Toxicology of Selected Food Additives
Food Toxicology
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Learning Objectives
• Explore the national and international agencies that study the safety of food additives
• Review the use, safety review, and toxicology of saccharin, cyclamate, aspartame, BHA/BHT, sulfites, and MSG.

Agencies and Safety of Food Additives
• Joint FAO/WHO Expert Committee on Food Additives (JECFA)
• 1950 by FAO of United Nations and WHO
  – Assess safety of chemical food additives internationally
• Independent scientists
  – International

Agencies and Safety of Food Additives
• Codex Alimentarius Commission (1960)
  – Establishes international food standards
    • CODEX GENERAL STANDARD FOR FOOD ADDITIVES (GSFA) ONLINE DATABASE
    • http://www.codexalimentarius.net/gsfaonline/index.html?lang=en
  – Protect health and promote international food trade
  – Use JECFA for tox evaluation

Agencies and Safety of Food Additives
• Federation of American Societies for Experimental Biology (FASEB)
  – Does external safety evaluation for FDA since 1958
  – Did much of GRAS and “prior sanctioned”
  – Independent scientists

Agencies and Safety of Food Additives
• EEC Scientific Committee for Food (SCF)
  – European group similar to FDA
  – Reviews food safety issues
  – Independent scientists

Focus Food Additives
• Saccharin
• Cyclamate
• Aspartame
• BHA/BHT
• Sulfites
• MSG

Saccharin
• Discovered in 1869 (accidentally)
• 300x sweeter than sugar
• Heat-stable, long shelf life
• Originally used for diabetics
• Slightly bitter/metallic aftertaste
• Synergistic w/other sweeteners
• 1:10 ratio w/cyclamate popular

Saccharin
• Controversial from beginning
• Harvey Wiley (FDA) wanted to ban
  – “Anybody who says saccharin is injurious to health is an idiot”
    --President Theodore Roosevelt
• Banned for short time
• Reinstated-WWI
  – Sugar shortage
• Used extensively in WWII
• 1958 given GRAS status

Saccharin
• 1972 -Two studies indicated bladder carcinogen, rats
• 1972 - Removed from GRAS status
• 1977 - Banned by FDA
• Major public outcry
  – A million letters to congress
  – 100,000 letters to FDA

Saccharin
• 1977 Saccharin Study and Labeling Act
  – Declared moratorium on ban
  – Required warning label on products
• Hundreds of studies on saccharin
  – Epidemiological and chronic bioassays
  – No effects in humans
• 2000 - ban repealed

Saccharin

• Acute toxicity
  – 15-17 g/kg, rat/mouse
  – 5.8 g/kg rabbit
• ADI = 2.5 mg/kg bw - FAO/WHO

Conclusions

• Bladder carcinogen in rats
• Epigenetic/promoter
• Species specific due unique protein
• High doses, long exposure
• Mechanism - cell proliferation

Cyclamate

• 1937-discovered by grad student
• 30x sweeter than sugar
• Less bitter aftertaste than saccharin
• Heat-stable
• 20x cheaper than saccharin
• 1950-dietetic aid-Abbott Labs

Conclusions

• 1955-NAS reported safe for human consumption
• 1958-given GRAS status by FDA
• 1968-70-two studies showed bladder cancer
• 1968-taken off GRAS status
• 1970-banned from all uses

Cyclamate

• 500 new studies showed no cancer
• FDA still would not approve
  – “could not show it was not a carcinogen”
• SOT position paper stated this was
  “a classical example of how NOT to interpret toxicology data”

Cyclamate

• 1984-petition to reinstate based on 15 new epidemiological studies
  – Showed neither saccharin nor cyclamate cause bladder cancer
• 1985-FDA Cancer Assessment Committee exonerated cyclamate
• 1985-NAS exonerated cyclamate
• Still banned

**Cyclamate**

*Why is it Still Banned?*

• Approved in 40 countries
• NAS, WHO, EEC consider safe
• FDA scientists consider safe
• Example of FDA failure to admit mistake?
• Politics not good science?

**Aspartame**

*Nutrasweet*

• 1960 - discovered by Searle scientist by accident
  – Gastric peptide: N-L-a-aspartyl-L-phenylalanine
  – 1-methyl ester
• 180x sweeter than sugar
• Dipeptide
• aspartic acid,
  – Phenylalanine
• No sweet effect separately

**Aspartame**

• Enhances flavors of fruits
• Shelf-life 6 months
• Better for dry formulations
• Not heat-stable, sweetness varies with pH and temp
• Natural product safety
  – Found in dairy, meat, cereal, grains, vegetables

**Aspartame**

• 1974 - petition as food additive
  – 113 supporting studies (most ever)
• Approved but stayed
  – Concerns about brain damage, mental retardation and endocrine disruption
  – Phenylalanine neurotoxicity
  – Aspartic acid/glutamate neurotransmitters
• All studies on brain/endocrine negative
• Approved by FDA 1981
• Label must indicate “phenylketonurics: contains phenylalanine”
• ADI = 40 mg/kg bw - FAO/WHO

A Taste of Controversy
Aspartame

Other

• Breaks down into
  – 50% phenylalanine
  – 40% aspartic acid
  – 10% methanol
• Aspartic acid transaminated to glutamate
  – Both neurotransmitters
• Diketopiperazine metabolite

Aspartame

Conclusions

• All toxicology studies negative at relevant doses
  – Ongoing scientific study
• May be idiosyncratic responses
  – Migraine headaches
  – Urticaria (hives)
• Endorsed by AMA, Am A Pediatrics, Am Diabetic Assoc, Am Dental Assoc

Phenolic Antioxidants

• Butylated hydroxyanisole (BHA)
• Butylated hydroxytoluene (BHT)
  – Synthetic antioxidant chemicals
  – Antimicrobial properties
  – Prevent oxidation (rancidity) of fats
  – Oxidized fat
    • Off taste and smell and health hazards

Phenolic Antioxidants

• Used in a variety of foods
  – Dry cereals, dry mixes, dry soups, potato flakes, crackers, meat and fish, beer and many others-cosmetics
- Markedly increase shelf life of dry cereals from 2 to 50 days
- Greatly reduce cost of products

**Phenolic Antioxidants**

- GRAS status in 1958, later modified
- Tolerances are now set for each food
  – 0.02% of fat/oil content
- ADI =
  0.3 mg/kg BHA
  0.125 mg/kg BHT

**Phenolic Antioxidants**

**Toxicology Concerns**

- Liver enlargement
- Stored in fat
  – Slowly excreted-BHT
- Slow DNA/RNA synthesis *in vitro*
- Reduce cell growth *in vitro*
- Cause chromosomal anomalies *in vitro*
  – Conflicting studies
- Idiosyncratic sensitivity

**Phenolic Antioxidants**

**Carcinogenicity**

- Positive lesions in rat forestomach
- Negative in species w/o forestomach and NCI rat study
- Positive in fish
- Effects seem to depend on dose, timing, tissue and species
- Protective for several carcinogens

**Positive Effects of BHA/BHT**

- Inhibit cytochrome P450 activation
- Induce Phase II enzymes
  – Epoxide hydrolase
  – Glutathione S-transferase
  – UDP-glucuronyl transferase
Health Effects of Oxidized Fats

• Vitamin E deficiency
• Oxidative damage to cell membranes
• Mutagenic, carcinogenic and cytotoxic

Sulfites
• Antioxidant and antimicrobial
• Prevent enzymatic and non-enzymatic browning of food
• Used since ancient times
• Amount added to food limited by taste (500ppm), nutritive value and law

Sulfites
Problems
• Destroy thiamin (Vit B1) in food
• Small percentage of individuals are sensitive to free sulfite
  – <1% of consumers
  – 5% of asthmatics
• Symptoms can be severe to mild
  – Anaphylactic shock, death, hives, stomach ache

Sulfites
• GRAS in 1958
• 1986 GRAS status revoked on fresh fruits and veggies
  – Categories of food that could not be readily labeled
    • Salad bars, grocers
• 1987 all packaged food and alcoholic beverages >10ppm required label
• ATF - wine <350ppm (avg 150)

Sulfites
Other
• Help retain nutrients - carotene
• Prohibited from use on fresh meats/veggies and thiamine foods
  – Retains color but not safety
Monosodium Glutamate (MSG)

- Flavor enhancer
- Discovered in 1907 from kombu (kelp soup)
- Synthesized from fermented starch, sugar cane, sugar beets
- 5th basic taste “umami” (savory)

Monosodium Glutamate

- Sodium salt of glutamic acid
  - One of the most common aa in food/body
  - Glutamate 1/5 body protein
- Consume 0.5-1.0g/da free glutamate
- Consume 20g/da bound glutamate
- Very small fraction from MSG
- Glutamate foods - cheese, meat, peas, tomatoes, mushrooms, etc.

Chinese Restaurant Syndrome

- Anecdotal self diagnosed condition
- Onset - 20 min, duration - 2 hr
- Flushing, paresthia, chest pain, labored breathing, dizziness, sweating, headache, nausea, vomiting
- MSG Symptom Complex

Chinese Restaurant Syndrome

- Many controlled studies fail to confirm
- Double-blind placebo to people that were sensitive
  - Equal symptoms at any dose
- 43% of 3000 surveyed - some discomfort after any meals
- 1-2% allergy/intolerance not CRS

Monosodium Glutamate

- Glutamate: brain neurotransmitter
• Injected MSG: brain lesions in young rats
• No effect orally at any dose up to 40% in diet for adult rodents, dogs, rabbits, monkeys
• No effect-humans - 120g/da

Safety Studies: MSG
  – Small percentage of population may be sensitive to high doses (CRS)
  – Problems w/ severe untreated asthma (CRS)
  – No major health problems
• ADI = unspecified
  – Safest category

MSG
Conclusions
• CRS not reproducible
• Some allowance given based on epidemiology
• Small % allergic or intolerant
• Neurotransmitter not a problem
• All agencies regard as safe
• GRAS status