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Paper Title: Food Additives
Module 35 Safety aspects and Allergenicity of food additives

1. Introduction

Food additives are special chemicals that are added into our food supply on purpose, and they are meant to be in the food at the time of consumption. Additives include preservatives for extending shelf life, flavoring and coloring for improving taste and appearance, and nutritional supplements such as vitamins and minerals. The contaminants from manufacturing, storing and packaging processes are also considered as indirect food additives. Food additives are generally intended to provide important benefits to the producer or consumer of foods. But sometimes these additives cause unwanted or unhealthful effects. Often these undesirable effects of food additives are due to their excessive or accidental use; usage at an inappropriate stage of production, processing, or storage; or from a lack of purity or quality. Extensive research has been conducted on many additives to show they are safe for consumption and are effective for their prescribed function. For other additives, widespread and long-term use by food processors has demonstrated safety and efficacy.

Whether a chemical is synthetic or ‘‘natural’’ has no bearing on its toxicity. Therefore, this area of food safety concerning naturally occurring contaminants needs to be explored further to determine if the risk from natural contaminants is really low. Naturally occurring seafood toxins and mushroom toxins are relatively common causes of acute food borne disease. The effects of human exposure to natural toxins are difficult to study because consumption of naturally occurring toxins is variable and often cannot be determined. Also, excessive natural toxin consumption generally results in long-term or chronic illness whose source can be difficult to trace.

Both international organizations and local governments generally evaluate the safety of food additives. The goal of local assessment is to take into account local food supply and cultural differences in dietary habits that may influence the intake of food additives.

Food additive intake assessment has three major goals:

1. Monitoring the intake of chemicals and relating it to the acceptable daily intake (ADI) values.
2. Identifying consumer groups that may be at risk for food additive intake close to or higher than the ADI values
3. Provide information for the regulatory bodies for reassessing the food additive regulations in case of high intake in all or some consumer groups.

2. Food Allergenicity

Many people have uncomfortable reactions to various foods, and this is often considered to be due to food additives and other artificial chemicals, such as pesticide residues, rather than to the food itself. This discomfort is usually called allergy by nonmedical persons, but there are also nurses and doctors who use the term *allergy* when they mean various kinds of untoward reactions to foods without knowing the mechanisms of such reactions. Strictly, an *allergy* is a harmful physiological reaction caused by an *immunologic mechanism*. If the mechanism is not an allergic one but the reaction resembles allergic reaction, the term *intolerance* is often used. The symptoms mimic those seen in allergic reactions, but the amount of agent producing the reaction is small enough not to cause a *toxic reaction*. When the mechanism is not known, it is better to talk about *hypersensitivity*, which can mean both allergic reaction and intolerance. There are several foods and food additives that can cause both immunologic and nonimmunologic reactions indistinguishable from each other.

For example, fish can act both as nonspecific histamine liberators and as true allergens. Tuna, mackerel, and certain cheeses contain histidine and tyrosine to such an extent that histamine and tyramine produced by decarboxylation from them can cause allergic-type symptoms in atopic people (Royal College of Physicians and the British Nutrition Foundation, 1984). Among food additives, cinnamon and nitrogen mustard are the most well-known causes of both allergic and non-allergic reactions.

Table 1 Terminology of Hypersensitivity Reactions

Terminology	Description
Hypersensitivity	A small amount of a substance produces symptoms that can be objectively verified and repeated.
Allergy	Immunologic mechanisms are involved in the pathogenesis of symptoms.
Atopic allergy	The reaction is mediated by immunoglobulin E.
Intolerance	A small amount of a substance produces a reaction similar to or closely resembling a true allergic reaction, but immunologic mechanisms are not involved.

2.1. Intolerance and Other Nonallergic Reactions

- Nonspecific histamine liberation—Cocoa, citrus fruits, strawberry, etc.
- Intestinal diseases—Gluten intolerance produces abdominal and skin symptoms.
- Primary or acquired enzyme deficiency—Diarrhea and colic in lactase deficiency.
- Microbes and their toxins—Bacteria, viruses, yeasts, molds, and fungi cause a diversity of
- gastrointestinal symptoms.
- Psychological causes may underlie various kinds of skin, gastrointestinal, and other reactions.

3. Excessive Food Additive Intakes and Population Risk Groups

Currently there is a public debate concerning food additive usage, including food safety, the health risks associated with food additives, and the wholesomeness of food. The food industries assessments suggest that the food currently available is safe if placed in a historical context. The scientific debate regarding additive-associated risks is concerned with the difficulties of epidemiological studies performed in this area, comparisons of the toxicities of processed and unprocessed foods, appraisals of the resource priorities for scientific investigations, and critical evaluations of the methods of analysis. Despite the factors employed to ensure a minimum human sensitivity to the additives in food, particular sections of the population are susceptible to additive associated clinical disorders or toxic responses, some of which are usually thought to have an allergic origin. Excessive intakes have often been suggested for infants and children. The applicability of safety studies has been specifically assessed for infants and children and the different dietary patterns in relation to age and the consequences for intake of food chemical reported.

However, it is likely that the exposure to food additives and the individual's susceptibility expressed as an undesirable response are not separate phenomena, and that the latter could be mediated by

allergic reactions. The following considerations should be taken into account when estimating the potential or maximum additive intakes or identifying population subgroups exposed to unacceptable risk:

1. When a food additive is known to be present in a food but cannot be detected in analysis, the maximum additive concentration is assumed to be equal to the lower limit of detection. This method enables estimation of the potential average intake.
2. Intake estimation can also be achieved by multiplying the highest additive concentration determined by analysis with the amount of the food item or food group under consideration. This value may underestimate the additive intake because consumption of food varies. When the two extreme figures—maximum food additive concentration and maximum food consumption—are combined to give an estimate of intake, the calculated value is probably an overestimate.
3. In order to increase the accuracy of estimating the maximum intake value it is necessary to combine the additive concentration of analyzed meals with the true food consumption. Thus, once the population subgroup at risk of excessive food additive intakes is identified, the maximum intakes can be accurately estimated by conducting a duplicate meal study.

Because young men have the greatest demand for food, it may by thought that they also have the highest food additive intakes. However, a comparison of food consumption on a weight-to-body-weight basis indicates that children have the greatest intake of food. Moreover, children consume large quantities of certain food items such as sweets and soft drinks that contain high concentrations of additives. Generally, when food items are identified as being consumed in large quantities by children, the respective additive regulations should be adjusted to permit lower maximum additive levels than those allowed in other foods.

On rare occasions some individuals can experience adverse reactions to food additives. A small percentage of asthmatics can react to sulfites, substances used to prevent certain foods from browning. Also, a very small number of individuals, one or two of every ten thousand, are sensitive to FD&C Yellow No. 5, used as a food coloring, causing itching and hives.

Monosodium glutamate (MSG), commonly found in Chinese foods, can also cause adverse reactions in small groups of people. The symptoms, usually mild, include body tingling or warmth, and chest pain. These symptoms are usually mild and often last less than an hour.

Lastly, people with a rare genetic disease known as phenylketouria (PKU) should avoid foods sweetened with aspartame. Aspartame is made from two amino acids, one being phenylalanine. Individuals with PKU cannot metabolize this amino acid, and if consumed can cause serious side effects including tissue damage.

The best advice to any individual that has adverse reactions to any food additives is to read labels carefully and avoid these products whenever possible. If an adverse reaction does occur, be sure to contact your physician immediately.

4. REGULATION OF FOOD ADDITIVE USAGE

4.1. Safety of Food Additives

Food additives approved by the FDA are considered to be safe for human consumption, and many processed food manufacturers claim that there is no solid evidence to show direct association between food additives and human health. However, the U.S. government has claimed that safety aspects of food additives are not fully known.

“any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food…. Such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures … to be safe under the conditions of its intended use….” Thus with uncertainty about the safety of the consumption, the safety of the food additives and preservatives should be carefully examined once more before eating them.

In addition to the previously mentioned health problems of consuming modern synthetic preservatives, other food and color additives have been linked with allergic reactions, cancer, asthma, and birth defects. For example, sulfites used to prevent discoloration are shown to cause allergic reactions, according to the FDA. Once a person develops sulfite allergies, it can potentially lead to fatal respiratory distress.

BHA and BHT is most frequently used food additive in processed foods e.g. in processed cereals. These chemicals are usually added to prevent oxidation of fats and oils in food. Oxygen tends to react with BHA and BHT before oxidizing fats, which in turn keeps the food from going rancid. Although the United States Food and Drug Administration (FDA) have approved BHA and BHT along with about 3,000 food additives for consumption, they have been shown to cause a number of health problems. Some studies claim that synthetic preservatives worsen Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) symptoms in those affected. Other studies also show that certain persons may have more difficulty with digesting and metabolizing the compounds of BHA and BHT, which results in behavioral changes and other health problems.

Additionally, most fruit juices that are often marketed to parents of young children contain additives, including preservatives, artificial sweeteners and colorings. A study reports that preservatives such as sodium benzoates may cause increased hyperactivity in 3-year-old and 8/9-year-old children. The increase of the hyperactivity was about 50% greater for those children who regularly drank fruit juices with additives than those who drank juice without additives.

Concern about the possible effects of food additives on health, including cancer, is one reason that many people are now interested in organic foods. Organic foods are often promoted as an alternative to foods grown with conventional methods that use chemical pesticides and herbicides, hormones, or antibiotics. These compounds cannot be used for foods labeled as "organic." Organic foods, as defined by the US Department of Agriculture (USDA), also exclude genetically modified foods or foods that have been irradiated.

4.2. Food Safety Regulations

Today, food and color additives are more strictly studied, regulated and monitored more than any other time in history. The FDA sets safety standards, determining whether a substance is safe for its intended use. Rigorous testing is done to determine the amount of safe levels of different food additives. Additionally, food manufacturers must prove to the FDA their product is safe before it is put on the market.

The majority of direct food ingredients are used on the basis of a determination that they are GRAS or prior sanctioned. Review of some items on the GRAS list has indicated that the majority present no significant hazard with normal use, although only a small percentage have been thoroughly evaluated. The other direct food additives used in foods have been approved, and their uses are regulated by the FDA.

Food safety in India is ensured by Government of India’s Ministry of Health under the provisions of Prevention of Food Adulteration Act & Rules previously, which at present is under Food Safety

Standards Act. They are responsible for Food Laws and the rules therein. State government, Food & Drug Administration (FDA), which carries out surveillance using food inspectors, does the enforcement. There are food analysis laboratories, both state and central, which verify the authenticity of food products. Any food safety legislation or standard, requires involvement of several aspects including Research & Development, Information & Documentation, Education & Training, Quality Assurance Program, Codex & International Norms, Advisory System, Planning, Enforcement and Surveillance. Various activities take place at different places such as education & research institutions, government laboratories, data bases including international & national, industry production and quality evaluation centers, and finally state level enforcement and surveillance departments. Due to the complex nature, any change in standards and enforcement has to be properly planned and executed after careful consideration of all these factors.

There are different sets of regulations everywhere. Each country has its own set of rules for regulating food additives for example, US FDA Guidelines & Regulations gives the American regulations for food additives. Thus anyone producing and marketing food products in the US must abide by them. India has its own set of regulations under Food Safety Standards Act. Each country has a set of regulations. When an Indian company wants to export to US, then it will have to follow the US regulations. When it wants to export to Australia their rules have to be followed. So there might be difficulties trying to follow many sets of regulations.

A group of countries may have a common regulation for example, European Union Directives, which give regulations for countries affiliated to it. This allows free exchange of food products across those EU countries. It avoids confusion because of many different regulations being followed for different countries. For international trade we have Codex, SPS, TBT regulations. Under the WTO agreements, common regulations have been arrived at for those countries signatories to the agreement and this allows the international trade without much problems. FAO/WHO has come up with Codex rules, which are accepted by these countries.

4.3. Food Additives: Approval Process

Any new additive before approving must undergo rigorous toxicity studies, including acute and chronic studies involving biochemical evaluation, teratogenic studies, reproductive studies besides the LD50 tests. In the US, Delaney Clause governs the approval of any food additive, under which the additive is banned if found to be carcinogenic, under any condition or level, a very difficult zero risk condition.

However, exposure assessment is very important in determining the risk involving any additive under the modern practice of determining safety. The Risk Analysis, adopted nowadays involves, risk assessment, wherein the Hazard is identified & characterized, Exposure is assessed and thus risk is characterized. Once the Risk is assessed, it must then be managed so hazardous conditions do not arise. Finally the risk must then be communicated.

4.3.1. General Principles of Food Safety Risk Management

1: Risk management should follow a structured approach.

2: Protection of human health should be the primary consideration in risk management decisions.

3: Risk management decisions and practices should be transparent.

4: Determination of risk assessment policy should be included as a specific component of risk management.

5: Risk management should ensure the scientific integrity of the risk assessment process by maintaining the functional separation on risk management and risk assessment.

6: Risk management decisions should include clear, interactive communication with customers and other interested parties in all aspects of the process.

7: Risk management should be a continuing process that takes into account all newly generated data in the evaluation and review of risk management decisions.

4.4. Regulatory Authority

Numerous research studies have confirmed that appropriate use of many additives is safe for human health and provides a benefit to the processor, preparer, or consumer. Other additives are considered safe and efficacious due to successful widespread use over many years. Multiple federal agencies, laws, and regulations work together to ensure the safety and efficacy of thousands of food additives, but there are great differences in how many of these additives are regulated. The Food, Drug and Cosmetic Act of 1938 gives the U.S. Food and Drug Administration authority to regulate foods, ingredients, and their labeling.

The 1958 Food Additives Amendment to the FD&C Act requires FDA approval for the use of new additives prior to its inclusion in food. Also this Amendment requires the additive manufacturer to prove an additive's safety for its recommended use. Food additives are defined as substances which may, by their intended uses, become components of food, either directly or indirectly, or which may otherwise affect the characteristics of the food. The term specifically includes any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding the food, and any source of radiation intended for any such use (FDA, 1998a). This definition does not include some classes of additives such as pesticide chemicals for raw agricultural products, new animal drugs, certified colors, or colors exempt from certification. These additives are similarly regulated, but under other laws or acts. Additionally, food additives that have a history of safe usage are exempted from the regulation process described in the Food Additives Amendment. One group of these additives is known as ''generally recognized as safe'' (e.g., salt, vitamins). They have been generally recognized, by experts, as safe based on their extensive history of use in foods before 1958, or based on published scientific evidence. Another group of exempted additives is designated as prior sanctioned additives. These are substances that the FDA or U.S. Department of Agriculture (USDA) had determined were safe for use in specific foods prior to 1958 (e.g., sodium nitrite to preserve meat). Other important federal regulation of food and color additives is described in the 1960 Color Additive Amendment to the FD&C Act, the 1990 Nutrition Labeling and Education Act, and the 1996 Food Quality Protection Act. Current good manufacturing practice (CGMP) regulations can limit the quantity of food and color additives used in production. Manufacturers may only use the amount of an additive necessary to achieve a desired effect.

In the case of pesticides for foods and animal feeds, the U.S. Environmental Protection Agency and the FDA have regulatory responsibilities for the approval and monitoring of pesticide use. Three major legislative acts describe the authority of the EPA and FDA to regulate pesticide chemicals (EPA, 1998). The Federal Insecticide, Fungicide and Ro- denticide Act prescribes that the EPA is responsible for registering or licensing pesticide products for use in the United States. The Federal Food, Drug and Cosmetic Act govern the maximum level of pesticide residues allowed in or on specific human foods and animal feeds. In 1996, the Food Quality Protection Act (FQPA) amended these two acts in several respects. For example, to assess the risks of pesticide residues in foods or feeds, the FQPA requires that the combined exposure from dietary and other nonoccupational

sources be considered. Also, when setting new or adjusted tolerances for pesticides, the EPA must consider any special risks to infants and children.

4.5. Monitoring

Federal regulations are in place to determine if an additive is safe and effective under its prescribed uses. Also, regulations may stipulate the permitted food uses or usage levels for hundreds of additives. Nevertheless, the usage and labeling of food additives may be monitored through analytical testing and label review of finished products or ingredients. Improved chemical analytical methodology has resulted in faster extraction and identification of additives from foods. Many testing protocols can now detect chemical concentrations of very low levels (e.g., parts per billion) and with increasing discrimination.

4.6. Labeling

The risks or benefits of food additives and ingredients must be clearly displayed for consumers. The FD&C Act requires, in virtually all cases, a complete listing of all the ingredients of a food. The Nutrition Labeling and Education Act, which amended the FD&C Act, requires most foods to bear nutrition labeling and requires food labels that bear nutrient content claims and certain health messages to comply with specific requirements. Two of the exemptions from ingredient labeling requirements have resulted in special product labeling efforts to protect the health of consumers. First, the act provides that spices, flavorings, and colorings may be declared collectively without naming each one. One exception is the artificial color additive FD&C Yellow No.5. This chemical must be specifically identified in the ingredients statement of finished foods because a small percentage of the population may be allergic or sensitive to the additive. Second, FDA regulations exempt from ingredient declaration incidental additives, such as processing aids, that are present in a food at insignificant levels and that do not have a technical or functional effect in the finished food. One important example of an incidental additive is peanuts. An increasing number of products are identified that they ‘‘may contain peanuts.’’ While peanuts or peanut-derived ingredients were not intentionally added to these products, residues from peanut use in processing on nearby equipment or previous production runs may have contaminated these products with peanut residues. Since peanuts are one of the leading causes of allergenic responses to foods, many companies have chosen to label some products with ‘‘may contain peanuts.’’ Some processors have elected to process products with peanuts in separate locations from their product lines that are not to contain peanuts.

Some foods may be identified or labeled to contain additives that can improve public or individual health. Many ready-to-eat breakfast cereal products are fortified with several vitamins and minerals. A quantity of these substances is added to the cereal so that a consumer may expect to consume 25 to 100% of the recommended daily intake of that nutrient from a defined size serving. Additives that can improve human health are sometimes advertised elsewhere on finished product packaging besides the ingredients list and nutritional label. Advertising claims that imply better health through consumption of a food product additive are permitted for specific additives, ingredients, or inherent compounds. As one example, regular consumption of folic acid can be advertised as beneficial for preventing neural tube defects in newborn babies.

Allergic people who are highly sensitive to soy, rape, egg or sunflower seeds might react to lecithin. The origin of lecithins derived from the most common allergenic foods (as defined in local legislation) must be declared on food labels. Hypersensitivity to sulphites is relatively well described, especially in people with asthma, and they may also trigger skin reactions such as hives (urticaria). When used at levels of or above 10mg per kg, sulphites have to be labelled on pre-packed foods within the EC.

5. Conclusion

Only seldom have food additives been shown to cause true allergic (immunologic) reactions. Adverse effects due to various pharmacological or other mechanisms are much more common. The individual tolerance may be decreased for one reason or another, and it may fluctuate from time to time. There is no simple and all-embracing diagnostic method to study adverse reactions to ingested additives. Better knowledge of the mechanisms underlying these reactions is the only basis for more dependable tests.

The function of preservatives often falls into three different categories: prevention of bacterial or fungal growth, prevention of oxidation, and prevention of natural ripening of fruits and vegetables. According to the FDA, consumption of food that is manufactured with preservatives is almost inevitable. Recently, food irradiation has become more common in order to preserve meat and dairy products. In the process, due to potential microbes existing in the food, food is exposed to high-energy radiation to kill microorganisms, bacteria, viruses, and insects. However, the labeling for irradiation is not required. Similarly, many of these modern synthetic preservatives are often labeled as ingredients for “freshness” while their true meanings and dangers are concealed from consumers.

The present-day perception that major risks may be associated with the food supply seems to be the result of several factors. First, current analytical capabilities allow the detection of mere traces of potentially hazardous substances in foods. Even a few decades ago such levels of detection were not possible. Second, the food laws in the United States focus considerable attention on food additives at the expense of naturally occurring chemicals in foods (although naturally occurring substances can be food additives in some instances). While food additives should be thoroughly tested for safety, the lack of testing of naturally occurring chemicals has resulted in a loss of perspective on the comparative hazards associated with food additives.