Food and Chemical Toxicology 107 (2017) 37–46

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Our unrequited love for natural ingredients

George A. Burdock*, Wendan Wang

Burdock Group, 859 Outer Road, Orlando FL 32814, United States

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form
31 May 2017
Accepted 3 June 2017
Available online 6 June 2017

Keywords:
GRAS
Natural
Synthetic
Artificial

ABSTRACT

Naturally sourced food ingredients have been the beneficiary of legal, regulatory and consumer preference as the result of a widely shared assumption of safety. However, the natural substances consumed in modernity may have little to do with the historically consumed part of the plant or even the plant itself. Further, our initial impression of a safe plant derivative may well be false as the result of the use of different growth conditions or, changes in harvesting and processing conditions that may have brought about a higher level of toxic constituents. Despite the variability of plant constituents, manufacturers' standards are set according to the content of commercially desirable properties, rather than presence of potentially toxic constituents. Why then, after all the potential reservations regarding naturals, is there such an enmity toward synthetic chemicals (including single chemical fermentation products), which have been tested in a systematic manner for potential toxic effects and whose composition is well known as the result of consistent manufacturing techniques and analytical controls? The authors will describe the paradigms used for natural products safety review and compare them with the safety criteria required for an "artificial" food ingredient.

Contents

1. Introduction

Natural ingredients (or naturally-sourced ingredients) hold a favorable place in subsistence as well as technologically advanced societies as products of a sympathetic and beneficent Mother Nature as a source of articles for healing, nutrition or sensory gratification. Even the 1958 Food Additive Amendment of the Food Drug and Cosmetic Act [21USC342] provides an accommodation for natural (unprocessed) foods in §402 as follows:

> SEC. 402. [342] A food shall be deemed to be adulterated - (a) (1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the

* Corresponding author.
E-mail addresses: gburdock@burdockgroup.com (G.A. Burdock), wwang@burdockgroup.com (W. Wang).

http://dx.doi.org/10.1016/j.fct.2017.06.006
0278-6915/

Table 1
Natural or naturally-derived substances for which limitations exist.

Substance	Limitation[a]	Reference
Almond, bitter	Free from prussic acid	21CFR182.20
Artemisis (wormwood) *Artemisia* spp.;	Finished food [must be] thujone free	21CFR172.510
Cedar, white (arborvitae), leaves and twigs (*Thuja occidentalis* L);		
Cherry pits (*Prunus avium* L. or *P. cerasus*)	Not to exceed 25 ppm prussic acid	21CFR172.510
Cinchona, red, bark *Cinchona succiruba* Pav. Or its hybrids	In beverages only; not more than 83 ppm total cinchona alkaloids in finished beverage	21CFR172.510
Neurotoxic shell fish poison	0.8 ppm (as Brevetoxin-2- equivalent)	Kotsonis and Burdock, 2013
Red algae	Maximum allowable level for iodine is 0.05%	21CFR184.1121

[a] A limitation imposed on the basis for concern of a possible toxin present, not a limitation based on foods in which the substance may be used.

> substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health …

That is, a food may contain a non-added (i.e., naturally present) deleterious (i.e., poisonous, toxic or carcinogenic) substance, so long as the conventional use of the food does not result in injury (otherwise, it would be unlikely to be called a "food"). In some instances, the Food and Drug Administration (FDA) has placed upper limits (called *tolerances* or *action levels*[1]) (Table 1), that a toxic substance, that is not an added substance and, might have been formed or incorporated into the food during growth and normal metabolic processes essential to the normal development of the organism and not as the result of human actions.[2]

Nature is far from benign, with many toxins in foods including, but not limited to glycyrrhizic acid in licorice, tomatine in tomatoes, cucurbitacin in the *Curcurbitacea* family (zucchini, cucumbers, pumpkins, squash, melons and gourds), goitrogens in *Brassica* spp., cyanogenic glucosides in cassava which release hydrocyanic acid, *alpha*-amylase inhibitor in beans and wheat (Dolan et al., 2010). Because there are so many foods with the potential to contain endogenous toxins, many foods are marketed with no regulatorily articulated limits for possible toxins present. To illustrate the point of no articulated limits for toxins, an example is provided in the amount of glycoalkaloids (α-solanine and α-chaconine) in the nightshade family of edible plants (e.g., potato, tomato and eggplant), which may be enhanced as the result of cross-breeding. Glycoalkaloids in potatoes can also be increased through abusive harvesting and handling techniques. Also, phototoxins and photomutagens may be present in cold-pressed oils of citrus fruits and in vegetables (carrots, parsley, celery and parsnips), especially under poor storage conditions that allow bacterial growth on the vegetables (Kotsonis and Burdock, 2013). These potentially harmful substances become adulterants when they occur in such quantities as to "ordinarily render it (i.e., the food) injurious to health" (Food Safety Council, 1982).[3] Thus, the Food, Drug, and Cosmetic Act contains five separate standards by which the safety of the eight categories of food substances are evaluated and regulated by three U.S. government agencies. The five standards are: "ordinarily injurious," "may render injurious," "safe under conditions of intended use," "necessary for the protection of public health," and "to the extent necessary to protect the public health." "Ordinarily injurious" and "may render injurious" are thresholds of prohibition, while the other three are benchmarks for licensing, but all in one form or another were designed to accommodate naturally occurring toxicants. At this point however, there should be an understanding of the context in which the 1958 Food Additive Amendments was debated and how the lenient treatment of naturals was conceived.

In the early 1950's, there was considerable public pressure to subject food ingredients to some sort of systematic regulatory (safety) review. It should be noted that at the time (i.e., pre-1958), FDA had no way of ensuring that chemicals added to food were safe before they were consumed by the public. In order for FDA to take action against a substance of doubtful safety, FDA typically had to prove (under §402 of the Act) that the chemical was toxic and its presence in food might be injurious to health – a process that mandated safety testing to be conducted on the chemical. Thus, FDA was viewed as a slow and unresponsive regulatory agency (Degnan, 1991). Congress (the famous Delaney Committee[4]) was led to believe there were as many as 500 to 800[5] ingredients currently in use, although the number was actually quite a bit higher, with approximately 1400 flavor ingredients alone. While most of the consumer uproar was over highly publicized added chemical ingredients, such as sodium benzoate, formaldehyde and borax (all used as preservatives[6]) and the presence of pesticides in food, it is little wonder there was no obvious angst over naturals. Vociferous opponents of pesticides and synthetic food ingredients testifying before Congress included J.I. Rodale[7] (whose company still exists today, with much the same outlook) and even the widow of Dr. Harvey Wiley, who objected to the presence of any synthetic materials in bread, especially ones that made bread softer (White, 1994). Although testimony was at times sensationalistic, cooler heads prevailed and a voice of reason from Dr. Anton Carlson (an

[1] Tolerances are enforceable, action levels are not.

[2] Refer to Hutt et al. (2014) *in re* the discussion of mercury in fish.

[3] When tolerances, specifications, etc., do not address a potentially toxic substance in a food or ingredient, the agency may invoke the "general safety standard" (21CFR170.3(i)) "*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."

[4] Named for Congressman James J. Delaney of New York.

[5] A list of 840 chemicals often cited in the literature was actually a condensed list compiled by Commissioner Dunbar and was one of several such lists (White, 1994).

[6] Dr. Harvey Washington Wiley, the iconic investigator who publicized the presence of added ingredients in the food supply which led to the 1906 Pure Food and Drug Act, warned an anxious public that "… weak or diseased stomachs may suffer temporary or permanent injury from even minute quantities of preservatives." At a time late in the 19th and early 20th Centuries when borax and formaldehyde were commonly used preservatives in food, Wiley was nothing short of a zealot and wanted to equate all "chemical additives" with "poisonous" and regarded addition of a chemical to food in any amount as intolerable (i.e., no observance of the maxim "the dose makes the poison"). However, at the time of the hearings in the early 1950's, when considerable progress had been made in pharmacology (i.e., ingredient testing) and food science, Wiley's passionate dicta against chemicals in food were seen as anachronistic (White, 1994).

[7] Rodale was then editor of *Organic Gardening* and *Organic Farmer* and later editor of *Prevention Magazine* (White, 1994).