# The Shortcomings of FDA's Additives Regulations

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UNWRAPPED Conference

June 14, 2019

# Disclosure

- Clients include public interest organizations and food additives companies
- Co-authored food additive petitions requesting FDA revoke approval for food contact substances such as long-chain perfluoroalkyl substances, perchlorate, ortho-phthalates and carcinogenic flavors

# Take home message, Part I

- Chemicals in food are regulated
- Strong safety standard: Reasonable certainty of no harm
- Unlike EPA-regulated chemicals, food additives and food contact substances must be shown to be safe before used
- Safety assessment in based on risk: hazard and exposure are considered; benefit of the chemical is not considered

# FDA regulates chemicals in food

- Food Additive Amendment of 1958 to the Food Drug and Cosmetic Act of 1938
- Intended to protect the public from harmful chemicals
- Requires affirmation of safety and testing before chemicals are used in or on foods
- Two purposes:
  - to protect the health of consumers by requiring manufacturers of food additives and food processors to pretest any potentially unsafe substances that will be added to food, and
  - to advance food technology by permitting the use of food additives at safe levels.

# Definition of food additive

"The term 'food additive' means 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 (**including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food**; and including any source of radiation intended for any such use), if such substance is not…"

# Direct additives or Ingredients

**Breaded chicken nuggets, macaroni and cheese, corn and chocolate pudding.**

Ingredients (not listed in order)

Carrageenan, butylated hydroxytoluene, modified food starch, natural flavors, chicken breast, water, bleached wheat flour, whole wheat flour, salt, spices, soybean oil, whey protein, yeast, microcrystalline and carboxymethyl cellulose, disodium phosphate, monocalcium phosphate, sodium acid pyrophosphate, sodium caseinate, sodium phosphate, cellulose gum, citric acid, garlic powder, guar gum, gum Arabic, lactic acid, maltodextrin, potassium chloride, sodium bicarbonate, whey protein concentrate, yeast extract, soy lecithin, beta carotene, dextrose, dried sweet whey, acetic acid esters of mono-and diglycerides with maltodextrin, annatto, turmeric and red cabbage extract, corn, chicken

# Indirect additives or food contact substances

**Food contact article:**
yogurt cup


**Food contact materials:**

- Plastic(s)
- Metal
- Glass
- Paper
- Cardboard
- Coating
- Adhesives
- Printing inks
- …and many more

**Food contact substances:**

- Monomers
- Polymers
- Oligomers
- Additives
- Pigments
- Solvents
- Impurities
- Reaction by-products
- Degradation products
- …and many more

**Chemicals**

- Phthalates
- Bisphenols
- Perchlorate
- N-methyl pyrrolidone
- Benzophenone
- Styrene
- Tetramethyl bisphenol F
- Fluorinated chemicals (PFAS)
- BHA/BHT
- Toluene
- And many more….


SUGAR
SUGAR
SUGAR
SUGAR
NOTICE


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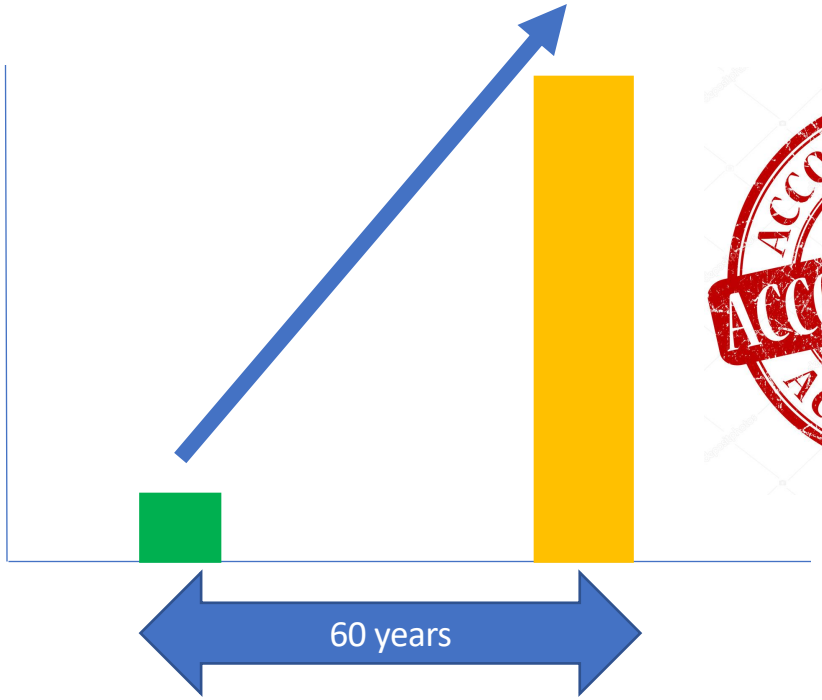
# Goal 1: To advance food technology

- 1958: 842
- 2019: > 10,000




# Goal 2: To protect the health of consumers

FROM THE CONGRESSIONAL RECORD

- Main concern: chemicals might cause **harmful effects after being consumed for months or years**
- Surgeon General: the lack of adequate information on the **chronic health effects** of chemicals precluded understanding the extent of the public health impact.
- Discussions of lawmakers at the time reflect an understanding that some chemicals could pose potential health hazards and that **co-exposure to chemicals is the norm** because many additives are present in the diet.

# Goal 2: To protect the health of consumers

A CHEMICAL MUST BE SAFE

- Safety is define as **reasonable certainty of no harm**
- It is based on the concept of **risk** which considers exposure and hazard
- Chemicals known to cause cancer in man or animals **must not** be added to food

# Statutory requirements of safety assessment

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 that, 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 (21CFR §170.3(i)).

# Shortcoming #1: Overlooked statutory requirements

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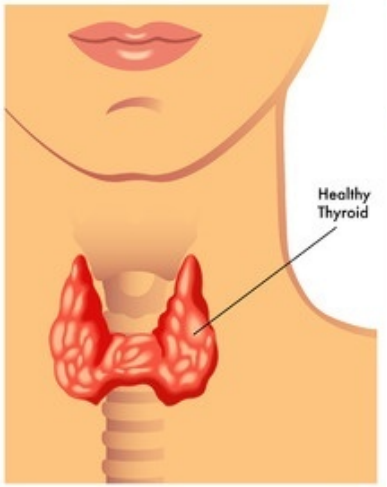
# FDA regulation to implement ‘cumulative effect’

At 21 CFR §170.18, FDA describes how to set tolerances (e.g., safe dose or acceptable daily intake) for related food additives:

“*Food additives that cause similar or related pharmacological effects* ***will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects*** *and will be considered as related food additives*.”




Perchlorate, Nitrates, Thiocyanates, 2-methyl-3-thioacetoxy-4,5-dihyrofuran, Allyl isothiocyanate, Brominated vegetable oil, Butylated hydroxyanisole (BHA), Butylated hydroxytoluene (BHT), Delta-dodecalactone, Ethoxyquin, Ethyl isovalerate, FD&C Red No. 3, Ferrous fumerate, Heptyl paraben, Ketone musk, Neotame, Potassium bromate, Potassium iodide, Potassium nitrate, Sodium acetate, Sodium nitrite, Tocopherols, Tumeric oleoresin, Vitamin D-3

# Shortcoming #1: Overlooked statutory requirements

- FDA has neither followed its regulation nor fully implemented its legal mandate to consider the cumulative effect of pharmacologically-related substances.
- FDA doesn’t have guidance on what pharmacological effect means
- Risk assessment is done one chemical at time

# Shortcoming #2: Generally Recognized as Safe

- "The term 'food additive' means 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 (**including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food**; and including any source of radiation intended for any such use), 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**;…"

# Shortcoming #2: Generally Recognized as Safe

- https://publicintegrity.org/federal-politics/why-the-fda-doesnt-really-know-whats-in-your-food/

- https://www.youtube.com/watch?time_continue=26&v=yvvvPTksIJ4

# Shortcoming #2: Generally Recognized as Safe

- Intended for common food ingredients, the exception may have appeared reasonable in 1958
- FDA and industry have stretched it into a loophole that has swallowed the law
- The exemption was interpreted as allowing manufacturers to make safety determinations that the uses of their newest chemicals or new uses of chemicals in food are safe **without notifying the FDA**
- There are an estimated 1000 chemicals in food that neither FDA not the public know about, **including food contact substances**

**Most new chemicals uses are self-certified as GRAS and some are voluntarily submitted to FDA for review of their safety assessment**

# Shortcoming #3: Outdated science

**Questionable assumption: low exposure is toxicologically insignificant**

FDA's recommended testing guideline for FCS

- **No toxicity studies are recommended** if incremental exposure are at or less than 0.5 ppb (i.e., 1.5 ug/person/day) in the diet
- **Genetic toxicity testing (in vitro)** if cumulative exposure in the diet greater than 0.5 ppb but not exceeding 50 ppb (150 ug/p/d):
- **Genetic toxicity testing (in vitro) + Subchronic oral toxicity study in 2 species** if cumulative exposure between 50 ppb and 1 ppm (3 mg/p/d)
- **Submit a food additive petition and include: 90-day oral toxicity study in rodent and non-rodent species; comparative ADME studies** if cumulative exposure greater than 1 ppm

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**Questionable assumptions result in data gaps**

Reproductive Toxicology 42 (2013) 85–94

Contents lists available at ScienceDirect

Reproductive Toxicology

# Data gaps in toxicity testing of chemicals allowed in food in the United States☆

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- Less than 38% of FDA-regulated additives have a published feeding study.
- For chemicals directly added to food, 21.6% have feeding studies necessary to estimate a safe level of exposure and 6.7% have reproductive or developmental toxicity data in FDA's database.
- Less than 27% food contact substances had published feeding study

# The exposure is too low => Toxicologically insignificant

Common conclusion by FDA reviewers of safety assessment of food contact substance:

> Based on a lack of exposure to the FCS and a lack of new exposure to the impurities of the FCS expected to be toxicologically significant, Toxicology has no safety concerns for this proposed use.

**It's unclear how toxicologically significant is defined**

# Impurities listed in safety assessment of PFAS used to grease-proof paper in contact with food

**Table 2: Exposure Estimates for Impurities in the FCS**

| Impurity | Typical residual (dry basis, mg/kg) | Basis of Exposure | DC (ppb) FCN 518 | EDI (ug/p/d) FCN 518 | EDI (µg/p/d) FCN 487 | EDI (ug/p/d) FCN 314 |
|---|---|---|---|---|---|---|
| FCS oligomers | | From Microwave use | 0.2 | 0.6 | 1.5 | 1.5 |
| $C_6$-$C_{18}$ Fluorinated telomer iodides (FTI) | <184(total) | 100% of residual | 0.0048 | 0.014 | 0.69 | <0.008 |
| Allyl alcohol | 1853 | LOD of method | 0.05 | 0.15 | 0.81 | 0.021 |
| $C_6$-$C_{18}$ Fluorinated iodohydrins (FI) | <61 (total) | 100% of residual | 0.0016 | 0.005 | 0.23 | <0.003 |
| Tetramethyl succinonitrile (TMSN) Breakdown product from AIBN | 171 | | - | AIBN Regulated in § 176.170 | | |
| $C_6$-$C_{18}$ Fluorinated epoxides (FE) | <61 (total) | 100% of residual | 0.0016 | 0.005 | 0.23 | <0.003 |
| $C_6$-$C_{18}$ Fluorinated alcohols (FA) | 2989 | Migration results FCN 518 | 0.1 | 0.3 | 0.17 | 0.12 |
| ECH | 2.3 | 100% of residual | 0.00006 | 0.0002 | 0.009 | 0.0001 |
| 2,3-Dichloro-1-propanol (2,3-DCP) | 8.2 | 100% of residual | 0.00021 | 0.0006 | 0.03 | 0.0003 |
| 1,3-Dichloro-1-propanol (1,3-DCP) | 9484 | Migration results from FCN 518 | 0.0088 | 0.03 | 0.012 | 0.004 |
| 3-Chloro-1,2-propanediol (3-CPD) | 3355 | Migration results from FCN 518 | 0.014 | 0.04 | 0.13 | 0.03 |
| TETA | <84 | Residual level from 518 | 0.0022 | 0.007 | 0.15 | 0.08 |
| Perfluorooctanoic acid (PFOA) | 57 | 100% of residual | 0.0015 | 0.005 | 0.2 | Not determined |
| Perfluoroacid congeners | 114 | 2 x PFOA residual level | 0.003 | 0.009 | 0.4 | Not determined |
| Perfluorinated alkanes | | Migration Results FCN 518 | 0.1 | 0.3 | - | - |
| Sodium hypophosphite monohydrate | | | | Essentially zero | Essentially zero | Essentially zero |
| Sodium metabisulfite | | | | Essentially zero | Essentially zero | Essentially zero |
| Sodium sulfate | | | | Essentially zero | Essentially zero | Essentially zero |

Food contact substance (FCS) 2-propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine (CAS Reg. No 464178-90-3). Food Contact Notification 518

# Take home message, Part II

- FDA has the authority to regulate safety of chemicals in food
- But, the lack of full implementation of the law and its own regulations, together with outdated scientific principles and an overstretched loophole has diminished public confidence in food safety
- Therefore, legislative and administrative changes are needed to
  - close the GRAS loophole and rein in rampant conflicts of interest;
  - update risk assessment framework using modern science, including approaches to mixture toxicity and cumulative effects; and
  - develop a post-market systematic review of the safety of chemicals


Thank you!
Questions?
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