GRAS, Safety Assessment and Regulatory Strategy

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March 1, 2017

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What is a Food Additive?

- Section 201(s)

"Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . ."

if such substance is not:

Generally recognized as safe (GRAS)

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What is GRAS?

. . . if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . .

Compliance With A FDA Food Additive Regulation

- FDA authorization is binding on FDA and industry
  - Food additive regulation or food contact notification
  - Authorization provides a safe harbor
    - Precludes FDA action if use is in compliance (food additive)
  - Once FDA has made a rule or allowed a notification to become effective it must follow procedures to:
    - Modify the regulation
    - Revoke the regulation
  - Manufacturing changes may raise new safety issues

GRAS and Other Determinations

- Binding on the manufacturer who makes the determination but not on FDA
- Non-zero risk of FDA action
  - Conduct assessments following FDA guidelines
  - Ensure COI is addressed
- Greatest risk may not be FDA action
  - NGO activity
- GMPs and intended use

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Implications of GRAS Status

"Food additives" must be preapproved by FDA (§ 409)

A GRAS substance is not a food additive, by definition

A GRAS substance does not require premarket clearance by FDA

GRAS Factors: Section 170.30

- Views of qualified scientific experts
- Common knowledge in the scientific community about the safety of the substance
- Same quantity and quality of scientific evidence required for food additive approval
- Based on published studies

The Easy Cases

- GRAS for Direct Use in Human Food
  - 21 C.F.R. Part 182
  - 21 C.F.R. Part 184 – Affirmed as GRAS
- GRAS for Use in Food Contact Applications
  - 21 C.F.R. Part 186
- GRAS for Animal Feed
  - 21 C.F.R. Part 582 – same listings as human food
  - 21 C.F.R. Part 584
- Must still consider safety

Options

- "Self-Determination"
  - Manufacturers may develop "self-determined" GRAS opinions without consulting FDA
  - Once GRAS determination has been reached, there is no requirement that FDA approve the conclusion
  - May use GRAS Panel
- GRAS Notification to FDA
  - Not Approval - Receive "No Questions" letter from FDA
  - Majority include GRAS Panel
  - Voluntary program in place since 1997 proposal

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FDA's Burden Regarding GRAS

- FDA has no special status regarding GRAS

- FDA must prove a use is not GRAS to take action
- Safety
  - Public availability of data?
  - New data available?
- General recognition
  - Substantive questions?
  - Partially hydrogenated oils notice
  - Caffeine in nontraditional uses

Establishing Safety for Packaging

- Establish potential migration of FCS (and impurities) to food based on calculation or testing
- Apply consumption factor and food type distribution factors to migration data to determine dietary exposure
- Dietary exposure determines the typical amount of toxicology data required to establish safety

When We Think of GRAS, We Think of…

- A substance
  - Human and animal food ingredients
  - Processing aids
  - Food contact polymers
  - Polymer additives
- But the use is the thing

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New Uses

- New monomers
- New additives
- New temperature range
- New molecular weight range
- New manufacturing process—maybe
  - FCN
  - New impurities
- How do these changes relate to safety

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When The Regulation Doesn’t Quite Fit

- There is no close enough standard in reading regulations or food contact notifications or prior sanctions
- Compliance with a food additive authorization has nothing to do with safety
- When you don’t quite meet the listed specification
- When the identity isn’t exactly the same
- When the use is just a bit “different”

Examples: Identity

- A reactor is not sufficiently cleaned to remove residual material from a production run for a non food contact material
- A production run using a naturally derived mix of fatty acids produces a mix of alkyl derivatives with a slightly different mix of chain lengths
- A new catalytic system permits greater control of polymeric structure

Examples: Manufacturing Changes

- Internal manufacturing specifications require “food grade” reactant
  - FCC compliance is specified
  - An out of spec shipment with higher impurity levels is received and processed
- A manufacturing process incorporates a new pathway for chemical synthesis
  - New impurities result
- A processing aid is substituted for a similar compound in the manufacture of a feed ingredient
  - The properties of the new compound result in higher residual levels than typical

Key Factors in the Assessment

- New residuals or increased exposure?
- Changes in material properties?
- Changes in use?
- Changes in toxicity?
- Length of exposure? Use versus exposure?
- Changes in the basic science?

Risk Assessment for All Chemicals

Natural or Synthetic


Risk
=
Hazard
x
Exposure


Risk
=
Hazard
x
Expo
sure

Safety Standard:
Reasonable Certainty of No Harm

FD&C Act Section 409(c)(3)(A)

(3) No such regulation shall issue if a fair evaluation of the data before the Secretary -

(A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided*, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal...

Safety Review of Polymers

- The main exposures are generally to oligomers and monomers
- Oligomer exposure to species below MW of 1000. (Based on H atomic weight, halogen substitution may increase this limit)
- Safety data specifically on oligomers is acceptable
- Safety data on monomers may be acceptable depending on structural analysis
- If safety review has been previously performed on some oligomers only new oligomers considered

Chemistry/Exposure Review

- Verify FCS identity and identity of constituents
  - Specific manufacturing process
- **Estimate consumer exposure**
  - 100% migration (repeat use vs. single use)
  - Migration levels (or modeling) * Consumption Factors
  - Other limits include food type
  - Typical assumption of 10 grams of food in contact with 1 sq. inch of food contact material
  - Goal is a suitably conservative estimate
- Limitations in use based on safety

Consumer Exposure

Dietary Concentration (DC)

DC = CF x <M>

CF, the consumption factor, represents the ratio of the weight of all food contacting a specific packaging material to the weight of all food packaged.

<M> is the migration into food.

What Are Consumption Factors?

- Consumption factors represent the fraction of all food consumed that is packaged in a specific material.

$$CF = \frac{weight\ of\ \ food\ contacting\ a\ specific\ \ packaging\ material}{weight\ of\ \ all\ \ food\ \ packaged}$$

- Subject to change to accommodate market trends.
- Can be as specific as data will allow.
- Can be subdivided according to type of food or type of package.

100% Migration

In some cases where the use level of the FCS is low, it may be possible to dispense with migration studies altogether by assuming 100% migration of the FCS to food.

- Single-use articles require:
  formulation information or
  chemical analysis for concentration of residual migrant in the FCS

100% Migration Calculation

An example: Adjuvant Y is added at a level not to exceed 0.01 wt-% to polypropylene (PP) films (not to exceed 2 mil, or 0.002 in)

-the CF for PP is 0.04

-the density of PP is 0.9 g/cm^3

-assume 10 g of food contacts 1 in^2 of PP

Migration is calculated as follows:

$$\langle M \rangle = \frac{0.01 \text{ g Y}}{100 \text{ g PP}} \times \frac{0.9 \text{ g PP}}{\text{cm}^3} \times \frac{16.4 \text{ cm}^3}{\text{in}^3} \times 0.002 \text{ in} \times \frac{1 \text{ in}^2}{10 \text{ g food}} = 2.95 \times 10^{-7} \frac{\text{g Y}}{\text{g food}}$$

= 300 ppb

Dietary Concentration (DC) is calculated as follows:

DC = CF x <M> = 0.04 x 300 ppb = 12 ppb

TABLE I - CONSUMPTION FACTORS (CF)

	Package Category	CF	Package Category	CF
A. General	Glass	0.1	Adhesives	0.14
	Metal- Polymer coated	0.17	Retort pouch	0.0004
	Metal- Uncoated	0.03	Microwave susceptor	0.001
	Paper- Polymer coated	0.2	All Polymers[(a)]	0.8
	Paper- Uncoated and clay-coated	0.1	Polymer	0.4
B. Polymer	Polyolefins	0.35[(b)]	PVC	0.1
	-LDPE	0.12	-rigid/semirigid	0.05
	-LLDPE	0.06	-plasticized	0.05
	-HDPE	0.13	PET[(c,d)]	0.16
	-PP	0.04	Other Polyesters	0.05
	Polystyrene	0.14	Nylon	0.02
	EVA	0.02	Acrylics, phenolics, *etc.*	0.15
	Cellophane	0.01	All Others[(e)]	0.05

[(a)]Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).
[(b)]Polyolefin films, 0.17 (HDPE films, 0.006; LDPE films, 0.065; LLDPE films, 0.060; and PP films, 0.037).
[(c)]PET-coated board, 0.013; thermoformed PET, 0.0071; PET carbonated soft drink bottles, 0.082; custom PET, 0.056; crystalline PET, 0.0023; PET films, 0.03.
[(d)]A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[(e)]As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

Modeling Exposure

- Numerous Migration Modeling Tools Available
  - Basic Equations for Fickian Diffusion
  - Migratest Lite; Migratest EXP
  - Polymer focused
  - Can Vary Time Temperature and (in some cases) Food Type
- Challenges of Paper Containing Materials
- Food Consumption Data and Models Can Also be Used

Migration Testing

- End tests are not migration testing
- Migration testing typically uses a food simulant
  - 10% ethanol aqueous and acidic food
  - 50% ethanol fatty food (PVC, PS, PET)
  - 95% ethanol fatty food (olefins and EVA)
  - Food oil
  - Miglyol
  - Tennax

Migration Testing

- Initial treatment at the highest temperature for two hours and sample held at a lower temperature for 10 days to represent storage
- COU-A 121C then 40 C
- COU-B 100C then 40C
- COU-C 66C or 100C(30 min) then 40C
  - Supports C-G
- COU-D 66C (30 min) 40C
- COU-E 40C 240hrs
- Usually sampled at 2hrs, 24hrs, 48 hrs, 96hrs and 240hrs

Migration Testing

- COU-F 20C 240 hrs
- COU-G 20C 120 hrs
- COU-H 100C 2hrs then 40C
- Numerous modified protocols for special applications

- Usually sampled at 2hrs, 24hrs, 48 hrs, 96hrs and 240hrs

Food Type Distribution Factors

- F_T = Percentage of a food contact material in contact with different food types (aqueous, acidic, fatty, alcoholic)
- Combined with migration data from the appropriate simulant
- Available in FDA guidance for polymers and other materials

Migration into Food <M>

- Based on results from migration studies and FDA food type distribution factors (f_T)
- Concentration in food:

  $<M> = (f_{aq}+f_{ac})M_{10\%\ EtOH} + (f_{al})M_{50\%\ EtOH} + (f_{fat})M_{fat}$

  (μg/kg food)
- Migration modeling
  - Fickian diffusion
  - Migration database
  - Migratest

Special Considerations

- Wet-end paper additives
- Polymers
- Microwave testing
- Heat susceptor technology
- Colorants for polymers

Consumer Exposure

Dietary Concentration (DC)

DC = CF x <M>

(μg/kg food)

Estimated Daily Intake (EDI)

EDI = DC x 3 kg/person/day

(μg/p/d) or (μg/kg bw/d)

Cumulative EDI

Toxicology Review

- Identify pivotal data (most sensitive species/sex/endpoint)
- Determine if sufficient quality data exists to support safety
- Determine if data raise additional questions
  - Indications of more significant toxic endpoints
- Consider sensitive subpopulations
- Review raw data to verify internal consistency
- Minimal SAR review may indicate a need for in-depth SAR review or for additional specialized testing

The Role of the Knowledge Base

- Qualified experts bring the bigger picture
  - Not just what the available data means but whether there is enough of it
  - Regulatory guidelines are the result of expert judgement and analysis
- Everything need not be explicitly tested
  - Reasonable certainty of no harm (acceptable uncertainty)
  - FDA has no data “requirements” just recommendations
- Expert judgement based on common knowledge is a valid basis for GRAS status

Toxicology Testing Regimen:

Minimum Toxicity Tests	Exposure Level (micrograms/person/day)
Literature Search	<1.5
Ames Assay	>1.5<150
Mouse Lymphoma Assay or In vitro Chromosome Aberration Assay	>1.5<150
Third Mutagenicity Assay	>150<3000
Subchronic Toxicity Test with Rodents	>150<3000
Subchronic Toxicity Test with Non-rodents	>150<3000
Repro study w/ teratology phase	>3000
One-Yr toxicity test with non-rodents	>3000
Carcinogenicity study with rodents	>3000
Chronic tox/ carcinogenicity study with rodents	>3000

GRAS Read Across

- Focusing on the differences while leveraging similarity
  - Consider the starting point
    - Existing approvals
    - What is/was GMP?
    - What is publically known about the manufacture?
    - What do the possible variations mean?
  - Consider the changes
    - Consider new publically available data
    - Include non-public information
- Document the review and decision
- Address possible conflict of interest

Threshold of Regulation

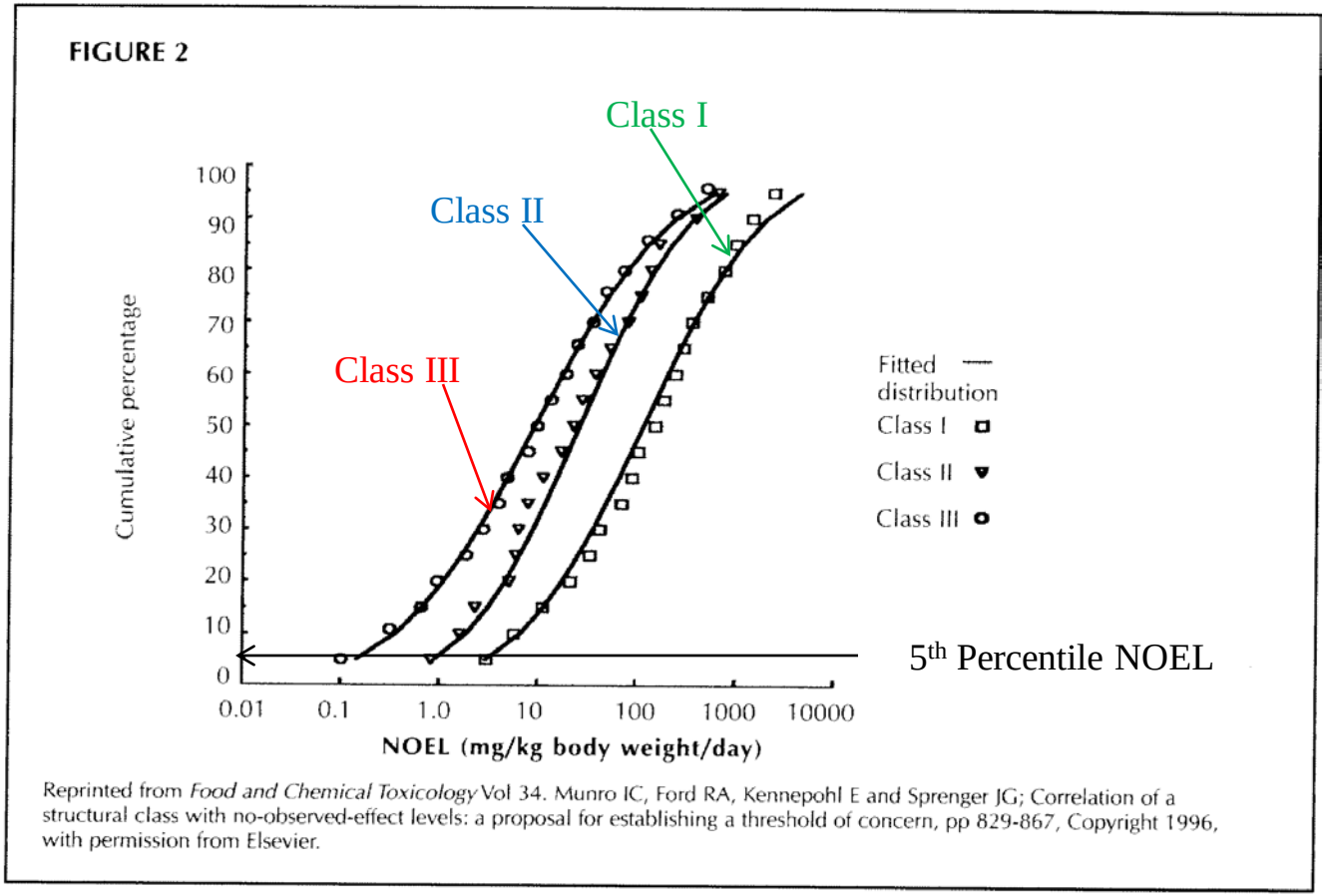
- 1995 rule allows FDA to exempt a food-contact material from regulation if:
  - Either:
    - Use results in dietary exposure of 0.5 ppb or less, or
    - Cleared as direct food additive and exposure from food-contact use is less than 1% of Acceptable Daily Intake (ADI)
  - And:
    - Not a carcinogen and it does not have impurities that are potent carcinogens (TD50 < 6.25 mg/kg b.w./day)
  - 21 C.F.R. § 170.39
- TOR listings are not proprietary
- A TOR exemption must be confirmed by FDA

Threshold of Toxicological Concern

- Risk Assessment Framework
- Safe human exposure thresholds for defined chemical classes 1800, 540, and 90 mcg/p/d (180, 240)
- Based on a representative and robust toxicological knowledgebase
- Conservatively derived 5th percentile NOAEL, 100-fold safety factor
- Actual data must be considered first

Kroes et al. 2004

TTC Non Cancer Analysis



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TTC Meets the GRAS Factors

- Common Knowledge About the Safety of the Substance/ Published Studies
  - TTC is the subject of studies authored by recognized experts and published in the scientific literature
- The Same Quality and Quantity of Data as Food Additive Decisions
  - TTC does reflect “common knowledge in the scientific community” with respect to establishing the safe level of exposure to a substance based on toxicological data on substances with analogous structures
  - Based on the whole body of toxicological data
  - TTC does not require toxicological data on the specific substance
- Views of Qualified Scientific Experts
  - Designed to be applied by knowledgeable experts

Strategic Factors

- Time to market
  - GRAS ~60 days
  - FCN ~180days +
- Cost
  - GRAS
  - FCN
  - Number of determinations
- Risk
  - Basic risk
  - Uncertainty in assessment
  - Competitors
  - NGOs
  - Customers

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Regulatory Strategy U.S.

- Regulatory interpretation
- Intake estimate (Incremental and Cumulative)
  - Potential Data requirements
  - Ease of assessment
- Toxicology assessment (high level)
  - Potential data requirements
  - Ease of assessment
- Regulatory Pathway(s)

Questions?

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