

# Dietary Supplements: Safety, Quality & Efficacy

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Policy Director





## Recent successes include leading efforts to:

- ✓ Remove artificial trans fat from food;
- ✓ Secure a guidance on sales of powdered pure caffeine to public;
- ✓ Prompt investigations into categories of misleading supplement claims;
- ✓ Challenge rollbacks to school nutrition standards in court;
- ✓ Require calorie labeling at chain restaurants;
- ✓ Keep food safe through passage and implementation of the Food Safety Modernization Act.

## Our Core Values

### **We are:**

- focused on system change;
- effective and resourceful;
- independent and rigorous;
- persistent yet flexible.

# Crackdown Urged on Supplements Marketed as Opioid Withdrawal Aids

CSPI Investigation Shows Manufacturers Can't Support Claims

December 8, 2017



NatraCet is one of the eight opioid addiction dietary supplements that CSPI investigated.

The Center for Science in the Public Interest today urged the [Federal Trade Commission](#) and the [Food and Drug Administration](#) to take enforcement action to protect consumers from dietary supplements that are marketed as opioid withdrawal aids.

## The New York Times

# Supplements Claiming to Ease Opioid Addiction Come Under Scrutiny

By [Sheila Kaplan](#)

Dec. 8, 2017

## Guidance for FDA Staff and Industry

## Marketed Unapproved Drugs – Compliance Policy Guide

Sec. 440.100  
Marketed New Drugs Without Approved NDAs or ANDAs

# Current Dietary Supplement Marketplace Failures

## *First Principles*

**For any consumer product, consumers have a right to:**

- 1) Expect a product is safe to consume as directed;
- 2) Expect a product does what it claims to do and there is adequate scientific evidence to back up those claims;
- 3) Know that what is on the label is inside the package & that it is not adulterated with other or substandard ingredients;
- 4) Expect that limitations of the product's efficacy are clearly communicated and that safety concerns (such as drug interactions) are also made clear;
- 5) Expect that if there is a reaction to a product that affects a number of consumers OR is serious that both the industry or regulator will act quickly and effectively to protect consumers.

# Basic Reforms for Supplements Oversight

**Greater Transparency:** Product listing and registration

**Addressing High-Risk & Tainted Supplements:** Third-party premarket safety tests, with spot audits by the FDA of specific classes of products that pose a “high risk” because of their ingredients, contaminants, susceptibility to being adulterated, or the likelihood of affecting vulnerable groups (e.g., infants), and mandatory recall authority over tainted supplements.

**Consumer empowerment and better event tracking:** Meaningful product labeling, including changes to the clarity, prominence, and font size of disclaimers, warning labels pertaining to drug interactions, and a 1-800 number for direct reporting of adverse events by consumers to the FDA on the label of products.

**Adequate oversight:** Improved resources for FDA

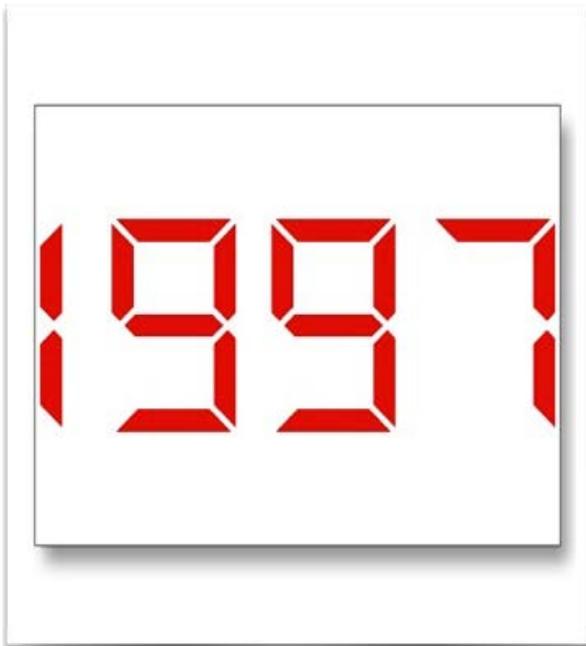
# Generally Recognized As Safe

**A substance is GRAS for a certain use in food if that use is... generally recognized as safe by experts based on common knowledge.**

- General recognition of safety of a use of a substance can be established through “**scientific procedures**” (or for a substance used in food before 1958, based on that use of that substance in food).
- FDA defines “**safe**” to mean that “there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”
- The “**common knowledge**” element requires: 1) data and information necessary to establish the scientific evidence must be “generally available;” 2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use.
- Determinations are for specified conditions of use, based on exposures in food.

# GRAS Listing and GAP

- Immediately after FFDCA, FDA published a partial list of GRAS substances.
- Although the law did not *require* premarket approval re GRAS, manufacturers would generally seek informal review before marketing substances by writing FDA to request an “opinion letter” on the GRAS status of a substance for a particular use, called an affirmation of GRAS status.
- A 1972 FDA rule formalized the opinion letter practice: companies could petition FDA to affirm the GRAS status of a substance, subject to notice and comment, called “GRAS Affirmation Petitions” (GAPs).
- While not strictly mandatory, the GAP was the “primary mechanism for manufacturers to protect themselves from FDA enforcement actions.”
- In the few instances that industry made private GRAS determinations, manufacturers would commission safety reviews by reputable scientific organizations to address the “obvious regulatory risks” self-determinations then posed.



- In a 1997 proposal, FDA said it would no longer officially review ingredients for safety.
- While some companies do submit notices to FDA, if FDA raises questions, the company can withdraw it and the ingredient can be used in food anyway.
- FDA also said industry's decisions can be based on secret "expert panels" and weakened the requirements for published, peer-reviewed safety data.
- The final rule issued in 2017 replicated these serious problems.

# “Generally Recognized as Safe”

ACME  
FOOD  
CORP.

“Let’s add a new ingredient – Schweety-x -- to our Cinnamon Crunchi-pops!”

We can voluntarily submit safety data to FDA.

We can secretly “self-determine” that it is “generally recognized as safe” (GRAS).

But  
is it  
safe?

FOOD INGREDIENT SAFETY  
ASSESSMENT TODAY ...

I THINK IT'S SAFE.  
YOU?

I THINK IT'S SAFE.  
YOU?

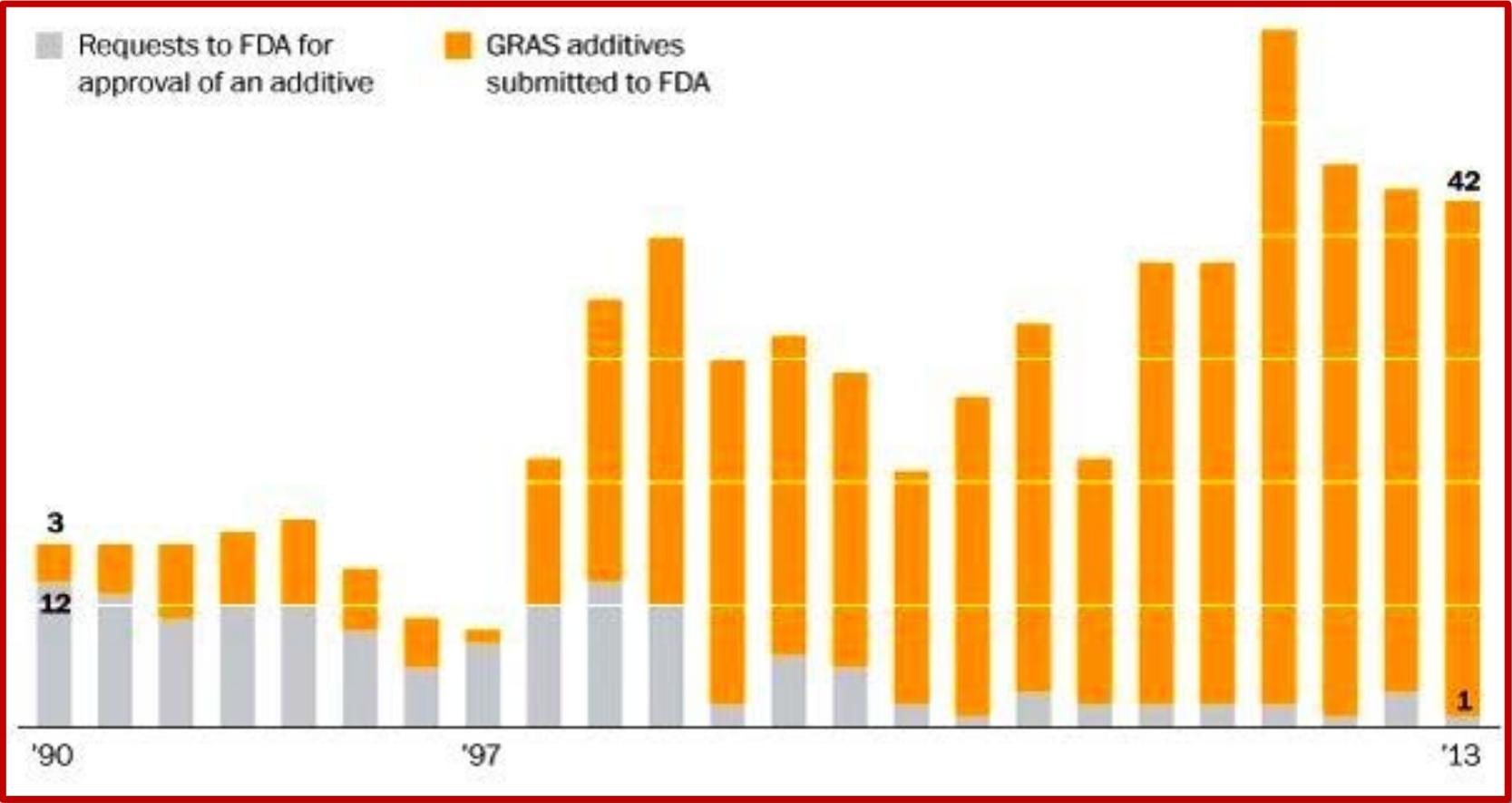
IT'S ALL GOOD.

GREAT!  
LET'S USE  
IT IN FOOD.

ACME FOOD CORP  
SCIENTIST #1

ACME FOOD CORP  
SCIENTIST #2

# How GRAS Took Over

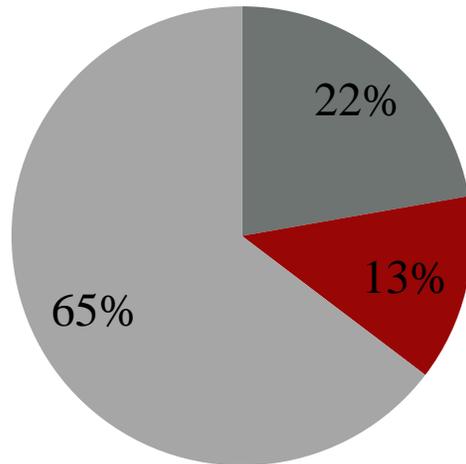


Source: Graphic by Kimberly Kindy and Cristina Rivero for the Washington Post, August 17, 2014. Data Sources: Natural Resources Defense Council, Food and Drug Administration, Center for Science in the Public Interest, Pew Charitable Trusts.

# Conflict-laden secret panels decide the safety of ingredients

## Who Decided Safety: 451 Notices to FDA (‘97-’12)

22% were made by an employee of an additive manufacturer;  
13% by an employee of a consulting firm to the manufacturer; and  
64% by an expert panel selected by consulting firm/manufacturer.



## JAMA Internal Medicine

### Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe

Out of Balance **FREE**

Thomas G. Neltner, JD<sup>1</sup>; Heather M. Alger, PhD<sup>1</sup>; James T. O'Reilly, JD<sup>2</sup>; Sheldon Krimsky, PhD<sup>3</sup>; Lisa A. Bero, PhD<sup>4</sup>; Maricel V. Maffini, PhD<sup>1</sup>

**“This is the opposite of what the law intended... [GRAS] assessments need to be based on publicly available information where there is agreement among scientists...It has got to be more than three employees in a room looking at information that is only available to them.”**

**—Deputy FDA Commissioner for Foods Michael Taylor, 2014**

*Kindy, Kimberly. “Food additives on the rise as FDA scrutiny wanes.” *The Washington Post*, Aug. 17, 2014. [Emphasis added.]*

# The 2017 FDA final rule essentially ratified 20 years of poor practice.

So we are suing on the theory that the rule, by permitting secret GRAS, illegally sub-delegates FDA's mission to assure the safety of food to private companies without oversight.



Case 1:17-cv-03833-VSB Document 44 Filed 09/12/18 Page 1 of 18

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

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CENTER FOR FOOD SAFETY, BREAST  
CANCER PREVENTION PARTNERS,  
CENTER FOR SCIENCE IN THE PUBLIC  
INTEREST, ENVIRONMENTAL DEFENSE  
FUND, and ENVIRONMENTAL WORKING  
GROUP,

Plaintiffs,

- against -

TOM PRICE, SECRETARY, DEPARTMENT  
OF HEALTH AND HUMAN SERVICES;  
SCOTT GOTTLIEB, COMMISSIONER,  
UNITED STATES FOOD AND DRUG  
ADMINISTRATION; and UNITED STATES  
FOOD AND DRUG ADMINISTRATION,

Defendants.

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USDC SDNY  
DOCUMENT  
ELECTRONICALLY FILED  
DOC #:  
DATE FILED: 9/12/2018

17-CV-3833 (VSB)

**OPINION & ORDER**



# Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry

## 2016 Draft Guidance

- An NDI notification is required unless all dietary ingredients “have been present in the food supply as an article used for food in a form in which the food has not been chemically altered” (21 U.S.C. 350b(a)(1)).
- Guidance, p. 23: “The purpose of the NDI notification requirement, which is to ensure that dietary ingredients that have not been widely consumed **receive a safety evaluation before reaching the marketplace.**”
- *Id.* “In addition, substances added to conventional foods must meet the safety standards for conventional food ingredients, **which are more demanding than those that apply to dietary ingredients used in dietary supplements.**” (“reasonably expected to be safe v. “reasonable certainty of no harm”)

# “Secret” GRAS: 2011 v. 2016 Guidance

## 2016 Guidance...

**Am I required to submit an NDI notification for a dietary ingredient that is an NDI, but has been (a) listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food or (b) approved as a direct food additive in the U.S.?**

- No...[if] the direct food additive or GRAS substance (1) has been used in the food supply (i.e., in conventional foods) and (2) is to be used as a dietary ingredient without chemical alteration. If the NDI has been legally marketed in the U.S [or outside the U.S.], as an ingredient for use in conventional food and ...introduced into the food supply as a result of such marketing, it would be exempt from the notification requirement... the NDI adulteration standard still applies, and voluntary NDI notification may be advisable.

## ...versus the 2011 Guidance:

2011 language [emphasis added]: “Am I required to submit a NDI notification for a dietary ingredient that has been listed or **affirmed by FDA as generally recognized as safe (GRAS)** for direct addition to food, **self- affirmed as GRAS** for direct addition to food, or **approved as a direct food additive** in the U.S.?”

# GRAS v. NDI: Some Differences

GRAS	NDI
Should use published data (“principles” ok under final rule)	Not required to use public safety documentation
Timeframe: 180+ days	75+ days
Allow for conditions of use in foods	Allow for conditions of use in supplements
Must be able to be used in foods (and in supplements without chemical alteration)	Could be used for dietary ingredients that can’t be used in foods due to properties
“No questions” letter	NDI authorization

# GRAS v. NDIs for Supplements

- 22 And many legal advisors and consultants have
- 1 told companies **that GRAS affirmation is a good option**
  - 2 **to NDI filing under certain conditions. There are**
  - 3 **probably six to seven times more GRAS affirmations than**
  - 4 **there are NDI notifications to date, post-DSHEA, which**
  - 5 **is an indication of the shift toward GRAS because**
  - 6 **there's more clarity about the overall process and a**
  - 7 **lack of an authoritative ODI list.**

**Panel 1 Presentations: What Evidence is Necessary to Show that an Ingredient was Marketed Before October 15, 1994?** Public Meeting to Discuss the Development of a List of Pre-DSHEA Dietary Ingredients, 10/3/17; [Panel 1.1](#) - Loren Israelsen

# Is GRAS a good substitute for an NDI?

- Not if self-affirmed (FDA should clarify that an NDI required)
- Not if it is only “legally marketed” and not used in food (that is NOT “present in the food supply”); or is a substance can’t really be used in foods
- Not if it marketed outside the U.S. (same statutory problem)
- GRAS fails to address safety for mixtures of ingredients
- Only if GRAS notification fully considered appropriate conditions of use for supplement, not just food (NDIs also based on conditions of use)
- Only if GRAS notification fully considered all dietary exposures (food and supplement) for “cumulative effects” (incl chemical and pharmacological)

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**Generally Recognized as Secret:**  
Chemicals Added to Food in the United States

**AUTHORS:**

Tom Neltner, J.D.  
Maricel Maffini, Ph.D.  
*Natural Resources Defense Council*

## Substances withdrawn from FDA review show up in food and supplements anyway.

- Epigallocatechin-3-gallate (EGCG) | leukemia in fetuses | 25 products.
- Gamma-amino butyric acid (GABA) | exposures > “safe” levels | 5 products.
- Sweet lupin protein | serious allergic reactions | >20 products lack a warning.
- Theobromine | testicular degeneration & delayed bone formation | >20 products.

## In addition, GRAS Is Generally Broken

- Rampant conflicts of interest (draft guidance not yet finalized and structurally weak due to secrecy loophole).
- The Redbook, FDA's toxicology guide, is not scientifically current and effort to update is stalled.
- FDA fails to account for vulnerable populations or to adequately take cumulative effects into account.
- There is no systemic lookback to re-examine the safety of an ingredient when concerns emerge.
- Resulting lack of public confidence in the safety of food chemicals.

## GRAS Notices

[FDA Home](#) [Generally Recognized as Safe](#) [Food Ingredient & Packaging Inventories](#) [GRAS Notices](#) [GRN No. 822](#)



## GRN No. 822

<b>Substance:</b>	Curcumin
<b>Intended Use:</b>	For use as an ingredient in a variety of food categories, excluding infant formula and foods under the 100 mg/100g.
<b>Basis:</b>	Scientific procedures
<b>Notifier:</b>	Laurus Labs Private Ltd. 2nd Floor, Serene Chambers Road No: 7 Banjara Hills, Hyderabad 500 034, Telangana India
<b>FDA's Letter:</b>	Pending



We absorb very little of the curcumin we eat.

## CURCUMIN

Curcumin is the compound in turmeric that makes curry powder and mustard yellow. Can it also boost your brain and memory, relieve your aches and

He—like others—has patented a curcumin formulation that is designed to be better absorbed. And some brands add a black pepper extract that keeps the body from clearing the curcumin too quickly. (The extract “can also interfere with the metabolism of many drugs,” notes Cole.)

But it's not just whether curcumin is absorbed or retained by the body that matters. In tests this year, [consumerlab.com](http://consumerlab.com) found that some supplements had just one-tenth as much of curcumin's active ingredients (curcuminoids) in each dose as others. And no one would know that from the labels.

Assuming you can find a supplement that has enough curcumin that your body can absorb or hold on to, what can it do? It's far too early to tell.

For example, in one study of Cole's formulation, 30 healthy, cognitively normal adults aged 60 to 85 who took 400 mg a day for a month scored better on only 1 of 10 cognitive tests than 30 similar people who got a placebo. (They were slightly better able to subtract by 3s.)<sup>2</sup>

However, in another study of the formulation, taking 2,000 mg a day improved blood flow through arteries, which might lower the risk of stroke and heart failure.<sup>3</sup>

pains, or protect your cells against deterioration, as some supplement companies claim?

“The big problem with curcumin is that what little we normally absorb is rapidly cleared, so very little reaches our tissues to do much,” explains Gregory Cole, professor of neurology and medicine at UCLA.

That may explain in part why so few trials in humans have been successful. For example, even though high doses of curcumin reduced Alzheimer's plaque in mice, Cole found no evidence that it did the same when he examined the cerebrospinal fluid of 36 Alzheimer's patients.<sup>1</sup>

“Maybe that was because we failed to reach blood levels of curcumin that were comparable to the levels we could produce in the mice,” Cole explains.



<sup>1</sup> *Alzheimers Res. Ther.* 4: 43, 2012.

<sup>2</sup> *J. Psychopharmacol.* 29: 642, 2015.

<sup>3</sup> *Aging.* 9: 187, 2017.

Thank you.

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