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

- Preservatives
  - Antimcrobial
  - Antibrowning
  - 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

Food additive NH_4HCO_3

- 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

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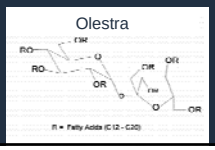
Regulated Food Additive

- 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)



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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

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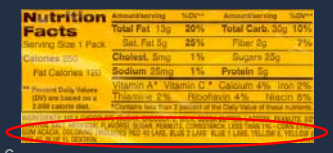
Color Additives

- 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



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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

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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)

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Contaminant Tolerances

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

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Contaminant Action Levels

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

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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

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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)?

FDA
Red Book 2000
Click Here

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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.

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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.

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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

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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

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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

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Concentrations in Food

Direct Additives

- Determined by manufacturer
- Assume highest level allowable
- Assume processor uses GMP and does not abuse levels

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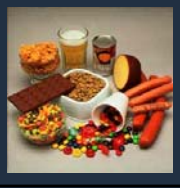
Regulatory Food Categories (43)

- 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



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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)

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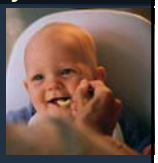
Food Consumption Surveys



- 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

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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”

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Estimated Daily Intake

- Establish EDI
- Assign Concern Level (CL)

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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****

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Toxicity Categories

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

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Concern Levels and Exposure Levels

A	B	C	CL
<0.05	<0.025	0.0125	I
0.05	0.025	0.0125	II
1.0	0.5	0.25	III

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

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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

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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

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CLs and Toxicity Testing

CL II

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

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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

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Toxicity Tests	Concern Level		
	I	II	III
Short-term for genetic toxicity	X	X	X
Metabolism and pharmacokinetics		X	X
Short-term rodent toxicity	X		
Subchronic rodent toxicity		X	X
Subchronic non-rodent toxicity		X	
Reproduction with teratology		X	X
One-year non-rodent toxicity			X
Rodent carcinogenicity			X
Chronic rodent toxicity/carcinogenicity			X

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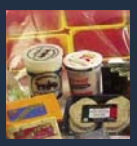
Indirect Food Additives

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



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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

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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

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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)

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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)

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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

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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

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Food Type Distribution Factor (fT)

	AQU	ACID	OH	FAT
• Glass	0.08	0.36	0.47	0.09
• Metal, polymer coated	0.16	0.35	0.40	0.09
• Metal, uncoated	0.54	0.25	0.01	0.20
• Paper, polymer coated	0.55	0.04	0.01	0.40
• Paper, uncoated	0.57	0.01	0.01	0.41
• Polymer	0.49	0.16	0.01	0.34

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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

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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

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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

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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

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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

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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

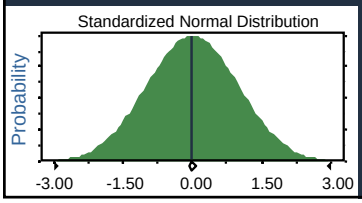
Delaney Clause

- 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

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Carcinogenic Constituent

Diethylstilbestrol (DES) Proviso

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

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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

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Interpretation of Delaney

- Must be primary carcinogen
- Secondary carcinogenesis not considered evidence

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Secondary Carcinogenesis

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

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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

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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