FDA's Missed Opportunities to Tackle Endocrine Disrupting Chemicals in Food

Maricel V. Maffini, Ph.D.

Collaborative on Health and the Environment

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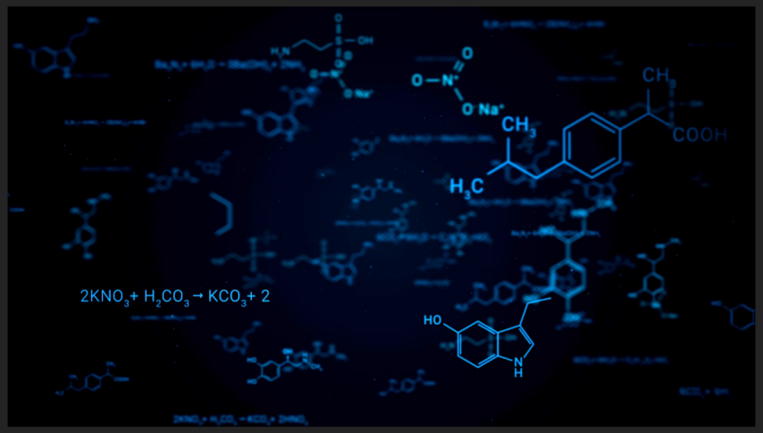


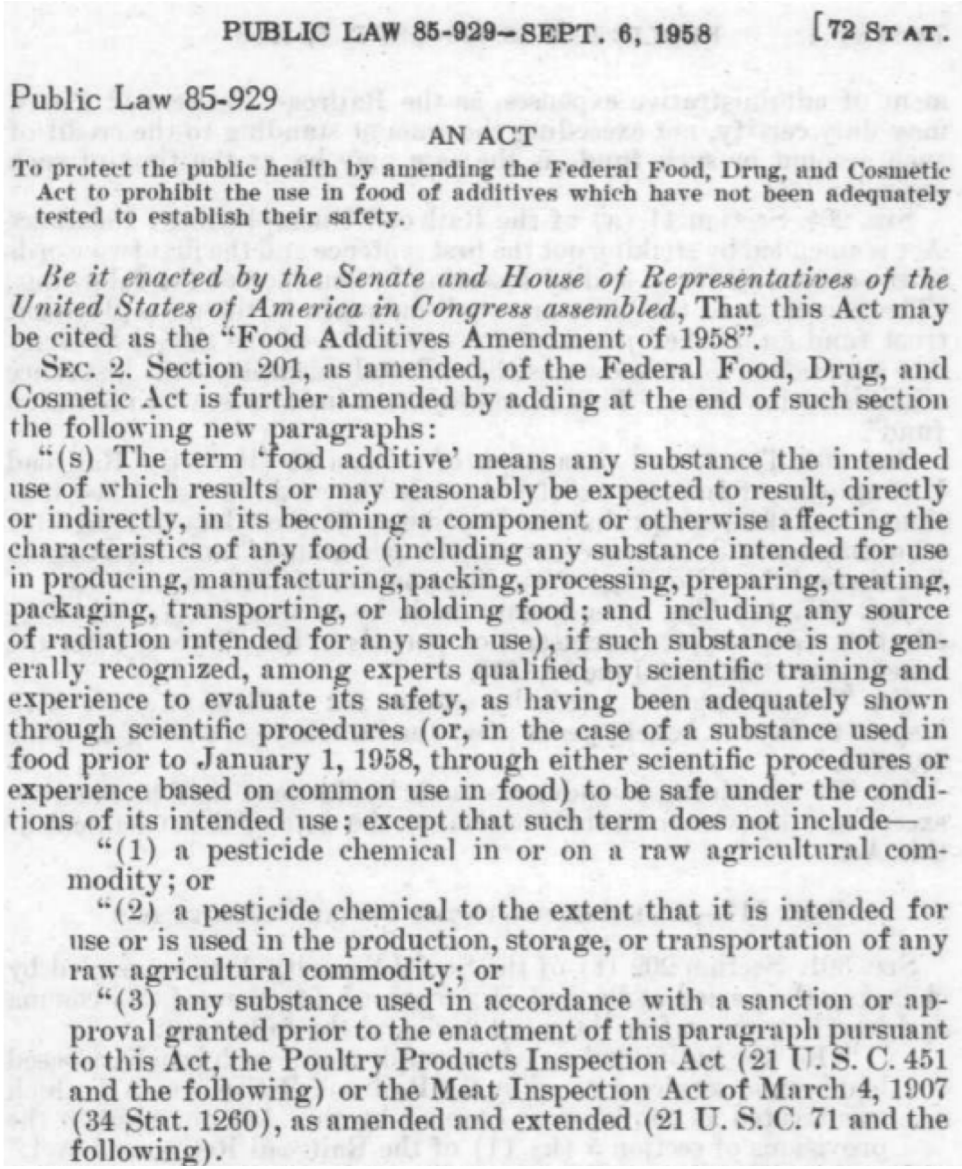
Outline

- The Food Additive Amendment
- FDA's regulatory responsibilities and definition of safety
- Approach to endocrine disrupting chemicals in food
- Examples of endocrine disruptors allowed in food
- Latest news and opportunities on phthalates and BPA

Disclosure: clients include non-profit organizations and private companies. Opinions are my own.

The Food Additive Amendment of 1958 to the Food Drug and Cosmetic Act of 1938

An act to protect the public health, to prohibit the use in food of additives which have not been adequately tested to establish their safety.



PUBLIC LAW 85-929—SEPT. 6, 1958 [72 STAT.

Public Law 85-929

AN ACT

To protect the public health by amending the Federal Food, Drug, and Cosmetic Act to prohibit the use in food of additives which have not been adequately tested to establish their safety.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Food Additives Amendment of 1958".

SEC. 2. Section 201, as amended, of the Federal Food, Drug, and Cosmetic Act is further amended by adding at the end of such section the following new paragraphs:

"(s) 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; except that such term does not include—

"(1) a pesticide chemical in or on a raw agricultural commodity; or

"(2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or

"(3) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act (21 U. S. C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U. S. C. 71 and the following).

The food additive amendment

- Protect the health of consumers by requiring manufacturers to test potentially unsafe substances
- Advance food technology by allowing food additives at safe levels
- Give FDA regulatory authority
- Require affirmation of safety before chemicals are allowed in or on food
- Assess safety based on risk
- Prohibit carcinogens regardless of exposure

SAFE

UNSAFE

What does safe mean?

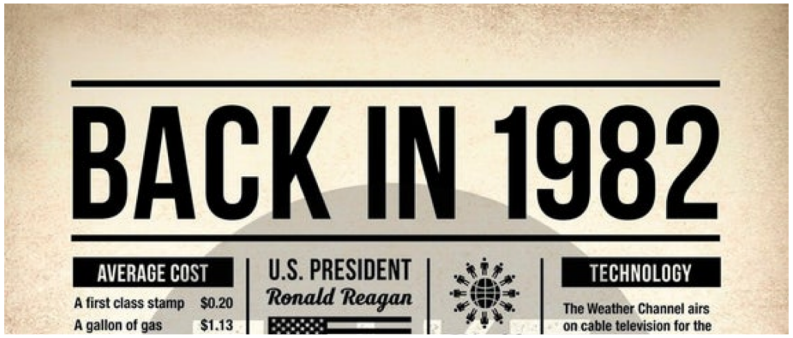
There is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use

Must consider three factors:

1- Probable consumption

2- The **cumulative effect** of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in the diet

3- Safety factors



FDA LEADER IN CHEMICAL SAFETY ASSESSMENT

TOXICOLOGICAL PRINCIPLES

for the Safety Assessment
of
Direct Food Additives
and
Color Additives Used in Food

FDA RECEIVED FIRST WARNINGS ON ADDITIVES IMPACTS

1- Behavior

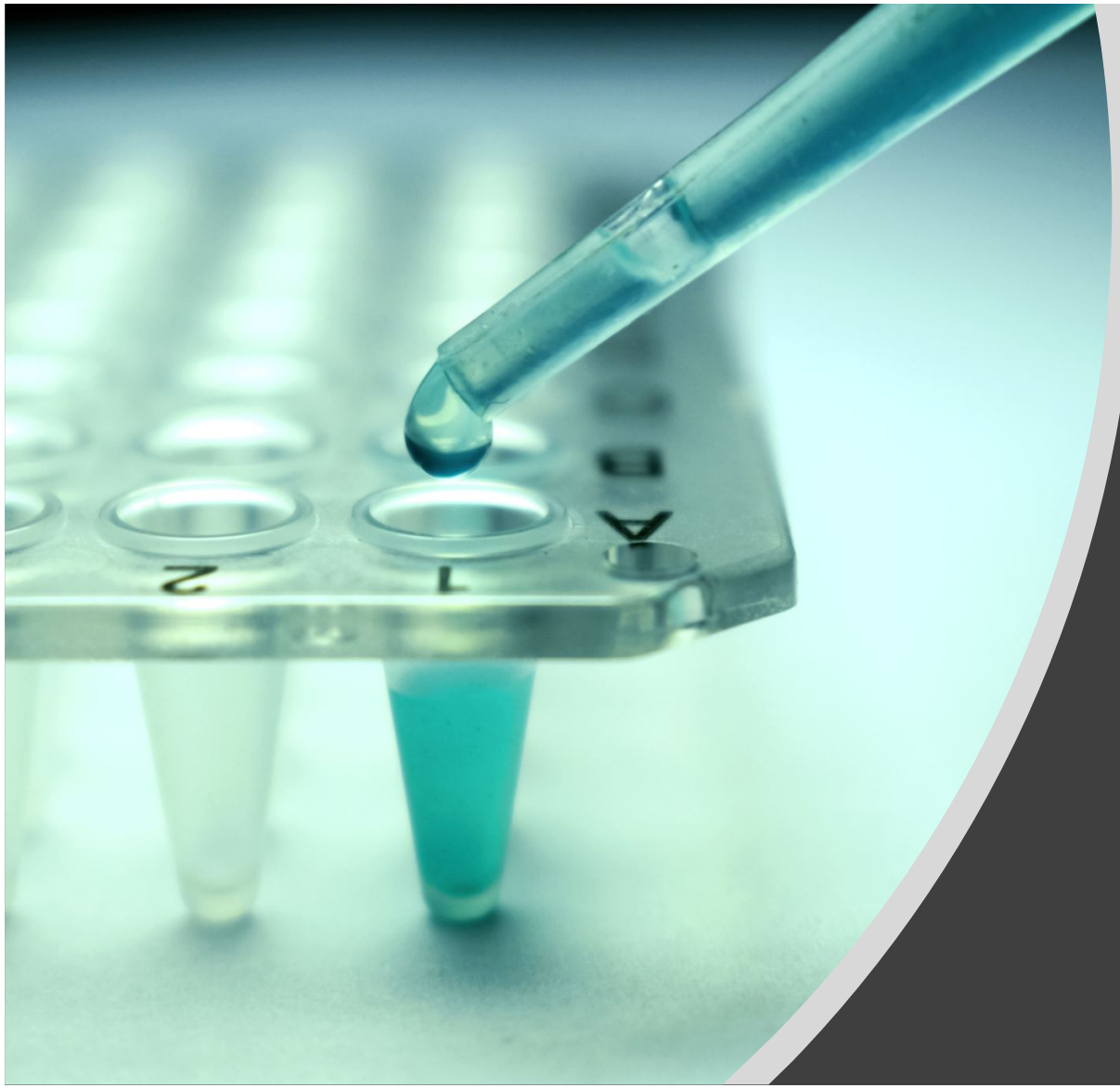
2- Endocrine system

3- Vulnerable/Susceptible populations

4- At ALL levels of exposure

5- How the body absorbs, processes, and eliminates chemicals

Maffini et al. 2013. Looking Back to Look Forward



FDA guidance for chemical testing

GUIDANCE DOCUMENT

Guidance for Industry and Other Stakeholders: Redbook 2000

Toxicological Principles for the Safety Assessment of Food Ingredients

JULY 2007

Specific toxicity studies

- Short-term genetic toxicity
- Acute oral toxicity
- Short term toxicity
- Subchronic toxicity
- Chronic toxicity
- Carcinogenicity
- Combined chronic toxicity/carcinogenicity
- In utero exposure phase for addition to carcinogenicity
- Reproduction and developmental toxicity
- Neurotoxicity

Additional studies

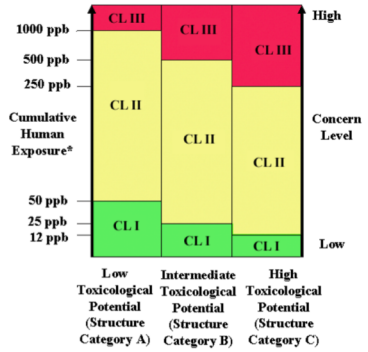
- Metabolism and pharmacokinetic
- Immunotoxicity

Human studies

Consider proxy for endocrine disruption testing

[Guidance for Industry and Other Stakeholders: Redbook 2000]

IV. Concern Levels (CL) as Related to Human Exposure and Chemical Structure



III. Recommended Toxicological Testing Summary Table for Additives Used in Food

Toxicity Tests[a]	Concern Level Low (I)	Level Intermediate (II)	Concern Level High (III)
Genetic Toxicity Tests	X	X	X
Short-term toxicity tests with rodents	X[c]	X[a,c]	X[a,c]
Subchronic toxicity studies with rodents		X[c]	X[a,c]
Subchronic toxicity studies with non-rodents		X[c]	X[a,c]
One-year toxicity studies with non-rodents			X[c]
Chronic toxicity or Combined chronic toxicity/carcinogenicity studies with rodents			X[c]
Carcinogenicity studies with rodents			X
Reproduction studies		X[c]	X[c]
Developmental toxicity studies		X[b,c]	X[b,c]
Metabolism and Pharmacokinetic studies (available in PDF (90 KB)from 1993 Draft Redbook II)		X[b]	X[b]
Human studies (available in PDF (86 KB)from 1993 Draft Redbook II)			X[b]

[Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food]

Toxicology recommendations for food contact substances: Guidance for industry

Guidance is silent on endocrine screening or testing

- Based on thresholds of estimated exposures
- As a minimum
  - At or less than 0.5 ppb in the diet (1.5 µg/p/d): no safety studies recommended if substance is not mutagen or carcinogen
  - Exposure >1.5 but < 150 µg/p/d (0.5-50 ppb in diet): genetic toxicity testing recommended
  - Exposure >150 but < 3 mg/p/d (50ppb-1ppm in diet): genetic toxicity; subchronic oral toxicity tests in 2 species. The results of these studies will help determine whether longer-term or specialized safety tests (e.g., metabolism studies, teratogenicity studies, reproductive toxicity studies, neurotoxicity studies, and immunotoxicity studies) should be conducted.

https://www.fda.gov/media/153239/download

FDA REVIEW

In 2014, FDA completed a review of how the agency evaluates the harmful effects of chemicals in foods, cosmetics, dietary supplements, animal food/feed and veterinary drugs.

The review included interviews of current and former FDA employees involved in all aspects of the agency's chemical safety assessment program.

AREAS OF CONCERN IDENTIFIED

1- Lacks processes to identify and manage endocrine disruptors

2- Data gaps on effects of chemicals at low doses

3- Lacks understanding of chronic toxicological effects

4- Inadequate assessment of sensitive populations at greater risk

5- Needs to consider exposure to mixtures and related chemicals.

OFVM Chemical Safety Assessment Review: Report of the CFSAN Working Group

SOME RESPONSES FROM FDA's SCIENTISTS

1c. Where do we most need to increase our scope and depth of expertise to improve our programs?

-No specialist for endocrine disruptors, although some overlap from in-house staff (developmental, neurotox, etc.).
-Endocrine disruption and pharmacokinetic modeling.
-But things like hormones (endocrine disruptors), nanotechnology, carcinogens, and biotechnology; we need narrow expertise.

Need to expand: endocrine chemistry expert
We need to bring in specialized toxicologists. We need to move into areas for endocrine disruptors

6- Are the program's risk assessment and safety evaluation methods (a) in keeping with the current and emerging state of the art and, (b) recognized as such by the external scientific and stakeholder communities?

Outdated. Certainly little internal guidance on endocrine disruptors. Need updated guidance on infant safety, especially for food packaging.
There may be three areas where we are not aligned with emerging state of the art:
1. Risk assessment for carcinogenic impurities - we don't have a way to recognize the non-mutagenic carcinogens. For example at EPA, if they look at the mechanism of carcinogenic action and determine it is
2. Low dose hypothesis - Agency is aware of it and may have published a paper on it, but currently we are not
operating under this hypothesis.
3. Endocrine disruptors - currently our particular Division does not actively force the notifiers to screen for endocrine disruption. It's an emerging state of the art and sometimes the notifier will voluntarily screen chemicals for endocrine disruptors, but not always.

7a. What do you see as some of the emerging issues and questions in chemical safety review?

Endocrine disruptors

Do we need to re-evaluate the review process for specific types of chemicals that have raised issues (endocrine disruptors)?
-How to screen for endocrine disruptors? How to recognize endocrine disruptors? How to prevent them from entering the food supply?
-New issues have come up (e.g., endocrine disruptors) that are not just environmental issues any more. The toxicology, microbiology, physiology, and pharmacology fields are getting involved; these issues are merging together.

IN 2012-13, ENDOCRINE DISRUPTION WAS CONSIDERED AN **EMERGING** ISSUE
FDA WAS STILL UNPREPARED TO DEAL WITH EDCs, LOW DOSES AND CHRONIC EFFECTS

Known and likely EDCs allowed in food

Food contact substances

- Perchlorate
- PFAS
- BPA
- Phthalates
- Parabens

Ingredients

- Soy isoflavone extract
- Catechins from green tea extract
- Resveratrol

Soy Isoflavone extract

- Ingredient in performance bars, mature adult meal replacements, and beverages at a level of 25 milligrams per serving

Daniel M. Sheehan, Ph.D.
Director, Estrogen Base Program
Division of Genetic and Reproductive Toxicology
and
Dan Doerge, Ph.D.
Division of Chemistry

We are writing in reference to the application for GRAS status for isoflavones, such as genistein, by ADM. We oppose GRAS status because there is abundant evidence that some of the isoflavones, including genistein and equol, are toxicants. This is true for a number of species, including humans. Additionally, the adverse effects in humans occur in several tissues and, apparently, by several mechanisms.

Genistein is clearly estrogenic; it possesses the chemical structural features necessary for estrogenic activity (Miksicek, 1998; Sheehan and Medlock, 1995; Tong, et al, 1997) and induces estrogenic responses in developing and adult animals and in adult humans. In rodents, equol is

Additionally, isoflavones are inhibitors of the thyroid peroxidase which makes T3 and T4. Inhibition can be expected to generate thyroid abnormalities, including goiter and autoimmune thyroiditis. There exists a significant body of animal data that demonstrates goitrogenic and even

As the benefits are not under consideration, the addition of isoflavones to foods needs to considered just as would the addition of any estrogen or goitrogen to foods, which are bad ideas.

GRAS Notification 1

trans-Resveratrol

trans-Resveratrol is intended to be added to bottled water that are fortified with minerals, vitamins, herbs, electrolytes, or other such ingredients at levels up to 10 ppm.

The structural similarity of resveratrol to that of the synthetic estrogen agonist, diethylstilbestrol, suggest that resveratrol might also function as an estrogen agonist. *In vitro* experiments in cell culture indicate that resveratrol acts as an estrogen agonist under some conditions, and an estrogen antagonist under other conditions. Initial concerns

In summary, available *in vitro* data indicate that resveratrol has complex estrogenic and antiestrogenic effects depending on the biological environment. Resveratrol appears to act consistently as an antiestrogen to breast tumors under physiological conditions. These data suggest that resveratrol may have beneficial effects if used as a chemopreventive agent for breast cancer. Results from an *in vivo* study

GRAS Notification 224

Catechins from Green Tea Extract

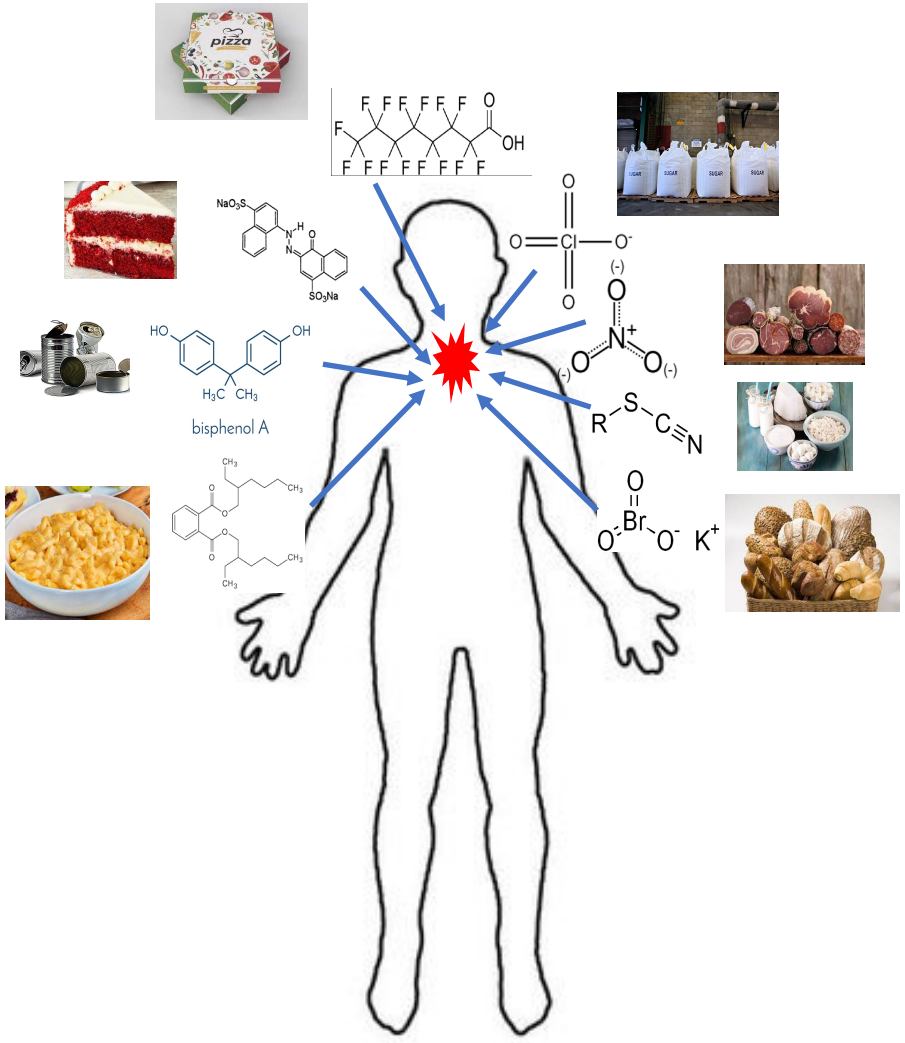
- Ingredient in bottled teas, sport drinks, carbonated soft drinks and juices at levels up to 540 milligrams per serving
- Highly purified extract contains >95% of EGCG (epigallocatechin gallate), the active ingredient

2. Similarly, the weights of Spleen, Testis (dose related) Pituitary and Thyroid/Parathyroid glands are significantly reduced in male rats. The authors considered these organ weight differences as spurious, incidental and unrelated to the administration of test articles.

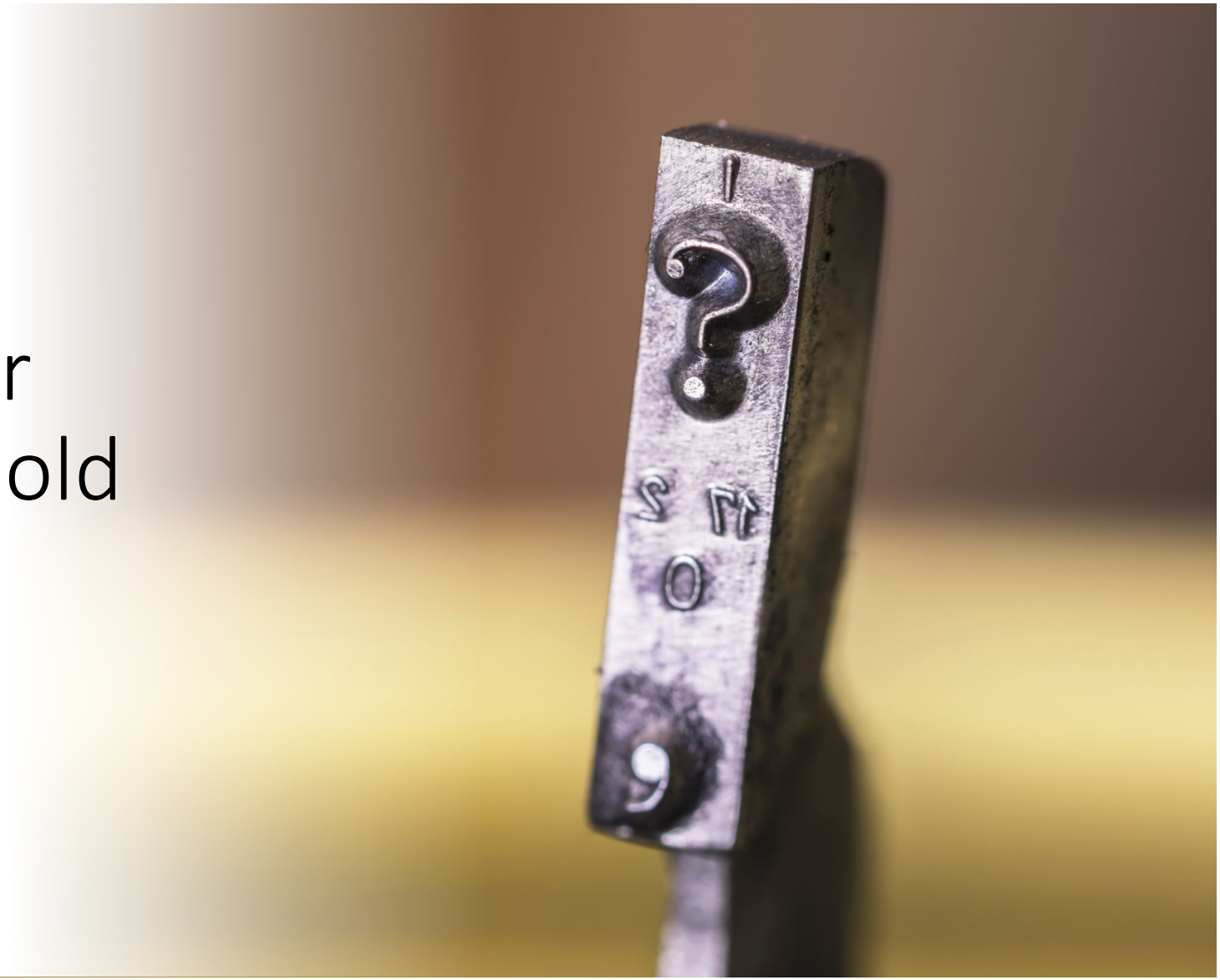
12. Goitrogenic effects: In a 13 week study, goiters were observed in F344 rats administered GTC in their diets. The incidence of thyroid lesions were higher in males than in females. The NOEL of GTC was considered to be 0.625% in males and 1.25% in

GRAS Notification 225, 259

Must do: Cumulative effect of chemicals with similar biological effects, and assess them as a class



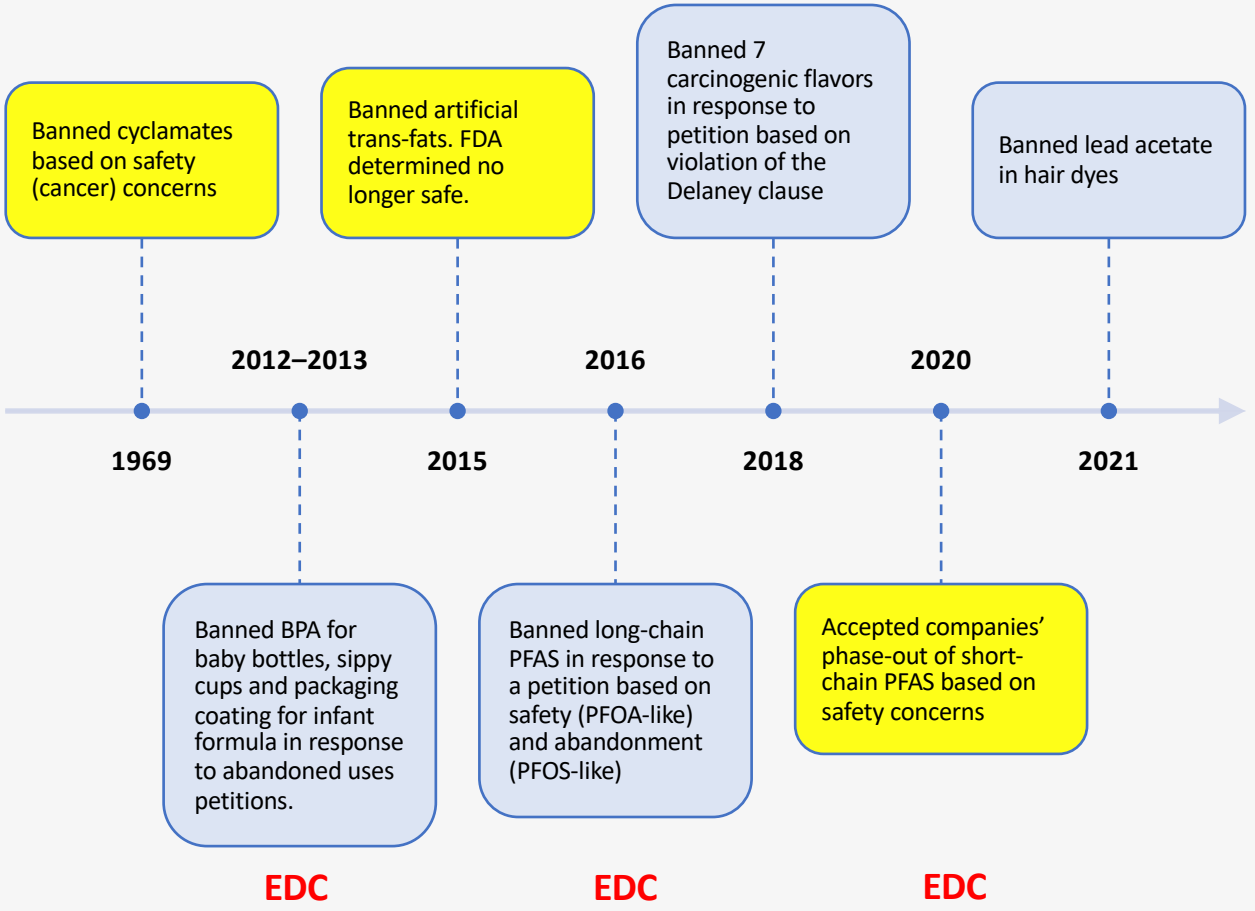
No regular review of old decisions



Lack of systematic reassessment

Actions taken by FDA to restrict or eliminate uses

Petitions as a tool to force reassessment of old decisions



Lack of systematic reassessment

	EDC	EDC
Petitions submitted and denied	**Perchlorate** (2014-2022) Court ruled in favor of FDA. FDA maintained that the amount of the thyroid disruptor in the diet is not of public health concern	**Phthalates** (2016-2022) FDA denied petitions to revoke uses of phthalates in contact with food including banning those unsafe for use in toys
Pending petitions	**PFAS** (2021) Citizen petition requesting that FDA ban all forms of PFAS that biopersist in the human body	**Lead as additive in food contact materials** (2021) Citizen petition requesting FDA to prohibit lead as an additive; lower the maximum lead allowed in bottled water

FDA ruling on phthalates – May 19, 2022

- FDA denied two NGOs petitions to ban the use of more than two dozen phthalates based on safety concerns
- The same day, FDA partially granted an industry petition claiming most uses were abandoned
- Final rule: FDA left 9 phthalates allowed for use in contact with food without performing safety assessments
  - **DEHP, DINP, DCHP, DIOP**, DIDP, DEP, Diallyl phthalate, Butyl phthalyl butyl glycolate, Ethyl phthalyl ethyl glycolate
- Petitioners objected and commented on FDA's decisions and requested a public evidentiary hearing to examine the evidence
- FDA published a request for information on eight phthalates. Any person can submit information (regulation.gov docket FDA-2022-N-0571)

FDA decisions leave ortho-phthalates in food and our safety in limbo

FDA agreed to reevaluate safety of BPA (May 3, 2022 (cont')

- Petitioners: Environmental Defense Fund, Breast Cancer Prevention Partners, Clean Water Action, Consumer Reports, Endocrine Society, Environmental Working Group, Healthy Babies Bright Futures, Maricel Maffini, and Linda Birnbaum
- Petition is based on safety concerns.
- Rationale:
  - Substantial body of studies of the health effects of dietary BPA exposure published since 2013
  - EFSA's safety assessment establishing a tolerable daily intake (TDI) of 0.04 ng/kg bw/day (from 4 µg/kg bw/d).
  - FDA exposure estimate for the US population older than 2 years: mean: 200 ng/kg bw/d; 90th percentile: 500 ng/kg bw/d
  - Based on FDA's own exposure estimates, the average American is exposed to more than 5,000 times the proposed safe level of 0.04 ng BPA/kg bw/day set by the EFSA Expert Panel.

FDA agreed to reevaluate safety of BPA

- We asked FDA to revoke uses of BPA for adhesives and coatings and strictly limit migration of the substances into food from various plastic food contact articles.
- We proposed a specific migration limit for BPA in food of 0.5 ng/kg.
- We proposed to add new section a “General limitation of use 4,4'-Isopropylidenediphenol” with the following restriction on use of BPA:

Except as specifically described in parts 175, 176, and 177, for any use of the 4,4’-Isopropylidenediphenol, CAS Reg. No. 80-05-7, as a constituent in a food contact article that may migrate into food, the substance is subject to a specific migration limit of 0.5 ng/kg of food. If the specific migration limit is below the limit of quantification (based on 95% confidence that the false negative rate is less than 5%) using the most sensitive method, the concentration must be below the limit of quantification.

Timeline

- Filing date: May 3, 2022
- FDA must publish the filing in the Federal Register within a month, and request public comments (~60 days)
- FDA has a legal obligation to respond to the petition in 180 days after filing. It will likely take 1 year+
- July-August (?): Public comment period. Anyone can submit comments. Please consider submit your support for the petition
- Regulations.gov

Thank you!

drmvma@gmail.com