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- 2000 - ban repealed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

Saccharin

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

Cyclamate

- 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

Aspartame

- 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

  - Destroys Vitamin E
- ADI = 0.7 mg/kg bw
- 37 mg/120lb person
- EDI = 6-10 mg

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 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

Other Concerns

- 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

- 1980 FASEB, 1986 FDA, 1991 EEC, 1992 AMA
  - 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