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Toxicology of Processed and Packaged Foods

A.N. Srivatsa and T.R. Sharma
Defence Food Research Laboratory, Mysore-570 010

ABSTRACT

Modern food production, processing and preservation use a large number of additives at various stages. These include food sweetners, preservatives, colours, antioxidants and pesticides. In addition, the foods come in contact with packaging materials which by themselves contain a large number of additives. Some of these are potential sources of hazards to consumers. This paper is a review of investigations which have been carried out on some of the additives, the migration of additives from packing systems and naturally occurring toxic substances as possible health hazards.

1. INTRODUCTION

The aim of science and technology is the improvement of quality of life of the common man. Towards this goal, great strides have been made in providing adequate and nutritious food to man. This has been possible mainly due to the advances in the fields of manufacture, processing and preservation of foods. Large scale use of several preservatives and other additives has contributed in this endeavour.

Despite their enormous benefits, some of these food additives, chemical preservatives and additives of packaging materials are without absolute guarantee of safety for the consumers.

Thus, the human diet in addition to major macro-nutrients (namely, proteins, fats and carbohydrates) and micro-nutrients (namely, vitamins and trace elements) may also contain some of the anutrient compounds which do not undergo any energy yielding metabolism. These anutrients find their way into the food as (i) naturally occurring toxins, nitrosamines, polycyclic hydrocarbons, (ii) deliberately added additives at various stages like antioxidants, flavours, colours, (iii) products of processing like heterocyclic pyrolysis and (iv) from the packaging systems as migrants.

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Since the safety of the consumer is of primary importance and concern, these compounds are subjected to exhaustive toxicological investigations for their short-term and long-term risks. The hazards of consumption of anutrient compounds which are added for various purposes or are naturally present, include allergies, carcinogenicity and mutagenecity in addition to causing other diseases.

The elaborate procedures and available information have eventually contributed towards the establishment of safety precautions and legislative action.

However, establishing toxicity itself is a difficult task since foods are complex heterogenous systems of low moleculer weight compounds, protein-lipid complexes and fragmented cells of animals and plants. The more important difficulties in evaluating the toxicity are (i) interference of food components with the end-point for detection, (ii) administering the food components to the testing systems particularly *in vitro* assay systems, (iii) identification of a suitable food as a control, and (iv) difficulty in administering large doses of food to experimental animals without nutritional imbalance.

These difficulties hinder accurate prediction of the toxicity of any particular component. Hence, the usual method is to utilise the quantitative data from mammalian *in vivo* systems and qualitative information from *in vitro* test systems.

It is also important to note that there is an inter-relationship between nutrition and observed toxicological parameters, in the nature and incidence of various hazards.[1,2] Inspite of the above constraints, abundant data has been collected with respect to various components and levels of safety have been established with respect to additives.

2. NATURAL CONTAMINANTS

Natural fungal and microbiological contamination of foods are common and some have attracted wide attention.[3]

Aflatoxins have been subjected to extensive studies since no other mycotoxin has comparable carcinogenicity.[4] Of the several species, ducklings are the most susceptible to Aflatoxin B1, the extensively investigated and the most potent toxin. Human liver cells become susceptible[5] at 10 μg of B/ml. In case of aflatoxins, toxic hazard is characterised by periportal necrosis and bile duct proliferations.[6] The exact mechanism of action of aflatoxins is yet to be conclusively established. It inhibits DNA and RNA and protein synthesis in endoplasmic reticulum and yet there is no co-ordinated concept of the sequence of events.[5]

(i) Ochratoxin A – This toxin has been investigated as a hepatoxin from *A ochracecus* and *P viridicum*.[7,8] Although found in moulds on cereals and vegetables, there is no proof of human susceptibility.

(ii) Rubra toxin – P rubum is widely found and is experimentally established to produce toxin, causing lesion of liver, kidney and nervous systems.[9]

3. POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons (PAHs) are an important group of carcinogens and are widely distributed in several foods. PAHs result from products of incomplete combustion of organic materials which can interact to combine into complex structures. From atmosphere, they enter the food systems through air, soil and water. They are also found in fresh and decaying vegetables and meat. Nearly 122 different PAHs have been identified.[10] A principal source of PAHs is factory smoke and hence vegetables grown in and around industrial areas contain more PAHs.[11] Thus, large scale industrialisation and other factors contaminate a number of sources.

Another important source of PAHs is the grilling or broiling of meats particularly when the meat pieces are directly exposed to open flame.[12] When the fat is allowed to drip on the flame, considerable quantities of PAHs are formed.

Smoking is a traditional method of preservation of meat of various types. The use of charcoal or firewood produces PAHs on food. A possible way of minimising this while smoking is to pass the smoke through water, so that the PAHs could be sedimented.[13]

Of the several PAHs, the most potent carcinogen is identified as 3,4-benzopyrene. Most of the animal studies on benzopyrene have been to assess its effects when in contact with skin and lungs and little information is available on the hazards of oral ingestion.

From limited data, it is possible that high levels of ingestion by man can produce tumours of oesophagus, stomach, intestine and other organs.[14] Again, there is paucity of information regarding the interaction of benzopyrene with other carcinogens such as nitrosamines.

4. DIRECT AND INDIRECT ADDITIVES

4.1 Pesticides

Use of pesticides is one of the contributory factors in increasing the food grain production. The large scale use of pesticides has also resulted in distribution of these chemicals, their decomposition products and metabolites in body tissues.

The safety of pesticides have to be viewed with respect to (i) delayed neurotoxicity, (ii) hepato carcinogenicity, (iii) toxic effects of pesticide impurities, (iv) effect of pesticide mixtures, (v) effect of diastereoisomeric mixtures and (vi) interaction of pesticide components before and during cooking.[15-17]

During cooking, pesticide residues can interact with components of food to give complex products which can be toxic, as in the case of chlorinated pesticides where it is probable that the transchlorination may take place forming polychlorinated polycyclic hydrocarbons which are considered toxic and mutagenic.[18] In prepared foods, the amount of organochlorine residues is generally very low.[19]

4.2 Direct Additives

Food processing industry, uses a number of food additives to improve colour, flavour, preservation and physico-chemical performance. In order to clear the anxiety concerning hazards, to preclude unsafe materials from diet and to formulate specific legislative requirements, food additives have been subjected to intensive toxicological evaluation. A few important additives are given below.

4.2.1 Sweetening Agents

Sugar is a good source of energy in human food and an essential nutrient. But it has been implicated as a major cause of dental decay, diabetes and ischaemic heart diseases. In recent times, there is also a growing demand for non-calorific sweetners for reducing/maintaining body weight for clinical and other reasons. This can be met with synthetic, non-calorific sweetening agents. There is a growing necessity for sweetening agents in soft drink industry. Sweetening agents are some of the most investigated additives of food processing.

(i) Saccharin – The oldest of the sweetening agents, saccharin, was introduced by Ramsen and Fahlberg in 1879. Saccharin found a ready application in soft drink and processing units, since it had an economic advantage inspite of the disadvantage of a bitter after taste.[20] Saccharin has been subjected to sereral investigations independently and in combination with cyclamates.[21,22] It has been found in experimental animals that saccharin in the proportion, widely used can promote bladder tumour[23] if used in conjunction with cyclamates.

By itself in very high doses, it is reported to be carcinogenic.[24,25] This has promoted a cautious approach in several countries on the use of saccharins such as the compulsory notification of saccharin warning in U.S.A.

(ii) Cyclamate – Cyclamate is far less sweet than the saccharin but it does not leave a bitter after taste. Due to its lower sweetness it is required in large quantities. Long term studies on the effects of cyclamates have provided inconclusive results.[26] Inspite of several studies and surveys carried out on cyclamates and saccharin, it is difficult to state in unequivocal terms the safety or otherwise to humans. Further work is necessary to provide positive and conclusive answers. There are other sweetners like aspartame and acesulfame K. These are reported to be of very low toxicity and are permitted for limited use.[27]

4.3 Nitrates and Nitrites

Nitrates and nitrites are principally used for curing and preserving various meat products and canned meats. They are also permitted in cheese.[28,29] The permitted levels vary between 100 to 500 ppm is case of nitrates and 10 to 200 ppm in case of nitrites. The active component nitrite prevents the growth of *Cl botulinum* and also imparts a red colour to cured meat, by reaction of nitrus oxide and myoglobin and also with haemoglobin. It also gives a specific cured flavour in case of ham and bacon. Since both fish and meat slowly liberate free amines, nitrites react with secondary and tertiary amines, yielding nitrosomines, which can possibly induce tumours.[30] Exhaustive investigations have revealed that only four volatile nitrosamines namely dimethylnitrosamine (DMN), diethynitrosamine (DEN), nitrosopiperidine and nitrosopyrrolidine are present in the food and DMN is generally the commonest nitrosamine.[31] It is also reported that the rate of reaction is catalysed by several compounds such as chlorides, thiocyanates, aldehydes and vitamin B_6 and inhibited by ascorbic acid, bisulphite and a number of thiol compounds.[32,33] Approximately 25 per cent of ingested nitrate is excreted through saliva and this is reduced to nitrite by oral bacteria.[34,35] High incidence of tumour is found in laboratory animals even in very low doses of ingestion of nitrosamines.[36] The important outcome of several studies is the toxicological effects of nitrates and nitrites, due to the formation of nitrosamines in stomach under the acidic conditions.[37]

As a result of several observations, it has been inferred that nitrosamines are formed in several ways and has been confirmed by *in vitro* and *in vivo* studies. Hence, nitrosamines pose a real carcinogenic hazard to humans. Though nitrates can be ingested through vegetables and water,[38] the high risk groups are those who consume large quantities of processed protein foods, preserved by addition of nitrates and those having high levels of thiocyanate in saliva. In practice, the danger is generally minimised since the man ingests nitrates and or nitrites in amounts much lower than those levels studied in experimental animals at present.

4.4 Antioxidants

Several antioxidants are regularly used as food additives in various processed foods to prevent changes in flavour, quality and nutritive value, resulting from the oxidation of edible fats.

Of these, butylated hydroxy anisole (BHA) and butylated hydroxy tolune (BHT) are extensively used and were generally regarded as safe but later investigations have revealed contradicting results.[39-41] These studies have increased the responsibility in the matter of selection of antioxidants, since these are very important and indispensable ingredients in many food processing operations.

4.5 Monosodium glutamate

Monosodium glutamate (MSG) is a popular chemical added to enhance flavour. This additive attracted attention after the so called Chinese Restaurant Syndrome in which the affected patients showed neurological and behavioural changes. As a result of several subsequent studies, it has now been accepted that new born infants are more susceptible than older adults.[42]

4.6 Sulphiting agents

Sulphiting agents are widely used as preservatives either as sulphites or metabisulphites, especially in beverages and to prevent browning in other products. Used at different permitted levels depending upon the product, sulphite is a reactive and irritant chemical and has been critically reviewed for the toxic effects.[43,44] Presently it can be concluded that it does not pose toxic effects to majority of human beings[45] except in case of asthmatics, in whom, it may be a source of irritancy.

4.7 Food Colours

Food colours have long and historical association with food processing. No other group of compounds have been more exhaustively investigated than the colours, probably because of their supposed association with coal tar.[46]

It was presumed that the sulphated triphenyl methane, xanthine and azo compounds would be potentially carcinogenic because they were close to the polycyclic aromatic compounds of the types found in coal tar. Subcutaneous sarcoma was also considered to be the true index of carcinogenicity by oral administration.[47] Subsequently this method was abondoned since a hypertonic solution of glucose, common salt and surface active solution also produced local sarcomes.[48]

The colours that are used in various processed foods and beverages are yellow, orange, red and brown which are based on azo compounds, black colours based on bis azo compounds with two azo compounds. In addition to these, a large number of colours Amaranth, Blue FCF, Sunset Yellow and Green are being used to give different shades. Often the food colours are mixtures of more than one component.

The food colours have been exhaustively investigated. Poncean 3R and Poncean MX produced hepatic tumours when orally administered and were immediately banned in U.K. and U.S.A.[49]

A large number of studies have been able to confirm that several colours such as Brown FK, Red 10B, Red 2G, Red G, Lissamine Fast Yellow 2G, Orange G, Poncean 4R and DN generally undergo reduction by gasto intestinal microflora.[50,51] This can cause mild non-significant effects at very high levels and do not present a very serious hazard at the levels consumed.[52]

Amaranth C (Red dye) is a widely used colouring material which has attracted maximum attraction, due to its reported teratogenecity.[53] But several subsequent studies carried out by Food and Drug Authority and British Industries Biological Research Association revealed contradictory conclusion.[54] However, the use of Amaranth is being critically evaluated in several countries.

The food colours permitted for use in India (at max. levels of 0.2 g/kg of food) are as follows.

Colour	*Name*	*Chemical class*
Red	Poncean 4 R	Azo
	Carmoisine	"
	Fast red E	
	Amaranth	
	Erthyrosine	Xanthene
Yellow	Tartrazine	Pyrazolene
	Sunset yellow FCF	Azo
Blue	Indigo carmine	Indigoid
	Brilliant blue FCF	Triaryl methane
Green	Green S	Triaryl methane
	Fast green FCF	Triaryl methane

5. PACKAGING MATERIALS

During the last three decades, plastic packaging is sweeping the food packing field and flexible packing systems are being developed and used for every conceivable food replacing older metal cans. Though the primary functional requirement of adequate packing is to protect the food from hazards of insects, microbes, oxidation gas/vapour contamination and moisture, it is essential that the packaging itself be free from any possible contaminants to the foods.

Unlike in the case of direct additives to foods, there is lack of information regarding the quantum of additives, in case of packaging materials; the migration from packaging system into the food poses very difficult and complex problems. Since the type and nature of migration varies with the particular basic packaging design, geometry of the pack, type of food, the conditions and period of storage and the total quantity added to the packaging materials, it is difficult to establish the accurate toxicity standards. The packaging systems can be broadly classified into four groups based on possible extractables/migrations into food :

(i)	Glass	:	Extraction or solution of alkalies, silicates and salts.
(ii)	Paper	:	Abrasion of the whole paper by dry solids, extraction of wax, coatings.
(iii)	Metals	:	Chemical reaction leading to dissolving of metals, specially tin or lead and residual migration of tin coatings.
(iv)	Plastics	:	Migration of monomers, low molecular weight, oligomers, catalysts, antioxidants, various additives like plasticisers, colourants, antistatic agents, UV absorbers etc. and their decomposition products.

Much of the work relates to the plastics, since plastics have been playing a very significant role in food packaging and to contaminants like lead and tin in metal cans.

5.1 Metals

Lead forms a principal source of contaminant from solders of cans and from water containing high amounts of lead.

Lead has no significant beneficial nutritional role and generally leads to anaemia resulting from induced defects in haeme formation, renal damage and mental disturbances.[55] Lead in diet is clearly a hazard to health.

In several countries, there is a drastic reduction in the permissible limit of lead.[56] The canning industry has initiated stops to reduce lead soldering.

Fresh fruits and vegetables contribute very significant amounts for contamination by tin. However, canned vegetables, fruit juices and meat products substantially increase the tin content in diet, due to defective lacquering of cans, corrosion and other factors as tin is an important component of the can material.

Tin at 5 ppm level reduced longevity of female rats and increased incidence of fatty degeneration of the liver and of vacoule changes in renal tubules of both male and female rats.[57] Though tin has relatively low order of toxicity, long term effect on human beings is yet to be fully worked out and as such does not pose any major health hazard.

Use of aluminium for food packaging in the form foils, cups, caps and cans is widespread. Aluminium is naturally present in fruits and vegetables.[58] Large intakes of aluminium were shown to induce gastro-intestinal absorption[59] and can become toxic.

5.2 Polymers

Considerable data have been generated with respect to flexible packaging material based on high polymers. No other packaging attracted as much attention and underwent as many safety evaluations as the polymeric packaging materials.[60] Criticisms and investigations of polymer packaging have been growing at a galloping rate all over the world, leading to several legislative measures, since food packaging is more than a simple covering of the product. It includes especially in flexible packaging systems, a primary material directly in contact with food, followed by a secondary, tertiary and quaternary packaging which function in totality to protect against static and dynamic stress to permit economic and efficient handling and to preserve the food in the best possible state.

Polyvinyl chloride, used for packing in various forms of rigid, semi-rigid and flexible systems, is perhaps the most critically evaluated polymer, due to the reported carcinogenicity of the residual unpolymerised vinyl chloride monomer in the finished product. Due to technological necessity and to meet specific end uses, the finished PVC contains a very high proportion of plasticisers and other additives. This has resulted in detection of significant amounts of migrants in model food systems, leading to initial banning of PVC in some countries. Consequently, specific manufacturing processes were developed to reduce the vinyl chloride monomer level to less than 1 ppm, resulting in the reconsideration of legislative measure and fixing safe limits in the basic polymer as well as in finished packing.

Amongst the various plasticisers used, diesters of phthalic acid have been exhaustively investigated.[61] The acute toxicity of phthalate esters is low but chronic administration has caused liver enlargement, changes in hepatic enzyme activity and testicular atrophy in experimental animals.[62]

Extensive studies have also been carried out with respect to packaging materials in contact with food such as polyolefins, polyesters, polyamides and adhesives which are used for laminating purposes.[63]

In view of the difficulty in quantifying the individual migration of each additive component in food from packaging material, regulating agencies, on the basis of available data have adopted the system of fixing the maximum limit of total migration of additives in model food systems. It generally does not exceed 60 mg/kg of food for polymers in most of the countries including India.

High molecular weight polymers are the backbone of flexible packaging industry. Monomers are physiologically inert but caution has to be exercised with respect to selection of additives such as plasticisers, catalysts, antioxidants, colourants and adhesives.

6. CONCLUSION

Food Toxicology has made great strides in endeavouring to protect the safety of the consumer. The voluminous data and extensive long-term and short-term investigations of the processing and packaging aids in food technology have posed a very serious question; are unprocessed foods safer than processed foods?

For this purpose the status of the natural/unprocessed foods has to be clearly assessed, as natural foods do not ensure any degree of absolute safety. There are several toxicants and contaminants of plant and animal origin present in the food, which can render the food unsafe, unless these are properly eliminated. The preparation and cooking methods, themselves, can pose hazards, as in the case of charcoal broiling of meat and formation pyrolysates of amino acids.

Food toxicology hence becomes important due to the new advances in food processing and availability of new additives and packaging materials as the decisions have to be made at human levels, considering the interaction of potentially hazardous chemicals and other dietary factors.

It will be more appropriate and may be faster if methods can be evolved to predict toxicity on the basis of chemical and molecular configuration, which determine such activity.

Further, clear cut knowledge of mechanisms of the rates of absorption excretion and tissue distribution of the various anutrients can greatly enhance the knowledge involved in predicting the hazards.

Finally, the extrapolation of animal studies can be more useful if followed by studies in human tissues in culture or in long-term storage.

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