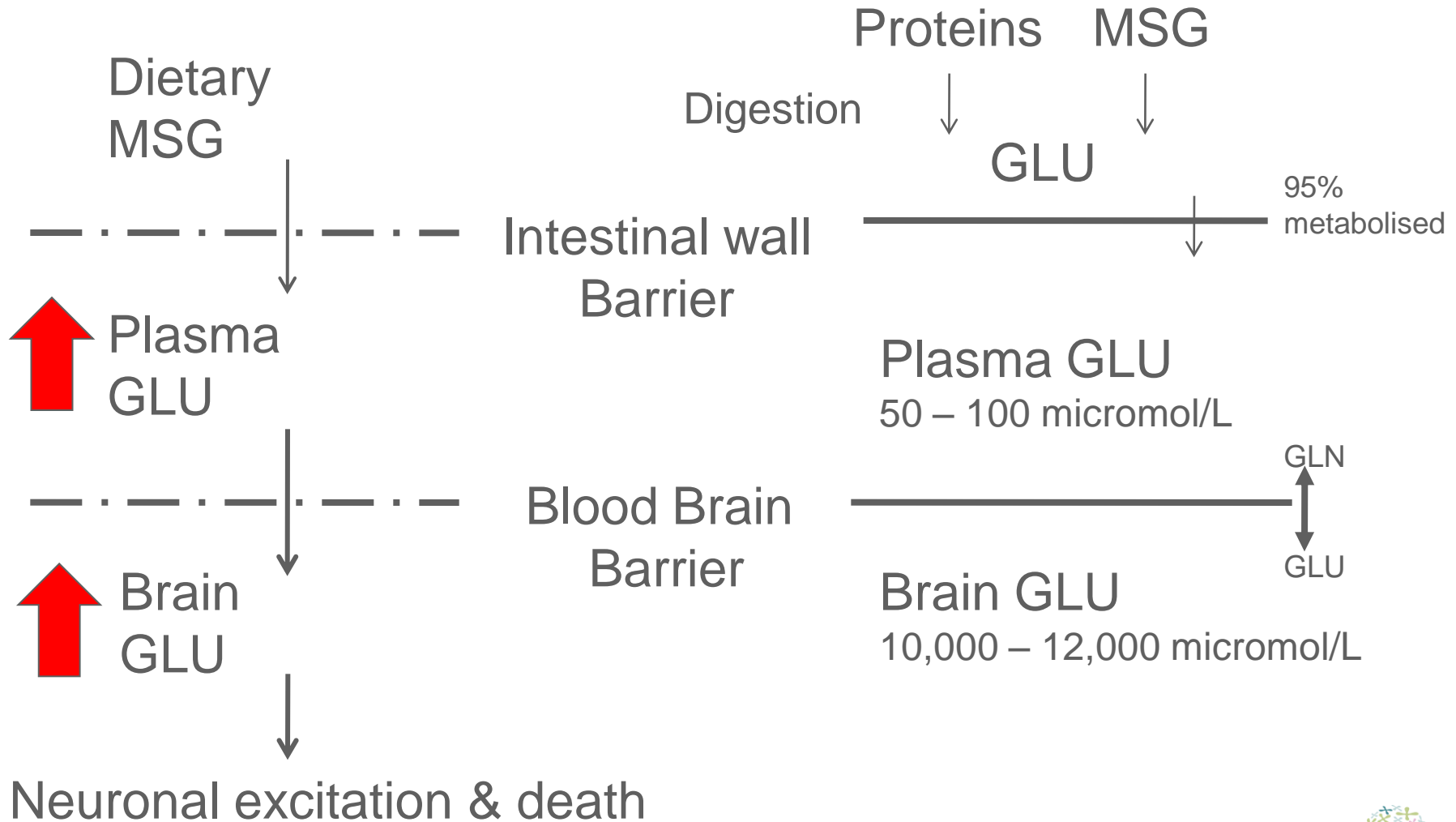
- Extensive toxicological database
- Long Term *Dietary* studies – incorporated into feed/water
 - Up to 4% in diet of rats
 - Up to 10% in diet of dogs
 - No adverse effects (**2.5g/kg bw/d**).
 - (1000x higher than human exposure)
- No adverse effect on reproduction/development
- No genotoxic or carcinogenic potential

- Taste perception
- Intermediary metabolism – Krebs cycle to produce energy for cellular reactions, fuel reserve
- Neurotransmitter (endogenously formed)
- Concentration of Glutamate in body fluids
 - Plasma 50 – 100 micromol/L
 - Brain 10,000 – 12,000 micromol/L
 - Extracellular Fluids 0.5 – 2 micromol/L
- BBB is impermeable to glutamate, even at high concentrations.
- Glutamate – glutamine trafficking at blood brain barrier to maintain endogenous concentrations

- At least 59 studies reviewed by JECFA.
- Species, doses, mode administration
- Mice (most sensitive species)
 - Extremely large oral bolus doses (gavage) of **1g/kg BW**, or when injected, caused lesions in the brain.
 - Threshold levels causing effect : 100 – 130 micromol/dL. (**1000 – 1300 micromol/L**)
 - Not when given in the diet
 - Oral ED50 in neonatal mouse is **500 mg/kg bw by gavage**
- Only observation from feed was when deprived of food and water o/n, then given solutions of 40% MSG as sole water source

Concern

Science



- High plasma levels not recorded after bolus doses of 150 mg/kg bw (10g adult)
- (*Largest palatable dose for humans (3.6g) causes nausea*).
- Infants no more at risk than adults (metabolised effectively)
- Not transferred through the placenta
- The human brain is unaffected by the plasma (GLU) following high dose MSG intake
- No dose of MSG has yet been given to humans high enough to induce CNS effects.

- **‘Chinese restaurant Syndrome’**
 - Anecdotal reports from 1960’s.
 - After eating Asian food (containing many ingredients.....)
- Acute, temporary:
 - Tingling neck, forearms, chest
 - Headache, Nausea
 - Palpitation, Chest pain
 - Bronchospasm
 - Drowsiness
- **‘MSG complex syndrome’** – includes protein hydrolysates, other natural sources of GLU.
- Continued reports..... In 1995 FDA commissioned a review – Federation of American Societies for Experimental Biology (FASEB).

- Double-blind, cross-over studies, dose-response studies of pure MSG, and of MSG in food matrix.
- Advertised for MSG sensitive individuals:
 - From a population of \cong 25 million
 - Total inquired = 178
 - Total entered = 132
- None of the individuals who claimed a sensitivity to MSG actually showed this sensitivity when tested under blinded conditions

[Geha RS et al. J Allergy Clin Immunol 106:973-80, 2000]

- Controlled double blind crossover trials failed to demonstrate an unequivocal relationship between CRD and consumption of MSG.
- [Subset that responds, within 1 hr exposure, when exposed to oral bolus dose of 3g in the absence of food] (*relate to single dose challenges in capsules /simple solutions – not relevant for prediction of adverse effects from food uses*). ??
- Did not consider evidence regarding sensitivity of asthmatics compelling.
- **FDA accepted conclusion that serious neurotoxicological effects from MSG is limited to animals given very large doses by parenteral, pharmacologic or other non-dietary conditions of use.**

- FSANZ (2003) Monosodium glutamate : A safety assessment. Food Standards Australia New Zealand. Technical Report Series No 20, June 2003
- JECFA (1988) Toxicological evaluation of certain food additives. 31st meeting of the FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 22.
- JECFA (2006) Safety evaluation of certain Food Additives Prepared by 63rd meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additive Series 54
- SCF (1991) Reports of the Scientific Committee for Food. First series of food additives of various technological functions (Opinion expressed on 18 May 1990) Twenty fifth series. EUR 13416EN Luxembourg.
- FASEB 1995 Analysis of Adverse Reactions to Monosodium glutamate

- Overwhelming evidence from a large number of scientific studies MSG is safe for general population at levels incorporated into various foods. This has been confirmed by a number of expert bodies.
- Small % of population *may* experience a mild hypersensitivity to large amounts in one meal; no convincing evidence for serious reactions.
- *‘If you suspect you might be reacting to MSG, should be confirmed by appropriate clinical assessment’..... ‘Obtain dietary advice’*
- *MSG, hydrolysates, tomatoes*