Food Additive Safety Assessment

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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
  – Sucrose, salt, corn syrup, dextrose

Six Categories of Food Additives

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

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
  – Leaves FDA some leeway
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
  - [Amount of food consumed daily] x [concentration of additive in food]
- EDI = concentration (C) x 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

- 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

Food Consumption Survey 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

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05</td>
<td>&lt;0.025</td>
<td>0.0125</td>
<td>I</td>
</tr>
<tr>
<td>0.05</td>
<td>0.025</td>
<td>0.0125</td>
<td>II</td>
</tr>
<tr>
<td>1.0</td>
<td>0.5</td>
<td>0.25</td>
<td>III</td>
</tr>
</tbody>
</table>

- 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
  – Ames assay, etc

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.

Toxicity Tests

<table>
<thead>
<tr>
<th>Toxicity Tests</th>
<th>Concern Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Short-term for genetic toxicity</td>
<td>X</td>
</tr>
<tr>
<td>Metabolism and pharmacokinetics</td>
<td>X</td>
</tr>
<tr>
<td>Short-term rodent toxicity</td>
<td>X</td>
</tr>
<tr>
<td>Subchronic rodent toxicity</td>
<td>X</td>
</tr>
<tr>
<td>Subchronic non-rodent toxicity</td>
<td>X</td>
</tr>
<tr>
<td>Reproduction with teratology</td>
<td></td>
</tr>
<tr>
<td>One-year non-rodent toxicity</td>
<td></td>
</tr>
<tr>
<td>Rodent carcinogenicity</td>
<td></td>
</tr>
<tr>
<td>Chronic rodent toxicity/carcinogenicity</td>
<td>X</td>
</tr>
</tbody>
</table>
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 on 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

<table>
<thead>
<tr>
<th>Total fraction of diet in contact with container</th>
<th>Glass</th>
<th>Metal, polymer coated</th>
<th>Metal, uncoated</th>
<th>Paper, polymer coated</th>
<th>Paper, uncoated</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>0.08</td>
<td>0.17</td>
<td>0.03</td>
<td>0.21</td>
<td>0.10</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Material</th>
<th>AQU</th>
<th>ACID</th>
<th>OH</th>
<th>FAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>0.08</td>
<td>0.36</td>
<td>0.47</td>
<td>0.09</td>
</tr>
<tr>
<td>Metal, polymer coated</td>
<td>0.16</td>
<td>0.35</td>
<td>0.40</td>
<td>0.09</td>
</tr>
<tr>
<td>Metal, uncoated</td>
<td>0.54</td>
<td>0.25</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>Paper, polymer coated</td>
<td>0.55</td>
<td>0.04</td>
<td>0.01</td>
<td>0.40</td>
</tr>
<tr>
<td>Paper, uncoated</td>
<td>0.57</td>
<td>0.01</td>
<td>0.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Polymer</td>
<td>0.49</td>
<td>0.16</td>
<td>0.01</td>
<td>0.34</td>
</tr>
</tbody>
</table>

EDI of Indirect Food Additives

\[
\text{EDI} = \text{CF} \times \left( \frac{fT_{\text{aqueous/acidic}} \times \text{ppm in 8\% EtOH}}{\text{CF}} \right) + \left( \frac{fT_{\text{alcoholic}} \times \text{ppm in 50\% EtOH}}{\text{CF}} \right) + \left( \frac{fT_{\text{fatty}} \times \text{ppm in corn oil}}{\text{CF}} \right) \times 3kg/\text{person/day} = \text{mg/person/day}
\]

- \(\text{CF}\) = consumption factor
- \(fT\) = food type distribution factor
- 3 kg = daily food consumption

Indirect Additives

EDI Summary

\[
\text{EDI} = \text{(sum of } fT\text{s x extraction data in ppm) x 3kg/person/day x CF}
\]

- 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
- 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

- **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