Food Additive Safety Assessment
Food Toxicology
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Learning Objectives
• Understand the background and principles of safety assessment of food additives.
• Review the quantitative assessment of dietary exposure to food additives and the development of concern levels.
• Explore the basics of testing related to food additive safety.
• Explore the relationship between food type & food packaging in food additive safety assessment.
• Understand the interaction of the Delaney Clause and food additive regulation.

Food Additive
• A substance which may, by its intended use, become a component of food, either directly or indirectly, or which may otherwise affect the characteristics of food.
  – Includes any substance intended for use in producing, manufacturing, processing, preparing, treating, packaging, transporting or holding food, and any source of radiation intended for such use.

Scope of Food Additives
• ~3000 additives
• ~1800 flavoring agents
• Texturing agents used in highest quantity
• Soft drinks are biggest market
• 4 direct food additives = 93% of total
  – Sucrose, salt, corn syrup, dextrose

Six Categories of Food Additives
• Texture
  – Emulsifiers
  – Stabilizers
• Miscellaneous
  – Enzymes
  – Catalysts
  – Solvents
  – Propellants
• Preservatives
  – Antimicrobial
  – Antibrowning
  – Antioxidant
• Nutritional
  – Vitamins/minerals
• Flavor
  – Flavor enhancers
  – Sweeteners
  – Nat/syn flavors
• Color

Consumption of Food Additives
• 139 lbs/year/person
• 5 lbs/year if remove common ones
  – Spices, sugars, salt, honey, pepper, mustard, dextrose, etc
• 75% people concerned about food additives
• 60% try to avoid
• 6% could name one

Consumption of Color Additives
• Estimated max = 53 mg/da
• Estimated average = 15 mg/da
• About 10% of foods contain food coloring

Food Additives Numbering Systems
• E System
  – Developed by the European Economic Community (EEC)
• Number and description
  – e.g. “E123 Amaranth, Colour – Red”
• Additives considered safe and allowed between countries
• Nutrient additives
  not included

Food Additives Numbering Systems
• International Numbering System
• Developed by Codex Alimentarius
  – Commission Committee on Food Additives and Contaminants
  – Broader than E system
  – e.g. “491 Sorbitan Monostearate; Emulsifiers and Stabilisers; salts or Esters of Fatty Acids”
• Does not imply toxicology approval
  – INS largely E w/o E in number
  – 23 functional classes

Food Additives
• Direct food additives
• Certified color additives
• Exempt color additives
• Unintentional additives
  – Tolerance based; Action level based

Exempt Chemicals
• GRAS (Generally Recognized as Safe)
  – From scientific studies or wide usage
  – Salt, vitamins, etc.
  – GRAS - qualified experts determined safe
  – May not be FDA decision (GRAS)
  – Company can self-proclaim (GRAS)
• “Prior Sanctioned” before 1958
  – Prior sanctioned – approved by FDA/USDA prior to 1958
  – Sodium nitrite, etc.

GRAS Ingredients
• Not food additives
• Exempt for pre-market clearance but must be supported by safety data
• Exempt from Delaney Clause
• GRAS list in CFR is not inclusive
GRAS Ingredients: 1997 Changes
• Not all GRAS petitions will be rigorously reviewed
• Company will submit intention to list as GRAS
• FDA may or not review
• Speeds process and better directs resources

Regulated Food Additive
• Food additives that are not color, or GRAS, or prior sanctioned
• Require FDA approval
• Scientific data that no harm will occur
  – “Redbook” guidelines
• Must justify function
• 32 categories (C&D)

Food Additives Approved Since 1970
• Sucralose acetate isobutyrate 1999
• Sucralose 1998
• Olestra 1996
• Gellan gum 1990
• Acesulfame K 1988
• Polydextrose 1981
• Aspartame 1981
• TBHQ 1970

Color Additives
• Same testing as food additives
• Not eligible as GRAS
• Tested at all FDA concern levels
• Two types
  – Certified - by FDA chemists for purity
  – Exempt - mostly naturally occurring

Certified Color Additives
• Prefix of FD&C
  – Two exemptions: Orange C, Citrus Red 2
• Every batch must be FDA certified
• Aromatic amines, aromatic azos
– Unusually nontoxic for these compounds

**Exempt Color Additives**
- Usually naturally occurring (25)
  - Dried algae, beet powder, grape skin extract, fruit juice, caramel, etc.
- Lack precise chemical identity
- Fade readily, lack intensity and uniformity
- Higher levels required
- Used less (except caramel)

**Contaminant Tolerances**
- For unavoidable contaminants
- Acceptable level established
- Any food cannot exceed level
- Enforceable levels
  - PCB, metals, Nitrosochemicals

**Contaminant Action Levels**
- Informal tolerances
- Not legally enforceable
- Allow flexibility between different foods (e.g. aflatoxin)
- Based on estimated exposures

**Unintentional Food Additives**
- Packaging materials
  - BHA/BHT, PCP, polymers, metals
- Processing chemicals
  - PAH (from cooking), solvents (from extractions)
- Environmental
  - Natural and anthropogenic
  - Pb, Hg, pesticides, fumigants

**Tests Required**
- FDA Redbook Guidance
- *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*
- What is the safe dose (ADI)?

**Definitions**
- **Reference Dose (RfD):** An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
  - Can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

- **Acceptable Daily Intake (ADI):**
  The amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects.

### Safety Testing of Food Additives

- **Acute/Short-term = LD_{50}, DRC**
- **Subchronic - MTD**
- **Chronic - NOAEL, ADI, RfD**
- **Carcinogenic/Mutagenic**
- **Developmental toxicity**
- **Immunotoxicity**
- **Neurotoxicity**
- **Metabolic, analytical, etc.**

### Estimating Exposures

- Must establish Estimated Daily Intake (EDI) for:
  - Direct food and color additives
  - Indirect food additives
- The sum of EDIs for an additive from all sources cannot exceed the RfD/ADI

### Direct Food Additives

- Estimated daily intake
  - \([\text{Amount of food consumed daily}] \times [\text{concentration of additive in food}]\)
- \(\text{EDI} = \text{concentration (C)} \times \text{intake (I)}\)
- Sum of all sources of additive in food and non-food
- Unique number for each direct additive

**Direct Food Additives**

**Estimating Consumption**

- Level of additive in food category
• Daily intake of each food category containing additive
• Distribution of intakes in population groups
• Exposure from non-food sources

Concentrations in Food

Direct Additives
• Determined by manufacturer
• Assume highest level allowable
• Assume processor uses GMP and does not abuse levels

Regulatory Food Categories (43)
• Baked goods and baking mixes
  – Ready to eat and ready to cook products
  – Doughnuts, bread, croissants, cake mix, cookie dough
• Beverages - alcoholic
  – Beer, wine, liquor, cocktail mix

Food Categories (43)
• Beverages - nonalcoholic
  – Special/spiced teas, soft drinks, coffee substitutes, fruit/vegetable drinks
• Breakfast cereals
  – Ready to eat and instant, regular hot cereals
• Of 43 total; see CFR 21, 170.3(n)

Food Consumption Surveys
• National Food Consumption Survey
  – USDA 1987-8
• Continuing Survey of Food Intakes by Individuals
  – USDA 1985-91
• Estimates of Daily Intake
  – NAS/NRC 1979
• FDA Total Diet Study 1987

Problems
• 3 – 14 day snapshots
• Lack of detail
  – Age, ethnic group, food groups
• Some are outdated – food groups
• Not always “user friendly”
Estimated Daily Intake

- Establish EDI
- Assign Concern Level (CL)

Food Safety Concern Levels (CLs)

- Three levels - CLI, CLII, CLIII
- Based on “structure-activity” relationships to known toxic chemicals
- Based on structural and functional groups
  - Category A, B, C
- Based on exposure level****

Toxicity Categories

- Category A
  - Low toxic potential
- Category B
  - Intermediate or unknown toxicity
- Category C
  - High degree of toxic concern

Concern Levels and Exposure Levels

- Values in ppm (mg/kg) in food
- Much more emphasis on exposure
- Lower exposure - less testing

Food Additive Safety Summary

- Estimate daily intake (EDI)
- Determine toxicity rating (A, B, C)
  - C = higher toxicity
- Assign CL (I, II, III)
  - III highest concern,
    - Most testing
    - Exposure carries more weight
- CL determines toxicity tests required

CLs and Toxicity Testing

CL I
- Short-term repeated dose study
  - Not less than 28 days
- Short-term carcinogen tests
  - Genetic toxicity
CLs and Toxicity Testing

CL II
• Subchronic - 90 da - 2 species
• Multigeneration (2) reproduction study with teratology phase
• Short-term carcinogen

CLs and Toxicity Testing

CL III
• Carcinogen studies - rats and mice
• Chronic feeding study - 1yr - may be combined with carcinogen study
• Chronic study in non-rodent - 1yr
• Multigeneration (2) reproduction with teratology phase
• Short-term carcinogen study

Indirect Food Additives
• Not added directly to food
• May enter food through migration of packaging materials, holding containers or processing surfaces
• Cans, cardboard, plastics, glass, etc.

Estimates of Indirect Additive Migration

Extraction Methods
• Solvents simulate food types
• Aqueous/acidic food - 8% EtOH
• Alcoholic food - 50% EtOH
• Fatty food - corn oil or synthetic triglyceride
• Expose solvent to packaging material to extract

Indirect Additives Extraction Temperatures
• Different temps based projected processing method
• Retorted foods
  – 212°, 250°, 275° for 2 hrs and held 238 hr at 120°
• Refrigerated foods
  – Same but held at 70°
• Frozen foods
  – Same but held 120 hrs
Indirect Food Additives

Exposure Estimates

- Extraction data = how much in food
- Extraction data is converted to exposure estimates using
  - Consumption Factors (CF)
  - Food-type-distribution factors (fT)

CFs and fTs

- Consumption factor (CF) = amount of US diet that comes into contact with different kinds of holding materials (paper, metal, polymer)
- Food type (fT) = the fraction of food types for which each packaging material is used (aqueous/acidic, fatty, OH)

Consumption Factors

Total fraction of diet in contact with container

- Glass 0.08
- Metal, polymer coated 0.17
- Metal, uncoated 0.03
- Paper, polymer coated 0.21
- Paper, uncoated 0.10
- Polymer 0.41

Food-Type-Distribution Factor (fT)

- Estimate of fraction of food types for which different types of packaging is used
  - Aqueous, acidic, alcoholic, fatty
- Performed for each package category
  - Glass, metal, paper, polymer

Food Type Distribution Factor (fT)

- Glass
- Metal, polymer coated
- Metal, uncoated
- Paper, polymer coated
- Paper, uncoated
- Polymer

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EDI of Indirect Food Additives

- EDI =
  \[ CF \times [(fT_{aqueous/acidic} \times ppm \text{ in } 8\% \text{ EtOH}) + (fT_{alcoholic} \times ppm \text{ in } 50\% \text{ EtOH}) + (fT_{fatty} \times ppm \text{ in corn oil})] \times 3\text{kg/person/day} \]
  = mg/person/day
  - CF = consumption factor
  - fT = food type distribution factor
  - 3 kg = daily food consumption

Indirect Additives

EDI Summary

- EDI =
  \[ \text{sum of } fTs \times \text{extraction data in ppm} \times 3\text{kg/person/day} \times \text{CF} \]
- Total of EDIs cannot exceed ADI

Indirect Food Additives

Toxicity Testing

- Negligible migration (< 0.05ppm) and EDI < 0.15mg/person/day
  - Acute toxicity studies only
- Migration 0.05-1.0ppm
  - Subchronic studies; 2 species
- Migration > 1.0ppm
  - Chronic studies; 2 species
  - Carcinogenicity
  - Multigenerational reproduction
  - Teratology

Threshold of Regulation

- New legislation on indirect food additives - 1997
- Concentrations <0.05 ppb and not carcinogenic
- Exempt from full-blown pre-market evaluation and petition review
- Assume negligible risk

FDA Modernization Act 1997

- Indirect food additives can be marketed 120 days after notifying FDA
- Burden of objection on FDA
- Significantly streamlined process
- FDA must review much faster
Dietary Supplements

• Regarded as food
• Not food additives or drugs
• Lesser standard of safety
  – DS: no history of unsafe use
  – Additive: demonstrated safety
• No FDA unapproved
  health claims
  – Would then be a drug
  – Different safety testing

Delaney Clause and Food Additives

• Prohibits FDA approval of regulated food additives shown to cause cancer by appropriate tests
• Appropriate tests are usually animal studies

Delaney Clause

• Applies to:
  – Regulated food additives, color additives and drugs
• Does not apply to:
  – Unavoidable contaminants, GRAS substances, prior sanctioned ingredients or non-functional trace contaminants

FDA Carcinogenic Constituent Policy

For Non-functional Carcinogenic Contaminants of Food Additives

• Delaney is not invoked
• Health effects may be negligible
• Probabilistic RA model

Carcinogenic Constituent Policy Risk Assessment Model

• Upper bound lifetime risk in humans < 1 in $10^6$ above background
• Many conservative estimates made in model
  – Possibly over estimates risk by million-fold

De Minimis Concept

• De minimis non curat lex
  – “The law does not concern itself with trifles”
• First involved insect and worm fragments in food
  – Cannot completely avoid
• Later applied to carcinogenic contaminants in food additives
**De Minimis Concept**

- Most recently courts have not allowed FDA to invoke *de minimis* because Delaney language is specific
- FD&C orange 17
- Pesticide residues
  - Resulted in FQPA changes

**Carcinogenic Constituent**

**Diethylstilbestrol (DES) Proviso**

- Permits addition of carcinogenic substances to animal feeds if no residues end up in edible tissues

**Interpretation of Delaney: Food Additives**

- RA cannot be used if food additive is carcinogenic
- Zero tolerance policy
- Very strict regulation
- FDA requires clear, unequivocal, reproducible evidence for cancer
- Few substances banned

**Interpretation of Delaney**

- Must be primary carcinogen
- Secondary carcinogenesis not considered evidence

**Secondary Carcinogenesis**

- Nutritional, hormonal, physiological imbalances are secondary causes of cancer
- Secondary carcinogens only contribute to increase (promote) effect
- No evidence of direct genotoxicity

**Secondary Carcinogenesis**

- BHA
  - Chronic irritation = tissue damage = hyperplasia = cell proliferation = increased chance for mutation and cancer
- Xylitol and sorbitol
  - Calcium imbalance in gut exacerbated by fermentation of sugar alcohol

**Substances Banned by Delaney**

- Packaging materials - Flectol H, mercaptimidazoline
- Food additives - safrole, cinnamyl anthranilate, thiourea, diethylpyrocarbonate (forms urethane)
- Primary carcinogens
Carcinogenic Food Additives

- BHA, xylitol, sorbitol, methylene chloride, TCE, melamine, formaldehyde, nitrilotriacetic acid, diethylhexyl phthalate, bentonite
- All listed by National Toxicology Program and International Agency for Regulation of Carcinogens
- All secondary carcinogenesis
  - FDA approved

Delaney Clause

- Because of the strict nature of the Delaney Clause, the FDA requires clear and unequivocal proof that an additive is a carcinogen