Food Additive Safety Assessment

Food Toxicology
Instructor: Gregory Möller, Ph.D.
University of Idaho

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
  - Antimcrobial
  - 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

- 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

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

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

- 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.

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

AQU	ACID	OH	FAT
0.08	0.36	0.47	0.09
0.16	0.35	0.40	0.09
0.54	0.25	0.01	0.20
0.55	0.04	0.01	0.40

0.57 0.01 0.01 0.41
0.49 0.16 0.01 0.34

EDI of Indirect Food Additives

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

Indirect Additives

EDI Summary

- EDI =
  (sum of fTs 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

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