The Toxicity of Food Additives

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.

Introduction

The development in food technology and food processing led food additives play an important role in providing a safe food supply as well as meeting the consumers' need.

Food additive means any substance, either natural or synthetic, intentionally added to food for a technological purpose in the processing, packaging, transport or storage of such food. The technological functions of food additive include but not limited to the following:

-enhancing the safety and quality by the inhibition of microbial growth;

-extending the shelf-life by protection against any oxidative deterioration;

-enhancing the flavour and odor;

-stabilizing or retaining the colour; and

-improving the texture and consistency of a food, etc.

Food additive is not normally consumed as a food by itself and not normally used as a typical ingredient of the food. The intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its byproducts becoming a component of or otherwise affecting the characteristics of such foods. The term does not include contaminants or substances added to food for maintaining or improving nutritional qualities as well as seasonings such as salts, herbs and spices. There are many types of food additives and the commonly used ones include preservatives, antioxidants, sweeteners, colouring matters, flavour enhancers, thickeners, emulsifiers, etc.

The use of food additives is justified only when such use has an advantage, does not present an appreciable health risk to consumers, does not mislead the consumer, and serves one or more of the technological functions set out by Codex and the needs set out from and only where these objectives cannot be achieved by other means that are economically and technologically practicable. Food additives can be derived from plants, animals, or minerals, or they can be synthetic. They are added intentionally to food to perform certain technological purposes which consumers often take for granted. There are several thousand food additives used, all of which are designed to do a specific job in making food safer or more appealing.

International standards for the safe use of food additives

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

The safety assessments completed by JECFA are used by the joint intergovernmental food standard-setting body of FAO and WHO, the Codex Alimentarius Commission, to establish levels for maximum use of additives in food and drinks. Codex standards are the reference for national standards for consumer protection, and for the international trade in food, so that consumers everywhere can be confident that the food they eat meets the agreed standards for safety and quality, no matter where it was produced. JECFA reviews all of the safety concerns related to food additives with several determinations; including cytotoxicity, genotoxicity, carcinogenicity, reproduction and developmental toxicity and induction or potential of inducing mutagenicity. Once a food additive has been found to be safe for use by JECFA and maximum use levels have been established in the Codex General Standard for Food Additives, national food regulations need to be implemented permitting the actual use of a food additive.

The International Conferences on Harmonization, Organization for Economic Cooperation and Development, European Food Safety Authority, and the U.S. Food and Drug Administration issue guidelines for the rules and regulation of safe use and also publish lists of approved food additives. The food additives are specially screened for cytotoxicity, genotoxicity, mutagenicity, and hepatotoxicity by various methods. The food additive safety studies are carried out by cytogenetic evaluation in which gene mutation assay, long-term carcinogenicity tests, reproductive and developmental toxicology tests, hyperactivity, anxiety, and depression activity tests are performed. The limitations of these studies are inappropriate in vivo follow-up assay and specificity of subjects. Furthermore, the main challenge is that there are no uniform guidelines on the status of these agents across the various regions or worldwide. We briefly discuss the two main organizations that review the safety of food additives in use.

European Union

In order a food additive to be authorized in the EU, a reasonable case of technological need, no hazard to consumers at level of proposed use and no misguidance to consumers should be demonstrated. To evaluate whether the newly released food additive has an effect on health; The European Commission is required a consultancy from Scientific Committee on Food (SCF). SCF is the organization that review questions relating to the toxicology and hygiene in the entire food production chain for consumer health and food safety issues. The evaluation process by the SCF requires administrative, technical, toxicological data and references (European Commission Health & Consumer Protection Directorate, 2011). The toxicological data obtained from experimental studies have a crucial role for consumers' health due to the presence of any additive in food. During the general toxicological evaluation of food additives, While EU has Guidelines for the Safety Assessment of Food Additives the new guidance documents have been published as Joint FAO/WHO Expert Committee on Food Additives (JECFA) (IPCS/JECFA, 1987) is still valid. The aim of toxicological testing should provide sufficient information relevant to average consumer and vulnerable populations such as suppressed immune deficiency people, young age, pregnancy, diabetes, etc. The testing conditions depend on the chemical structure, proposed levels of use in food. The human data is obtained from epidemiology, medical use and volunteers but; for newly submitted food additives experimental data is commonly derived from laboratory animals. For evaluation of the safety of food additives, core studies are required such as; metabolism/toxicokinetics, sub-chronic toxicity, genotoxicity, chronic toxicity, carcinogenicity, reproduction and developmental toxicity.

US

It is noted that regulation of the food additives in US depends upon specifics of the intended use in toxicology research and application specific food categories, populations intended to consume those foods, and the anticipate health claims to be made. The definition is a bit different than the rest of the world. In general, food additives 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 food additive 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. It should be noted that an additive that is intended to impart color when added or applied to a food is regulated separately as a color additive.

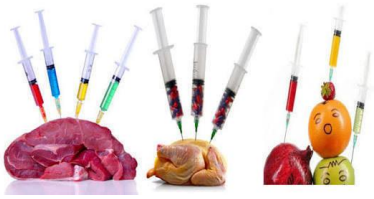
There are some principles apply. First, the agency presumes that some toxicological information is necessary for every food additive. Most of the toxicological studies are derived from animal studies. Second, the agency introduced a term called a level of concern (LOC) which is similar to the term risk. 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. As stated the LOC is analogous to risk. In other words 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 ("Toxicological Principles for the Safety Assessment of Food Ingredients" (Redbook 2000) is the new name of Redbook I which was previously published in draft form in 1983. Redbook 2000 provides information about toxicological data of food ingredients which are submitted to Center for Food Safety and Applied Nutrition and Office of Food Additive Safety for industry and other stakeholders. Food and color additives, food contact substances (which are also defined as indirect food additives) and substances classified as generally recognized as safe (GRAS) are the components of food ingredients (U.S. Food and Drug Administration, 2007)). The category is ranked based on toxicity, which is centered on three categories: A (low toxicity), B (moderate toxicity), or C (high toxicity). In category assignments, the additives are classified based on chemical structure, number and amount of unidentified components in the additive, and 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.

The output of the toxicological studies (from animal studies) can be used to extrapolate to provide information on human exposure. Thus, identifying the Acceptable Daily Intake (ADI), defined as the dose level at which the food additive produces effects on the health of the animals, is critical. The highest level at which no adverse effect on the health of the animals is observed is called the NOAEL (No-Observed-Adverse-Effect-Level). An ADI is developed by dividing the NOAEL obtained from these studies, by an appropriate 'uncertainty' factor, which is intended to take account of differences between the animals and humans. NOAEL is divided by

a safety factor (conventionally 100) to account for the differences between animals and human, and sensitivity between humans, such as gender- and age- differences. The 100-fold safety factor is based on the need to take into account both the differences in species and differences in toxicokinetics and toxicodynamics. The ADI which is then 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.

In rest ,we briefly discuss about some of the direct food additives which may have adverse impact on our health if consumed higher than recommended daily intake.

Preservatives



Nitrates and Nitrites

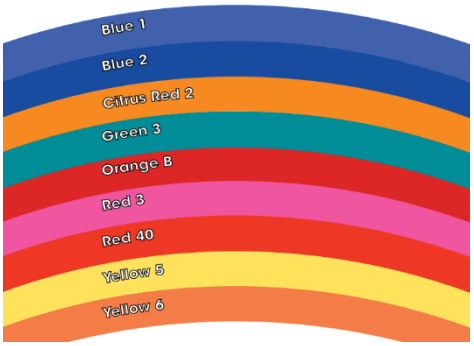
Nitrite is consumed in the diet, through vegetables and drinking water. It is also added to meat products as a preservative. The potential risks of this practice are balanced against the unique protective effect against toxin-forming bacteria such as *Clostridium botulinum*. Although the preservatives which are permitted in foods are considered to be without potential adverse effects there have been concerns about the safety of nitrites. Nitrite, in high concentrations, is undoubtedly toxic to humans. The principal toxic effect is oxidation of oxyhemoglobin to ferrihemoglobin, leading to methemoglobinaemia. This can be fatal, particularly in newborn infants in which the methemoglobin-reducing capacity is low, leading to so-called 'blue baby syndrome' . There has been established concern regarding the use of nitrates and nitrites as preservatives in cured and processed meats, fish, and cheese. The American Medical Association statement also highlighted the risk of gastrointestinal or neural cancer from the ingestion of nitrates and nitrites, which (although not carcinogenic themselves) may react with secondary amines or amides to form carcinogenic N-nitroso compounds (NOCs) in the body. In 2006, the International Agency for Research on Cancer classified ingested nitrates and nitrites, in situations that would lead to endogenous nitrosation (production of NOCs), as "probable human carcinogens" (Group 2A). In 2015, the International Agency for Research on Cancer specifically classified processed meat (which includes meat that has been salted, cured, or otherwise altered to improve flavor and preservation) as "carcinogenic to humans" (Group 1). Such processing can result in the increased formation of NOCs, and there is convincing evidence linking consumption of processed meats with colorectal cancer. In addition, high maternal intake of nitrite-cured meats has also been linked to an increased risk of childhood brain tumors in the offspring, especially tumors of the astroglia. FDA regulations currently allow up to 500 ppm of sodium nitrate and 200 ppm of sodium nitrite in final meat products. However, no nitrates or nitrites can be used in food produced specifically for infants or young children.

Nitrates, can also disrupt thyroid function by blocking the NIS and thereby interfering with essential iodide uptake. Although its relative potency is much lower than that of other common NIS inhibitors, nitrate is still a significant concern, given that combined exposures from food and water may account for a larger proportion of NIS inhibition than from perchlorate exposure and NIS inhibitors may act together additively.

TBHQ

TBHQ is a common preservative that manufacturers use to prolong their products' shelf lives. A recent study has assessed the harmful effects of TBHQ on the immune system. The study compared laboratory toxicology testing (ToxCast) results with data from previous animal tests and epidemiological Trusted Source studies. The ToxCast results and available animal study data confirmed that a common food preservative called tert-Butylhydroquinone (TBHQ) might negatively affect immune system functioning. The antioxidant preservative tert-butylhydroquinone (TBHQ) showed activity both in ToxCast assays and in classical immunological assays, suggesting that it may affect the immune response in people. It appears that the pre-market safety evaluation of the TBHQ was inadequate that is due to fact that immunotoxicity testing is not thorough investigated as an integral part of chemical safety assessment. Therefore, FDA should prioritize and integrate updated immunotoxicity testing to identify harmful chemicals into standard safety assessments to protect public health and well-being. It should be noted that there are so many other preservatives can be included in the list because of their proven toxicity.

Synthetic Food Colors



Synthetic artificial food colors are added to foods and beverages for aesthetic reasons, and the resulting brightly colored products are appealing to young children in particular. In some cases, these colors serve as substitutes for nutritious ingredients, such as in fruit juice drinks that contain little or no actual fruit. Nine AFCs currently are approved for use in the United States: Blue 1 (Brilliant Blue FCF, E 133) , Blue 2 (Indigotine, E132), Green 3 (Fast Green FCF, E 143), Yellow 5 (Tartrazine, E 102) Yellow 6 (Sunset Yellow FCF), Red 3(Erythrosine,E127), Red 40 (Allura Red, E129), Citrus Red 2, and Orange B (which are called rainbow of risks). FDA data

indicate that the use of AFCs increased more than fivefold between 1950 and 2012, from 12 to 68 mg per capita per day.

Over the last several decades, studies have raised concerns regarding the effect of Artificial food colours (AFCs) on child behavior and their role in exacerbating attention-deficit/hyperactivity disorder symptoms. Elimination of AFCs from the diet may provide benefits to children with attention-deficit/hyperactivity disorder.[131] Although the mechanisms of action have not yet been fully elucidated, at least one AFC, Blue 1, may cross the blood-brain barrier. Overall, however, further work is needed to better understand the implications of AFC exposure and resolve the uncertainties across the scientific evidence. The available literature should be interpreted with caution because of the absence of information about the ingredients for a number of reasons, including patent protection.

The FDA has set acceptable daily intakes for each of the AFCs. However, these standards, as well as original safety approval for the color additives, are based on animal studies that do not include neurologic or neurobehavioral end points.

Summary of some of the research and literatures (all references are provided) show Red 3 causes cancer in animals, and there is evidence that several other dyes also are carcinogenic. Three dyes (Red 40, Yellow 5, and Yellow 6) have been found to be contaminated with benzidine or other carcinogens. At least four dyes (Blue 1, Red 40, Yellow 5, and Yellow 6) cause hypersensitivity reactions. Numerous microbiological and rodent studies of Yellow 5 were positive for genotoxicity. Toxicity tests on two dyes (Citrus Red 2 and Orange B) also suggest safety concerns, but Citrus Red 2 is used at low levels. The inadequacy of much of the testing and the evidence for carcinogenicity, genotoxicity, and hypersensitivity, coupled with the fact that dyes do not improve the safety or nutritional quality of foods, indicates that all of the currently used dyes should be removed from the food supply and replaced, if at all, by safer colorings. It is recommended that regulatory authorities require better and independent toxicity testing, exercise greater caution regarding continued approval of these dyes, and in the future approve only well-tested, safe dyes.

While the effects of these AFCs have been observed in children, a thorough reassessment of AFCs is warranted to determine whether there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.

As for several other synthetic food colors, some studies such as ‘Southampton study’ have raised so much concern. In this study six colors (unset yellow (E110), quinoline yellow (E104), carmoisine (E122), allura red (E129), tartrazine (E102) and ponceau 4R (E124)) have attracted attention because of a claimed effect on children's behavior. The UKFSA commissioned the ‘Southampton study,’ which investigated the effect of mixtures of six synthetic food colors (one of which was Sunset Yellow FCF) and also contained a preservative (sodium benzoate) on the

behavior of children. However, it should be bear in mind this study was done in combination of sodium benzoate.

Artificial Sweeteners

Artificial sweetener is a food additive that duplicates the effect of sugar in taste, but usually has less food energy. In addition, to its obvious benefits of low food energy, animal studies have convincingly proven that artificial sweeteners cause weight gain, brain tumors, bladder cancer and many other health hazards. U.S. Food and Drug Administration has approved aspartame, acesulfame-k, neotame, cyclamate and alitame for use as per acceptable daily intake (ADI) value. But up to now, breakdown products of these sweeteners have controversial health and metabolic effects. Some of these controversial sweeteners are briefly discussed in here.

Aspartame

It is an artificial, non-saccharide sweetener, L-aspertyl-L phenylalanine methyl ester that is a methyl ester of the dipeptide of the amino acids aspartic acid and phenylalanine. Aspartame is a low calorie sweetener used to sweeten a variety of low and reduced calorie foods and beverages including low calorie tabletop sweetener as well as for use in gum, breakfast cereal and other dry products. Aspartame provides energy of 4 calories per gram. Aspartame is unstable if subjected to prolong heating and therefore cannot be used in baking or cooking. It also decomposes in liquids during storage.

After ingestion, aspartame breaks down into natural residual components, including aspartic acid, phenylalanine, methanol and further break down products including formaldehyde, formic acid and diketopiperazine. High level of the naturally occurring essential amino acid phenylalanine is a health hazard to those born with phenylketonuria (PKU) a rare inherited disease. Therefore, the phenylalanine level statement or aspartame is required sweeten products. While carcinogenicity studies of aspartame were conducted by Nalt Toxicological Programme (NTP) in 2 strains of transgenic mice, and it was concluded that aspartame exposure was associated with increase in cancer in either male or female mice (NTP 2005). Based on government research reviews, European Commissions Scientific Committee on Food and joint FAO/WHO expert committee on food additives, aspartame has been found to be safe for human consumption by more than ninety countries worldwide.

Acesulfame—k

This high intensity sweetener is potassium salt of 6-methyl-123-axathiazine-4(3H)-one 2,2-dioxide with molecular formula$C_4H_4KNO_4S$ and molecular weight of 201.24. It is a white crystalline powder, approximately 120 times sweeter than sucrose and has high water solubility. Acesulfame—k is heat stable, so can be used in cooking and baking.

Acesulfame—k is not metabolized in the human body, thus it provides no calories and does not influence potassium intake despite its potassium content. The breakdown product of ace-k is acetoacetamide known to be toxic if consumed in very large doses because human exposure to this breakdown product would be negligible. The USFDA concluded that no further testing of it was necessary.

Saccharin

It is a non-nutritive sweetener of 1,2-benzoisothiazol-3-(2H) on 1,1 dioxide. Saccharin has an unpleasant bitter or metallic off taste. As the parent compound is only sparingly soluble in water, the sweetener is usually used as the sodium or calcium salt. Both salts are highly water soluble, 0.67 gms/ml.of water at room temperature. It is about 300 times sweeter than sucrose.

The FDA tried to ban saccharin in 1977 because animal studies had showed that it caused cancer in rat (mainly bladder cancer). Many studies have since been performed on saccharin. However, no study has ever shown a clear causative relationship between saccharin consumption and health risks in human at normal doses. Though some studies have shown a correlation between consumption and cancer incidence. While, saccharin is currently permitted for use under an interim regulation that specifies the amounts of saccharin permitted in beverages, processed food, and sugar substitute and requires that the product level must state saccharin in the ingredient declaration and specify the amount use some countries unilaterally ban the use of saccharin as a sweetener.

Stevia rebaudiana

Stevia is a natural herb. This zero calorie sweetener mainly containing steviol glycoside which is 200 to 300 times sweeter than sucrose. Human body does not metabolize these sweet glycosides, so obtains no-calories from stevia. It is noted quite contrary to artificial sweetener, the glycoside does not completely break down in heat (unless the temperature goes above 200^oC)which makes stevia an excellent sweetener for cooking and baking. Some studies have indicated that stevia tends to lower the elevated blood pressure. It also significantly improves nutritional status of diabetic patients, but these studies are not comprehensively reviewed scientifically.

Conclusion

The food additives being used should present no risk to the health of the consumer at the levels of use. Therefore, the use of food additives is justified only when such use has an advantage, does not present a hazard to health of and does not deceive the consumer, as well as serves some of the required technological functions and needs, and only where these objectives cannot be achieved by other means which are economically and technologically practicable. The toxicity of food additives is generally low. The major food safety concern of food additives is in fact due to their chronic exposure at levels above the safety reference. However, many of the new and old food additives have to be reviewed and screened for cytotoxicity, genotoxicity, mutagenicity, and hepatotoxicity, long-term carcinogenicity tests, reproductive and developmental toxicology tests, hyperactivity, anxiety, and depression activity tests by various methods. Due to development of new methods, and arrival of new human studies the accuracy of all previous studies must be critically reviewed and shared openly with public.

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