

**Chemical food safety in  
the U.S. - analysis of  
FDA's scientific basis for  
assessing chemical risk**

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# Topics

1. Current focus of U.S. public interest community
2. Comparison of U.S.'s and Europe's approaches
3. Four packaging chemicals of special concern
4. Kids' brains as a priority
5. Summary



# A. Current focus of U.S. public interest community

1. Implementing FDA Food Safety Modernization Act (FSMA)
2. Closing “Generally Recognized as Safe” (GRAS) loophole
3. Modernizing FDA’s science
4. Limiting specific direct additives
5. Limiting specific food contact substances

*Disclaimer: Public interest community is varied. These comments are my perceptions.*

# A.1. Implementing FDA Food Safety Modernization Act (FSMA)

- ▶ Final rulemaking due in Fall of 2015 as part of lawsuit settlement.
- ▶ In September, FDA revised proposed rulemakings and requested additional comment on:
  - ▶ Produce Safety Rule
  - ▶ Hazard Assessment and Risk Management Preventive Controls Rule for Human Food and for Animal Food
  - ▶ Foreign Supplier Verification for Importers Rule

## A.2. Closing “Generally Recognized as Safe” (GRAS) loophole

- ▶ Statutory exemption that industry has stretched so today almost all new additives go through loophole.
  - ▶ An estimated 1,000 of 10,000 additives not reviewed by FDA
- ▶ Allows companies to decide that an additive is safe and use it in food without informing the agency.
  - ▶ 56 companies marketed 275 additives as GRAS without FDA review
  - ▶ Most were dietary supplement ingredients expanding to be used in conventional food
- ▶ Safety standard for GRAS is same as food additives but pivotal safety data must be published. However, the data is often hard to find and limited to toxicology not exposure.

## A.2. Closing GRAS loophole (cont.)

- ▶ Of voluntary notifications submitted to FDA:
  - ▶ Agency finds flaws in about 20% of determinations
  - ▶ Company employee made 22% of decisions
  - ▶ Consultant made about 13% of decisions
  - ▶ Expert panels decided the rest
  - ▶ One of 10 people served on 75% of expert panels
  - ▶ Additives remain in food even when FDA has safety concerns
- ▶ FDA has no policy or rule limiting conflicts of interest
  - ▶ But is planning to release draft guidance soon
- ▶ Many determinations rely on professional judgment rather than analytical studies.
- ▶ Lawsuit pending seeking to force FDA to finalize its 1997 proposed rule governing the voluntary program.

## A.2. Closing GRAS loophole (cont.)

*“We cannot require anything, as this is a voluntary program and we don’t want to frighten anyone away. Having said that, we would typically [sic] tell any notifier that their submission would have to address the total dietary exposure from new and current uses, [h]ow else could you conclude that the uses were safe, without a notion of what total exposure is[?]”*

FDA reviewer of GRAS notice in  
email to manufacturer’s consultant

## A.3. Modernizing FDA's science

- ▶ 2013 article in food industry journal compared 1982 recommendations of a FDA-convened expert panel to agency's current guidance and rules:
  - ▶ Most recommendations not implemented
  - ▶ Problems found in 9 areas including:
    - ▶ Behavioral impacts (behind EPA and OECD)
    - ▶ Endocrine systems (behind EPA and OECD)
    - ▶ Subpopulations (children, pregnant women, and hypersensitivity) (behind EFSA)
    - ▶ Toxicological insignificance
    - ▶ Personal bias and conflicts of interest (behind EFSA)
    - ▶ Reassessment and consistency across substances (behind EFSA)

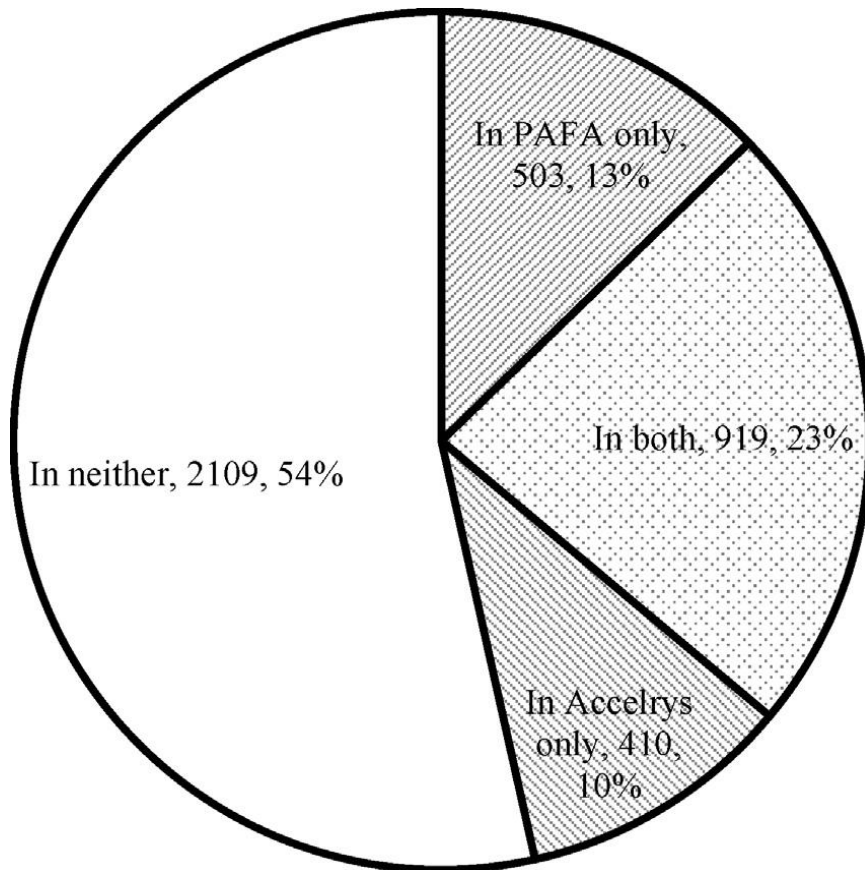


## A.3. Modernizing FDA's science (cont.)

- ▶ A 2013 article in *Reproductive Toxicology* journal compared additives to three toxicology databases including FDA's.
- ▶ Most additives determined to be safe based on professional judgment rather than published feeding toxicology studies.
- ▶ For chemicals directly added to food:
  - ▶ 21.6% have feeding studies necessary to estimate a safe level of exposure; and
  - ▶ 12.5% of additives that FDA recommended having reproductive or developmental toxicity study had data in agency's database.

## A.3. Modernizing FDA's science (cont.)

Percentage of FDA-approved direct additives with and without feeding toxicology studies



PAFA is FDA's  
database.

Accelrys is  
commercial database  
initially developed by  
U.S. National Institute  
for Occupational  
Safety and Health

## A.3. Modernizing FDA's science (cont.)

- ▶ FDA assessment of its science published in August 2014
- ▶ Opinion survey of FDA's scientific staff showed confusion and dissension. A consultant reviewer highlighted key concerns:
  - ▶ Risk assessment - risk management distinction
  - ▶ Fundamental concepts of a rigorous safety assessment program
  - ▶ Difference between data requirements and assessment methodology to be applied to those data
  - ▶ Leadership role for FDA in adopting new scientific approaches

## A.4. Limiting specific direct additives

- ▶ Artificial *Trans* Fats
  - ▶ Long-standing GRAS determination by manufacturers not FDA
  - ▶ FDA proposed to remove GRAS status
  - ▶ Industry is fighting
- ▶ Caffeine
  - ▶ Alcoholic drinks
  - ▶ Energy drinks
  - ▶ Waffles, jelly beans, syrup and now, in a shaker
- ▶ Artificial colors
- ▶ Quorn - fungal protein substitute for meat

## A.5. Limiting specific food contact substances

- ▶ Bisphenol-A
- ▶ Perchlorate
- ▶ Long-chain Perfluorinated Compounds
- ▶ *Ortho*-Phthalates



Will discuss each in more detail later

## B. Comparison of U.S.'s and Europe's approaches

1. What does safe mean?
2. Who evaluates science?
3. Who makes decisions?
4. Direct additives v. food contact substances
5. FDA's scientific assessment of packaging



## B.1. What does safe mean?

For U.S. additives, “*Safe or safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. . . . In determining safety, the following factors shall be considered:

- (1) The **probable consumption** of the substance and of any substance formed in or on food because of its use.
- (2) The **cumulative effect** of the substance in the diet, taking into account any **chemically or pharmacologically related** substance or substances in such diet.
- (3) **Safety factors** which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.” (21 CFR 170.3(i))

## B.1. What does safe mean? (cont.)

For Europe, “In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment.”

“Measures . . . shall be proportionate and no more restrictive of trade than is required to achieve the high level of health protection chosen in the Community, regard being had to technical and economic feasibility and other factors regarded as legitimate in the matter under consideration.”

Considerations include:

- (a) not only to the probable immediate and/or short-term and/or long-term effects of that food on the health of a person consuming it, but also on subsequent generations;
- (b) to the probable cumulative toxic effects;
- (c) to the particular health sensitivities of a specific category of consumers where the food is intended for that category of consumers. (Reg No 178/2002, Articles 7 and 14)





## B.3. Who makes safety decision?

- ▶ In U.S., FDA unless the food manufacturer determines the use is “generally recognized as safe.”
- ▶ In Europe, the European Commission makes the safety management decision.



## B.4. Direct additives v. food contact substances

- ▶ In U.S.,
  - ▶ until 1997, the safety assessment and approval requirements were the same for direct and indirect additives (food contact substances).
  - ▶ In 1997, Congress created an alternative review process for food contact substances allowing agency to issue “no objection” letters to a company for their substance’s use.
- ▶ In Europe, food contact substances other than specific categories such as plastic additives require pre-market approval.



## B.5. FDA's scientific assessment of packaging

- ▶ Consumption Factor
  - ▶ Based on final product use
  - ▶ Does not consider exposure from bulk packaging or food handling equipment
  - ▶ FDA updating
- ▶ Migration Testing
  - ▶ Not done for dry food because of 50 ppb assumption
- ▶ Toxicology Requirements
  - ▶ Depends on exposure
  - ▶ Only an *in vitro* DNA toxicity test or, if low enough, may not be needed

## C. Four packaging chemicals of concern

- ▶ Bisphenol-A
- ▶ Perchlorate
- ▶ Long-chain Perfluorinated Compounds
- ▶ *Ortho*-Phthalates

# C.1. Bisphenol-A

- ▶ In 2009, Congress provided \$30M to NIEHS to invest in BPA research that will lead to better understanding of the public health consequences of BPA
- ▶ NIEHS and FDA created CLARITY-BPA: “Consortium Linking Academic and Regulatory Insights on the Toxicity of Bisphenol A”
  - ▶ Multi-year project of scientists from FDA and 12 NIEHS-funded academic investigators to enhance the utility of a perinatal 2-year GLP chronic toxicity study on BPA for regulatory decision-making by incorporating a wide range of doses and disease-related endpoints that are not usually covered, including behavior, immune function, cardiac, reproductive tract, cancer, thyroid and mammary gland
  - ▶ The study is ongoing but some results have already been published and more will continue to trickled down for the next 2-4 years.
  - ▶ Early this year, FDA investigators published preliminary results from a 90 day subchronic study performed ahead of the 2-year chronic study. They concluded that BPA was safe.

## C.2. Perchlorate

- ▶ Perchlorate is pervasive in food, people and breast milk.
- ▶ Perchlorate inhibits thyroid gland's uptake of iodine. Risk is particularly serious to fetuses and breast-fed infants where mother has low iodine intake.
- ▶ In 1963, FDA approved for use in rubber gaskets.
- ▶ Sodium hypochlorite (bleach) also degrades to perchlorate.
- ▶ In 2005, FDA allowed dry food plastic packaging made by Ciba (now BASF) to contain up to 1.2% perchlorate as anti-static agent.
  - ▶ No migration testing. Used 50 ppb assumption
  - ▶ 83-fold math error in Ciba application
  - ▶ Additional 3.3-fold error in FDA's announcement of decision

## C.3. Perfluorinated compounds

- ▶ From 1963 to 1990, FDA approved five categories as food additives to use in greaseproofing paper.
- ▶ From 2002 to 2006, FDA allowed five additional categories as food contact substances.
- ▶ In 2010, companies voluntarily suspended 2002-2006 uses at FDA's request. Uses approved from 1963-1990 not affected.
- ▶ U.S. and European manufacturers withdraw from market.
- ▶ In U.S., EPA tentatively concluded that more protective levels are needed than even EFSA determined to be safe.
- ▶ China and India manufacturers start production. Use in U.S. could begin immediately without notifying FDA.



## C.4. Phthalates

- ▶ Before 2000, FDA approved 31 ortho-phthalates as plasticizers in plastics for food packaging and food handling equipment.
- ▶ In 2011, Congress:
  - ▶ Banned six types of phthalates from children's products; and
  - ▶ Directed Consumer Products Safety Commission (CPSC) to convene panel to evaluate safety of phthalates and their alternatives.
- ▶ In 2014, CPSC Expert Panel concluded that:
  - ▶ Ortho-phthalates with 3 to 7 carbon chain lengths linked to male reproductive problems. Advised CPSC to ban common forms of these.
  - ▶ Other *ortho*-phthalates linked to developmental problems.
  - ▶ Use in food packaging needs to be reconsidered.
- ▶ Two 2013 exposure studies showed phthalates in food.

## D. Kids' brains as a priority

- ▶ Safety evaluation for additives must consider “the **cumulative effect** of the substance in the diet, taking into account any **chemically or pharmacologically related substance or substances** in such diet.”
- ▶ Requirement does not appear to be systematically followed in U.S. or EU for chemicals impacting common organ.
- ▶ Children's brain development seems particularly sensitive, especially when chemicals affecting thyroid are considered.
  - ▶ EFSA 2013 model identified > 100 pesticides impacting thyroid and nervous system
  - ▶ FDA toxicology database identified 44 direct additives
  - ▶ NIH, EPA, FDA Tox 21 *in vitro* testing program identified > 200 chemicals that activated or inhibited thyroid receptor:
    - ▶ 66 direct additives
    - ▶ 107 chemicals used as food contact substances
    - ▶ 86 pesticides

# E. Summary

- ▶ Chemical safety assessment should be done by diverse group of scientists with disclosed and limited conflicts of interest. Government must review decision (applies to U.S.).
- ▶ Cumulative risk assessment considering cumulative biological effects must be done to comply with the law (applies to U.S. and EU).
- ▶ Systematic reassessment of chemical safety is needed to keep up with the latest scientific knowledge and exposure (applies to U.S.).



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