



GENOTOXICITY OF HEAT INDUCED CONTAMINANTS IN FOOD

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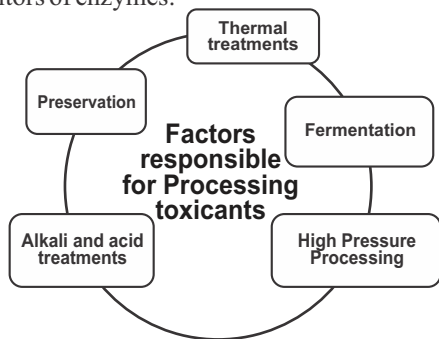
Abstract

Food contains various types of mutagens and carcinogens and consist both initiators and promoters of carcinogenesis. Some mutagens are formed during the thermal processing such as polyaromatic hydrocarbon (PAH), acrylamide, heterocyclic aromatic amine (HCA), acrolein, trans fatty acid (TFA), furan, 5-hydroxymethylfurfural (HMF) and chloropropanols etc. These heats induced contaminants are considered to exert adverse toxicological effect on human. Most of the contaminants have been recognized as environmental pollutants. The carcinogenic and genotoxic potential of heat induced contaminants have been evaluated regularly by International Agency for Research on Cancer (IARC), which has come to conclusion that many heat induced toxicant present in cooked foods are possibly (2A) or probably (2B) carcinogenic to human on the basis of both high dose, long term animal studies and in vitro & in vivo genotoxicity test. Yet, there is insufficient scientific evidence that these genotoxic compounds really cause human cancer, and no MRL (maximum residue limit) has been set for their presence in cooked foods. However, the competent authorities in most western countries recommend minimizing their occurrence. The review focuses on generation of heat induced toxicants and its health effect on human bodies.

Key words: IARC, Genotoxic, Toxicants and Carcinogen.

Introduction

The factor responsible for the food processing including thermal treatments (frying, toasting, roasting, evaporation, burning, sterilization and pasteurization), preservation (irradiation, pickling, freezing), fermentation, acid and alkali treatments and high-pressure processing greatly expanded food supply capacity in modern times. Commercial food production in the United States is subject to FDA oversight and must meet strict cleanliness and safety standards. Sometimes specific food processing methods are considered in the category of food additives, as they may intentionally alter the nature of the food. Home cooking is one important method of food processing. Cooking enhances the palatability (e.g., flavour, appearance, texture) and food stability; it also enhances food digestibility. It also destroys toxic microorganisms and disables toxic substances such as inhibitors of enzymes.

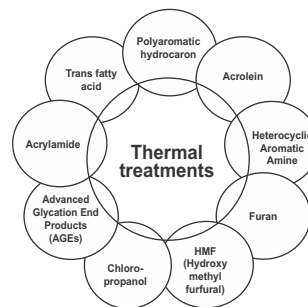


Maillard reaction in the food products:

A variety of chemical reactions take place concurrently during heating and cooking, and one of the main reactions is the Maillard reaction. It is a very complex reaction to the reduction of sugars and amino acids. It is known that the

Maillard reaction produces more than 550 volatile compounds that contribute to flavours and aromas while non-volatile products such as melanoidins contribute to browning color in cooked foods. Compounds produced during Maillard reactions, however, have adverse physiological effects or potential risks to health (Lineback and Stadler, 2009). This complex reaction, which involves reducing sugar and amino acids, has been the subject of intense research for many years, which has been prepared by heating for the formation of characteristic flavours, aromas, and colours (browning) in foods prepared by heating (Maillard, 1912).

Heat-derived compounds can create a risk for human health. For some years, adverse effects from neo-formed contaminants have been the subject to increased attention mainly acrylamide, nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons, furanic compounds (Furan, HMF) and advanced glycation end products (Lineback & Stadler, 2009; Quelhas *et al.*, 2010; Viegas *et al.*, 2012b).



ADVANCED GLYCATION END-PRODUCTS (AGES)

A heterogeneous group of highly reactive chemical compounds are advanced glycation end-products (AGES). They also called glycotoxins. AGES can occur naturally in

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animal tissues, but when they reach high levels in the body, they become pathogenic. The pyrrole is heterocyclic AGEs produced by the lysine-amino-group reaction with 3-deoxyglucosyl. Pyrrole is an effective predictor for the "advanced stages" of Maillard reaction. The first amino acid derivative of the advanced Maillard reaction formed from the oxidative cleavage of Amadori products was the N- π -carboxymethyllysine (CML). This constitutes 3–10% of Amadori products (Buser and Erbersdobler 1986).

Formation of AGEs: Non-enzymatic glycation of proteins, lipids, and nucleic acids is the primary formation process. The formation of AGEs accelerates markedly during high-temperature cooking processes such as frying, roasting and grilling. Cooked red meats, poultry, fish and eggs found high levels of both CML and methyl glyoxal (MG). High fatty foods such as butter, margarine, and mayonnaise have also been reported to contain significant amounts of AGEs.

Toxicity of AGEs: The dietary AGEs (dAGEs) are poorly absorbed, their potential effects on human health have been overlooked. Experimental animal and human research, however, have shown that dAGEs are consumed and make a significant contribution to the AGE reservoir of the body (Uribarri 2010). It is highly oxidative and inflammatory acts on human health due to the deleterious effects of AGEs. It can be involved in the development of a number of diseases i.e. diabetes and resistance to insulin, cardiovascular and kidney diseases, hypertension, and Alzheimer's disease.

POLYAROMATIC HYDROCARBON (PAH)

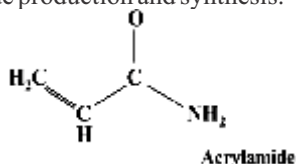
There is a large amount of polycyclic aromatic hydrocarbons in the world. They are present in many foods, in water, dirt, dust, and. PAHs have been linked to carcinogenic effects for over 200 years. The correlation between the high incidence of scrotal 134 cancer in chimney sweeps and their constant interaction with chimney soot was reported in 1775 by Percival Pott, an English physician (Liaronow *et al.*, 1938).

Formation of polyaromatic hydrocarbon: The high levels of PAHs in vegetable oils may be due to endogenous processing, with only a minor role being played by environmental contamination.

Toxicity of PAH: Benzopyrene identified as probable human carcinogen (Group 2A) by International Cancer Research Agency (IARC 1973) and has recently been reclassified as human carcinogen by the WHO. Benzopyrene alone is not mutagenic and carcinogenic, but must first be converted into active metabolites. Initially, this metabolic process requires a P450-mediated oxidation of cytochrome, creating a 7,8-epoxide. In addition, the 7,8 epoxide undergoes an epoxide hydrolase-mediated hydration, creating the 7,8-diol that produces the corresponding diolepoxide after further oxidation by cytochrome P450.

ACRYLAMIDE

Acrylamide (2-propenamide, $\text{CH}_2=\text{CH}-\text{CONH}_2$) is a compound of synthetic vinyl produced as an intermediate in polyacrylamide production and synthesis.



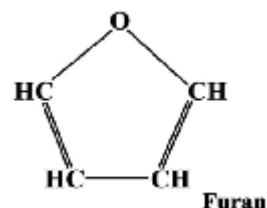
Formation of acrylamide: It was discovered in 2002 by the Swedish National Food Authority and the University of

Stockholm, significant amounts of acrylamide form when certain foods are cooked at temperatures normally above 120°C and low humidity. Acrylamide is also found in various foods that are high in baked or fried carbohydrates, including French fries, potato crisps and biscuits. The most important components for acrylamide formation are the reducing sugars and asparagine and also formed from acrolein and acrylic acid, especially when fats are heated at high temperature in lipid-rich foods (Claus *et al.*, 2006, Stadler and Scholz, 2004).

Toxicity of acrylamide: Studies on epidemiology showed that mothers, infants and other children were the most frequent. Acrylamide has been listed by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans" (Group 2A). The National Toxicology Program (NTP) determined in 2011 that acrylamide is reasonably expected to be a human carcinogen (NTP, 2011).

FURAN

Furan is a colourless chemical ($\text{C}_4\text{H}_4\text{O}$) with a low molecular weight of 68, a high volatility with a boiling point of 31°C, and insoluble water. Furans are a major class of compounds that form in food during the reactions of Maillard (Maga, 1979).

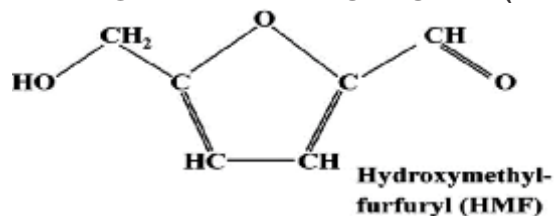


Due to their volatile composition and difficult identification with analytical methods, it was not considered to be a common food contaminant. Scientific reports, however, illustrated the presence of furan in a wide variety of foods, such as coffee, dried or jarred foods, baked goods, and baby foods in particular. Furan is classified as "possibly carcinogenic to humans" (Group 2B) according to the IARC and the study of this compound is a major concern (EFSA, 2004a).

Formation of furan: The mechanism of furan formation in foods is minimal. Different studies suggest numerous reactions to occurrence such as thermal degradation of sugar reduction or certain amino acids, and ascorbic acid thermal oxidation, polyunsaturated fatty acids, and carotenoids.

Toxicity of furan: According to animal experiments, furan is quickly and thoroughly absorbed from the intestine and lung. Because of its low polarity, it can move through biological membranes and penetrate different organs. Apparently, furan causes tumours in rats and mice, and the main target organ is the liver. Experiments showed an increase in hepatocellular adenomas and carcinomas based on the dosage of furan. Even, at the lowest dose of furan tested, high incidence of cholangiocarcinoma (2 mg/kg b.w.) (Vranova and Ciesarova, 2009; IARC, 1994).

HYDROXYMETHYLFURFURAL (HMF)

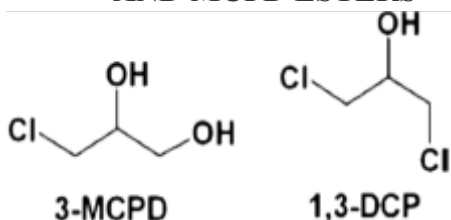


Hydroxymethyl furfural (5-hydroxymethyl-2-furaldehyde, HMF) is naturally formed during heating and is an intermediate in the Maillard (MR) reaction. HMF molecular formula is $C_6H_6O_3$ with 126.11 g/mol molecular weight, and the melting point ranges from 32 °C to 34 °C. HMF is considered one of the key food quality evaluation metrics. HMF is created when carbohydrate rich goods are heat treated and subsequently processed (Morales, 2009).

Formation of HMF: HMF is derived from monosaccharides by the mechanism of dehydration and cyclization of acid-catalysed. HMF is formed by the intermediate of Maillard reaction and also from the degradation of hexoses. HMF formation depends on temperature, water activity, pH, acidity, bivalent metal content, organic or inorganic acids, or salts. During caramelization, the reduction of carbohydrates is directly affected by 1, 2 enolization, dehydration and cyclization reactions. The order of HMF formation is caramelization requires higher temperatures than the Maillard reaction, and various sugars have a different impact on HMF formation (Morales, 2009).

Toxicity of HMF: HMF does not possess a serious health risk in cell systems, even though the highest concentrations in specific foods approach the biologically effective concentration range. The major concern for HMF is related to its conversion to sulphoxymethyl furfural (SMF) by sulphonation of the allylic hydroxyl function of HMF catalysed by sulfotransferases (SULTs). The resulting sulphate ester can induce genotoxic and mutagenic effects through a highly electrophilic allyl carbocation (Abraham, 2011; Capuano & Fogliano, 2011).

CHLOROPROPANOLS (3-MCPD, 2-MCPD) AND MCPD ESTERS



Chloropropanols and their carboxylic acid esters (chloroesters) are contaminants that are formed during the processing and manufacture of certain foods and ingredients (Hamlet *et al.*, 2009). 3-Monochloropropane-1,2-diol (3-MCPD), 1,3-dichloro-2-propanol (1,3-DCP), and their isomers 2-MCPD and a couple of, 2,3-DCP are the known components of group chloropropanols. 3-MCPD and 2-MCPD found in hydrolyzed vegetable proteins (HVP) manufactured by acid hydrolysis (Velisek *et al.*, 1979; Abraham *et al.*, 2013; Barocelli *et al.*, 2011).

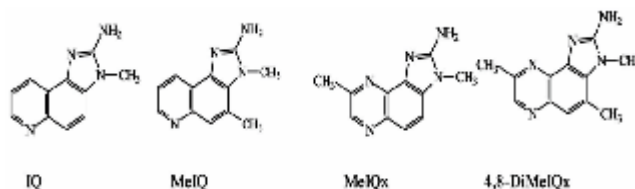
Formation of monochloropropanols: There is different path for the formation of 3-MCPD, counting on the reactants. It might be formed from acid and glycerol or acylglycerols or acid and propenyl alcohol but the foremost probable formation in foods is from common salt (chlorine source) and glycerol (Hamlet *et al.*, 2009). Dolezal *et al.*, 2004 reported that 3-MCPD formation depends on temperature and reaches the highest value when the model system was heated at 230 °C for 20h.

Toxicity of monochloropropanol: The EU Scientific Committee concluded that the 3-MCPD should be considered a genotoxic, carcinogen and since it had been impossible to

work out a secure threshold dose, residues in food should be undetectable using the foremost sensitive analytical method (EC 1997). 1,3-DCP was hepatotoxic, caused variety of tumours in several organs in rats, and was genotoxic in vitro (Schlatter *et al.*, 2002a, b).

HETEROCYCLIC AROMATICS AMINE (HCAs)

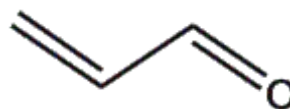
Sugimura, a Japanese scientist, first detected the carcinogenic and mutagenic heterocyclic aromatic amines (HCAs) in fish and meat cooked at temperatures above 150 °C and more than 25 HCAs in cooked meat products (Nagao *et al.*, 1977; Sanz *et al.*, 2008). Heterocyclic aromatic amines are powerful mutagens in cooked meat and fish from few ng/g to some µg/day levels. (Sugimura, 2002).



Formation of heterocyclic aromatic amine: HCAs can be categorized into two major groups known as amino imidazoarzenes (AIAs) or imidazoquinolinone (IQ) and amino carbolines i.e. non-IQ HCAs. The AIAs are the most important class of cooked foods produced by heating and it is involving in the reaction of free amino acids creatine, creatinine and hexoses during the cooking of foods at traditional cooking temperatures (150–300 °C). We have an imidazo group that is associated with a quinoline, quinoxaline, or pyridine (Jagerstad *et al.*, 1983; Sugimura and Adamson, 2000; Busquets *et al.*, 2004; Kizil *et al.*, 2011).

Toxicity of heterocyclic aromatic amine: Salmonella mutagenicity varied more than 160,000 times between the strongest and the weakest HCAs, influenced by the number and positions of exocyclic substituents, especially the 2-amino-group of the imidazo part of the molecular structure found in the HCAs (Nagao *et al.* 1977). HCAs were found to be active carcinogens that cause a number of histological tumours in the multiple organs after long-term oral administration (Eisenbrand and Tang, 1993; Sugimura *et al.*, 1993). It is interesting that some HCAs caused colon tumours (PhIP, IQ, MeIQ), mammary gland (PhIP, MeIQ) and prostate (PhIP), common cancers in western countries associated with western lifestyle.

ACROLEIN



Berzelius, 1839 had described aldehydes from the product of glycerine thermal degradation which is also called as acrolein (2-propenal). Acrolein is produced during the heating of food from carbohydrates, vegetable oils and animal fats, and amino acids and present in the atmosphere all the time. Acrolein was identified in samples from fat pyrolysis in the early 1960s. Acrolein has been identified in various foods as a volatile component of the aroma.

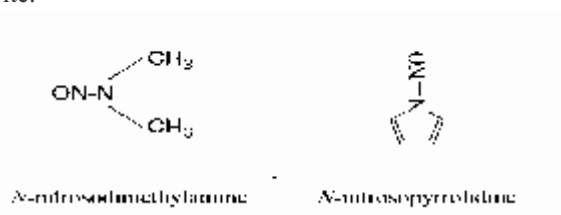
Formation of acrolein: Chemical reactions responsible for formation of acrolein is heat-induced dehydration of glycerol,

cleavage of dehydrated carbohydrate *i.e.* retroaldol, lipid peroxidation in PUFA and Strecker degradation of methionine and threonine. Esterbauer *et al.*, 1991 said that acrolein is produced by frying foods in oils. Acrolein was stated to be formed from different amino acids and polyamines during food processing (neutral pH and 100°C) (Shibamoto, 2009).

Toxicity of acrolein: Acrolein is commonly found in outdoor air and indoor air pollution as it is derived from lipids like cooking oils, lipid-rich foods such as beef and pork that are processed at high temperatures, and acrolein is mostly concerned with inhalation toxicity. A clinical study on social worker found that the average threshold of sensation distress level ranged from 0.09 (eye irritation) to 0.30 mg/kg (breathing rate, throat irritation) and 0.15 mg/kg (0.35 mg/m³) of nasal irritation (Weber-Tschopp *et al.*, 1977). Often found were eye and nasal pain, growth depression, histopathological respiratory tract changes (Feron *et al.* 1978), as well as Alzheimer's disease (Calingasan *et al.*, 1999) were found.

NITROSAMINES

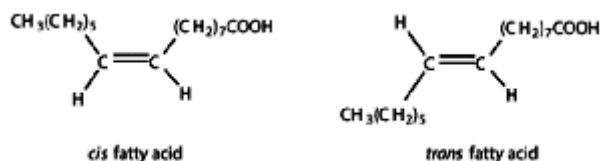
Nitrites react with the secondary amines of nitrosamines. Sodium nitrite is used to preserve the herring meal that has been found to be a nitrosamine source in milk. In the fish meal, methylamines reacted to dimethyl nitrosamine with sodium nitrite.



Formation of nitrosamines: Nitrosamines are formed by direct flame in cured meats, smoked fish, and soy protein products. The secondary amines that react with nitrous acid are considered to be the main chemical reaction for N-nitrosamine formation. (James and Kenneth, 1975; Richard and Phillip, 1975).

Toxicity of nitrosamines: A large group of N-nitrosoamines, *i.e.* NDMA (N-nitroso dimethylamine), NDEA (N-nitroso diethylamine), NPYR (N-nitroso pyrrolidine) and NPIP (N-nitroso piperidine) in food are carcinogenic instability. The main forms of N-nitroso compounds in food, however are non-volatile (e.g. proteins containing N-nitrosated peptide links, such as N-nitrosoproline) that are non-carcinogenic or non-mutagenic but may serve as precursors to volatile carcinogenic nitrosamines (Margaretha and Kerstin, 2005). The main sources of access are beer, meat products and fish (Michael and Gerhard, 2009). After dimethyl nitrosamine was given, Barnes and Magee (1954) documented liver damage and liver tumours in rats.

TRANS FATTY ACIDS (TFA)



There are saturated and unsaturated fatty acids in foods that contain lipids. Many unsaturated fatty acids that occur naturally are located in the form of cis. The trans isomers of

unsaturated fatty acids are trans fatty acids. The cis and trans forms refer to the position of the hydrogen around the double bonds on the fatty acid chain. When the atoms are on the same physical side of the chain, they are referred to as being in the cis position; they are in the trans position on the opposite sides of the chain. Foods with partially hydrogenated edible oils are major sources of dietary trans fatty acids.

Formation of trans fatty acids: TFA isomers are generated by thermal treatments of fats and oils such as deodorisation, cooking and frying. Heating primarily leads to configurations trans-18:2 and trans-18:3. Throughout frying, the degrees of TFA formation depend on the frying condition and the frying material. TFA production is generally lower when partially hydrogenated fats are used, but high initial content of these acids results in a greater concentration of trans isomers in fried food.

Toxicity of trans fatty acid: Refined edible oils contain a small amount (0–2%) of trans fatty acids. Trans fat is found in various foods such as fast foods, frozen snacks, bakery goods and margarines. Fast food contains very high levels of trans fat, and 10–25 g of trans fat can be eaten in one day. Customers who have a daily habit of eating fast food have a daily intake of about 5 g of trans fat. This level of daily intake of trans fat is associated with increased risk of ischemic heart disease by 25% (Stender *et al.*, 2006). Cardiovascular disease, sudden death, and probably diabetes mellitus is associated with TFAs. TFAs have harmful effects on plasma lipoproteins, which increase levels of low-density lipoprotein (LDL) and decrease levels of high-density lipoprotein (HDL).

Conclusion and Future Prospects

Thermal processing of food is necessary to make the food digestible and palatable, to ensure microbial health and to create a distinct taste, aroma and texture. The nutritional effects of thermal treatment of food are very complex. The effects of thermal treatment may be nutritionally beneficial, for example by increasing the bioavailability of bioactive components from the modified food matrix; however, some of these bioactive components, especially water-soluble vitamins, may also be beneficial. And there are a variety of toxic compounds produced during heating and cooking, but the question remains from a dietary health perspective, which toxicants are of major concern in foods. Specific compounds have been identified in animal studies at high doses in foods with mutagenic, carcinogenic or neurotoxic properties. During thermal processing, however, chemical changes are a very complex phenomenon. Interdisciplinary knowledge is required to understand the effect on different nutrients as well as the development of various chemical toxic compounds and their effect on health. Contribution of different disciplines and knowledge is very crucial in many areas such as agronomy, analytical chemistry, food science, food processing, toxicology, epidemiology, nutrition, and consumer research. Therefore, a strong interdisciplinary research project and effort are required to focus on this complex thermal processing issue.

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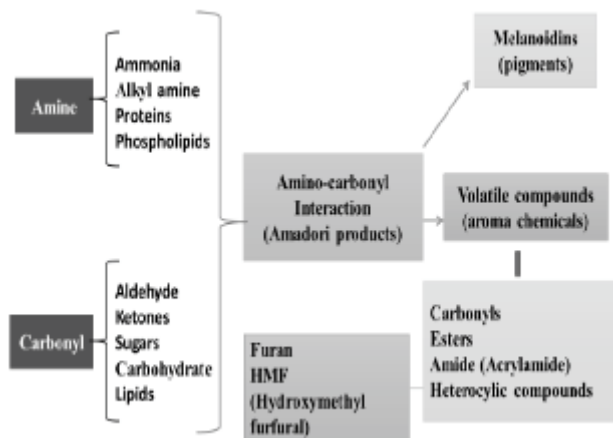


Fig. 1: General scheme of Maillard browning reaction (Maillard, 1912)

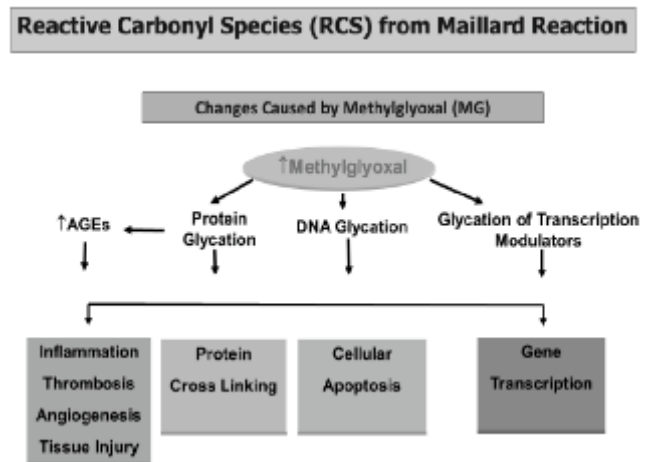


Fig. 2: Toxicity of methylglyoxal (Ramasamy *et al.*, 2006)