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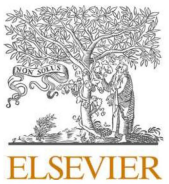

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Review of the standards of proof (of safety) for FDA regulated consumer products and how the generally recognized as safe criteria could be applied to cosmetics

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ABSTRACT

The Modernization of Cosmetics Regulation Act of 2022 (MoCRA) amends the Food, Drug and Cosmetic Act (FDCA), elevating the standard of proof of safety (better known as a "safety standard") for cosmetics to the standard of a "reasonable certainty … [of] … safe."a standard equal to that of food ingredients. The standards of the proof of safety differ for various classes of FDA-regulated product categories *e.g.*, cosmetics, dietary supplements, food ingredients and food itself. This manuscript describes the various standards of proof, the essential differences between the standards, key elements required to achieve a particular standard and, compares the standards to more familiar legal terms such as "a preponderance of the evidence" or "beyond reasonable doubt." The standards of proof for these product categories are also ranked according to increasing threshold for achievement of "safe" status. Lastly, this manuscript suggests how the requirements for the high standard of a "reasonable certainty of safe" (or "reasonable certainty of no harm") might be met.

1. Introduction

The Modernization of Cosmetic Regulation Act (MoCRA) represents a dramatic change in the level of proof of safety of cosmetics – from an undefined "adequate substantiation of safety" to the equivalent of "a reasonable certainty of no harm" the high standard of proof required for food ingredients. To better understand the magnitude of the qualitative leap required by MoCRA, this manuscript will illustrate the differences in product safety standards and standards of proof of safety for dietary supplement ingredients, colors, food ingredients and food and; compare them to more familiar terms for standards of proof required in civil and criminal law. For these proofs of safety, the statute, subsequent regulations, and guidance documents attempt, but often fall short of definitive descriptions of the characteristics and qualification of the safety decision makers, the decision makers' degree of certainty and the rigor of the information on which the decision is based; the objective of this manuscript is to fill those gaps.

2. Cosmetics – history, definition and regulation

2.1. Tragic events precipitating legislative intervention

The first national law governing foods and drugs was the Pure Food and Drug Act of 1906 (a/k/a the "Wiley Act") and was passed largely in response to Upton Sinclair's book, *The Jungle,* which exposed nefarious practices in the meat packing industry. Theodore Roosevelt, a Progressive and President at the time of passage, had a first-hand experience with the tainted drugs and food sent to the troops in Cuba during the Spanish-American War (1898) in which Roosevelt was a colonel in the "Rough Riders". However, the 1906 Pure Food and Drug Act focused on food and drugs and did not address cosmetics (FDA, 2019).

The oversight to not address cosmetics in the 1906 Act became obvious in the 1930's with a series of widely publicized tragic incidents. In 1932, *Koremlu,* advertised as a safe and permanent depilatory and although mostly applied only to the upper lip of women, repeated use resulted in significant loss of body hair and paralysis from the thallium acetate in the depilatory, despite the fact that the toxicity of thallium was widely known at the time (Kallet and Schlink, 1933; Kay, 2005). The following year, 1933, a mascara with the seductive name "Lash Lure",

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caused an allergic reaction in some users resulting in blisters, abscesses and ulcers on the face, eyelids and eyes, and in some users, the reaction was sufficient to lead to blindness (Kay, 2005). Also during this period, consistent use of a beautifying face cream (*Gouraud's* Oriental Cream), left users with "bluish-black gums and loose teeth" as the result of mercury poisoning from the ingredient calomel (mercury chloride) in the product (Eschner, 2017). Public outrage over these and other incidents, precipitated a total reformation of the 1906 Pure Food and Drug Act, which was re-named the Food, Drug and Cosmetic[1] Act of 1938.

2.2. Cosmetics – definition and examples

What is a cosmetic? A cosmetic is defined in the 1938 Food Drug and Cosmetic Act (FDCA) in section 201(i) as follows:

> §201(i) The term "cosmetic'' means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

The definition specifically excludes soap, which eventually became the domain of the Consumer Product Safety Commission (CPSC).

Products included in the definition of a cosmetic are shown in Table 1. In the left column of the table, there is a list of products with which consumers would be familiar as cosmetics, such as hair and nail products, perfumes, eye liner, etc. On the right, there is a list of products, some of which may not normally be thought of as cosmetics, such as toothpaste and breath mints.

Toothpaste is a cosmetic when advertised to clean the teeth, but it is an over-the-counter drug if the label states that it can remove plaque or kill germs. Toothpaste, breath mints, lipstick, and lip gloss, are all cosmetics, despite the fact they are swallowed like any food. Prior to the implementation of MoCRA, manufacturers of these (ingested) products were only obligated to meet the much lower standard of proof of safety for cosmetics (an "adequate substantiation of safety"), rather than the standard of "a reasonable certainty of no harm" for food ingredients. While breath mints may seem functionally equivalent to chewing gum and candy, the latter two are both foods (FDCA §201(f)). The reader should be aware that all colors, whether used in cosmetics, supplements, foods or drugs, must be approved *via* a color additive petition by FDA. The reader should also note there is no such term in the regulator's lexicon as "cosmeceutical", a marketing term. "… the cosmetic industry uses this word to refer to cosmetic products that have medicinal or drug-like benefits" (FDA, 2022a).

Table 1
Examples of cosmetic products.

- Hair and nail products
- Tanning products without sunscreen
- Skin moisturizers
- Perfumes
- Shaving cream
- Eye liner
- Bath oils, tablets and salts
- Hairspray, shampoos, tints and rinses
- Underarm deodorants, but not antiperspirants
- Feminine deodorant sprays and douches
- Foot powders and sprays
- Beard softeners
- Toothpaste
- Breath mints
- Lipstick, and lip gloss, but not lip balm (if a claim is made)
- Eyelash and eyebrow adhesives, glues and sealants
- Bubble bath
- Leg and body paints
- Tattoo inks
- Baby wipes
- AND - any components thereof (except colors, which must be approved by FDA *via* a color additive petition).

[1] Emphasis added.

Even though the category of cosmetics was added to the Food Drug and Cosmetic Act in 1938 [Public Law: 75–717], the statute addressed adulteration and labeling of cosmetics, as opposed to criteria for proof of safety:

Sec. 601 [21 U.S.C. 361] A cosmetic shall be deemed to be adulterated:

(a) If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual …
(b) If it consists in whole or in part of any filthy, putrid, or decomposed substance.
(c) If it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.
(d) If its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health.
(e) If it is not a hair dye and it is, or it bears or contains, a color additive which is unsafe within the meaning ….

The standard of proof for safety of cosmetics was not articulated until nearly 40 years later, in 1975 (Federal Register 40:8917 March 3, 1975) and incorporated into the CFR.

21CFR740.10 Labeling of cosmetic products for which adequate substantiation of safety has not been obtained.

(a) Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel:

Warning – The safety of this product has not been determined.

However, the standard of proof, "adequate substantiation of safety" was poorly conceived as it did not define the terms used, including a description of what must be considered in a decision of safety or the qualifications of the decision-makers. There had been attempts to clarify the 1975 standard of "adequate substantiation of safety" and in 2013, Congress proposed an upgrade to the cosmetic standard of proof of safety to the same used for food ingredients, to "a reasonable certainty of no harm" (House of Representatives, 2013) and other provisions now included in MoCRA. That bill, however, did not make it to the President's desk.

2.3. Modernization of Cosmetics Regulation Act (MoCRA)

Signed into law on December 29, 2022, as part of the Consolidated Appropriations Act of 2023, MoCRA became Public Law 117–328, amending the Food Drug and Cosmetic Act and mandating sweeping changes in the regulation of cosmetics and personal products. The upgrading of the standard of proof of safety of cosmetics, which many have argued was long overdue, because cosmetics represent a wide cross-cutting category of products that are applied to some very absorptive areas of the body, sprayed or otherwise introduced into various orifices on a daily basis and often for a lifetime. Among the requirements in this amendment to the FDCA, is an elevation in the standard of proof (of safety) from the original indeterminate standard of an "adequate substantiation of safety" for cosmetics and their ingredients, to a new standard, a "reasonable certainty … [of] … safe" – clearly, an upgrading to a standard of proof of safety shared with food ingredients.

Importantly, unlike the 1975 attempt, MoCRA better defined how the standard of proof of "Adequate Substantiation of Safety" should be determined. MoCRA mandates that to achieve the standard of proof, it must include three important features:

> First, the standard requires that the determination of safety must include tests or studies, research, analyses or other evidence or information (presumably empirical), on which the decision of safety is based.
>
> Secondly, the decision makers on safety must be experts qualified by scientific training and experience (equivalent to a peer-reviewed safety assessment).

Third, the qualified experts must conclude the threshold of "a reasonable certainty of safety" has been met.

The statute (MoCRA §608(c)(2)) precludes a challenge that the ingredients must be safe at any level of use, but only that the ingredient must be safe at those concentrations and consequent levels of human exposure that "are customary or usual"; that is,

> The Secretary [*i.e.*, the Commisioner of FDA] shall not consider a cosmetic ingredient or cosmetic product injurious to users solely because it can cause minor and transient reactions or minor and transient skin irritations in some users.

This provision avoids the troublesome "safety *per se*" interpretation that had resulted in at least one Supreme Court case (*United States* v. *Lexington Mill and Elevator Company* 232 U.S. 399 (1914)). The new standard also encourages consideration of cumulative exposure from daily use (sometimes for a lifetime) and precludes minor or transient reactions (such as minor skin irritation) as meeting the threshold of no longer safe (MoCRA §608(c)(2)).

As noted, the standard of proof of "reasonable certainty," is based upon "tests or studies, research, analyses or other evidence or information." This evidentiary requirement is important because it gives an opening for FDA to demand empirical evidence of the data on which a finding of safety is based, rather than inferred safety based on the behavior of similar substances, such as the method referred to as "read-across" which predicts the potential toxicity of one substance, knowing the toxicity of a structurally similar substance (Andersson, 2017). Although not as substantive as direct, empirical evidence, the read-across method may be admissible as providing corroborative evidence of safety as allowed for demonstrating the safety of food ingredients as cited in 21 Code of Federal Regulations (CFR) 170.30(b) and (c). The concept of "corroborative" evidence is elaborated on in FDA guidance (FDA, 2022b), in that, "… qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to 'corroborative' information."

Importantly, MoCRA goes a step further than §201(s) of the FDCA (*i.e.,* for Generally Recognized As Safe or GRAS) in describing scientific requirements. The concept of general recognition of safety originated in the new-drug provisions of the 1938 Act and the idea was carried forward in the pesticide chemicals amendment of 1954, then later improved and incorporated into the Food Additives Amendment of 1958 (Goodrich, 1960). One of the requirements for generally recognized as safe (GRAS) cited in FDCA (§201(s)) and the regulatory requirement for "Eligibility for classification as generally recognized as safe (GRAS)" provided in 21CFR170.30, requires that "scientific procedures," must be met and although not further defined in the statute, but is generally interpreted as being empirical scientific evidence. The concept of "scientific procedures" is however, defined in 21CFR170.3(h): "Scientific procedures include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use." As noted above, while corroborative information may be employed in the decision-making process, the experts must be able to conclude that the substance is not harmful in the absence of the corroborative information.

MoCRA makes the scientific element clearer by referring specifically to "tests or studies, research, analyses or other evidence or information; " this provision leaves no question as to what is required for the scientific element. Equally important, MoCRA has no provision for exemption from data requirements on the basis of historical use of the substance, such as is permitted for a conclusion of GRAS; that is, there is no "grandfather clause" conferring safe status solely on the basis of historically safe use (Kennedy and Burdock, 2016).

MoCRA imposes a tight timeline for such a comprehensive characterization of ingredients: the Advanced Notice of a Proposed Rule is due December of 2024, and the final rule is due December of 2025. This timeline may be difficult to meet for companies that do not start planning and prioritizing those substances to be tested, because the lead times and time to completion of critical information can be lengthy (Table 2). Understanding the requirements of "reasonable certainty" and planning ahead to meet the deadline for submission of data and a persuasive argument for safety is essential, as these deadlines are usually inflexible because it is seen as unfair to companies that submitted their data in a timely manner.

2.4. *Reasonable certainty – a term of art and the concept underlying cosmetic and food ingredient safety*

What does "reasonable certainty" mean? According to the dictionary at the Lawinsider.com (2023) website:

> Reasonable certainty means you are persuaded based on a rational consideration of the evidence and that you have a high degree of confidence in this decision.

To put "reasonable certainty" in context, reasonable certainty in the legal arena is a higher standard of proof than the "weight of evidence", but less than "beyond a reasonable doubt"(Lawinsider.com, 2023). Therefore, as mentioned above, "reasonable certainty" in addition to having a legal definition, is an accepted term of art used by FDA since at least the passage of the Food Additive Amendment of 1958.

Table 2
Tasks which may be required to fulfill the mandate for "tests or studies, research, analyses or other evidence" on which to base a decision of safety.

Task[a]	Time (weeks)[b]
Stability study[c]	1–13
Acute eye irritation	4
Acute dermal toxicity	4
Dermal absorption	4
Mutagenicity and genotoxicity	8
Guinea pig maximization test/Buehler test[d]	8
Human sensitization study[e]	12
28–90 Day duration oral or dermal study[f]	10–40
Preparation of safety dossier	13
Expert Panel review	2

[a] Many of these tasks can be conducted simultaneously.
[b] Approximate.
[c] Stability under conditions of use and the medium for test animal administration.
[d] In place of these *in vivo* tests, FDA may accept i*n vitro* skin sensitization test (such as 442E of the OECD protocols).
[e] ~~a, b, c, d, e and f~~Likely required if animal or *in vitro* test are positive.
[f] Likely required if absorption is significant and/or the ingredient is used habitually.

3. What does it mean for something to be safe?

3.1. Safety – absolute and default positions

During the hearings pursuant to the Food Additive Amendment, Congress addressed the very fundamental meaning of the word "safe" and how it should be interpreted.

> The concept of safety used in this legislation involved the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not — and cannot — require proof beyond any possible doubt that no harm will result under any conceivable circumstances (HR. Report, 1958).

With this statement, the Congressional Committee made the distinction between "safety *per se*" or "harmless *per se*" and "safe for its intended use."

3.1.1. Safe at any level of exposure – safety per se

Must something be absolutely safe? NO. The concept that a substance should not produce harm at any level of exposure was supposedly foreclosed in a 1914 Supreme Court decision (*US* v. *Lexington Mill & Elevator Company* 232 U.S. 399 (1914)). This case was in response to the presence of residue from a flour bleaching agent, nitrogen peroxide, which can be toxic, but not in the amounts present in Lexington Mill's flour after treatment. However, the government interpreted the then prevailing 1906 law such that no detectable toxin should be present in the flour and the flour was therefore considered adulterated.

The Supreme Court concluded the government's interpretation of the 1906 law was an over-reach. The Court noted that according to the government's interpretation of the statute governing food at that time, all substances in food should be safely consumed in any amount and by all people, was an obvious impossibility. Further, the Supreme Court indicated that because the 1906 law "was a criminal statute, creating a new offense, it must be strictly construed and applied" [*i.e.,* the law was not subject to a loose interpretation] … and because the government could not demonstrate harm befell the consumers, interstate distribution [of the flour] was permitted" (Krinsky, 1976). As a result, a stricter interpretation of the law was imposed such that an adulterant must be of sufficient quantity in the food to render the article of food injurious to the consumer before it may be condemned as being adulterated.

Unfortunately, with the passage of the 1938 Food, Drug and Cosmetic Act, the concept of "harmless *per se*" was re-instituted by FDA and not overturned until the 1958 Additives Amendment, at which time the government was persuaded to abstain from the concept of safe at any level of use and in any circumstance, but employ the concept of safety-in-use or as more commonly said, "safe for its intended use" (Editorial Board Minnesota Law Review, 1962).

3.1.2. Safe as a default position?

May something be assumed to be safe if there is no data to the contrary? The answer is again, NO. A case in point is one in which a beverage company added potassium nitrate to its beverage, claiming that potassium nitrate was safe because it was already approved for addition to meat (*via* "prior sanction", 21CFR181.33) and there was no evidence indicating potassium nitrate was unsafe. The court decided that the lack of evidence of harm is not enough to declare something to be safe (*United States* v. *an Article of food*, 1985). The court's finding is captured in the antimetabole, "absence of evidence is not evidence of absence" (Marsh, 2019).

With certain exceptions, dispositive, empirical evidence is needed to declare something is safe, which discounts the value of corrobortive evidence alone, as proof of safety. The depth and breadth of the evidence required to meet a particular category standard of proof of safe is discussed in the following pages.

3.2. Safety as a relative value achieved through different standards of proof

3.2.1. Precedent for different standards of proof

The different standards of proof are illustrated in the drama accompanying the trials of O.J. Simpson; that is, Mr. Simpson was acquitted in the criminal trial of the murder of his ex-wife and her friend, having been found *not guilty* by the jury. However, in a subsequent civil trial, Mr. Simpson was found guilty of the wrongful death of his ex-wife and her friend and, was required to pay monetary damages. How can this be that he was not guilty in one trial but guilty in another?

In Mr. Simpson's criminal trial, the prosecution had the *burden of proof* to demonstrate it had met the standard of proof of *beyond a reasonable doubt* which is required for a criminal conviction.

According to the Cornell Law School Legal Information Institute (2023a,b):

> **Beyond a reasonable doubt.** The prosecution bears the burden (i.e., the "burden of persuasion) of proving that the defendant is guilty beyond all reasonable doubt. That is, the prosecution must persuade the jury that there is no other reasonable explanation that can come from the evidence presented at trial. The standard of proof, beyond all reasonable doubt, is much higher than the civil standard, called "preponderance of the evidence," which only requires a certainty greater than 50 percent.
>
> **Preponderance of the evidence**. To prove an element by a preponderance of the evidence simply means to prove that something is more likely than not. In other words, in light of the evidence and the law, do you believe that each element of his/her [claim/counter-claim] is more likely true than not?

In the criminal trial of Mr. Simpson, although the prosecution may or may not have met the standard of proof, of beyond a reasonable doubt, the prosecution most certainly failed to meet the *burden of persuasion* and the jury declared Mr. Simpson, not guilty. However, in the civil trial, the threshold for meeting the standard of proof is much lower, *preponderance of evidence*, for which the Plaintiff's attorneys met both the *burden of proof* and the *burden of persuasion.* So too, are there different standards of proof for products regulated by FDA.

3.2.2. The binary nature of safety versus the multidimensional nature of standard of proof

The FDCA §201(u) defines the term "safe" as referring to the health of man or animal — the presumptive interpretation of this statement is that "safe" is binary; that is, either something is safe, or it is not. How then, can various categories of regulated products (*e.g.*, cosmetics, dietary supplements, food ingredients) have different standards of safety? Further, the regulations differ on who can make the determination of what is safe, the credentials of the decision-makers, and what should be considered in determining safety.

The answer is that safety is not so much binary as it is relative to the intended use of the substance, and the differences between the various categories is not a difference in safety, but a difference in the standard of proof for each category to demonstrate safety. Standards of poof refer to the degree or level of proof required in a specific circumstance *i.e.*, intended use. The required degree or level of proof includes not only the quantity, but also the quality of proof submitted – all of which must be relevant to the point to be made (Karnavas, 2016).

> **Standard of proof:** the level of certainty and the degree of evidence necessary to establish proof in a criminal or civil proceeding (Merriam-Webster, 2023).

In the illustration with the seesaw balances (Fig. 1), to meet the standard of proof for safety (regardless of the substance category), a specific quantum of data (*i.e.*, the totality of information, including but not limited to quantity, type and quality of relevant data), must be

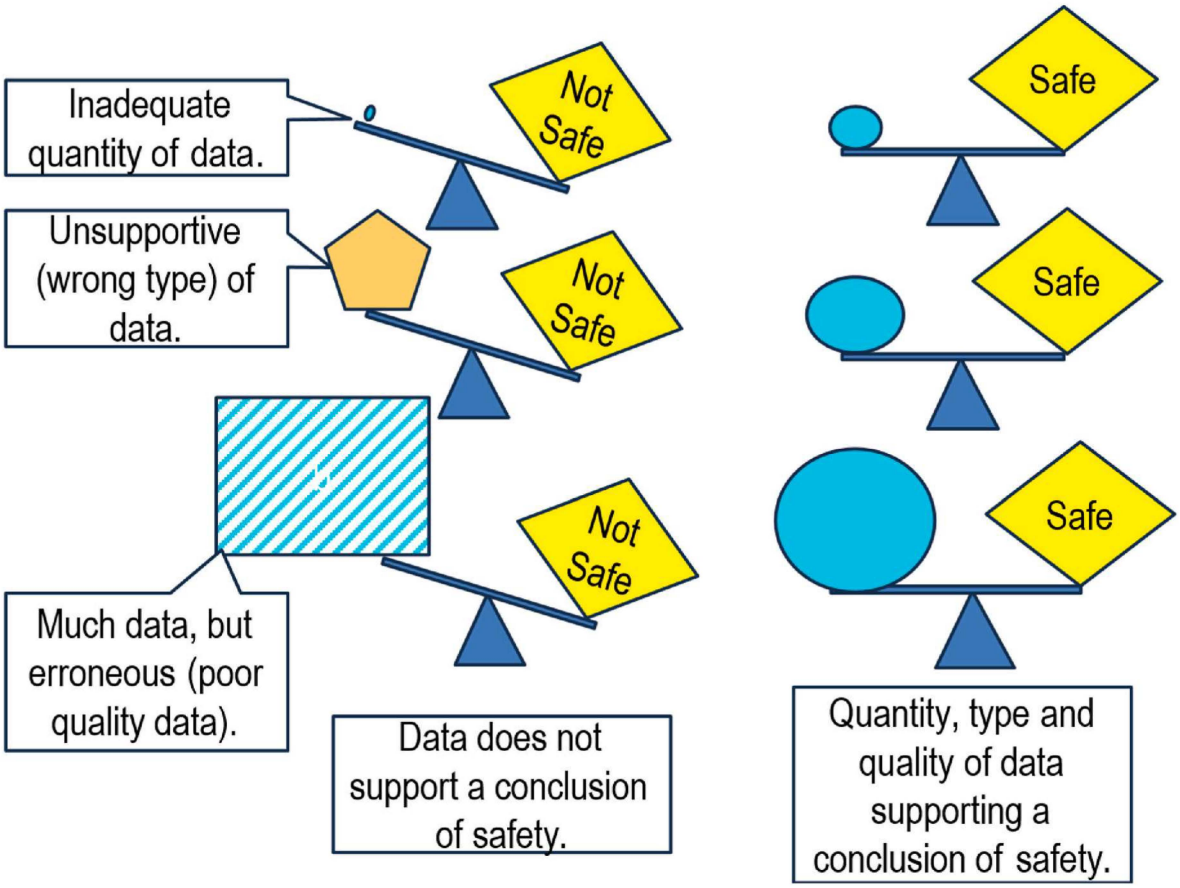

Fig. 1. Distinction between standards of proof and conclusion of safety.

submitted to achieve the standard of proof for a particular category. On the left side of this illustration, the quantum of data necessary to satisfy the standard of proof has not been met; that is, the quantum is inadequate (even though the threshold requirement might be quite low). For example, the data may be unsupportive (such as an orally administered test substance data for a dermally applied substance), or poor quality (*e.g., a* non-GLP study). However, on the right, the standard of proof has been met, including quantity, type and quality of data.

3.2.3. Standards of proof for safe use for various regulatory categories – statute versus regulation

As in criminal versus civil proceedings, there are different standards of proof to achieve the threshold for a decision on safety for various consumer products (Table 3). Some standards of proof were identified in the statute (FDCA) and others, by regulation, in Chapter 21 of the Code of Federal Regulations (21CFR).

The standard of proof, if any, cited in the FDCA may not be entirely clear or applicable in the mind of the Executive Agency mandated to implement the statute; as a result, the Executive Agency is allowed a degree of interpretation of the statute in promulgating the regulation. While an interpretation may result in some disparity between what is mandated in the statute and subsequently provided in the regulation, the interpretation by the Executive Agency is permitted by the Chevron Deference rubric (*Chevron U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 468 U.S. 837 (1984)) As a result of Chevron Deference, the finalized regulation instituting the MoCRA-mandated standard of proof (*i.e.,* reasonable certainty), may not faithfully reflect the wording of the statute. However, for the purposes of this discussion, it is assumed FDA will remain faithful to "reasonable certainty" in the amendment for cosmetics and will retain the spirit for food ingredients as in §201(s) of the FDCA.

Relevant to this discussion of MoCRA and the degree of fidelity FDA pays to the statute, the Chevron Deference decision is scheduled to come up for review by the Supreme Court in its 2023-24 session and may be overturned, thus forcing the FDA to a more literal interpretation of the statute.

3.3. Ranking of the standards of proof of safety for various categories

3.3.1. Standard of proof for safety of cosmetics prior to passage of MoCRA

In the hierarchy of standard of proof required to meet the threshold for a finding of safety, the lowest level is, "Adequate Substantiation" the previous standard for cosmetics – where there is no definition of "adequate" and no designation of the requirements (including qualifications) of the decision makers or the data requirements for a decision (Fig. 2).

> 21CFR740.10(a) Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel: Warning - The safety of this product has not been determined.

What is the level of proof for "adequate substantiation"? Referring to Karnavas (2016), the lowest threshold for evidence, "scintilla," (Latin for "spark") (Cornell, 2023c) indicates a hint or trace of something barely suggesting its presence but cannot be summarily dismissed and is somewhat less than "substantial evidence". However, scintilla is based in common law, not statutory law and is rarely used in federal or state courts (Cornell, 2023c). Therefore, in this regulatory context, preference is given to the term "substantial evidence," as described by the

Table 3
Current standards of proof of safety for product categories.

Product Category	Standard of Proof for Safety	Reference[a]
Cosmetic (pre-MoCRA)	General references to the cosmetics having been adulterated and "rendered injurious to health"	FDCA §601[b]
	Adequate substantiation of safety.	21CFR740.10
Cosmetic (post-MoCRA)	(1) ADEQUATE SUBSTANTIATION OF SAFETY.-The term 'adequate substantiation of safety' means tests or studies, research, analyses, or other evidence or information that is considered, among experts qualified by scientific training and experience to evaluate the safety of cosmetic products and their ingredients, sufficient to support a reasonable certainty that a cosmetic product is safe. (2) "SAFE.-The term 'safe' means that the cosmetic product, including any ingredient thereof, is not injurious to users under the conditions of use prescribed in the labeling thereof, or under such conditions of use as are customary or usual …	FDCA §608(c)(1)&(2)
	To be determined.	21CFR
Dietary Supplement	" … presents a significant or unreasonable risk of illness or injury …"	FDCA §402(f)(1)(A)
	"… reasonably be expected to be safe …"	FDCA §413(a)(1) & (2) & §413 (b) *et seq.*
	"… reasonably be expected to be safe …"	21CFR190.6(b)(4)
Color additive	[Secretary makes the final decision on use, but safety factors must be evaluated by] "… experts qualified by scientific training and experience to evaluate safety of color additives …"	FDCA §721(b)(5)(A)(iii)
	Safe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.	21CFR70.3(i)
GRAS substance	… experts qualified by scientific training and experience to evaluate its safety … to be safe under the conditions of its intended use …	FDCA§201(s)
	General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food.	21CFR170.30(a)
Food additive	… the Secretary shall consider … the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives …"	FDCA §409(c)(5)(C)
	Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.	21CFR170.3(h)(i)
Food	(f) The term "food'' means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.	FDCA §201(f)
	… 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 … [A presumption of safety].	FDCA §402(a)(1)
	Food has the meaning given in section 201(f) of the Federal Food, Drug, and Cosmetic Act: (1) Except for purposes of this subpart, it does not include: (i) Food contact substances as defined in section 409(h)(6) of the Federal Food, Drug, and Cosmetic Act; or (ii) Pesticides as defined in 7 U.S.C. 136(u). (2) Examples of food include: Fruits, vegetables, fish, dairy products, eggs, raw agricultural commodities for use as food or as components of food, animal feed (including pet food), food and feed ingredients, food and feed additives, dietary supplements and dietary ingredients, infant formula, beverages (including alcoholic beverages and bottled water), live food animals, bakery goods, snack foods, candy, and canned foods.	21CFR1.227

[a] References: CFR = Code of Federal Regulations, FDCA = Food, Drug and Cosmetic Act (as amended, 2022).
[b] Historical reference, changed with the passage of MoCRA.

following:

> Indirectly referring to substantial evidence as the threshold of admissibility, was the finding by the court of the following: "Mere uncorroborated hearsay or rumor does not constitute substantial evidence" (*Consolidated Edison Co.* v. *NLRB*, 305 U.S. 197 (1938)).
>
> Similarly, the court in *Richardson* v. *Perales*, 402 U.S. 389 (1971), said a finding should be "supported by substantial evidence," and that this was "more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion."
>
> In Degnan et al.(2015): "Substantial evidence" is the threshold required for judicial review of a food additive petition; the agency's final decision is subject to review in any U.S. court of appeals. A request for a hearing must demonstrate that a material and substantial issue of fact exists (*i.e.,* regarding the approval or denial of a food additive petition); unless the threshold is met, a hearing will not be granted (Degnan et al., 2015).

Therefore, the term "substantial evidence" became embedded in the regulations and is defined as meaning that the "… degree of relevant evidence which a reasonable person, considering the record as a whole, might accept as adequate to support a conclusion, even though other reasonable persons might disagree. This is a lower standard of proof than preponderance of the evidence" (4CFR28.61(d)).

Both scintilla and substantial evidence are lower standards of proof than "preponderance of the evidence" (Cornell, 2023d). "And 'substantial' in this connection does not mean 'preponderant evidence' or 'conclusive evidence'. Congress specifically discarded those terms [i.e., "preponderance" and "conclusive"] for the milder term 'substantial', which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion." (Hynson, Westcott and Dunning v. Richardson, 461 F.2d 215, 220 (4th Cir. 1972)); with which, the Supreme Court concurred (Weinberger v. Hynson, Wescott & Dunning, Inc., 412 U.S. 609 (1973)).

3.3.2. *Standard of proof for safety of dietary supplement ingredients*

For the purposes of clarity, a "dietary supplement" is the finished product consisting of the dietary ingredient(s) (the "actives," whether an old dietary supplement ingredient (ODI) or new dietary supplement ingredient (NDI) or both and the excipients (the "inactives" and including the capsule, coatings, etc.). For the purposes of regulation, dietary supplement ingredients (*i.e.,* the active ingredient, not the excipients or finished product) are broken down into two categories – (1) Old Dietary Ingredients (ODI), a supplement ingredient in use as such prior to passage of the Dietary Supplement Health and Education Act (DSHEA) October 15, 1994, and for which a notification to FDA is not required unless the method of manufacture has been changed (Pendergast et al., 2017; FDCA §413(a)(1)). Notification of an ODI is not required as the result of a presumption of safety (see also the section on Food, below) because of a history of (presumed) safe use — such an ingredient is "grandfathered". (2) New Dietary Ingredients (NDI) are those proposed for use since passage of DSHEA and FDA must be notified of their impending marketing.

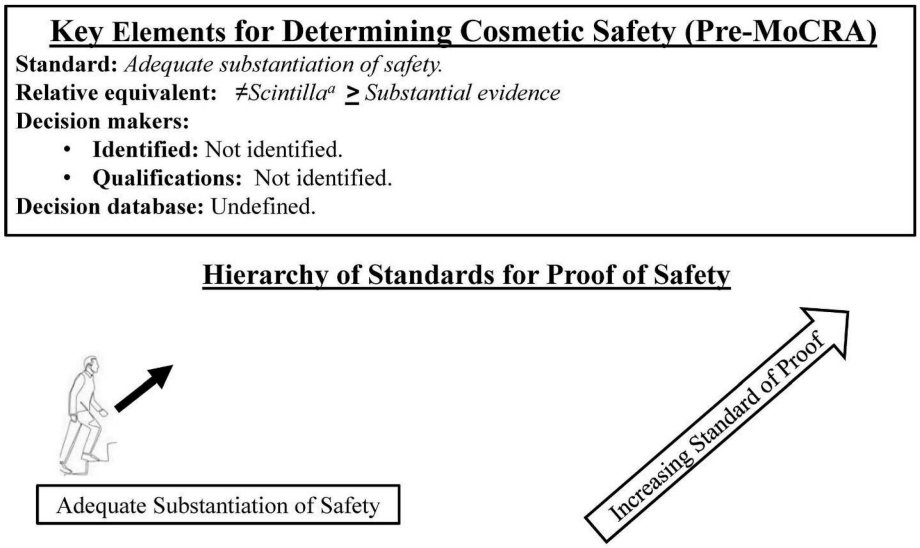

Fig. 2. The standard of proof and the meaning of safe for a cosmetic (Pre-MoCRA).

The Dietary Supplement Health and Education Act of 1994 (DSHEA, Public Law 103–417) is an interesting study in Congressional sausage-making. For example, the "reasonable expectation" standard, although not defined in the Act, likely arose from the Congressional statement regarding the benign nature of dietary supplements, as expressed in the Findings section of the Act (Section 2), "(14) dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare" — essentially a rebuttable presumption of the safety of dietary supplements and; because Congress was so convinced of the safe nature of dietary ingredients, it placed the burden on FDA to prove a dietary supplement was unsafe (Degnan et al., 2015).

In addition to the "reasonable expectation" standard in DSHEA, in §402 of the FDCA, "A food (*i.e.,* supplement) shall be deemed to be adulterated if it "… presents a significant or unreasonable risk of illness or injury" (§402(f)(1)(A)) and in §402(f)(1)(B), which refers to a "a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury …", and which, provides the Secretary substantial discretion (in §402(f)(1)(C)) to declare the NDI as posing "an imminent hazard to public health or safety"; such an administrative determination results in an immediate ban of the ingredient or product. This provision to allow immediate removal of a dietary supplement from the market was modeled on the *imminent hazard authority* for drugs in the FDCA and provides "greater discretion and authority to FDA to enforce safety requirements for dietary supplements and ingredients than are applicable to conventional food" (Hutt, 2005).

Despite the frequent reference to "reasonable" and "unreasonable" in the FDCA and in its own guidance, FDA has avoided defining these terms. In the final rule for Premarket Notification for a New Dietary Ingredient (FDA, 1997), FDA refers to comments requesting more definition be provided for the references to "reasonable/unreasonable" in the form of some sort of metric or standard such as provided for a food additive petition in 21CFR170.3(h) and (i) or that FDA should provide industry with samples of publications that are acceptable as evidence of safety. The comments also cited:

> … [further] that, in the absence of an appropriate scientific standard of evidence, manufacturers would be free to submit articles from questionable publications or unpublished materials to establish the safety of the new dietary ingredient.

To which the FDA responded:

> … contrary to what the comment asserts, the manufacturer or distributor is not required to do a complete literature search. It is required only to provide the basis on which [the manufacturer] has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe (section 413(a)(2) of the act). That is all that the regulation requires (FDA, 1997).

Therefore, the submitter is left to determine what "reasonable/unreasonable" means. The word "reasonable" is defined as the result of "sound judgment", "not exceeding the limit prescribed by reason", "judicious", "logical", "rational" and others. The meaning of "unreasonable" is largely defined in the context of the situation, although synonyms often mentioned in on-line dictionaries include "illogical", "capricious", "irrational", "subjective" and others (Thesauras.com, 2023).

Therefore, if it is logical to assume that for an NDI (Fig. 3), the standard is a "reasonable expectation of safety," is equivalent to the "preponderance of evidence" standard. The Justia website, in a discussion of evidentiary standards in civil cases, indicates that "some scholars define the preponderance of the evidence standard as requiring a finding that at least 51 percent (*i.e.* a probabilistic threshold of >0.5) of the evidence favors the plaintiff's position," a level of evidence lower than "clear and convincing evidence," an intermediate standard, whose probabilistic threshold is somewhere between >0.5, but less than the probabilistic value of 0.9–0.95 required for proof beyond a reasonable doubt (Gardiner, 2019; Ho, 2021; Justia, 2023). At the "Reasonable Expectation" level there is "some" evidence of safety and presumably no evidence the substance is unsafe at the intended level of use. Others have described this level as having more evidence supporting safety under the conditions of use, than there is contrary evidence or in the absence of non-supporting evidence. However, the identity and qualifications of decision makers or the scope and rigor of the database required is not described in the statute or regulation.

In addition, a dietary ingredient is granted safe harbor from the Delaney Clause (prohibiting carcinogens) by being declared a food (i.e., PL 103–417 §3(a) "a dietary supplement shall be deemed to be a food") and *not* a food additive (i.e., PL 103–417 §3(b) "Exclusion from definition of food additive") which appears in the FDCA §201(s) as "… except that such term does not include— (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement". The concept that a dietary supplement was a food and not a food additive was affirmed in *United States v. Two Plastic Drums ….Black Currant Oil* (984

Key Elements for Determining New Dietary Ingredient Safety

Standard: *Reasonable expectation of safety*

Relative equivalent: *Preponderance of the evidence* (*i.e.,* something is more likely than not).

Decision makers:

- **Identified:** Not identified.
- **Qualifications:** Not identified.

Decision database: Undefined.

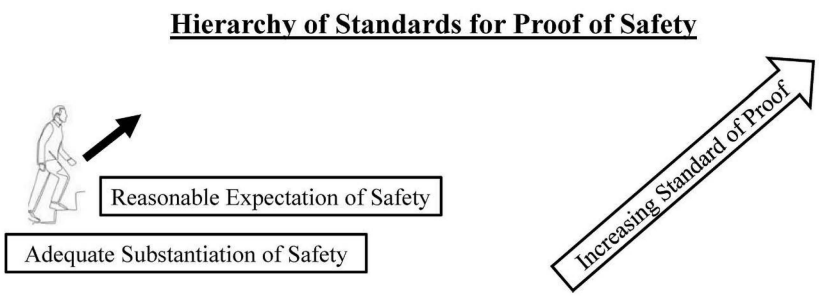

Fig. 3. The standard of proof and the meaning of safe for a new dietary ingredient.

F.2d 814 (1993)), wherein FDA claimed the black currant oil in capsules was an unapproved food additive; the court disagreed.

Ironically, excipients or "inactives" (such as preservatives, flavors, processing aids, binders and other agents supplying a technical function (21CFR170.3(o)) to the finished product (*i.e.,* the supplement) are not exempted in DSHEA from conformance with the standard of food ingredients, a "reasonable certainty of no harm", a higher standard of proof of safety than for the NDI itself (Fortin, 2022).

3.3.3. *Standard of proof for safety of a color*

From reasonable expectation, we move up the metaphorical steps of Increasing Standard of Proof to the "convincing evidence" plateau, the level of proof for colors (Fig. 4).

> 21CFR70.3(i) Safe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.

According to the Cornell University database (Cornell, 2023e), "clear and convincing evidence" is a medium level burden of proof which must be met for certain convictions/judgments (see also Ho, 2021). According to the 9th Federal Circuit, "clear and convincing" means that the evidence leaves you with a firm belief or conviction that it is highly probable that the factual contentions of the claim are true. Both sources agree this standard is more rigorous to meet than the "preponderance of the evidence" standard, but less of a rigorous standard than proving "evidence beyond a reasonable doubt" (U.S. Courts for the Ninth Circuit, 2017). Justia (2023) concurs with this comparison. In *Colorado* v. *New Mexico* (467 U.S. 310 (1984)) "clear and convincing" was determined as meaning that the evidence is highly and substantially more likely to be true than untrue. In other words, the fact finder must be convinced that the contention is highly probable (Cornell, 2023e).

A reading of the definition of "clear and convincing" in Fig. 4, we see that the definition is two-pronged, by referring to the persuasiveness of the evidence (that is, "convincing evidence") to support a conclusion of

Key Elements for Determining Color Safety

Standard: *Convincing evidence, …reasonable certainty no harm will result…at intended use.*

Relative equivalent: Greater than *Preponderance of evidence* but less than *Beyond reasonable doubt (i.e.,* reasonable certainty).

Decision makers:

- **Identified:** FDA Commissioner aided by
- **Qualifications:** "…experts qualified by scientific training and experience to evaluate safety of color additives…"

Decision database: Mandated by color additive petition details in 21CFR71.1

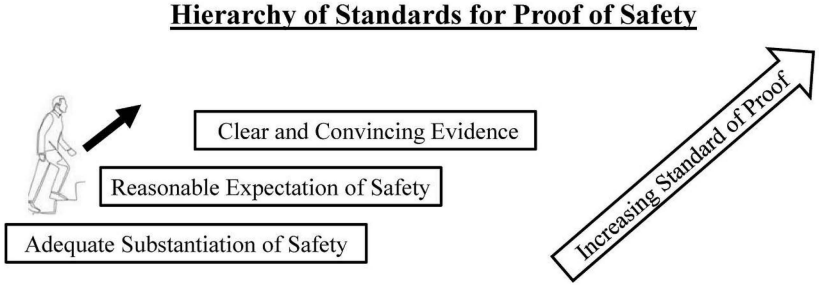

Fig. 4. The standard of proof and the meaning of safe for a color.

"reasonable certainty" – a higher level of confidence.

Key elements for determining for the color additive standard is a mandate for "convincing evidence" – a threshold for data quality, a demand for "reasonable certainty" and, for the first time in this series of comparisons, the decision makers are defined *i.e.,* competent scientists qualified by scientific training and experience, although their remit is to judge the applicability of the animal test data and the Secretary of HHS (*i.e.*, the Commissioner) makes the final decision and is required to consider the following in coming to his decision:

> 721 [21 U.S.C. 379e] (b)(5)(A) In determining, for the purposes of this section, whether a proposed use of a color additive is safe, the Secretary shall consider, among other relevant factors—
> (i) the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or devices, or cosmetics because of the use of the additive;
> (ii) the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet;
> (iii) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data; and
> (iv) the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug or devices, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive.

Therefore, the Secretary would seem to have the option of requiring variable safety factors for one application versus another *e.g.,* taking the safety factors from the experts, using the principles of "reasonably certain" and increasing or decreasing the more subjective "safety factor" proportional to other inputs such as methods of analysis, impurities, specific use, exposure, or cumulative effect.

Convincing evidence was applied as the threshold standard for the now abandoned GRAS affirmation process, a process which continued from 1974 through 1990. The regulations in force at that time (21CFR170.35(b)(3), 170.38(a), 170.38(b)(3)), required the commissioner to evaluate the petitions, using the standard of convincing evidence as to whether the substance was GRAS and exempt from the requirements of a food additive petition.

According to FDA, these industry sponsored GRAS affirmation petitions comprise approximately 20 percent of the substances in 21 CFR Part 184, but each required greater than 72 months for completion (Gaynor et al., 2006). Because the affirmation process proved to be too much of a burden on FDA resources, it was abandoned and the GRAS Notification process was substituted (Federal Register 62:18938 at 18939, April 17, 1997).

3.3.4. Standard of proof for safety of a food ingredient

The standard of proof for a food ingredient is "reasonable certainty" (Fig. 5). The term "reasonable certainty" (or "reasonable scientific certainty") is an abbreviated reference to a "reasonable certainty in the minds of competent scientists" which has become a term of art at least since the passage of the 1958 Food Additives Amendment. According to the lawinsider.com dictionary (Lawinsider Dictionary, 2023b):

> Reasonable certainty means you are persuaded based on a rational consideration of the evidence and that you have a high degree of confidence in this decision.
>
> Reasonable certainty means that you are persuaded based upon a rational consideration of the evidence. Absolute certainty is not required, but a guess is not enough to meet the burden of proof.
>
> Reasonable certainty as judged by the standards of a professional person. To put "reasonable certainty" in context, reasonable certainty is more convincing than the "weight of evidence" standard, but less than "beyond a reasonable doubt".

Key elements for meeting the food ingredient standard are: (1) Reasonable certainty, that is, there is a high degree of confidence in the decision. (2) The decision makers are defined as qualified, competent scientists. (3) The required decision database for a finding is the *identity* and *all* pertinent information.

Approval is for a specific use of the ingredient, not the ingredient *per se*, a concept expounded upon by FDA at least three times: '

> In the past, it has been too often assumed that a GRAS substance may be used in any food, at any level, for any purpose. As a result, the use of some GRAS food ingredients have proliferated to the point where their GRAS status has been brought into serious question (Federal Register 39:34194,Sept 23, 1974).

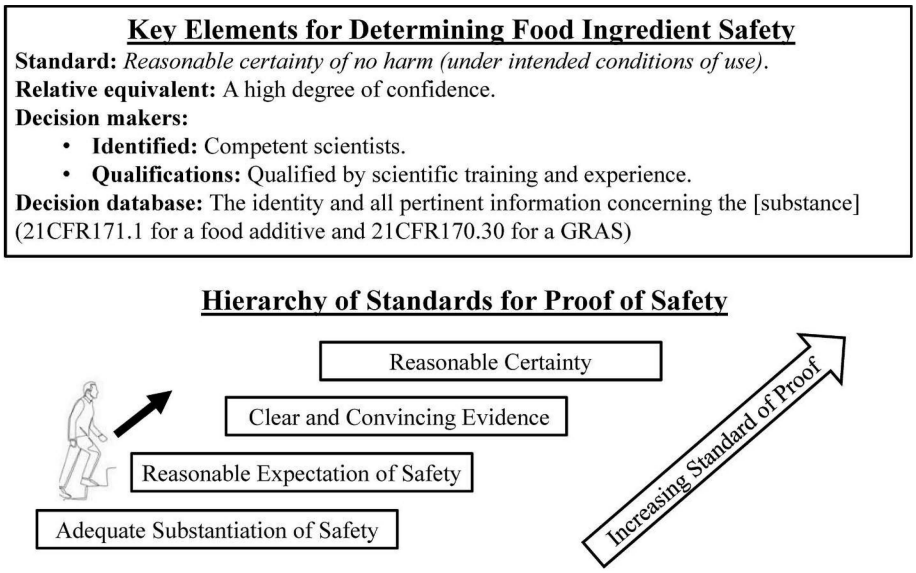

Fig. 5. The standard of proof and the meaning of safe for a food ingredient.

> … ingredients that have been present in the food supply for many years are now being added to beverages and other conventional foods at levels in excess of their traditional use levels or in new beverages or other conventional foods. This trend raises questions regarding whether these ingredients are unapproved food additives when used at higher levels or under other new conditions of use. (FDA, 2009, 2014).

The specific use includes to which food categories the ingredient may be added (as *per* the list provided in 21CFR170.3(n)) and at what concentrations – a rational and fact-based discussion of the mean and 90th percentile estimated daily intake (EDI) is required. Because the list of food categories was produced prior to 1972, more categories and subsets of categories have grown from the original 32 to the thousands of categories now provided in the intake profiles (amount, frequency and demographic) by individuals in USDA's What We Eat in America (WWEIA) Continuing Survey of Food Intakes by Individuals 2017–2018 (USDA, 2017). Trying to calculate an EDI on the basis of serving size results in gross errors, as serving size does not include how many daily servings are consumed nor the differences in eating habits of different categories of consumers (*e.g.,* sex, age) (Burdock, 2020). Also required for ingredient approval is a statement regarding the specifications of the ingredient and its manufacturing process, as a different manufacturing process may affect the specifications and ultimately, the safety of the ingredient. A statement regarding the substance's functionality (*e.g.,* buffering agent, processing aid or other functionality provided in 21CFR170.3(o)), has not been consistently required for GRAS notifications.

While "a reasonable certainty of no harm" is the legislatively mandated standard of proof for the safety of food ingredients, the FDA has prosecuted the contention that the standard of proof has not been met for a conclusion of generally recognized as safe (GRAS) until the requirement of "General Acceptance" has been met (Goodrich, 1960; Federal Register 62:18938, April 17, 1997)) and more recently, the concept of "General Availability" (*i.e.,* publication) has also been achieved (Federal Register 81:54960-55055, August 17, 2016).

3.3.5. *Standard of proof for safety of a food*

What is food? Because food is a social construct and as the result of cultural differences, considerable flexibility must be built into the definition of food.* In respect of these differences, the FDCA defines food in §201(f) as follows: "The term 'food' means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles for components of any such article." Because the tautological nature of this definition is not lost on anyone, the author's preferred definition is provided in Dolan et al. (2010):

> Foods are regarded as such because they are edible—they cannot be unpalatable or [acutely] toxic—and foods must have nutritional, hedonic or satietal value—otherwise there would be no point in consuming them. Therefore, in the absence of a spontaneous change or contamination, the concept of a "toxic food" *per se* would seem to be an oxymoron.

Therefore, food (Fig. 6) enjoys a "presumption of safety" – the standard used for foods, is the highest standard because it is demonstrated empirically time and again, in fact each time a bite of a ripe apple is taken, its safety has been proven once more. Thus, the term "poison food" is an oxymoron, unless that food has been rendered injurious through adulteration or is in a state of inedibility such as an unripe or rotten apple or a gene has been turned on rendering the food inedible such as the production of cucurbitacin in cucumbers.

> FDCA §402. [21 U.S.C. 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 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 … or (3) if it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food.

Therefore, a food is food, until the food becomes "injurious to health" or is "unfit for food".

3.3.6. *The effect of MoCRA on the hierarchy of standards of proof for safety*

To summarize, the standards of proof for demonstrating safety are relative and specific to the regulated product category (Fig. 7). Prior to MoCRA, the standard of proof for a cosmetic or cosmetic ingredient was largely undefined; the effect of MoCRA is to elevate the safety of a cosmetic ingredient from the definition of "adequate substantiation of

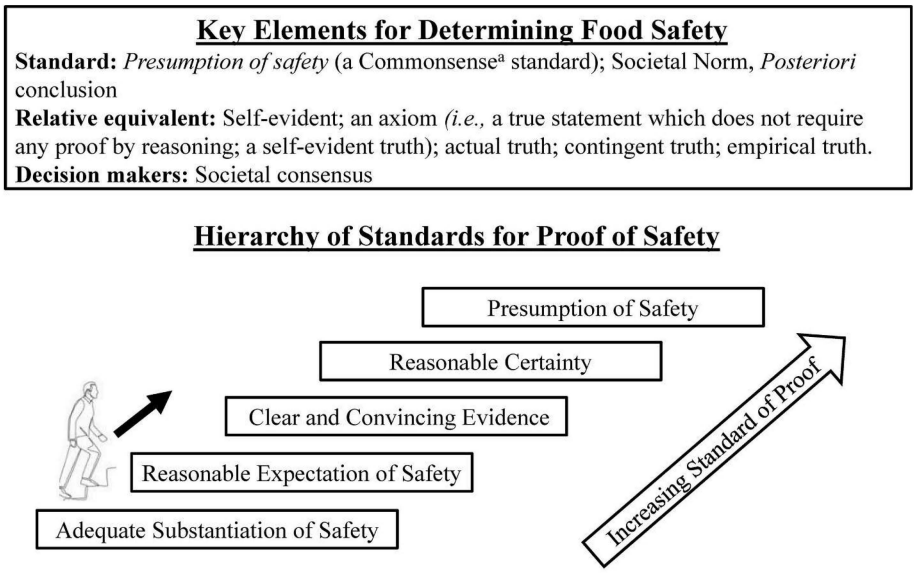

Fig. 6. Standard of proof and the meaning of safe for a food.

*See also https://disgustingfoodmuseum.com/ (site accessed 13Aug2023)

safety" to a "reasonable certainty … of safety"; putatively, the same high standard of proof applied to food ingredients – complete with the designation of the decision-makers, their credentials and a requirement for use of tests or studies, research, analyses or other evidence or information on which the decision of safety is based.

4. Preparing to meet the new standard of proof of safety for cosmetics

As the result of our experience over the last 30+ years, there are three main factors controlling the validity of a decision on "Reasonable Certainty of Safety" (1) the decision makers' expertise or credibility; (2) the degree of certainty of the decision makers and (3) the rigor of the evidence upon which the decision was based.

These factors are broadly represented in the Federal Rules of Evidence, Rule 702 (as amended), *Testimony by Expert Witnesses* (The Chief Justice The Supreme Court of the United States, 2023).

> Rule 702 (as amended) A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if the proponent demonstrates to the court that it is more likely than not that:
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
> (b) the testimony is based on sufficient facts or data;
> (c) the testimony is the product of reliable principles and methods; and
> (d) the ~~expert has reliably applied~~ expert's opinion reflects a reliable application of the principles and methods to the facts of the case.
> (Underlines and strikethroughs reflect the December 2023 amendments to Rule 702.)

4.1. The decision makers

4.1.1. The decision makers' expertise and credibility

Referring to the National Research Council's Reference Manual on Scientific Evidence, the authors of the chapter on toxicology (Goldstein and Henifin, 2000), suggest that the selection of an expert witness should be based on several qualities including peer-reviewed publications, certifications and memberships, advisory panels and university appointments.

In the context of establishing credibility, the number, type and quality of peer-reviewed publications are generally regarded as the *currency of credibility* for anyone claiming expertise. Certifications, such as the American Board of Toxicology demonstrates the ability to successfully complete a competitive and comprehensive examination on toxicology subject matter, while election to *Fellow* status of the Academy of Toxicological Science or the American College of Toxicology represents peer-recognition of an individual's expertise. Serving on advisory panels may only invite criticism of a possible conflict of interest. The credibility conferred by a university appointment needs to be judged on a case-by-case basis.

The European Chemicals Agency (ECHA, 2020) defines "competent person" as one who has, as a result of their training, experience and continued education, sufficient knowledge for the compilation of the respective sections of the Safety Data Sheet (SDS). This author's emphasis is placed on "respective" in the previous sentence, presumably indicating the fact the SDS addresses several areas (*e.g.,* chemistry, exposure, toxicology), and that the "competent person" should be able to adequately address the various areas included in the SDS.

Regarding the context of the decision-makers' expertise for a decision on "reasonable certainty of no harm", these persons must be competent scientists; that is, scientists specifically competent in the safety and risk assessment of substances introduced into or on the body. Further, while the decision-makers are experts, they are not expected to have expertise in every aspect of science. For example, if there is a question of a specific finding in a study, such as a pathology finding, a scientist with expertise in that particular area (such as a pathologist) can be consulted. In this case, there may be a pedagogical dialectic with the consulting pathologist and the decision-makers, where a question is approached from different perspectives and an issue resolved.

Does there have to be unanimity among experts? No. It would be expected there would be a consensus within a panel of experts, but once the finding of safety is made public, there may be some dissenters arguing that a finding of safety was erroneous or that the database was inadequate for such a finding. Whether this dissension has any basis or not depends on if the dissenters are qualified experts (emphasizing the word "qualified") and, is there more than one dissenter or just a single gadfly or two? Critical to the dissention is if the dissenters have presented any substantive data to support their claim and that the original

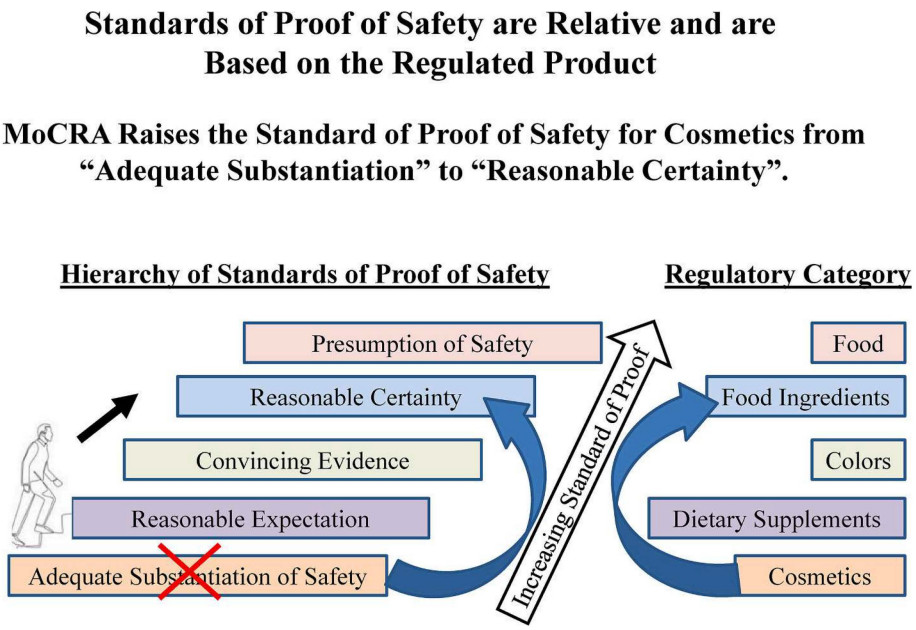

Fig. 7. The effect of MoCRA on the Hierarchy of a Standards of Proof and the Meaning of Safe for a Cosmetic.

claim of safety was contrary to the accepted and published scientific findings? Or is this a simple dispute in the faculty lounge? Fortunately, the boundaries of dissension have been addressed by FDA as follows:

> The proponent of the exemption (*i.e.,* of safety) has the burden of proving that the use of the substance is "generally recognized" as safe. To establish such recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance. Unanimity among experts regarding safety of a substance is not required. However, the existence of a *severe* conflict among experts regarding the safety of the use of a substance precludes a finding of general recognition (*mere* conflict among experts is not enough to preclude a finding of general recognition). (FDA, 1997)

> … although unanimity among experts regarding the safety of a substance is not required, "an ongoing scientific discussion or controversy about safety concerns raised by available data would make it difficult to provide a basis for expert consensus about the safety of the substance for its intended use." (FDA, 2022)

> While "mere conflict among experts is not enough to preclude a finding of general recognition [of safety]", it does not exist if there is a genuine dispute among qualified experts that the use of the substance is safe ("genuine dispute among qualified experts" precludes finding of general recognition, and no general recognition existed as a matter of law where there was a "sharp difference" of expert opinion) (FDA, 2022).

The truth of the matter is that there will always be gadflies, eager to criticize a decision. A good example is a study challenging the safety of aspartame. According to the authors of a chronic rodent study with aspartame, the study produced results contrary to the results produced in several well-controlled studies showing the safety of aspartame. However, upon closer scrutiny, the contrarian study had some flaws of a game-changing nature and FDA was not persuaded to withdraw approval (Magnuson et al., 2007).

4.2. The degree of certainty of the decision makers

The decision makers must commit to obtaining a high level of confidence in his/her decision of a reasonable certainty of safety. The decision should be one that could be made by anyone qualified in that particular field having reviewed the same data and should reflect the opinion of the decision maker's peers. If the science or technology is so advanced or so specialized there are no peers having coalesced around a particular school of thought, the decision maker might want to avoid the implication of speaking for the entire scientific community. Instead, the decision maker could utilize the phrase "high degree of certainty" in which the expert only testifies to the degree of confidence he has in his own opinion.

However, at the end of the day, the decision must be made on the data presented. Although any competent scientist would want to see the "critical mass" of data required for a decision of "reasonable certainty", the scientist cannot avoid decision-making in the absence of every scrap of data it is possible to generate – this is avoiding closure or suspending commitment. Unless the database is grossly inadequate, the decision maker must be capable of acting on the factual subject matter presented.

4.3. The rigor of the information upon which the decision is based

This last of the three factors controlling the validity of the decision, includes compliance with the requested information, thoroughness of the search for data, validity of the information and completeness of the dataset.

4.3.1. Compliance with requested information

Referring again to the requirements for food ingredients, the regulation in 21 CFR 170.30(b), states that general recognition of safety (*i.e.,* a finding of "reasonable certainty") based upon scientific procedures, shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. Therefore, if FDA applies the same principles of safety to cosmetic ingredients which shall meet the standard of proof for a reasonable certainty of no harm for food ingredients, the general requirements can be adapted from the published guideline for a food additive petition, some of whose requirements include identity of the ingredient (e.g., names, CAS number, name in commerce), proposed use of the ingredient, its intended technical effect and full reports of all safety investigations of the ingredient.

Compliance with requested information could be conceived almost as a quality assurance feature *e.g.*, rationalizing the lack of inclusion of some data such as Industrial Bio-Test reports of questionable veracity (Rosner and Markowitz, 2023) or the discredited chick embryo assay (Mazur and Jacobson, 1999). Lack of incorporation of other data could be rationalized such as elimination of pre-GLP generated data or studies that do not meet *core study values*.

4.3.2. Thoroughness of the search

A thorough search of the scientific literature is basic to finding the information on which a sound decision can be based. Our group has used a variety of databases in the past and have found commercial databases to be the most powerful. Free search engines including Google or PubMed are not going to compare with a commercial database. The search string should be documented and reproducible. Databases not connected to search engines can also provide helpful information including, but not limited to FDA's Substances Added to Food (formerly EAFUS), FDA Warning Letters, FDA food or color additive petitions held in abeyance, Threshold of Regulation (TOR) Exemptions, US International Trade Commission Harmonized Tariff Schedule, European Food Safety Agency, European Chemicals Agency, trade associations and even court cases.

4.3.3. Validity of the information

The validity of the data and information should meet at least minimum values upon which a decision can be based; however, not all the available safety data is of optimal quality and the reasons are many, including but not limited to:

- Studies conducted prior to (or in spite of) the requirement for good laboratory practice (GLP) in 1978 in the US.
- Lack of thorough identification and characterization of the test substance (e.g., purity, physical characteristics, source, methods for determination).
- Use of crude techniques/procedures for quantifying endpoints and later discovery of more relevant endpoints.
- The use of non-standardized protocols (compared with today's standards).
- The use of non-standardized test species or uniquely in-house animal colonies for which no historical data exist.

Still, some data generated for purposes other than a safety assessment (such as clinical reports or efficacy studies), cannot be ignored and may, in fact, shed additional light and may offer credible information from a different perspective even though the data may have been gathered for another purpose.

Clearly, it is necessary to vet data as having met at least minimal standards for inclusion in any assessment. Tools for judging the validity of these studies includes use of Klimisch criteria (Klimisch et al., 1997), or other sources of suggested methods for vetting data (OECD, 2005a, 2005b) or such as ToxRTool® (the latter being a toxicological data reliability assessment tool). We have found that although software can be very helpful, at the end of the day, decision making based on experience, is required. The point is not to ignore information, regardless of its positive or negative effect, but to qualify the information and its

contribution to the ultimate decision affecting the standard of proof.

4.4. How will this information be received by the FDA?

The US and EU take a very different viewpoint on chemicals in contact with humans. The EU takes a more proactive approach (observing the Precautionary Principle) and discourages the use of some substances before they have been proven to be harmful compared to US standards. The tipping point of what is considered safe or reasonable certainly of safe in one venue vs another, leaves the manufacturer in a "prisoner's dilemma" situation of how just how much *new* testing would be required (if extant information is deemed inadequate) as opposed to *over* testing and discovering an unresolvable finding.

In the absence of publication of an Advanced Notice of Proposed Rule by FDA it is impossible to know how FDA will handle these safety assessments; that is, will the assessments be treated like a food additive petition, which will invite comments prior to publication of the final rule, or will FDA treat these assessments as it does GRAS notices, where there is no provision for comment by the public. It will likely be the latter for several reasons, not the least of which is the lack of FDA resources to review the tsunami of data to be presented in response to MoCRA; as is, it takes two or more years to review a food additive petition and precisely the reason why Congress included a provision for outside experts to review food ingredients, the GRAS exemption, in the 1958 Amendment to the FDCA (Burdock and Carabin, 2004). The lack of FDA resources is critical because if FDA reviews the data, it will "own" the decision on safety; on the other hand, as in the GRAS notification process, FDA determines if the criteria for a GRAS has been met, avoiding a deep dive into the data supporting the GRAS conclusion and requiring only that the information supporting the safety determination be published. If there is any review outside of the panel of Experts, it might be journal reviewers or editors or, readers of the journal article describing the safety of the ingredient. However, to the author's knowledge, no GRAS conclusion has been overturned on the basis of a critique challenging the adequacy of the published data supporting the GRAS.

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5. Conclusion. Meeting the burden of proof and the burden of persuasion

Any successful dossier for a determination of safety-in-use provided to an expert panel, submitted to a state or federal agency, or simply providing documentation for the record, is more than a collation of documents and a narrative describing why the monographer feels the substance is safe for its intended use. For a successful dossier, the monographer must meet the *"burden of proof"* as well as the *"burden of persuasion"*. The burden of proof involves a thorough discussion of all the *relevant* evidence (direct, corroborative and antithetical) to meet the standard of proof. While there is clear statutory authority for marketing various products (*e.g.,* dietary supplements, cosmetics), and while the relevant agency may have promulgated guidelines describing the criteria to meet the standard of proof for various categories of products, no clear lines have been drawn to *guarantee* a product meets the standard of proof and there remains a great deal of subjectivity in the approval or compliance process. It is likely that more than one submission has failed in its objective because of this subjectivity. Therefore, because the "facts cannot always speak for themselves" the monographer must *also* meet the *burden of persuasion* and we have experienced considerable success by crafting what we identify as a *theory of approvability* (*or acceptability*), which we believe provides the final level of comfort to the decision-maker, regulator, and the public, auguring for approval.

Disclaimer

The author is an experienced toxicologist of 30+ years, is not a lawyer or able to provide legal advice. Any statements herein are intended to be an expression of opinion only, based on information available at the time, and should not be construed as a promise or guarantee. Because every safety and regulatory issue is slightly different, the examples provided herein may not apply to your specific situation.

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George A. Burdock: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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