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Food additive safety: A review of toxicologic and regulatory issues

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Abstract

Food is a very common source of toxicant exposure to humans. An unknown number of naturally occurring contaminants find their way into food. The most ominous are products of mold growth called mycotoxins, which include the carcinogenic aflatoxins. On the other hand, more than 2500 chemical substances are added to foods to modify or impart flavor, color, stability, and texture, to fortify or enrich nutritive value, or to reduce cost. In addition, an estimated 12,000 substances are used in such a way that they may unintentionally enter the food supply. The term "food additive" is a regulatory term that encompasses any functional substance that is normally neither consumed as a food itself, but is intentionally added to food (usually in small quantities) to augment its processing or to improve aroma, color, consistency, taste, texture, or shelf life. Additives are not considered "nutritional" even if they possess nutritive value. The purpose of the present review is to give an overview of the approaches to, and procedures involved in ensuring the safety of the US food supply in the context of food additives, with particular reference to the existing and emerging scientific and regulatory landscape and consumer perceptions.

Keywords

Food additives, safety, regulatory issues, toxicology

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Introduction

The Pure Food and Drugs Act of 1906 made illegal any food found to be adulterated (containing an "*added impure or . . . deleterious ingredient*") which may render the food injurious to health. This act provided regulatory authority to the federal government and allowed Harvey Wiley, MD of the US Department of Agriculture (USDA) and others to launch an initiative known as the "Poison Squad," to address food adulteration. The federal government, however, was required to show only a reasonable (not absolute) possibility that harm might result from an adulteration. This meant that, since the injurious effects of most food adulterants in humans are not known, results from studies in experimental animals would become the standard from which conclusions regarding possible harm to humans would be derived (Lane in Hayes' Principles and Methods of Toxicology, 2014).[1]

The Delaney Clause, which was introduced into US food safety law in 1958 (www.cfsan.fda.gov/~dms/opa2pmnt.html), stipulated that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal." Interestingly, Delaney has been a matter of contention ever since. In part, this is because it is now realized that

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virtually any substance in the food supply, even at a low level of exposure, might prove carcinogenic or otherwise toxic in some individuals at some time, and under some circumstances; hence the daunting challenge of food toxicology.

Accepting the insight of Paracelsus ("the father of toxicology") that everything is a potential poison—the dose being the crucial factor, the art and science of risk assessment becomes salient. However, where the human food matrix and eating is concerned, the tasks of hazard and risk assessment become complicated almost in exponential fashion. Variation in dietary patterns, lifestyle, age/stage of development, gender, genotype, physiology, and pathophysiology may represent significant confounds. Toxicokinetic and toxicodynamic studies reveal that different dose levels and interactions with other nutrients and bioactive moieties can produce varying responses in factors such as stability, solubility, absorption, protein binding, and metabolism of the additive in question.

Understanding that animal studies could demonstrate or potentially predict adverse effects not recognized in humans, combined with the advent of more accurate and sensitive analytical methods led, in the mid-20th century, to a series of amendments to the federal food safety law. The resulting watershed legislation, the Food, Drug and Cosmetic Act (FDCA) of 1938, required manufacturers to demonstrate the safety of a product marketed over state lines and be able to meet three standards: (1) standards (definitions) of identity, (2) standards of quality, and (3) standards regulating the fill of a container.

As defined in this act, a food is considered adulterated if it contains any added poisonous or deleterious substance that may *render it injurious to health*. Adulteration is defined as a food that bears or contains any added poisonous or deleterious substance; or if it bears or contains a pesticide residue, a food additive, or a new animal drug that is unsafe; or if it consists of, or is contaminated by any other substance that makes it unfit for food or renders it injurious to health; or if its container is composed of any poisonous or deleterious substance that may render the contents injurious to health; or if it has been intentionally subjected to radiation not conforming with regulation. The act distinguishes, however, between substances naturally present, such as those in food commodities, and those that have been added to the food. If the substance is naturally present in the food, the food is considered not to be adulterated under this regulation if the quantity of this substance does not *ordinarily render it injurious to health* (https://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/ucm132818.htm).

Today, with seemingly unprecedented pressures from consumers for accountability, rapid technological advances, and a dynamic regulatory milieu, it becomes more important than ever to support the extent to which consumers are able to make sound judgments on the safety and acceptability of food and recover their clearly shaken confidence in public health entities, in regulatory authorities, and in the components of the food supply chain.

Role of food additives in the diet

Everyone must eat! The human diet contains thousands of structurally diverse chemical substances, mostly of naturally occurring origin, plus substances purposely added such as nutrients, colorants, and flavor-imparting substances. More chemicals may become components of food during processing and during food preparation that bring about chemical changes and introduce compounds not normally found in raw agricultural products. Further, chemicals are added to achieve certain technical effects such as preservation, color, consistency (e.g. emulsification), flavoring, sweetening, and other physical effects. Additional substances often are introduced, usually in very small amounts that are largely by-products of agriculture and packaging (indirect additives). Among these are maybe pesticides, drugs used in food animal management, and substances that migrate from food contact surfaces (FCSs) and packaging. Our diet also contains other unwanted contaminants from natural sources such as microorganisms and their metabolites, and the substances that are innate to plants. Reviews of Frankos and Rodricks[1] and Kruger et al.[2] serve as resources for much of the conventional wisdom and "corporate knowledge" discussed in this review.

The Food Additive Amendment (1958) to the FDCA subjected food additives to regulatory scrutiny and gave the Food and Drug Administration (FDA) the authority to require information from manufacturers demonstrating that the additive is reasonably free of harm prior to its introduction into the food supply. Since that time, the FDA has delineated the types of toxicity and chemistry studies needed to assess the safety of food additives and generally recognized as safe (GRAS) substances. It is important to recognize that the safety assessment criteria for food additives and substances subjected to GRAS review are identical; the only substantive difference is time to market and the sources of experts reviewing the publicly available safety data. The objectives of this review are to summarize this information for the United States and to provide some guidance on how best to implement this guidance going forward in developing new or introducing ingredients that may be novel to the food supply. (Is this old cite truly appropriate or necessary here? Agree; let's drop it.)

The FDCA recognizes three categories of food constituents[3] and imposes substantially different regulatory and technical requirements for each category as follows:

1. substances intentionally added to food, both directly and indirectly,
2. substances that are natural components of food, and
3. substances that may contaminate food.

Food is consumed for nutritive value and sensory reward, that is, taste and aroma. Regulation of the US food supply depends upon specifics of the intended use in

specific food categories, populations intended to consume those foods, and the anticipate health claims to be made. Substances added either directly or indirectly to food can be legally introduced only if they have been shown by the manufacturer to be free from adverse effects under the conditions of use. A new product/ingredient may be regulated as a direct food additive or as a GRAS ingredient if the intent is for the ingredient to become a component of a food or if it affects the characteristics of a food. An additive that is intended to impart color when added or applied to a food is regulated separately as a color additive (https://www.fda.gov/ForIndustry/ColorAdditives/default.htm). Indirect food additives also fall under a separate regulatory category (21 CFR parts 175, 176, 177, and 178). Although not part of this review, a substance for a dietary supplement (new dietary ingredient) is an ingredient intended to supplement the diet by increasing the total dietary intake of that substance and is regulated as a new dietary ingredient (https://www.fda.gov/Food/DietarySupplements/ucm109764.htm). The supplement containing the dietary ingredient, however, must not be represented for use as a conventional food or as a sole item of a meal or the diet.

Direct and indirect food additives

Any substance that is reasonably expected to become a component of food is a *food additive* and is subject to premarket approval by the FDA, unless the substance is "GRASed" by experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use or meets one of the other exclusions from the food additive definition in section 201(s) of the Federal FDCA (FFDCA). Additives have been the subject of *food additive petitions* (FAPs) submitted to the FDA since 1958. Such petitions must contain sufficient information pertaining to safety to allow the agency to meet its criteria for approval.

Substances added to a food for a specific purpose are *direct additives and are identified on the ingredient label of the food to which the ingredient is added.* For example, the low calorie sweetener, aspartame, is a direct additive that is intentionally added to puddings, soft drinks, yogurt, and many other foods. An *indirect additive* becomes part of the food in very small amounts during processing, packaging, or storage. In general, additives serve valuable technical functions: (1) to maintain the nutritional quality of the food; (2) to enhance keeping quality or stability, with resulting reductions in food wastage; (3) to make food attractive to consumers; and (4) to provide essential aids during processing. At present, there are thousands of additives in the US food supply, most of which are indirect additives. By law, manufacturers must document that the amount of an additive in a food is below the threshold of observable adverse effects. However, unlike direct and indirect food additive, processing aids are not required to be declared on the ingredient statement.

Representative food ingredients including currently approved direct and indirect food additives with examples are listed in Table 1.

Legal burden for proof of safety

The Food Additive Amendment of 1958 stipulates that manufacturers ("petitioners") must satisfy the FDA's safety criteria prior to the marketing of a food additive. The safety standard is defined as "reasonable certainty in the minds of competent scientists that a substance is not harmful under its intended conditions of use." Although petitioners have a role regarding data submitted, the FDA, nonetheless, specifies or at least suggests the necessary safety criteria, including the type and quantity of data necessary to satisfy these criteria. In addition to information on chemistry and purity of the ingredient, the FDA requires information on intake, that is, exposure as a consequence of proposed uses within the dietary matrix and relative to the specific mechanisms of toxicity of the ingredient. Clinical studies may not be required. It is important to recognize that the goal of FDA is to ensure an adequate margin of safety between the expected concentration of the ingredient that produces adverse effects in animals and the expected exposure to the human population including sensitive subpopulations such as infants and the elderly. Any additive that is intended to have a technical effect in food is deemed unsafe under section 409 of the Act, unless it conforms to the terms of its approved use or to an exemption for investigational use. Any food that contains an unsafe food additive is considered adulterated under section 402(a)(2)(C) of the FFDCA.

A list of approved food additives for the European Union (EU) can be found in the following document (https://www.fsai.ie/uploadedFiles/Reg1129_2011.pdf).

Guide to safety assessment ("the Redbook")

Principles of safety evaluation

The currently preferred approach to safety assessment of food additives is compiled in a publication entitled *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*, commonly known as "the Redbook" originally published in 1982 (US FDA, 1982). Although attempts to better harmonize the agency's testing guidelines along international approaches have occurred in past revisions to the Redbook,[5,6] the overall approach for safety assessment of food additives remains organized around four basic principles. These principals are also emphasized in the safety assessment guidelines typically applied to pharmaceutical agents and advanced in section S (safety) by the International Conference on Harmonization (ich.org).

First, the agency presumes that some toxicological information is necessary for every food additive. Second,

Table 1. Food ingredients, their functions, uses, and examples.[a]

Type	Purpose	Examples of uses	Names found on product labels
Preservatives	Prevent food spoilage from bacteria, molds, fungi, or yeast (antimicrobials); slow or prevent changes in color, flavor, or texture and delay rancidity (antioxidants); maintain freshness	Fruit sauces and jellies, beverages, baked goods, cured meats, oils and margarines, cereals, dressings, snack foods, fruits, and vegetables	Ascorbic acid, citric acid, sodium benzoate, calcium propionate, sodium erythorbate, sodium nitrite, calcium sorbate, potassium sorbate, BHA, BHT, EDTA, and tocopherols (vitamin E)
Sweeteners	Add sweetness with or without extra calories	Beverages, baked goods, confections, table-top sugar substitutes, many processed foods	Sucrose (sugar), glucose, fructose, sorbitol, mannitol, corn syrup, high-fructose corn syrup, saccharin, aspartame, sucralose, and acesulfame potassium (acesulfame-K), neotame
Color additives	Offset color loss due to exposure to light, air, temperature extremes, moisture, and storage conditions; correct natural variations in color; enhance colors that occur naturally; provide color to colorless and "fun" foods	Many processed foods (candies, snack foods, margarine, cheese, soft drinks, jams/jellies, gelatins, pudding, and pie fillings)	FD&C blue nos. 1 and 2, FD&C green no. 3, FD&C red nos. 3 and 40, FD&C yellow nos. 5 and 6, orange B, citrus red no. 2, annatto extract, beta-carotene, grape skin extract, cochineal extract or carmine, paprika oleoresin, caramel color, fruit and vegetable juices, saffron (Note: Exempt color additives are not required to be declared by name on labels but may be declared simply as colorings or color added)
Flavors and spices	Add specific flavors (natural and synthetic)	Pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream, and BBQ sauce	Natural flavoring, artificial flavor and spices
Flavor enhancers	Enhance flavors already present in foods (without providing their own separate flavor)	Many processed foods	MSG, hydrolyzed soy protein, autolyzed yeast extract, disodium guanylate, or inosinate
Fat replacers (and components of formulations used to replace fats)	Provide expected texture and a creamy "mouth-feel" in reduced-fat foods	Baked goods, dressings, frozen desserts, confections, cake and dessert mixes, and dairy products	Olestra, cellulose gel, carrageenan, polydextrose, modified food starch, microparticulated egg white protein, guar gum, xanthan gum, and whey protein concentrate
Nutrients	Replace vitamins and minerals lost in processing (enrichment), add nutrients that may be lacking in the diet (fortification)	Flour, breads, cereals, rice, macaroni, margarine, salt, milk, fruit beverages, energy bars, and instant breakfast drinks	Thiamine hydrochloride, riboflavin (vitamin B_2), niacin, niacinamide, folate or folic acid, beta carotene, potassium iodide, iron or ferrous sulfate, alpha tocopherols, ascorbic acid, vitamin D, and amino acids (L-tryptophan, L-lysine, L-leucine, L-methionine)
Emulsifiers	Allow smooth mixing of ingredients, prevent separation, keep emulsified products stable, reduce stickiness, control crystallization, keep ingredients dispersed, and help products dissolve more easily	Salad dressings, peanut butter, chocolate, margarine, and frozen desserts	Soy lecithin, mono- and diglycerides, egg yolks, polysorbates, and sorbitan monostearate
Stabilizers and thickeners, binders, and texturizers	Produce uniform texture and improve "mouth-feel"	Frozen desserts, dairy products, cakes, pudding and gelatin mixes, dressings, jams and jellies, and sauces	Gelatin, pectin, guar gum, carrageenan, xanthan gum, and whey

(continued)

Table 1. (continued)

Type	Purpose	Examples of uses	Names found on product labels
pH Control agents and acidulants	Control acidity and alkalinity and prevent spoilage	Beverages, frozen desserts, chocolate, low acid canned foods, and baking powder	Lactic acid, citric acid, ammonium hydroxide, and sodium carbonate
Leavening agents	Promote rising of baked goods	Breads and other baked goods	Baking soda, monocalcium phosphate, and calcium carbonate
Anti-caking agents	Keep powdered foods free-flowing and prevent moisture absorption	Salt, baking powder, and confectioner's sugar	Calcium silicate, iron ammonium citrate, and silicon dioxide
Humectants	Retain moisture	Shredded coconut, marshmallows, soft candies, and confections	Glycerin and sorbitol
Yeast nutrients	Promote growth of yeast	Breads and other baked goods	Calcium sulfate and ammonium phosphate
Dough strengtheners and conditioners	Produce more stable dough	Breads and other baked goods	Ammonium sulfate, azodicarbonamide, and L-cysteine
Firming agents	Maintain crispness and firmness	Processed fruits and vegetables	Calcium chloride and calcium lactate
Enzyme preparations	Modify proteins, polysaccharides, and fats	Cheese, dairy products, and meat	Enzymes, lactase, papain, rennet, and chymosin
Gases	Serve as propellant, aerate, or create carbonation	Oil cooking spray, whipped cream, and carbonated beverages	Carbon dioxide and nitrous oxide

MSG: monosodium glutamate; FDA: Food and Drug Administration.
[a]Adapted from US FDA.[4] Overview of food ingredients, additives, and colors.

the amount of safety data required for a particular food additive is dictated by what is called a *level of concern* (LOC). Third, the LOC is based on the magnitude of potential human intake of an additive and its molecular structure: exposure data, if available, carrying greater weight than the structure alert. The fourth premise is that the initial evaluation of testing requirements can be adjusted when the data suggest that a significant or unexpected adverse effect is found to be associated with the ingestion of a particular additive. The results from toxicology studies are then utilized to calculate an acceptable daily intake (ADI) which is compared to the estimated daily intake (EDI). If the EDI is less than the ADI, the additive is determined to be safe under the proposed conditions of use.

An FAP should contain at least the following information for the additive (http://www.fda.gov/Food/GuidanceRegulation/Guidance Documents Regulatory Information/Ingredients Additives GRAS Packaging/ucm253328.htm):

- identity and composition,
- proposed use,
- use level,
- data establishing the intended effect,
- quantitative detection method(s) in the intended food,
- estimated exposure from the proposed use (in food, drugs, cosmetics, or devices, as appropriate),
- full reports of all safety studies,
- proposed tolerances (if needed),
- environmental information (as required by the National Environmental Policy Act (NEPA), as revised (62 FR 40570; July 29,1997))
- Consistent information should be presented throughout all sections of the petition, including those pertaining to,
- chemistry,
- toxicology,
- environmental science, and
- any other pertinent studies (e.g. microbiology).

Levels of concern: Direct food additives

The concept of "*LOC*" is fundamental to the safety assessment for direct food additives as suggested in the FDA Redbook. The LOC is akin to risk, that is, a predictive measure of the likelihood that a hazard presented by a particular additive may result in harm. The levels of concern for various anticipated intakes of direct additives, as given in Redbook II, are presented in Figure 1. A compound is assigned a level of expected toxicity based on its molecular structure into one of three categories: A (low toxicity), B (moderate toxicity), or C (high toxicity). Category assignments are based on a decision tree (Redbook II) related to the additive's (1) chemical structure, (2) number and amount of unidentified components in the additive, and (3) predicted metabolites. If fewer than 90% of the components of the additive have been structurally characterized, the additive is automatically placed into the highest toxicity category C. Examples of compounds in category A include simple aliphatic, acyclic, and monocyclic hydrocarbons; fats; fatty acids; simple aliphatic and noncyclic (saturated) monofunctional alcohols; ketones; aldehydes; acids; esters; ethers; and normal human metabolites of carbohydrates and

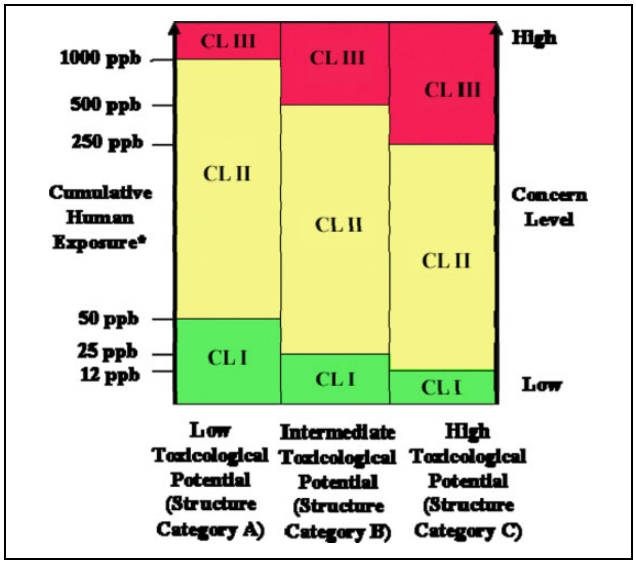

Figure 1. CLs as related to human exposure and chemical structure. *Cumulative human exposure is expressed as parts per billion (ppb; equivalent to microgram per kg diet) of daily dietary consumption of additives. Conversion of ppb to microgram per kg-body weight per day, divide by 20, assuming 3-kg daily diet (From US FDA Redbook[6]). CL: concern levels; FDA: Food and Drug Administration.

lipids. Category B compounds include nonconjugated olefins (excluding unsaturated fatty acids and fats); inorganic salts of iron, copper, zinc, and tin; amino acids; polypeptides; and proteins. Category C compounds are structurally varied and include organic halides; amides and imines; conjugated alkenes; polycyclic aromatic hydrocarbons; and compounds with nitro, N-nitroso, azide, and purine groups.

The LOC is derived based on anticipated human intake (Figure 1). The Redbook lists groups of studies that are required, as a minimum, to support safety assessment (Table 2) for each of the concern levels (CLs) I, II, and III. CL I compounds require a short-term feeding study (at least 28 days in duration) in a rodent species and short-term tests for carcinogenic potential. CL II requires testing in a 90-day feeding study in a rodent and a nonrodent species, a multigeneration reproduction study with a developmental toxicity phase, and a battery of short-term tests for carcinogenic potential. CL III compounds are required to undergo more extensive testing, in addition to the studies required for a CL II substance, carcinogenicity studies in two rodent species, and a chronic feeding study of at least 1 year in duration in a nonrodent species. These testing requirements are subject to modification based on the available data.

Threshold of regulation exemption: Indirect food additives (FCSs)

An FCS or an indirect food additive is any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food (https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/default.htm). Premarket approval of all FCS is required unless exempted. Under 21 CFR §170.39, if it is demonstrated that the substance used in a food contact article that may be expected to migrate into the food results in a dietary concentration of that substance at or below 0.5 ppb (corresponding to dietary exposure levels at or below 1.5 μg/person/day) that substance is considered by the agency to present no health or safety concern. Consequently, such substances are exempt from regulation as food additives because the substance is present at levels below the threshold of regulation ("TOR"). It is important to note that *carcinogens do not qualify for the TOR exemption*. The information on which the TOR is based must be submitted to the FDA. If the FDA concurs, the substance will be added to the list of approved TOR exemptions and will be exempt from regulation as a food additive because it becomes a component of food at a level that is below the TOR (https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/ThresholdRegulationExemptions/default.htm).

FCS (indirect food additive) notification

In 1997, the Food and Drug Administration Modernization Act of 1997 established a food contact notification (FCN) process to allow faster review of nonexempt FCS. FCN, because of similar safety standard to a petition, must contain sufficient scientific information to demonstrate that the FCS is safe for its intended use (21U.S.C.348(h)(l)). Regardless of whether an FCN or petition is submitted, the following information is required in addition to relevant information required in a direct FAP:

- Migration (extraction) data. Complete requirements, including extraction methodologies, are found in the FDA guidance document entitled, *Recommendations for Chemistry Data for Indirect Food Additive Petitions* (June 1995) and *Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations.*[7]
- Full reports of investigations made with respect to the safety of the additive, both published and unpublished.
- Evaluation of the safety of consumption of residues/extractables from the additive including determination of an ADI for the additive itself, calculations of its EDI in the total diet, and a comparison of the EDI to the ADI.

Recently, the FDA amended the food additive regulations by eliminating the use of three perfluoroalkyl ethyl containing FCSs as oil and water repellants for paper and paperboard for use in contact with aqueous and fatty foods. This deregulation, based on new data showing that the

Table 2. Recommended toxicological tests for additives used in food.

Toxicity tests	CL low (I)	CL intermediate (II)	CL high (III)
Genetic toxicity tests	X	X	X
Short-term toxicity tests with rodents	X[c]	X[a,c]	X[a,c]
Subchronic toxicity studies with rodents		X[c]	X[a,c]
Subchronic toxicity studies with nonrodents		X[c]	X[a,c]
One-year toxicity studies with nonrodents			X[c]
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents			X[c]
Carcinogenicity studies with rodents			X
Reproduction studies		X[c]	X[c]
Developmental toxicity studies		X[b,c]	X[b,c]
Metabolism and pharmacokinetic studies (available in 1993 Draft Redbook II)		X[b]	X[b]
Human studies			X[b]

CL: concern level.
[a]If needed as preliminary to further study.
[b]If indicated by available data or information.
[c]Including screens for neurotoxicity and immunotoxicity (available in PDF in 1993 Draft Redbook II).

safety profiles of structurally similar compounds suggested that there is no longer a reasonable certainty of no harm from the food contact use of these FCSs, was in response to a petition filed by a number of nongovernment organizations including the Natural Resources Defense Council, the Center for Food Safety, the Breast Cancer Fund, the Center for Environmental Health, Clean Water Action, the Center for Science in the Public Interest, Children's Environmental Health Network, Environmental Working Group, and Improving Kids' Environment.[8]

Estimated daily intake

Direct food additives. Petitioners need to supply sufficient data to develop a reliable estimation of the daily intake of the additive or the EDI. The EDI is determined by multiplying the dietary concentration of the additive by the total weight of food consumed by an individual per day (3000 g). For direct additives, the concentration is the amount recommended for each of the additive's technical applications. The estimated *all-person* and *all-user (only users of foods containing the additive)* total intake of the ingredient from all proposed food uses in the United States is summarized to generate the EDI by gender and age group for comparison with the ADI to generate the safety assessment for the ingredient. The goal is to ensure that the EDI for the 90th percentile all-user consumer of foods and/or beverages in which the additive is potentially present falls below the ADI. Thus, for each dietary item that contains the additive, data on the additive's maximum concentration and on human consumption rates for the food item, including that for the 90th percentile consumer, must be reported. If the EDI does not exceed the ADI, the additive is considered acceptable and should be approvable. The process of EDI determination for direct food additives, as outlined below, is detailed by Frankos and Rodricks.[1] The EU requires that the EDI is calculated for the 95th percentile (https://www.fsai.ie/uploadedFiles/Reg1129_2011.pdf).

In a dietary intake assessment, the concentration of an ingredient in food can be obtained from (1) the intended use levels of the substance in target foods (typical, recommended, or maximum use level); (2) the measured concentration in food as consumed, accounting for processing and storage losses of the ingredient; (3) the limit of detection (LOD) or limit of quantification (LOQ) of the analytical method, as appropriate, if the concentration in the food is nondetectable or nonquantifiable at the LOD or LOQ; (4) established limits for the substance (e.g. specifications in the CFR or the Food Chemical Codex) for undesirable impurities and contaminants in food ingredients; or (5) maximum levels for contaminants in foods adopted by a recognized standard-setting body such as the Codex Alimentarius Commission (http://www.fao.org/fao-who-codexalimentarius/standards/en/). The FDA typically uses the maximum intended use levels proposed to calculate a *worst-case* level of intake.

Of the number of sources of data available for use in estimating intake of substances in the diet, the FDA relies primarily on data taken from food consumption surveys, such as National Health and Nutrition Examination Survey (NHANES). These data are publicly available.

Food consumption surveys. The FDA uses nationwide food consumption surveys at the individual level to collect information on mean food intakes and the distribution of food intakes within subpopulations of individuals defined by demographic (age/gender) factors and health status (pregnancy, lactation). One or more methods, including food records or diaries, 24-h recalls, food frequency questionnaires, and diet history, are used.

The USDA initiated collection of nationwide food consumption data,[9] which, over time, transformed into the NHANES collecting data to measure the knowledge and attitudes about nutrition, diet, and health in the US population (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES became a continuous program in 1999, with

approximately 5000 individuals surveyed each year (NHANES I, II, and III). National Center for Health Statistics (NCHS) released data sets to the public in 2-year cycles. These dietary data are released in two files: a total nutrient intakes file and an individual food file (with detailed records of gram weights and nutrient values). Beginning in January 2002, NHANES studies collected data on two nonconsecutive 1-day recalls, the most recent of which involving 10,000 people for the years 2013–2014 is available for public use (http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx). Consecutive years of data collection are a nationally representative sample of the US population. It is well established that the length of a dietary survey affects the estimated consumption of individual users and that short-term 1-day dietary survey overestimates consumption over longer time periods .[10] In addition to collecting information on the types and quantities of foods being consumed, NHANES[11] collects socioeconomic, physiological, and demographic information from individual participants in the survey, such as sex, age, height, and weight and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population.

Estimates for the daily intake of ingredient represent projected 2-day averages for each individual from day 1 and day 2 of NHANES (NCHS, 2013–2014) data. Mean and percentile estimates are generated incorporating sample weights in order to provide representative intakes for the entire US population. *All-person* intake refers to the estimated intake averaged over all individuals surveyed, regardless of whether they consumed food products containing the ingredient, and therefore includes *zero* consumers (those who reported no intake of the food products containing the ingredient during the two survey days). *All-user* intake, a better estimate, refers to the estimated intake by those individuals consuming food products containing the ingredient. Individuals are considered users if they consumed one or more food products containing the ingredient on either day 1 or day 2 of the survey. The individual proposed food uses, default serving sizes, and the corresponding maximum use levels for specific foods as identified by food codes representative of each proposed use are chosen from the Food and Nutrition Database for Dietary Studies (FNDDS). In FNDDS, the primary (usually generic) description of a given food is assigned a unique eight-digit food code.[12,13] FDA Guidance for Industry: Estimating Dietary Intake of Substances in Food can be found at (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#mode).

Food contact substances. The EDI for indirect additives (FCS) is calculated using methods outlined in the *Recommendations for Chemistry Data for Indirect Food Additive Petitions* and the *Guidance for Industry: Preparation of Premarket Notifications for FCSs: Chemistry Recommendations*.[7] The EDI is based on a calculation of the amount of additive that could potentially migrate from the food contact material into various foods, and a subsequent calculation of the amount of those foods that would be consumed by a person each day. Other uses of the additive will be added to the calculated EDI to estimate the cumulative EDI (CEDI). The FDA uses the CEDI to assign a "LOC" to the compound which in turn dictates the extent of toxicological testing as specified in the FDA guidance entitled Preparation of Premarket Notifications for FCS: Toxicology Recommendations.[14]

For indirect additives, the LOC is based solely on anticipated human exposure. The agency recommends that the following toxicology studies be performed to assess the safety of an FCS (and its constituents if appropriate) with the indicated CEDIs:

1. CEDI < 0.5 ppb (<1.5 μg/day): No toxicity studies are recommended for an FCS or constituent with an estimated CEDI less than 0.5 ppb. However, information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in a comprehensive toxicological profile (CTP).
2. CEDI > 0.5 and < 50 ppb (>1.5 to <150 μg/day): The potential carcinogenicity of an FCS and/or constituent is evaluated using a battery of genetic toxicity tests (bacterial gene mutation and an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma thymidine kinase (TK) assay). Other information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in the CTP.
3. CEDI > 50 ppb and <1 ppm (>150 to <3000 μg/day): The potential carcinogenicity of an FCS and/or constituents with an estimated CEDI greater than 50 ppb but less than 1 ppm should be evaluated using the same genetic toxicity battery of tests plus an in vivo test for chromosomal damage using a rodent. The potential toxicity should be evaluated further by two subchronic oral toxicity tests, one in a rodent and one in a nonrodent species to provide an adequate basis for determining an ADI and to help determine the need for longer term or specialized toxicity tests (e.g. metabolism studies, teratogenicity, reproductive toxicity, neurotoxicity, and immunotoxicity studies). Other information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in CTPs.
4. CEDI > 1 ppm (>3000 μg/day): The agency requires that an FAP be submitted.

Table 3. Consumption factors.[a]

	Package category	CF	Package category	CF
A. General	Glass	0.1	Adhesives	0.14
	Metal-polymer coated	0.17	Retort pouch	0.0004
	Metal-uncoated	0.03	Microwave susceptor	0.001
	Paper-polymer coated	0.2	All polymers[b]	0.8
	Paper-uncoated and clay-coated	0.1	Polymer	0.4
B. Polymer	Polyolefins	0.35[c]	PVC	0.1
	LDPE	0.12	Rigid/semirigid	0.05
	LLDPE	0.06	Plasticized	0.05
	HDPE	0.13	PET[d,e]	0.16
	PP	0.04	Other polyesters	0.05
	Polystyrene	0.14	Nylon	0.02
	EVA	0.02	Acrylics, phenolics, and so on	0.15
	Cellophane	0.01	All others[f]	0.05

CF: consumption factor; FDA: Food and Drug Administration.
[a]From: US FDA;[7] Guidance to the Industry: Preparation of Premarket Submissions for Food Contact Surfaces: Chemistry Recommendations, December 2007.
[b]Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).
[c]Polyolefin films, 0.17 (HDPE films: 0.006; LDPE films: 0.065; LLDPE films: 0.060; and PP films: 0.037).
[d]PET-coated board: 0.013; thermoformed PET: 0.0071; PET carbonated soft drink bottles: 0.082; custom PET: 0.056; crystalline PET: 0.0023; PET films: 0.03.
[e]A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[f]As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

Estimating CEDIs. Estimates of indirect additive intake are derived by extraction studies with food-simulating solvents as described in the *Recommendations for Chemistry Data for indirect Food Additives Petitions*[15] and the FDA's *Guidance for Industry: Preparation of Premarket Notifications for FCSs: Chemistry Recommendations.*[7]

The design of the extraction experiments is discussed in the FDA guidelines[15,16] and includes the consideration of the type of extraction vessel used, the concentration of the sample used in the extraction, the thickness and surface area of the sample extracted, the volume of extracting solvent, the conditions of the extraction (food stimulant used), the time and temperature of the extraction, and the characterization of the substance extracted. The guidelines recommend that 3% ethanol be used to simulate extraction into both aqueous and acidic foods, that 8 or 50% ethanol be used for alcoholic foods, and that food oils (such as corn oil) be used to simulate extraction into fatty foods. The guideline lists specific polymers and fatty-food simulants that are appropriate for use. Importantly, the agency recommends that effort be made to mimic the intended use of the indirect additive.

Migration data gathered using these guidelines are intended to provide estimates of the higher level of migration to foods that might occur. The extraction data are used to calculate exposure to the additive, an estimate that depends not only on the extent of migration into food but also on the fraction of a person's diet that is likely to contact materials containing the additive. The *consumption factor* (CF) is used to describe that portion of the diet likely to contact specific packaging materials. The FDA defines the CF as the ratio of the weight of food containing the specific packaging material to the weight of all goods packaged with that material. Examples of CF values used by the agency for different packaging categories are shown in Table 3. The CFs for the FCSs are frequently revised as dictated by use pattern,[17] as exemplified by polystyrene, the CF for which was recently increased from 0.1 to 0.14. The minimum CF used by the agency is 0.05.

Before a CF value is used with the data on migration to derive an estimate of probable intake, information on the nature (aqueous/acidic, alcoholic, fatty) of the food that will likely contact the packaging material is needed. Food-type distribution factors(s) have been estimated by the agency for each type of packaging material, indicating the fraction of food contacting each material (aqueous/acidic, alcoholic, and fatty; Table 4). These values are used along with the CF values and migration data to estimate the expected migration (concentration) [M] of the new additive in food that contacts the specific packaging material as follows:

$$[M] = F_{\text{aqueous and acidi}c}\ (M_{10\%\,\text{EtOH}}) + F_{\text{alcohol}}(M_{50\%\text{EtOH}}) + F_{\text{fatty}}(M_{\text{corn oil}})$$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying [M] by CF. The EDI then is determined by multiplying the dietary concentration ([M]) by the total weight of food consumed by an individual per day (3000 g)

$$\text{EDI (mg/person per day)} = 3000\ \text{g/person per day} \times [M] \times \text{CF}$$

Table 4. Food-type distribution factors (f_T).[a]

		Food-type distribution (f_T)			
	Package category	Aqueous[b]	Acidic[b]	Alcoholic	Fatty
A. General	Glass	0.08	0.36	0.47	0.09
	Metal-polymer coated	0.16	0.35	0.40	0.09
	Metal-uncoated	0.54	0.25	0.01[c]	0.20
	Paper-polymer coated	0.55	0.04	0.01[c]	0.40
	Paper-uncoated and clay-coated	0.57	0.01[c]	0.01[c]	0.41
	Polymer	0.49	0.16	0.01[c]	0.34
B. Polymer	Polyolefins	0.67	0.01[c]	0.01[c]	0.31
	Polystyrene	0.67	0.01[c]	0.01[c]	0.31
	Impact	0.85	0.01[c]	0.04	0.10
	Nonimpact	0.51	0.01	0.01	0.47
	Acrylics, phenolics, and so on	0.17	0.40	0.31	0.12
	PVC	0.01[c]	0.23	0.27	0.49
	Polyacrylonitrile, ionomers, PVDC	0.01[c]	0.01[c]	0.01[c]	0.97
	Polycarbonates	0.97	0.01[c]	0.01[c]	0.01[c]
	Polyesters	0.01[c]	0.97	0.01[c]	0.01[c]
	Polyamides (nylons)	0.10	0.10	0.05	0.75
	EVA	0.30	0.28	0.28	0.14
	Wax	0.47	0.01[c]	0.01[c]	0.51
	Cellophane	0.05	0.01[c]	0.01[c]	0.93

FDA: Food and Drug Administration.
[a]From: US FDA;[7] Guidance to the Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations, December 2007.
[b]For 10% ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.
[c]1% or less.

The EDI is used together with information on exposure from all other uses of the indirect additive to establish the CEDI which is used to establish the level of toxicological testing recommended.

Toxicology testing in animals

The extent and types of toxicological studies required to support the safety of either direct or indirect food additives are dependent on both the EDI and the expected nature and potential for toxicity of the additive. Redbook II includes the following suggestions.

Short-term genetic toxicity studies. A modified battery including *Salmonella typhimurium* reverses mutation assay, in vitro mutagenicity in mammalian cells and in vivo cytogenetics.

Acute oral toxicity studies. Results of acute oral toxicity study will provide information on the type of toxicity (e.g. neurotoxicity and cardiotoxicity), identity target organ(s), and dose levels for longer term toxicity studies. The focus should be not on the number of animals that die at a given dose or LD_{50} determination but rather the toxic effects on organ systems and the potential recovery of the animals from the administration of high doses of the test compound.[18]

Short-term feeding studies. Short-term studies generally last 28 days in duration, with multiple dose groups of animals exposed repeatedly to the chemical in their diets. This type of study is required for CL I compounds and is useful for identifying the toxic characteristics and target organ(s) of an additive and as a range-finding study for subchronic and chronic studies to help set doses for these studies. Animals should be observed daily for overt signs of toxicity and necropsies are performed typically on all animals, including those that die during the course of the study.

Subchronic feeding studies. Subchronic feeding studies are required for CL II compounds and examine the toxicity (target organs, potency, etc.) of a compound in greater detail after repeated dosing of at least three dose groups of 20 rodents or 4 dogs/gender/group, generally for a period of 90 days. Blood and urine sampling is performed periodically throughout the studies for determination of insidious toxicity and to aid in target organ identification. At termination of the study, detailed necropsies and histopathology are performed on representative test (high dose) and control animals. The tests are designed to mimic human exposure and may involve administration in the diet, through drinking water, in tablets, or by gavage. Redbook II recommends that screening for neurotoxicity and immunotoxicity be performed and that rodents be single caged. Effects related to accumulation of the chemical in tissues should be evident, allowing for determination of a "no observable adverse effect level" (NOAEL) level. For a CL III

compound, the subchronic study helps dose selection for chronic study. For substances in CLs I and II, data from subchronic tests are often used for the ultimate determination of safety.[15,18]

Reproductive and developmental toxicity studies. Reproductive and developmental toxicity (DART) testing is required for compounds of CLs II and III and are conducted by exposing male and female rodents (20/gender/group) orally to the additive to determine its effects on a variety of endpoints including male and female gonadal function, estrous cycles, mating behavior, conception, parturition, lactation, weaning, and growth and development of the off spring. The mechanisms of any effects elicited are rarely apparent from the results of such testing; however, the data do provide information on the effects of the chemical on neonatal morbidity and mortality and on the teratogenic potential of the test substance.

Three test levels and a control group are included for parental animals of both generations (P and F_1). The animals in both generations are treated before mating, during pregnancy, and through weaning of the F_1 offspring. Selected F_1 offspring is treated during their growth into adulthood, mating, and production through weaning (21-days old) of an F_2 generation. For each generation, at least one litter should be examined. If toxicity is identified in the first litter, the study should be expanded. Animals should also be screened for neurotoxicity and immunotoxicity. A detailed assessment of male reproductive effects is also included.

In a teratogenicity phase of any multigeneration study, the test substance must be administered during in utero development. Multiple dose groups are included as well as a control. The dams are killed 1 day before parturition. The uterus is removed and examined for embryonic or fetal deaths, live fetuses, and any evidence of malformations of skeletal or soft tissues. Ovaries are examined for the number of corpora lutea. Live fetuses are weighed, sexed, and examined for external abnormalities. A selected number of fetuses are examined for soft tissue malformations, usually by random selection of one-third of the group. The remaining two-thirds of the fetuses are examined for skeletal defects.

Chronic toxicity and carcinogenicity studies. Chronic toxicity and carcinogenicity studies are required for a CL III food additive and are often combined into a single study. The studies are of lifetime duration in two rodent species lasting typically 104 weeks. The studies are usually designed to include several satellite groups for interim kills at 3, 6, and 12 months to determine the compound-related effects that are not due to aging. The Redbook II also recommends using 50 animals/sex/group, single housing of rodents, periodic observation of the animals for signs of onset and progression of toxic effects, hematological and organ function tests, and clinical examinations for neurological and ocular changes. Histopathology should be performed on all animals in the study.

Definitive evidence of carcinogenicity is difficult to establish from the results of a single study using a few dozen animals per group. Factors such as histological changes, sensitivity of the bioassay, and variability in background tumor incidence must also be considered. Other correlative information (e.g. results from short-term genotoxicity testing, structure–activity relationships, dose–response relationships, the number of strains and/or species tested, pharmacokinetic handling or metabolism of the compound, and the degree/site/incidence of the tumor response) is often used in the evaluation of the "weight of the evidence" of carcinogenic potential. Because the Delaney Amendment prohibits the use of carcinogenic food additives, the interpretation of carcinogenicity test results has an exceedingly important impact on the safety assessment process.

Human data (clinical studies)

Unlike drugs, under the FDCA, there is no requirement for obtaining clinical safety data for food additives. Instead, the safety assessment process for food additives can rest solely on the results from experimental studies. In cases where human data are available, however, the data should be incorporated into the safety profile of the food additive. In cases where human intake is expected to be relatively large, petitioners may choose to conduct human studies after a thorough completion of the nonclinical evaluation. Clinical studies for certain macro-ingredient food additives (e.g. noncaloric fat substitutes), however, may be required because high intake of macro-ingredients in rodents has been shown to induce alterations in normal physiology, leading to spurious toxicological effects of no consequence to humans.[19] Further, questions related to high levels of such additives reducing dietary caloric content and altering the micronutrient homeostasis are best answered in humans.

Environmental effects of food additives

A food additive can be introduced into the environment during manufacture, use, or disposal. Ingested additives can enter the environment via sewage. Chemicals used to produce food additives may also be added to wastewater treatment, manufacturing, or processing plants. Other routes of introduction for food additives include solid waste disposal in landfills, composing of foods, and incineration of solid wastes. The NEPA dictates that the FDA assesses the environmental implications of its regulatory decisions (CFR part 25, April 26, 1985). Petitioners are required to prepare an environmental assessment before the FDA will approve an FAP. Issues addressed include the intended use; physical/chemical properties; degree of metabolism following use; environmental fate in air, water, and soil; predicted

environmental concentrations; potential toxicological effects on aquatic and terrestrial species; and environmental implications of manufacturing and ultimate disposal.

Levels of introduction, rates of incorporation into soil, and environmental fate are evaluated to predict the final concentration of the additive in the relevant environmental media. When possible, processes that affect the transport and transformation of food additives are used when estimating the environmental concentration. Useful data include chemical stability (hydrolysis, photolysis), biodegradability, and mobility in waste media (water solubility, oil sorption, volatility). Once the amount of substance released into the environment has been estimated, the environmental assessment involves examination of available data on toxicity to animals, plants, and other organisms at the ecosystem level in each environmental compartment (air, freshwater, estuarine, marine, and terrestrial ecosystems). The toxicity database is then compared with the level of environmental exposure to arrive at an assessment of potential risk.[1]

Risk assessment

Acceptable daily intake

An ADI for human consumption of food additives, as accepted worldwide, is calculated as follows:

1. Most sensitive indicator (noncancer effect) of toxicity (point of departure) is identified.
2. Threshold or highest NOAEL is identified for the effect.
3. The NOAEL is divided by safety factors to arrive at the ADI.

It is assumed that individuals can be exposed to a daily intake of an additive at levels up to its human threshold or ADI for their full lifetime without significant risk for noncancer effects[1] (Porl and Abadin, 1995). The NOAEL represents the threshold of effect applicable to experimental animals. Uncertainties representing species variability of response in human beings compared to animals and among individuals more sensitive than others are adjusted by using safety factors. If the NOAEL is from a chronic toxicity study, a typical safety factor is 100 (l0 for each of the two major sources of variability). If the NOAEL is from a subchronic toxicity study, and a chronic ADI is desired, an additional factor of 10 is introduced. If the NOAEL is from a developmental/reproductive toxicity study revealing a type I effect, a factor of 1000 may be used or if the NOAEL is from a reproductive study, a factor of 100 may be considered since the reproductive study is classified as a chronic study. The magnitude of the "standard" safety factors can be altered if the data suggest human sensitivities or variabilities are reduced.[20] Data from clinical studies or from PK/PD studies, particularly concerning metabolic profiles, may provide the basis for such determinations.

Carcinogens and risk assessment

Additives shown to be carcinogenic when administered orally to laboratory animals are generally prohibited (Delaney Amendment). However, Congress passed special legislation in 1977 preventing the FDA from restricting the use of the artificial sweetener saccharin, even though it had been shown to induce tumors in laboratory animals in a limited number of studies (US Congress, 1977). In addition, two other carcinogens—vinyl chloride and acrylonitrile, both residual monomers—are allowed at very low levels (insert values and references) as a result of the plastics used in food-packaging materials. Such chemicals are considered by the agency to be "constituents" of the food-packaging material rather than additives. Residues of carcinogenic pesticides may contaminate foods through application directly on crops or from other environmental sources. Intrinsic constituents or unavoidable contaminants of foods, such as hydrazines in mushrooms or aflatoxin B_1 and polychlorinated biphenyls, are carcinogenic in long-term toxicological studies, but are permitted in foods only up to levels (provided level) that the FDA considers the lowest level generally attainable without resulting in severe economic losses or adverse effects on the food supply (National Research Council (US) Committee on Diet, Nutrition, and Cancer (1983)).[21]

Migrants from FCSs become food additives only if detected in food. Thus, the FDA has decided to use the risk assessment approach as a regulatory tool to deal with such agents. The FDA does not specify the detection limits or the analytical methods to be used. Instead, the agency is satisfied if the petitioner uses validated methods capable of detecting residues at concentrations sufficient to create daily intakes corresponding to lifetime risk no greater than 1×10^{-6}. The FDA has applied this approach to deal with carcinogenic manufacturing by-products that are present as impurities in food additives. If the additive is not carcinogenic when tested, trace amounts of carcinogenic impurities are permitted if their lifetime cancer risks do not exceed the one in a million criterion.[1]

The FAP

Once safety data have been generated for a potential new additive, an FAP is prepared according to guidelines found in Section 409(b)(2) of the FDCA. In general, five broad areas of information should be provided as follows:

1. identity of the additive,
2. proposed use of the additive,
3. intended technical effect of the additive,
4. analytical method of analysis for the additive in food, and
5. full reports of all safety investigations.

In addition, a petitioner may be asked to submit a description of methods, facilities, and controls used in the production of the additive, along with samples of the

additive and of foods in which the additive will be used. In the case of indirect additives, additional information on extraction and migration of the substance into foods is required. Details can be found in section 409 (b)(2) of the FDCA (https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm253328.htm).

GRAS substances

Reviews on the concept of GRAS include those of Frankos and Rodricks[1] and Kruger et al.[2,22] among others. The final ruling for GRAS was published in 2016 (Federal Register, August 17, 2016; 81(159):54960-55055). Under the 1958 food additive amendments to the FDCA, any substance intentionally added to food is a food additive and is subject to premarket approval by the FDA unless the use of the substance is GRAS (the GRAS provision; or otherwise excepted from the definition of food additive—e.g. color additive). Food ingredients that were in use prior to January 1, 1958 (baking soda, salt, pepper, vinegar) are also exempted.

Ingredients are classified as GRAS through "scientific evaluation procedure." The principal criterion for GRAS status is documentation that a substance is

> generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (. . . or experience based on common use in food) to be safe under the conditions of its intended use.

This, effectively, meant that the scientific safety standard to which a GRAS substance is held is virtually identical to that of a food additive with the only exception that all pivotal safety information must be publicly available. New uses of a substance that result in an increased intake must be re-justified [re-GRASed] by a new self-affirmation of the GRAS status.

By 1961, FDA amended its regulations to include a list of GRAS substances (GRAS notices; https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices). During the 1960s, many manufacturers requested FDA's opinion on whether their GRAS status was justified and received "opinion letters." In 1969, when the FDA removed cyclamate salts from its GRAS list as a result of safety questions, then-President Nixon directed FDA to reexamine the safety of GRAS substances. In the 1970s, the FDA conducted rulemaking to establish procedures to petition the FDA for a GRAS affirmation. A Select Committee on GRAS Substances conducted a "comprehensive review" of generally presumed GRAS substances and affirmed that most of these substances as GRAS but required a small number to be further tested and subject to petition and affirmation.[23]

To eliminate the resource-intensive rulemaking procedures, in 1997, FDA proposed to *replace the GRAS affirmation petition process* with a *notification procedure* ("GRAS notification"). Effectively, this meant that all future GRAS reviews would be "self-determinations" of GRAS status by the notifiers and the FDA may or may not be informed. The key elements of a GRAS review, as specified under sections 201(s) and 409 of the FDCA and the FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, continue to be technical evidence of safety and a basis to conclude that this evidence is generally known and accepted. Technical evidence can be derived either from scientific procedures or common use in food prior to January 1, 1958. Although the new GRAS notification process specifies both the format and scientific content, notification is not mandatory. In general, the FDA's response to a notification has been in one of three following categories:

1. The agency does not question the basis for the GRAS determination.
2. The agency concludes that the notice does not provide a sufficient basis for a GRAS determination (e.g. because the notice does not include appropriate data and information or because the available data and information raise questions about the safety of the notified substance).
3. The response letter states that the agency has, at the notifier's request, ceased to evaluate the GRAS notice.

As recently as October 2016, FDA issued a guidance document (Guidance for Industry: Frequently Asked Questions about GRAS for Substances Intended for Use in Human or Animal Food) that addresses common questions about the regulatory process and regulatory considerations regarding whether the use of a substance in human or animal food is GRAS (https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm061846.htm).

This guidance updates and replaces a previous guidance, entitled "Frequently Asked Questions about GRAS," that Center for Food Safety and Applied Nutrition issued in December 2004. This updated guidance refers to the provisions of a final rule published on August 17, 2016 (81 Fed. Reg. 54960) and addresses substances used in human food as well as substances used in animal food.

Safety evaluation of GRAS substances

The information critical in determining the safety of a GRAS substance must be publicly available and should include at a minimum as follows:

- *Description of the GRAS substance*: A review of the physical and chemical characteristics of the GRAS substance includes chemical name(s) (and synonyms), CAS registry number(s), and chemical structure(s) and a description of final product

characteristics includes established food-grade specifications for the principal components, related substances, by-products, impurities and contaminants, and batch analysis results showing compliance with established food-grade specifications.

- *Production process*: It includes documentation of good agricultural practice/good manufacturing practice (cGAP/cGMP), detailed process flow diagram for each step of the production process and operation parameters including critical control step(s) in the process, a list of raw materials including specifications and processing aids with food-grade and regulatory compliance documentation, critical control steps involved in the quality control process, description of potential impurities in the final product, and documentation of stability and shelf life.
- *Historical use, regulatory status, and consumer exposure*: A review of the history of use and/or natural occurrence of the ingredient in other foods along with an intake or exposure estimate, current regulatory status if any, proposed use and use levels utilized to calculate the EDI of the GRAS substance.
- *Intended effect*: It intended function in the food.
- *Analytical methodology*: For determining the quantity of the substance in or on food, and any substance formed in or on food because of its use.
- *Review of safety data*: Evaluation of the actual use of the product and issues that may contribute to the safety of the product; critical review from the published animal toxicology and clinical literature for safety information on primary components, related substances, secondary metabolites, impurities, and contaminants using relevant data for occurrence and/or levels present, estimated background intake, metabolic fate, and toxicological and pharmacological activity.
- *Safety assessment and GRAS determination*: Evaluation of the safety of consumption of the substance under its intended conditions of use including determination of an ADI for the substance as well as other components or contaminants and comparison of this ADI to the EDI of the substance from existing and proposed uses. As long as the EDI is less than (or approximates) the ADI, the substance can be considered safe under its intended conditions of use.

In addition to the substances approved by the FDA, another group of compounds which were independently affirmed as GRAS by the Flavor and Extract Manufacturers Association are included in the GRAS notice list (https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices). The largest numbers of compounds approved by the FDA are indirect additives used in the manufacturing of paper and plastic packaging materials. Exposure to these compounds occurs through migration out of the packaging and is therefore of an indirect nature. These additives are listed in 21 CFR parts 174–178. Although the FDA has published a list of GRAS substances, the agency realized that it was impractical to list all substances that could be considered GRAS.[3] The FDA can withdraw GRAS classification, as it did for partially hydrogenated oils (industrial trans fats) in 2015 when the evidence shows that these substances are no longer safe for its intended use (https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm449162.htm).

Food ingredients derived from chemically complex extracts

Natural products such as crude plant extracts, because of the presence of tens or even hundreds of compounds at very low concentrations and because the matrix molecules can modify bioavailability and the toxic responses of the active components, rendering a safety evaluation of individual compounds in such extracts are difficult at best and often impractical.[24] An approach to determining the safety of natural products involves: a review and analysis of the existing phytochemical and botanical literature, establishing the chemical composition of the raw material and the commercial product, determination of health-based levels of exposure for the identified compounds or compound, and utilization of published toxicology studies to establish safety of exposure to the extract through evaluation of the components/compound classes. A safety paradigm utilizing a thorough analytical elucidation of the composition of the complex natural product may allow a literature-based assessment of safety for individual components/classes of compounds comprising the botanical extract. Traditionally, safety determination of a complex natural product has relied on animal toxicology testing. Similar to that described for food additives, ADIs or safe levels of ingestion of the complex mixture can also be determined through scientific procedures described earlier. When the extract in the animals' diet exceeds 5% (w/w), however, the possibility that nutritional imbalance may contribute to the adverse effects observed must be considered.[25–28] In these cases, the concept of the 100-fold uncertainty (safety) factor is not appropriate in the determination of the ADI. Because the safety assessment of botanical substances is complicated by various factors including compositional diversity, lack of standardization of the botanical, lack of identity of the active ingredients, and the use of different formulations of the botanical in the article of commerce when compared with the test substance and/or its extracts, each new submission must be dealt with on a case-by-case basis.[29]

Color additives or food colorants

People consume food first with their eyes; color is an important part of that perception. A color additive, as defined by FDA regulations, is any dye, pigment, or other substance that can impart color to a food, drink,

pharmaceutical, or cosmetic or to the human body (https://www.fda.gov/forindustry/coloradditives/regulatoryprocesshistoricalperspectives/).

The assessment of color-imparting ingredients in foods was among the first public initiatives undertaken when, in 1881, the USDA's Bureau of Chemistry began research on the use of colors in food. Butter and cheese were the first foods for which the federal government authorized the use of artificial coloring. The Pure Food and Drug Act of 1906 reduced the permitted list of synthetic colors from 700 to seven: Ponceau 3R (FD&C red no. 1), amaranth (FD&C red no. 2), erythrosine (FD&C red no. 3), indigotine (FD&C blue no. 2), light green SF (FD&C green no. 2), naphthol yellow 1 (FD&C yellow no. 1), and orange 1 (FD&C orange no. 1).

Regulation

Food colors permitted by the FDA are classified as those subject to certification or those exempt from certification, both of which are subject to rigorous safety standards prior to their approval and listing for use in foods.

- *Certified colors* are synthetically or "artificially" produced and utilized because they impart intense, uniform color, are less expensive, and blend more easily to create a variety of hues. There are nine certified color additives approved for use in the United States. In general, these colors are stable with respect to exposure to pH, light, and heat. Importantly, each production batch of these colors is "certified" to meet specific standards.
- Colors that are *exempt from certification* include pigments derived from natural sources such as vegetables, minerals, or animals. These pigments are not stable in a broad range of pH, light, or heat. In addition, these substances are exempt from certification due to a broad variation in their innate characteristics. These additives are typically more expensive than certified colors and may add flavors to foods. Examples of exempt colors include annatto extract (yellow) often used in butter, dehydrated beets (bluish-red to brown), caramel (yellow to tan) often used in confections and soft drinks, beta-carotene (yellow to orange), and grape skin extract (red, green).

Today, any substance that is added to food to impart color to the food is a color additive (see color additive definition in section 201(t) of the FFDCA and 21 CFR 70.3(f) and the FDA's implementing regulations in 21 CFR part 70). Under section 201(t)(1) and 21 CFR 70.3(f), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food, except that such term does not include any material that the secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempted from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability are concerned. Any color additive is deemed unsafe unless its use is either permitted by regulation or exempted by regulation. In general, however, the safety criteria for color additives are identical to those used for food additives. Unlike the definition for food additive, however, there is no GRAS exemption for color additives and they are subject to the additional legal requirement (e.g. batch-by-batch certification by the FDA for synthetic colors) not found in the food additive regulations. Any food that contains an unsafe color additive is adulterated under section 402(c) of the FFDCA.

Following the passage of the Color Additive Amendment of 1960, 20 natural colors (comprising preparations such as dried algae meal, annatto extract, beet powder, grape skin extract, fruit juice, paprika, caramel, carrot oil, cochineal extract, ferrous gluconate, iron oxide, turmeric) were exempted from certification, whereas all the synthetic colors were required to be retested if questions regarding their safety arose. A provisional certification was given to those colors in use that required further testing. Currently, there are seven certified synthetic colors (FD&C colors blue no. 1, red no. 3, red no. 40, and yellow no. 5 are permanently listed, whereas FDB blue no. 2, green no. 3, and yellow no. 6 are provisionally listed) with unlimited uses; one permanently listed color (citrus red no. 2) is used only for coloring skins of oranges at 2 ppm, and several colors including green 1, green 2, orange B, red 2, red 4, and violet 1 were delisted due to concerns of their carcinogenicity and other chronic toxic effects (https://www.fda.gov/ForIndustry/ColorAdditives/default.htm).

Chemistry

Chemically, most food colors are water soluble aryl azo compounds that have vivid colors, especially reds, oranges, and yellows. They have excellent coloring properties, mainly in the yellow to red range, as well as good lightfastness. The lightfastness depends not only on the properties of the organic azo compound but also on the way they have been adsorbed on the pigment carrier.

Food coloring additives can be either *dyes* or *lakes*, depending on their solubility. *Dyes* are colors that have to be dissolved in water to function. *Lakes*, on the other hand, are a way of making soluble dyes insoluble, yet miscible or soluble in lipids, usually by adsorbing a dye on a substrate

of alumina hydrate. Lakes are quite stable, and typically used in products that do not have enough moisture to absorb the dye or where the potential for dye migration would be a hindrance. Application examples include oil-based products such as frosting, direct compression items such as chewable vitamins, and coated candies.

Childhood hyperactivity: A cautionary tale of toxicology and epidemiology gone awry

The "Feingold hypothesis" that food coloring additives were responsible for abnormal childhood behavior (hyperkinesis and learning disability) was popularized in the 1970s. Results from studies conducted by investigators other than Feingold demonstrated inconsistent and inconclusive results or were difficult to interpret due to inadequacies in study design. A consensus development panel of the National Institutes of Health concluded in 1982 that for some children with attention deficit hyperactivity disorder (ADHD) *and* confirmed food allergy, dietary modification may have produced *some* improvement in behavior (https://consensus.nih.gov/1982/1982DietHyperactivity032html.htm).

In 2007, synthetic certified color additives again came under scrutiny following publication of a study commissioned by the UK Food Standards Agency to investigate whether certain color additives cause hyperactivity in children (https://www.food.gov.uk/science/additives/foodcolours). Both the FDA and the European Food Safety Authority (EFSA) independently reviewed the results from this study and each concluded that the study does not substantiate a link between the color additives that were tested and behavioral effects (Background Document for the Food Advisory Committee: Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children March 30–31, 2011); EFSA concluded that the study provided only limited evidence that the additives had a negligible effect on the activity and attention of some children, and the significance of the effects was unclear. Because mixtures were tested, rather than individual ingredients, the observed putative effects could not be attributed to any individual additive. EFSA also noted that the effects observed were not consistent for the two age groups or for the two mixtures tested in the study (http://www.efsa.europa.eu/en/press/news/ans080314). In 2009, EFSA re-evaluated the safety of the six color additives used in the Southampton study and concluded that the available scientific evidence failed to substantiate a link between the color additives and behavioral effects.

Again, based on review of the data from all published studies, the FDA concluded that a causal relationship between exposure to color additives and hyperactivity in children in the general population has not been established. Almost half of the 33 studies trials reviewed by the FDA reported treatment-related effects based only on a parental rating outcome measure. Since only a single source outcome measure detected an effect, a lowered weighting/level of confidence was generally assigned to these study findings (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM248549.pdf).

Genetically modified foods

Kruger et al.,[2] Bawa and Anilakumar,[30] and others[31] have provided recent reviews of this topic. Existing conventional food crops and the products made from them, including those genetically modified or altered through conventional breeding/selection techniques to generate new varieties, are recognized to be safe. More recent technique of genetic engineering, process of removing a desirable gene from one organism or plant, and transferring it to a different organism or plant allows plant breeders to achieve improvements in food crops such as resistance to pests and/or enhanced nutritional value.[16] The new DNA introduced by genetic engineering produces a new protein, the safety of which is evaluated as part of the risk assessment process. Substances intentionally added to food via biotechnology to date have been well-characterized proteins, fats, and carbohydrates and are functionally very similar to other proteins, fats, and carbohydrates commonly and safely consumed in the diet and so will presumptively be GRAS.

The safety of a genetically engineered food crop or a product made from that crop is evaluated by comparing the nutritional and toxicological equivalence of the product to its conventional counterpart. Guidance for safety testing of genetically engineered products to assure that no unintended changes in the composition of the food could adversely affect human health has been published by authoritative scientific and regulatory agencies.[32–37] Differences between the conventional and bioengineered product are identified and the safety of the change is determined.[37] Very recently, the USDA determined that it will not regulate a mushroom genetically modified with the gene-editing tool CRISPR–Cas9, a new gene modifying tools that works within the host organism (https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf).

The FDA has provided guidance on the information that should be included in a safety and nutritional assessment (http://www.fda.gov/NewsEvents/Testimony/ucm115032.htm) of genetically engineered foods as follows:

- the name of the food and the crop from which it is derived,
- the uses of the food, including both human food and animal feed uses, the sources, identities, and functions of introduced genetic material,
- the purpose or intended technical effect of the modification and its expected effect on the composition or characteristic properties of the food or feed,

- the identity and function of any new products encoded by the introduced genetic material, including an estimate of its concentration,
- comparison of the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, anti-nutrients, and toxicants that occur naturally in the food,
- information on whether the genetic modification altered the potential for the bioengineered food to induce an allergic response, and
- other information relevant to the safety and nutritional assessment of the bioengineered food.

If a bioengineered food included a new protein derived from an allergenic source and consumers would not expect it to be present based on the name of the food, the presence of that allergen must be disclosed on the label.[38] Because FDA concludes that there is no basis to infer that foods developed by genetic engineering present any different or greater safety concern than foods developed by traditional plant breeding, labeling requirements for genetically modified foods are similar to conventional foods without the need to identify the "genetically modified" nature of the product.[37] Support for this conclusion also comes not only from a number of studies[33,34,39–59] but also from a lack of documented evidence that any approved, commercially grown genetically engineered crop has caused allergic reactions related to the transgenic component.[60]

Nanomaterials in food products

Nanotechnology is an emerging technology that can be used in a broad array of FDA-regulated products, including medical products (e.g. to increase bioavailability of a drug), foods (e.g. to improve food packaging), and cosmetics.[61,62] Materials in the nano range (i.e. with at least one dimension of approximately 1–100 nm) can exhibit different chemical and/or physical properties or biological effects compared to larger scale counterparts. In August 2015, FDA released a policy statement indicating that it will regulate nanotechnology products under existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction. FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science. To that end, the regulatory approach will have the following type of attributes[63]:

- FDA is maintaining its product-focused, science-based regulatory policy.
- FDA's approach respects variations in legal standards for different product classes. Nanomaterial use in food additives is looked at mainly from the safety standpoint whereas nanomaterials in drugs need to show benefits as well as acceptable safety profile.
- Where premarket review authority exists, attention to nanomaterials is being incorporated into standing procedures.
- Where statutory authority does not provide for premarket review, consultation is encouraged to reduce the risk of unintended harm to human or animal health.
- FDA will continue post-market monitoring. FDA will continue to monitor the marketplace for adverse effects from products containing nanomaterials and will take actions, as needed, to protect consumers.
- Industry remains responsible for ensuring that its products meet all applicable legal requirements, including safety standards.
- FDA will collaborate, as appropriate, with domestic and international counterparts on regulatory policy issues.
- Both for products that are not subject to premarket review and those that are subject to premarket approval, FDA will offer technical advice and guidance, as needed, to help industry meet its regulatory and statutory obligations.

International regulations and global harmonization

Food additive regulation in countries with existing procedures agrees with the general principle (1) that food additive safety can be reasonably assured by critically designed animal studies, (2) that the determination of safe level should be based on maximum dietary level producing no adverse effect in test animals, (3) that the intake of the additive will be below that which could produce harmful effects in animals, (4) that adjustment should be made to account for the safety of vulnerable populations, and (5) that the determination of safety must be based on the judgment of scientists qualified to render such determination. There is also universal acceptance that, for a major of new food additive, adequate animal studies are necessary to address potential mutagenicity, subchronic and chronic toxicity, reproductive and developmental toxicity, and carcinogenicity at a minimum.

Harmonization of food additive regulations, however, is an elusive goal because of major differences in global food use patterns, in the definitions of various additives and in current regulations. Magnuson et al.[64] have summarized the regulation and safety assessment of food substances in various jurisdictions. For example, the first major difference is that the only country with a GRAS list is the United States. This means that compounds considered GRAS in the United States may still need formal approvals in other countries. In a way, Japan has an informal GRAS approach in that natural products, either in plants or through fermentation, are considered inherently safe. Thus, a natural

compound that has undergone little testing in Japan but has been used safely in the Japanese population for years could require investigation if exported to the United States or to the EU. China considers nutrition enhancers, gum-based substances in chewing gum and flavoring agents as direct food additives whereas other countries do not.

Novel foods are not specifically defined in Japan or the United States, but are regulated as direct food additives or FCSs in the United States, whereas Japan has no authoritative statement. Many countries have specific definitions of novel foods and accompanying regulations. Flavoring agents do not require premarket notification in the United States and Canada and can be determined as GRAS or by consulting with the proper authorities, respectively. In Australia/New Zealand, China, the EU, Japan, and Mexico, flavoring substances are subject to approval as food additives. Indirect food additive regulations have little to no worldwide harmonization.

Japan has no definition of FCSs and Japan has established voluntary standards whereas premarket approval is required in most other countries. Enzymes and processing aids, although undefined or varyingly defined in various countries, are, for the most part, uniformly regulated either as direct additives or FCSs. Although many countries are studying specific safety regulations governing nanoscale materials in foods, none has established specific guidance beyond the general principles of food additive safety.

Because of similarities in food consumption patterns, attempts at harmonization have been more successful on a regional scale as exemplified by the common regulatory structures in member countries among Australia/New Zealand (which was suspended on December 1, 2016) and the EU communities. Globalization of populations and their respective food patterns necessitates greater efforts be directed toward global harmonization of food safety regulations to ensure safe consumption of food worldwide.

The future: Emerging strategies and new technologies

Toxicology and safety assessments require new strategies for evaluating risk that are less dependent on apical toxicity endpoints in animal models and rely in greater measure on knowledge of the mechanism of toxicity.[65] The National Research Council[66] has also recommended that safety testing of chemicals embarks on a departure from the emphasis on animal model-based evaluations of apical endpoints of toxicity toward an approach that is more focused on mechanisms of toxicity (adverse outcome pathways), kinetic knowledge of internal exposure, and modeling methods. Parallel to work related to this approach is efforts to develop appropriate novel methodologies to acquire such data. These methods include human stem cell cultures, 3-D cell cultures, organs-on-chips, models to study digestion, bioavailability, kinetics and biotransformation, and quantitative structure–activity relationship (QSAR) models.[67,68]

In addition, development of methods to describe concentration-dependent effects and long-term low-concentration exposure effects is increasingly important. The assessments of complex foods and ingredients such as those having to do with infant formula have to be approached on a case-by-case basis, depending very much on the nature and intended use of the food in question and the specific questions to be answered.

Novel and unconventional foods, and GMOs, present a challenge because of the complexity of the food composition.[69] This diversity of foods is recognized in the legislative approach adopted internationally and in the principle that safety assessment should be approached on a case-by-case basis. The ADI that typically includes a 100-fold safety margin when compared with the lowest NOAEL seen in toxicology studies does not seem feasible for the majority of novel foods. Complete freedom from risk is an unattainable goal, thus the circumstances and degree of exposure to the food in question become a crucial consideration.

In all cases of chemically defined substances or simple mixtures thereof, it may be possible to follow the traditional toxicological approach of feeding sufficiently high quantities to identify the NOAEL and to apply a safety factor of 100 in order to establish an ADI. However, when considering chemically definable compounds with a nutritional effect, for example, new sources of vitamins, minerals, and similar types of compounds, the requisite task obviously becomes far more nuanced.

The integration of derived toxicity data into a systems biology-type description (Hartung et al., 2013), referred to as modes of action or adverse outcome pathways, together with computer-based kinetic modeling is hoped to result in a risk or safety assessment that also has the effect of reducing the number of animal studies needed. When human-based cell or tissue cultures, or even human data, can be employed, a more direct relevance to the human situation can be obtained. This will allow a "fit-for-purpose" approach that can be flexibly adapted to the questions to be answered in safety assessments.

Other new approaches would allow addressing relevant organ-specific features, such as absorption and metabolism by recruiting test systems mimicking human organs and involving new findings on the gene, protein, and metabolite level. The intestinal system and the liver can be mimicked by 2-D and 3-D cell culture systems in bioreactors and for these systems organotypic tissues and functional units, for example, the intestinal villus. Also ex vivo viable human tissue can be used for screening purposes. Communicating micro-reactors and organs-on-chip approaches would also allow investigating the influence of distinct organs on each other, that is, intestine, liver, and adipocytes. New bio-barrier systems for intestine, placenta, and brain allow the investigation of transport phenomena as well as the influence on the coherence of these barriers. The choice of the adequate system depends on significance, sensitivity, robustness, and scientific validity of the system.[65]

Induced pluripotent stem cells derived from adult, differentiated cells may provide even better in vitro models to include in toxicology assessments. Since stem cell-derived in vitro systems can be stably maintained over prolonged periods of time in culture, these systems can be used in repeated dose toxicity studies in vitro.[70]

In silico modeling is already a prerequisite in many areas of the risk assessment field[71] and may end up as an integral part of toxicological assessment of foods and food ingredients. Nontesting data can be generated by several approaches, including grouping approaches, which consist of read across and chemical category formation, SAR, and QSAR.

Food ethics

We would be remiss if the realm of ethics was ignored. The collision of consumerism, public mistrust of the scientific establishment, the instantaneous flow of information (both accurate and inaccurate), and the predominance of emotion rather the evidence together mandates a consideration of universal values and morality as applied to food safety. Food additives can be, and are viewed through an ethical prism, seen as representing aspects of food ethics that is itself a branch of applied ethics. An important aim of applied ethics is to assess the extent to which generally accepted ethical principles are respected when applied in a specific context.[72] Building on this approach, ethical concerns may be examined in relation to the potential of food additives to affect respect for three principles: (1) consumer sovereignty, (2) consumer health, and (3) the rights and welfare of animals used in food safety evaluations. Corollaries related to the use of additives include as follows:

- technological need for their use,
- consumers not misled, and
- additives present no unreasonable hazard to consumers' health.

Whether the three preconditions for authorization of food additives listed above are adequately observed is ethically contentious. This condition may be compounded by the effects of food advertising, which may exert a significant influence on food choices. It is popularly estimated that hundreds of billions of dollars are spent globally on food advertising, an amount exceeding the national economies of the majority the world's countries. Given this enormous investment, the authenticity of the concept of consumer sovereignty may be legitimately under critical scrutiny. Similarly, simplistic journalism, ill-informed social media sources, and public misunderstanding or misperception of science complicate both individual health decisions and public health policy. Thus, the area of "food ethics" may be viewed as an emerging and necessary arena.

A final word

It can be argued that the science of toxicology is an accretion of provisional certainties. Amid the constantly modified protocols, novel technologies, and the orthodoxies, we must not lose sight of the case-specific requirements, the big public health picture, as well as scientific imagination and humility . . . all of which should be tempered by common sense and foundational knowledge and experience. Partitioning, specifying and distinguishing—all represent progress, but it is the integration and the application of synthetic wisdom "from 35,000 feet" that preserves judgment, common sense, and service ethics.

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