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Agnieszka Koszucka & Adriana Nowak

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REVIEW



## Thermal processing food-related toxicants: a review

Agnieszka Koszucka and Adriana Nowak

Institute of Fermentation Technology and Microbiology, Lodz University of Technology, Lodz, Poland

### ABSTRACT

Heterocyclic aromatic amines, acrylamide, 5-hydroxymethylfurfural, furan, polycyclic aromatic hydrocarbons, nitrosamines, acrolein, chloropropanols and chloroesters are generated toxicants formed in some foodstuffs, mainly starchy and protein-rich food during thermal treatment such as frying, roasting and baking. The formation of these chemical compounds is associated with development of aromas, colors and flavors. One of the challenges facing the food industry today is to minimize these toxicants without adversely affecting the positive attributes of thermal processing. To achieve this objective, it is essential to have a detailed understanding of the mechanism of formation of these toxicants in processed foods. All reviewed toxicants in that paper are classified as probable, possible or potential human carcinogens and have been proven to be carcinogenic in animal studies. The purpose of that review is to summarize some of the most frequent occurring heat-generated food toxicants during conventional heating, their metabolism and carcinogenicity. Moreover, conventional and microwave heating were also compared as two different heat treatment methods, especially how they change food chemical composition and which thermal food toxicants are formed during specific method.

### KEYWORDS

DNA adducts; DNA damage; carcinogenicity; Maillard reaction; Mutagenicity; thermal food treatment

### Introduction

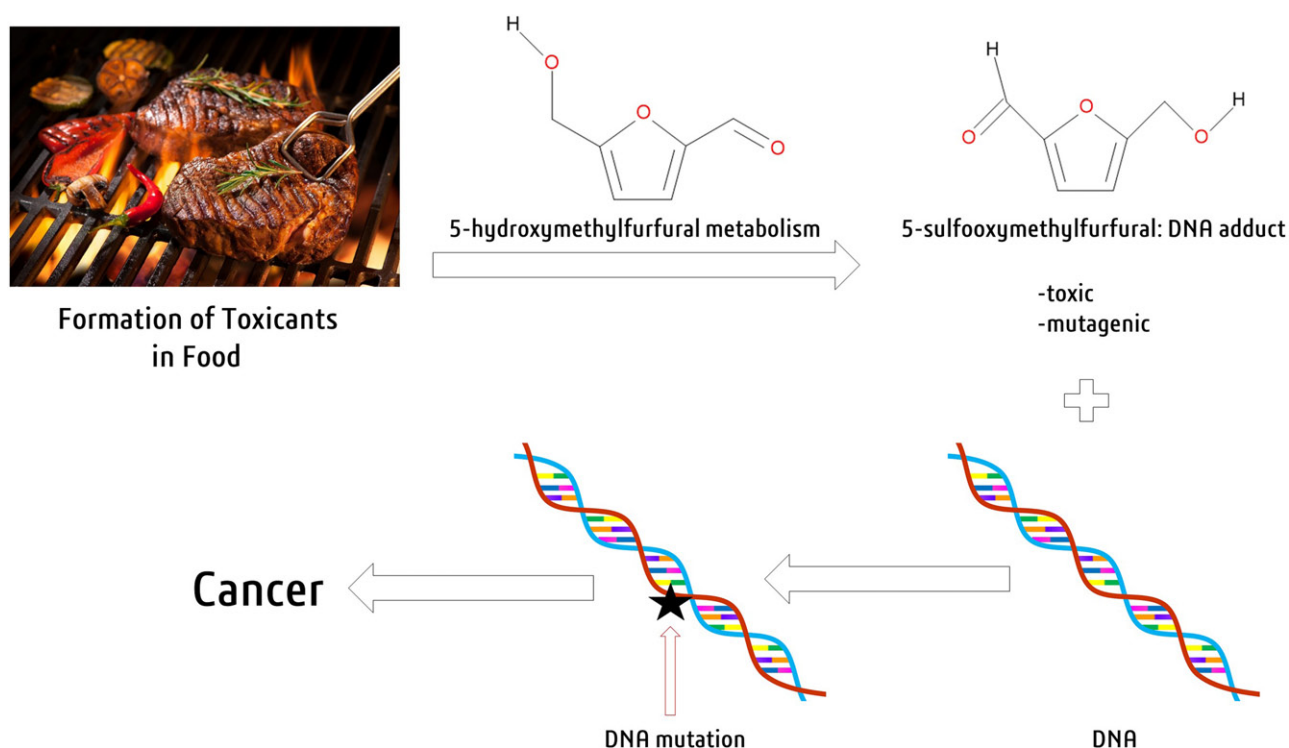
It has been known for a long time that formation of certain chemicals during food processing or preparation may pose a risk to human health. Technological developments and the use of the various industrial, as well home-cooking methods have led to a great number of different ways on how to use thermal treatment to achieve specific food qualities. Thermal treatment also changes the physical and chemical structure of macronutrients, e.g., starches and proteins with the generalized effect of better gastrointestinal digestion (Cartus and Schrenk 2017). However, thermal processing of food is known to generate potentially mutagenic and carcinogenic by-products in addition to desirable aromas, colors and flavors of active compounds (Fig. 1).

Thermal treatments have been reported to accelerate oxidative processes not only in lipids, but also in proteins due to their increasing effect on free radical production and decreasing effect on the food antioxidant protection (Santé-Lhoutellier et al. 2008). Numerous studies have been conducted on thermally generated food toxicants, ranging from identification, formation, toxicology and analysis (Wenzl, Lachenmeier, and Gökmen 2007).

Moreover, the heat treatment method also influences on thermal food toxicants formation (their type and level). Cooking process in a conventional oven consists of heating food by surrounding hot air, which is heated by a source of heat either electricity or gas. The physical processes of heat

transfer in a conventional oven are represented by radiation from the source of heat to the metal wall at the base of the oven, by conduction from the base to the other walls and by convection through the heated air currents set up in the oven to the food. Generally, the temperatures that are used in an oven range from 130 to 250 °C (Calabro and Magazu 2012). The working principle of a microwave dielectric heating is represented by polar molecules which rotate and transform electromagnetic energy into heat and thereby drive chemical reactions, which is different from the principle of conventional heating by conduction or convection (Fan et al. 2018).

The conventional blanching method is closely associated with the serious loss of weight and nutritional values of food products. To retain nutritional quality of food products, several researchers suggested the use of microwave heating as an alternative to conventional blanching method for food products. It can reduce the amount of nutrients lost by leaching as compared with hot water immersion. The amounts of protein, ashes, vitamin C, iron and phosphorus found in broccoli blanched by microwave were much higher than in the sample treated by hot water blanching and were closer to that of fresh broccoli (Chaparro, Diaz, and Paredes 2011). Daomukda et al. (2011) studied the effect of different cooking methods on physicochemical properties of brown rice. They concluded that the protein, fat and ash contents in rice cooked by microwave are retained at higher levels (8.49%, 2.45%, and 1.42%, respectively) than conventional



**Figure 1.** Role of thermally processed foodstuffs in causing cancer on the example of 5-hydroxymethylfurfural metabolism.

boiling and steaming methods. Substantial reduction in the energy consumption was observed with controlled cooking (using microwave oven) of unsoaked rice (14%–24%) and presoaked rice (12%–33%) compared with normal cooking. In a study carried out by Arab, Helmy and Bareh (2010), differences in chemical composition of chickpea flour before and after cooking are significant using different cooking treatments, namely cooking on a hot plate for 90 min, microwave cooking with power level 10 for 5 min, and frying in corn oil at 170 °C for 1 min. The obtained data shows that the fat and ash contents in chickpea cooked by microwave were decreased by 8.90 and 6.97%, respectively, compared with the traditional cooking practice (8.01 and 5.76%). Such decrease might be due to their diffusion into cooking water. Megahey, McMinn and Magee (2005) observed the influences of different baking conditions on quality in terms of texture of cake using microwave oven at 250 W and convection oven at 200 °C. Microwave-baked cake was found to possess high springiness, moisture content and the low firmness as texture attributes compared with the cake that baked in convection method. The quantitative analysis of phenolic compounds showed that microwave baking at the power of 500 W is a good level for retention of the compounds.

Microwave oven is able to heat up foods using the energy of oscillating electromagnetic wave, it is possible to do selective and quick cooking. But the penetration depth of microwave is under about a few inches or below the surfaces of foods. So, if the sizes of foods are small and the shape of foods is flat, the uniform heating through overall volume is possible. It will lead less loss of moisture contents and the greatest energy savings, and the nutrition of foods will be preserved very well (Puligundla et al. 2013). However, the process of microwave heating can accelerate the oxidative reactions

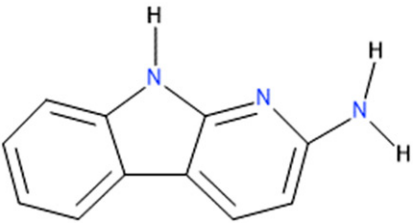
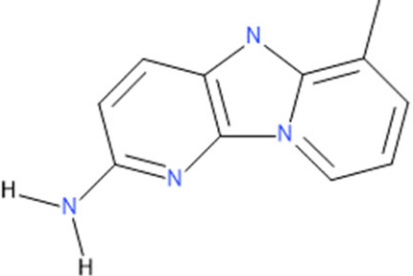
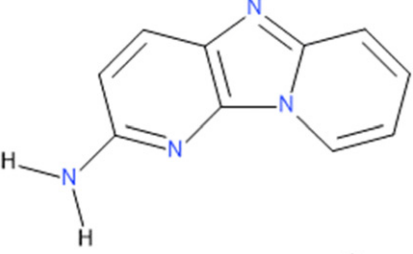
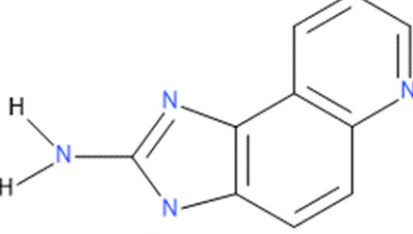
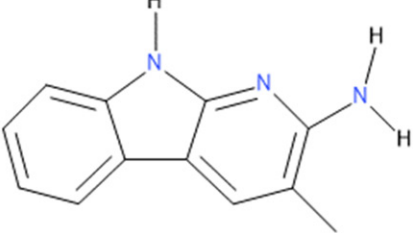
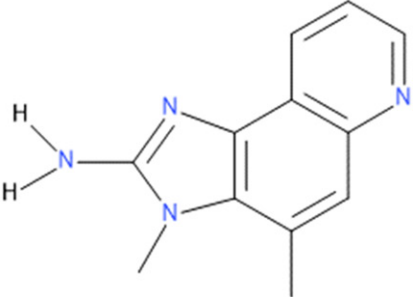
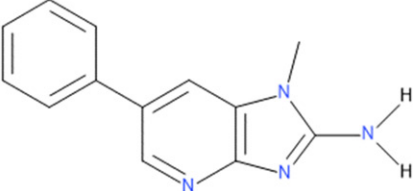
that promote the production of free radicals that rapidly react with atmospheric oxygen to produce hydroperoxides and secondary oxidation products. Different studies have aimed to evaluate the effects of microwave heating on food and its constituents, including the lipid fraction of animal fats and vegetable oils (Oueslati et al. 2010). Interestingly, the consumption of dietary antioxidants seems to play an important role in protecting against these degenerative events. Moreover, these antioxidants decrease the formation of heterocyclic amines that form during the frying of protein-rich food such as meat, eggs, and fish, and which are reported as animal carcinogens. However, other study showed that properly applied microwave heating can provide substantial support for nutritionally valuable oat meal preparation (Harasym and Olędzki 2018). Moreover, the different heating method can promote or hinder carbohydrate release in the digestive tract.

Close to 800 compounds have so far been identified that are formed *via* the Maillard reaction and lipid degradation of which some 50 were short-listed based on potential carcinogenicity and mutagenicity as calculated by toxicity prediction models. Due to the fact that there is a great number of thermal food-related toxicants, we have chosen the most frequent occurring during thermal food processing and described them.

### Heterocyclic aromatic amines (HAAs)

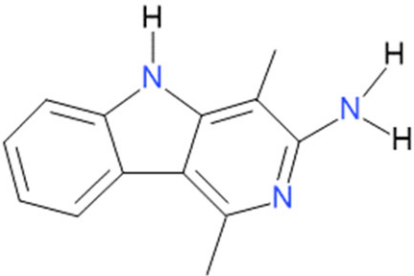
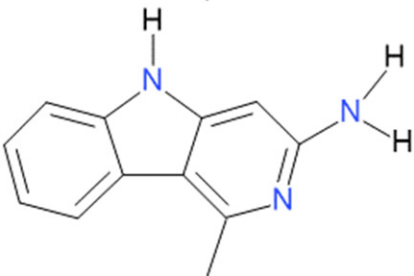
Heterocyclic aromatic amines were one of the first group of carcinogens isolated and identified in food following observations of mutagenic activity in cooked meat and fish by Sugimura et al. study in 1977. HAAs (Table 1) represent a large group of chemical compounds, many of which exhibit carcinogenic and mutagenic properties. They are typically produced as a result of high-temperature thermal processing

**Table 1.** Structures of various thermic and pyrolytic heterocyclic aromatic amines as representants of heat-generated food toxicants.

Structure	Abbreviation/Chemical name	IARC Classification
	AαC 2-amino-9H-pyrido[2,3-b]indole	Possible human carcinogen (group 2B)
	Glu-P-1 2-amino-6-methylpyridine[1,2-α:3',2'-d]imidazole	Possible human carcinogen (group 2B)
	Glu-P-2 2-aminodipyrido[1,2-α:3',2'-d]imidazole	Possible human carcinogen (group 2B)
	IQ 2-amino-3-methylimidazo[4,5-f]quinolone	Probable human carcinogen (group 2A)
	MeAαC 2-amino-3-methyl-9H-pyrido[2,3-b]indole	Possible human carcinogen (group 2B)
	MeIQ 2-amino-3,4-dimethylimidazo[4,5-f]quinolone	Possible human carcinogen (group 2B)
	PhIP 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine	Possible human carcinogen (group 2B)

(continued)

Table 1. Continued.

Structure	Abbreviation/Chemical name	IARC Classification
	Trp-P-1 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole	Possible human carcinogen (group 2B)
	Trp-P-2 3-amino-1-methyl-5H-pyrido[4,3-b]indole	Possible human carcinogen (group 2B)

and can be found in a wide variety of cooked protein-rich food products. Since the discovery of HAAs by Professor Sugimura in Sugimura 1977, more than 25 HAAs have been isolated and identified in cooked meat and almost all HAAs were proven to be carcinogens in toxicological studies (Sugimura et al. 2004).

HAAs are formed in grilled meats, fishes and tobacco smoke condensate, and they also occur in diesel exhaust. The HAAs are classified in at least 2 groups: thermic or IQ-type HAAs (100–300 °C) and pyrolytic or non-IQ-type HAAs (>300 °C) (Gibis 2016). IQ-type HAAs as thermic mutagens, they are classified into three subgroups based on their structure, imidazoquinolines, imidazoquinoxalines and imidazopyridines. They are formed by heat induced non-enzymatic Maillard reaction during conventional cooking temperatures between 150 and 300 °C involving reaction of creatine or creatinine, amino acids and hexose. Non-IQ-type HAAs, commonly referred to pyrolytic mutagens are typically formed at much higher temperatures, often above 300 °C, resulting in amino acid or protein pyrolysis (Kizil, Oz, and Besler 2011).

HAAs are potent mutagens which can play a crucial role in the etiology of cancer, as previous studies have shown them to be carcinogenic and genotoxic in long term animal studies and during DNA repair tests respectively (Jagerstad and Skog 2005). HAAs undergo oxidation at the exocyclic amine group by cytochrome P450 enzymes to form the genotoxic N-hydroxylated-HAA metabolites. These metabolites may react with DNA or undergo further metabolism to produce unstable esters that adduct to DNA (Turesky and Holland 2007). Special attention is given in the literature to the following carboline type of HAAs: MeAxC, AxC, Trp-P-1, Trp-P-2, Glu-P-1, Glu-P-2, and the aminoimidazo type of HAAs: IQ, MeIQ, PhIP. HAAs exhibit a clear *in vitro* activity inducing reverse mutations in *Salmonella* Typhimurium (Ames assay), morphological transformation in mouse fibroblasts, micronucleus induction in human cells, and DNA

strand breaks (comet assay) in human cells (Jagerstad and Skog 2005; Nowak, Ślizewska, and Klewicka 2012; Nowak et al. 2014), and genotoxic effects *in vivo* as DNA adducts (Arimoto-Kobayashi et al. 2006). Carcinogenicity studies in nonhuman primates with PhIP, MeIQ, and IQ could only demonstrate a carcinogenic action of IQ in the liver at doses of 10 and 20 mg/kg/day (Takayama, Thorgeirsson, and Adamson 2008). Differences in metabolism between rodents and primates account for the observed differences in the carcinogenic effects.

This conclusion is consistent with the International Agency for Research on Cancer (IARC 1987) that classified AxC, Glu-P-1, Glu-P-2, MeAxC, MeIQ, PhIP, Trp-P-1, Trp-P-2 as possible human carcinogens (Group 2B) and assessed IQ as a probable human carcinogen (Group 2A) (IARC 1993). Harman and norharman, although  $\beta$ -carbolines, are not considered as member of the HAA class in most publications as they lack an exocyclic amine group. The exocyclic amine group of HAAs can undergo metabolic activation by N-hydroxylation producing an intermediate (arylnitrenium ion) which has been implicated in general toxicity and DNA damage (Turesky and Le Marchand 2011).

### Acrylamide (AA)

Acrylamide ( $\text{H}_2\text{C}=\text{CH}-\text{CO}-\text{NH}_2$ ), an unsaturated amide with low molecular weight of 71.08 kDa, is a synthetic chemical used to form polyacrylamide used commonly in electrophoresis and as a component of cosmetics, textiles, paper and many other products. However, it is also found in various thermally processed foods, as an intermediate product of the Maillard reactions, known as browning (Zamani et al. 2017). An undesirable acrylamide concentration in heat treated foods by Swedish scientists in 2002 (Tareke et al. 2000) and since then the efforts to minimize the acrylamide content in foods have been in the forefront of the food safety authorities. Further analytical studies revealed that

processing of food rich in starch and protein subjected to frying, roasting or baking is the main source of AA (Kwolek-Mirek et al. 2011). The highest concern about acrylamide intake comes from the cereal grains-based products (such as biscuits, crackers or bread), breakfast cereals, coffee and especially, potato products (French fries and chips). Acrylamide is generated in food products containing high content of reducing sugars such as glucose and proteins especially rich in asparagine, amino acid, when heated at high temperature ( $>120^{\circ}\text{C}$ ) (Zamani et al. 2017).

In mammalian cells, acrylamide is metabolized by conjugation with glutathione either non-enzymatically or by glutathione-S-transferases and by epoxidation reaction mediated by cytochrome P-450 CYP2E1 (Fig. 2) (Kwolek-Mirek et al. 2011). The metabolite of that reaction is glycidamide which in contrast to acrylamide gives rise to stable adducts to DNA (Paulsson, Grawé, and Törnqvist 2002) and induces carcinogenesis. Another study suggested that acrylamide itself, but not its oxidative metabolite, appears to be involved in acrylamide-induced cellular transformation (Park et al. 2002).

Acrylamide is known to have neuro-, hepato- and genotoxic effects. Neurotoxicity occurs in both, the central and peripheral nervous systems, likely through microtubule disruption, which has been suggested as a possible mechanism for genotoxic effects of acrylamide in mammalian systems

(El-Assouli 2009). The genotoxic potential of acrylamide in food and its impact on cancer risk in humans is of great concern. Food mutagens cause different types of DNA damage. However, the effect of food mutagens in carcinogenesis can be modified by heritable traits, namely, low-penetrant genes that affect mutagen exposure of DNA through metabolic activation and detoxification or cellular responses to DNA damage through DNA repair mechanisms or cell death (Jagerstad and Skog 2005).

Practical advice for minimizing acrylamide formation specifically intended for industrial food application is continuously being updated into the “Acrylamide Toolbox.” This toolbox is essentially based on a compilation of scientific publications and advice, providing practical guidelines for reducing acrylamide formation as a function of the food product in question and is specifically intended for industrial food application (Confederation of the Food and Drink Industry of the EU 2011). The International Agency for Research on Cancer (IARC 1994) has classified acrylamide as probable human carcinogen (Group 2A) causing DNA damage and gene mutation; its prolonged exposure has induced gene mutations and chromosomal aberrations in germ cells of mice, chromosomal aberrations in germ cells of rats and forms covalent adducts with protamine in germ cells of mice *in vivo*.

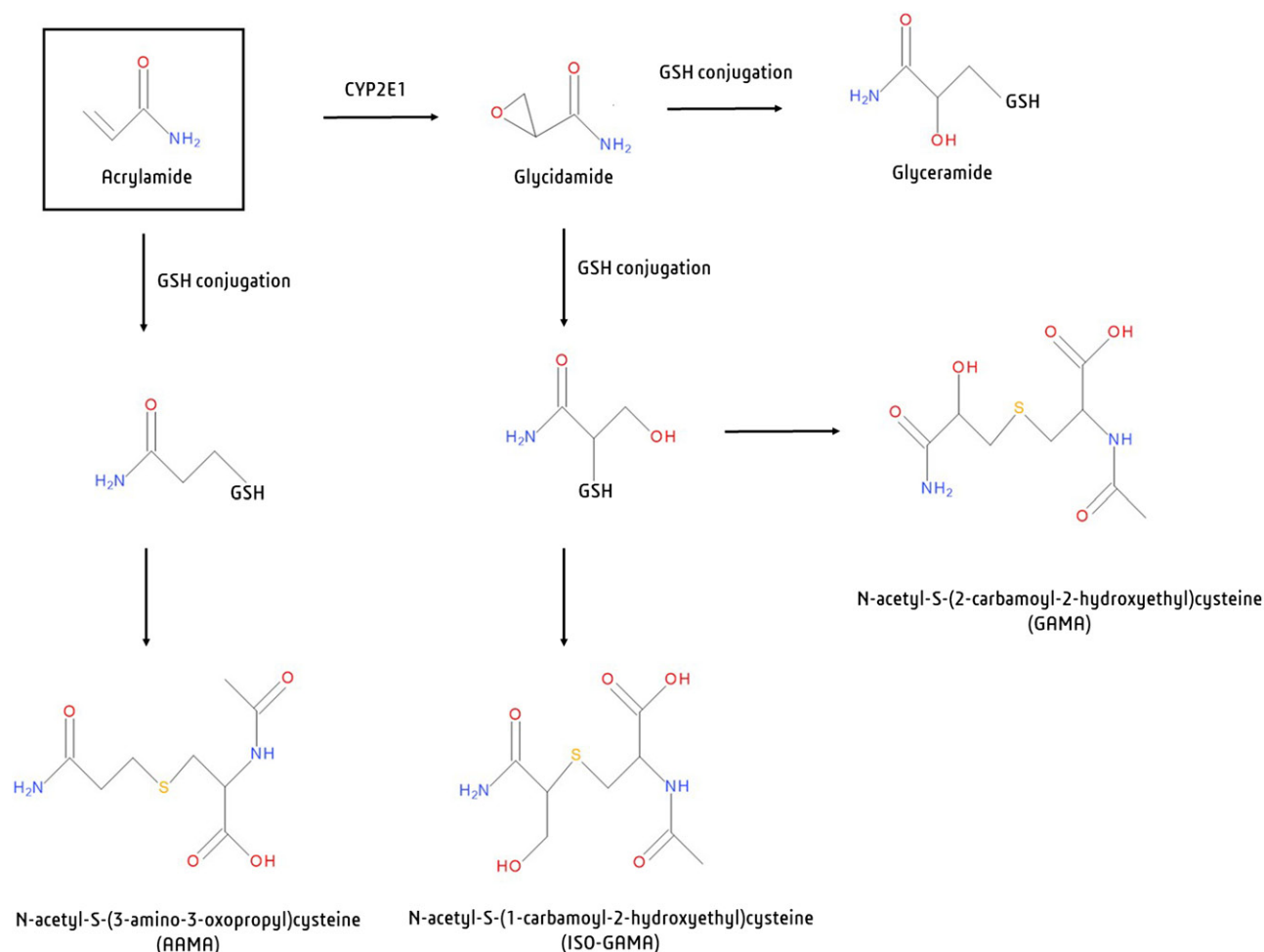


Figure 2. Acrylamide metabolism in animals (Sumner et al. 2003).



## 5-hydroxymethylfurfural (HMF)

HMF ( $C_6H_6O_3$ ) is known as one of the most common intermediate products of over-processed foodstuffs. Another point to be kept in mind is that the HMF in fruit juice, jam, honey, milk powder and infant formulas can occur not only as a result of Maillard reaction but also by heating hexose directly, typically above  $150^{\circ}C$ . HMF could be also found in bakery products, malt, coffee, and vinegar. In particular acrylamide and HMF can be regarded as the most important heat-induced contaminants occurring in bread and bakery products (Capuano and Fogliano 2011).

The main pathways to HMF formation in foods, which includes key intermediate 3-deoxyosone formation *via* 1,2-enolization and dehydration of glucose or fructose, and further dehydration and cyclization of 3-deoxyosone to yield HMF. Under dry and pyrolytic conditions an alternative pathway to HMF formation from fructose and sucrose has been proposed. It involves the formation of a highly reactive fructofuranosyl cation which can be effectively and directly converted to HMF (Perez Locas and Yaylayan 2004).

During metabolism, HMF has recently been converted *in vivo* to 5-HMF and it has shown to be bio-activated *in vitro* to SMF, through sulphonation of its allylic hydroxyl functional group and catalyzed by SULT in the presence of the sulpho-group donor PAPS. In SMF, sulfate is a good leaving group, producing a highly reactive intermediate that can react with DNA (Glatt and Sommer 2006). SMF is very unstable but, it has been recently detected in the blood of HMF treated mice indicating that HMF is metabolized to SMF *in vivo* (Monien et al. 2009). This pathway has been described in the literature for rodents, but it has not yet been confirmed for humans. In Caco-2 cell line, Delgado-Andrade et al. (2008) reported that absorption and transport of HMF is higher when cells are exposed to higher HMF concentration. In addition, the authors suggest that food composition, i.e. fiber content, might affect HMF uptake. The International Agency for Research on Cancer has not yet classified HMF as human carcinogen due to lack of conducted animal studies.

## Furan

Furan ( $C_4H_4O$ ) with low molecular weight of 68.07 kDa, is a cyclic dieny ether with a low boiling point  $31.4^{\circ}C$  and is poorly soluble in water. Its derivatives are naturally occurring compounds formed in many heat-processed foods and drinks; these compounds have low odor thresholds and significantly contribute to the sensory properties of heated foods and beverages above  $150^{\circ}C$ . The occurrence of furan in foods was established in the 1960s. Its industrial uses are mainly focused on synthetic purposes (Condurso, Cincotta, and Verzera 2018).

Recently, great attention has been paid to the presence of furan in foods by several international food organizations, such as the US Food and Drug Administration (US FDA) and the European Food Safety Authority (EFSA). In 2004 the US FDA reported the first results on furan occurrence in a several selected foods, mainly heat-processed baby foods

packaged in jars and cans (US FDA 2004). The European Food Safety Authority (2008) has reviewed the toxicity data on furan and found that the weight of evidence indicates that furan-induced toxicity is probably attributable to a genotoxic mechanism; its metabolism to cis-2-butene-1,4-dial is thought to be the main genotoxic route although the results of a recent publication question this evidence (Durling, Svensson, and Abramsson-Zetterberg 2007), hence warranting further studies in this field.

It has now been firmly established that furan in food can be formed by several different pathways, including the thermal degradation of carbohydrates, amino acids, ascorbic acid, and the oxidation of PUFAS and carotenoids (Yaylayan 2006). Perez Locas and Yaylayan (2004) suggested that ascorbic acid had the highest potential to produce furan, followed by some sugar/amino acids mixtures; reaction conditions, such as temperature, time and pH, can also affect the furan formation significantly.

Furan has been found to exhibit carcinogenic and cytotoxic activity on animals and harmful effects on human health (Byrns et al. 2006). It has been classified by the International Agency for Research on Cancer as Group 2B, as possibly carcinogenic to humans (IARC 1995).

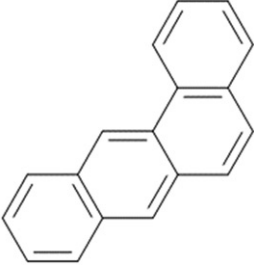
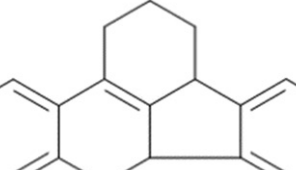
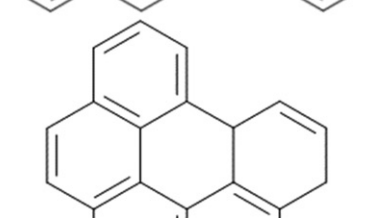
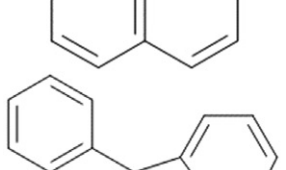
## Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (Table 2) constitute a large class of over 100 different organic compounds with two or more fused benzene rings. Most are weakly volatile and dissolve weakly in water. PAHs are created during incomplete combustion of coal, gas, oil wood, such as tobacco and food components more than  $120^{\circ}C$  and are considered ubiquitous environmental and food contaminants (EFSA 2008). Some PAHs are suspected to be produced by autogenous biosynthesis and can be already present in plants. High abundance of phenanthrene is observed in bark and twigs of *Vismia cayennensis* trees and authors consider a possible biological origin for these two PAHs (Krauss et al. 2005). However, origins of PAHs in fruits and vegetables remain mainly anthropogenic. Their transfer from contaminated environment (air and soil) to plants is described; influence of cooking processes is also presented.

Fruits and vegetables are mainly consumed as raw products but some of them are cooked before eating. Boiling, which is the most common cooking process for vegetables may induce a great decrease of the total PAHs content. For instance, PAHs proportion is reduced by 88% for potatoes and 81% for spinach after a boiling process (Abou-Arab et al. 2014). Some PAHs have been found in the boiling water of potatoes highlighting a possible transfer from the vegetables. PAHs formation during cooking processes depends on type of food, temperature of combustion, oxygen accessibility, time of cooking, and the kind of cooking process. During cooking, PAHs could be produced in plant by pyrolysis of organic matter such as proteins, lipids, steroids, and sesquiterpenes (Chen and Chen 2001).

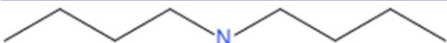
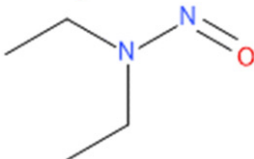
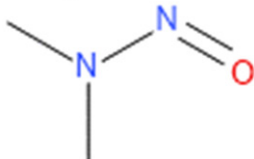
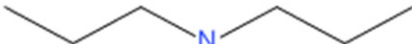
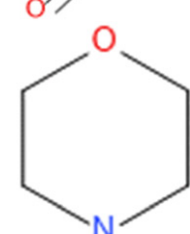
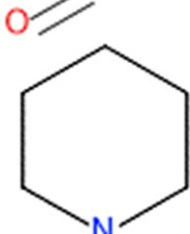
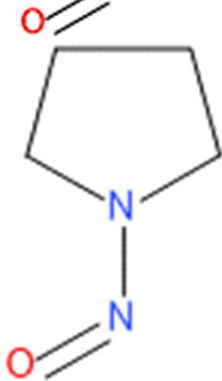
The first reaction of PAH metabolism is an epoxidation. PAH epoxides can conjugate with glutathione (detoxification

Table 2. Structure of various polycyclic aromatic hydrocarbons as representants of heat-generated food toxicants.

Structure	Abbreviation/Chemical name	IARC Classification
	BaA Benz[a]anthracene	Probable human carcinogen (group 2B)
	BaP Benzo[a]pyrene	Human carcinogen (group 1)
	BbF Benzo[b]fluoranthene	Probable human carcinogen (group 2B)
	BghiP Benzo[g,h,i]perylene	Potential human carcinogen (group 3)
	BjF Benzo[j]fluoranthene	Probable human carcinogen (group 2B)
	BkF Benzo[k]fluoranthene	Probable human carcinogen (group 2B)
	DBaA Dibenz[a,h]anthracene	Possible human carcinogen (group 2A)



**Table 3.** Structure of various nitrosamines as representants of heat-generated food toxicants.

Structure	Abbreviation/Chemical name	IARC Classification
	NDBA <i>N</i> -nitrosodibutylamine	Possible human carcinogen (group 2B)
	NDEA <i>N</i> -nitrosodiethylamine	Probable human carcinogen (group 2A)
	NDMA <i>N</i> -nitrosodimethylamine	Probable human carcinogen (group 2A)
	NDPA <i>N</i> -nitrosodipropylamine	Possible human carcinogen (group 2B)
	NMOR <i>N</i> -nitrosomorpholine	Possible human carcinogen (group 2B)
	NPIP <i>N</i> -nitrosopiperidine	Possible human carcinogen (group 2B)
	NPYR <i>N</i> -nitrosopyrrolidine	Possible human carcinogen (group 2B)

reaction). The epoxides which do not conjugate with glutathione are converted into phenols and diols. PAH metabolites are sometimes not sufficiently polar to be excreted. Therefore, they must be conjugated with glucuronic or sulfuric acids to be excreted (Abdel-Shafy and Mansour 2016). Because of their ability to cause gene mutation and cancer PAHs are the world's largest class of carcinogens known to date (EFSA 2008).

Mutagenicity/genotoxicity of BaP, DBaH, BaA, BbF, BkF, BkF, CHR, BghiP, and IP in animal somatic cells *in vivo* notably leads the Scientific Committee on Food of European Food Safety Authority to consider these compounds as potentially genotoxic and carcinogenic to humans through diet (EFSA 2008). Ubiquity of PAHs in food products and the carcinogenic potential of these compounds to humans *via* ingestion explain the need of their monitoring in food matrices. The International Agency for Research of Cancer has designed BaP as a compound of Group 1-carcinogenic to humans (IARC 2012), whereas DBaH has been classified as Group 2A-possible human carcinogenic, and other hydrocarbons as 2B-probable human carcinogenic (IARC 2010). Some PAHs, classified as non-carcinogenic compounds (Group 3), have shown effects on the immune system and endocrine regulation (Hylland 2006).

### Nitrosamines (NAs)

Nitrosamines (Table 3) as one kind of the most important toxic substances have been proven to be carcinogenic and mutagenic for humans, which can result in a series of diseases such as gastric, colorectal and esophageal cancer (Lee et al. 2006). Generally, humans are exposed to NAs that are mainly from various thermal processed foodstuffs above 130°C containing: marine fish, sausage, cured meat, drinking water, beer and so on. Their formation has been confirmed by the nitrosation reaction of a nitrosating reagent derived from either nitrites or nitrogen oxide with the N-containing substances (Yurchenko and Mölder 2005). Thus, the use of nitrites and nitrates applied as preservatives is also strictly controlled in meat industry.

Diet therefore contributes to nitrosamine-related cancers in three very different ways: (1) by modulating the *in vivo* synthesis of nitrosamines, and also by reducing the carcinogenicity of the nitrosamines to which man is exposed. (2) As a source of exposure to preformed nitrosamines, especially those not found in tobacco. While several hundred nitrosamines have been shown to be carcinogenic in animal studies, only a small number so far have been found that are specific to tobacco. As each nitrosamine has its own organ specificity, dietary nitrosamines could be responsible for tumors at sites in addition to those related to tobacco use. (3) As a source of amines and nitrite, which can react together in the stomach, mouth or intestine to form a variety of nitrosamines (Craddock 1990).

Human, rat, monkey and trout liver possess the capacity to metabolize NAs, and in most cases a lower metabolic capacity is observed in extrahepatic tissues, with a few notable exceptions. Methylbenzyl nitrosamine an esophageal

carcinogen in rats, is metabolized to a greater extent in the esophagus than in the liver. Considerable evidence has accumulated that the initiation of the carcinogenic process by this group of carcinogens is linked to the metabolic competence of the target tissues or cells to convert these carcinogens into mutagenic metabolites and to the binding of these metabolites to cellular DNA (Nowak, Kuberski, and Libudzisz 2014). In the study of García et al. (2008), NPIP and NDBA induced apoptotic cell death characterized by several parameters as well as Reactive Oxygen Species (ROS) production in the human leukemia HL-60 cell line. Apoptosis induced by carcinogens seems to have an important role in cancer development. Further studies are required to determine the NPIP and NDBA-induced cell death pathway.

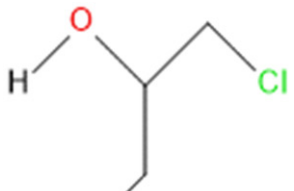


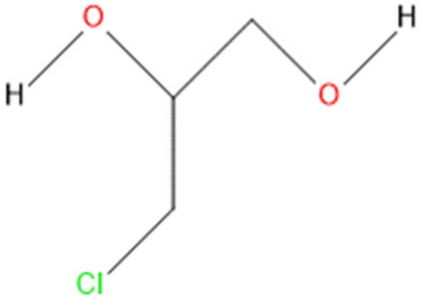
Nitrosamines have been classified by the International Agency for Research on Cancer (IARC 1987) according to the obtained results from numerous laboratory studies. NDBA, NDPA, NMOR, NPIP and NPYR are classified as the group of possibly carcinogenic to human in Group 2B. NDMA and NDEA are listed as probably carcinogenic to human beings in Group 2A. And the tolerance level of human exposure to NAs has also been strictly set in different countries (Andrade, Reyes, and Rath 2005). Thus, the sensitive and facile determination of trace NAs is of significant importance.

### Acrolein

Acrolein (C<sub>3</sub>H<sub>4</sub>O) belongs to the  $\alpha$ ,  $\beta$ -unsaturated aldehydes. The substance is a highly volatile (boiling point 52.5°C) colorless liquid with a melting point of 88°C, which dissolves very well in water. Acrolein is formed from amino acids, fats or carbohydrates during thermal food processing mostly over 150°C. During the preparation of carbohydrate-containing foods, acrolein can be formed in the course of the Maillard reaction. It occurs in fruits, for instance raspberries, grapes, strawberries and blackberries as well as in vegetables, tomatoes, fish and cheese. Furthermore, it can be detected in spirits and wines.

According to Abraham et al. (2011), the metabolism routes of acrolein consist of (1) epoxidation of the double bond followed by a conjugation with GSH, (2) Michael-type addition of water followed by oxidative degradation and (3) GSH addition to the double bond and an oxidative or reductive change of the aldehyde function. Acrolein reacts with SH groups as well as primary and secondary amines. Acrolein exposure may lead to GSH depletion and formation of adducts with thiol groups of cysteine residues and amino groups of proteins, nucleic acids and other cellular components (Cai, Bhatnagar, and Pierce 2009). In addition to this adduct formation, acrolein may also cause cross-linking between proteins as well as between peptides/proteins and DNA (LoPachin et al. 2009). Consequently, acrolein is highly cytotoxic *in vitro* and *in vivo*. In cell culture studies, acrolein ( $\geq 10$  mM) reduces the viability of numerous cell lines such as bronchial endothelial and epithelial cells, bronchial and cardiac fibroblasts, retinal pigment epithelial cells as well as neuronal cells (Yoshida et al. 2009). Furthermore, acrolein modulates several signaling pathways including

**Table 4.** Structure of various chloropropanols as representants of heat-generated food toxicants.

Structure	Abbreviation/Chemical name	IARC Classification
	1,3-DCP 1,3-dichloropropane	Possible human carcinogen (group 2B)
	2-MCPD 2-chloropropane-1,3-diol	No data
	2,3-DCP 2,3-dichloro-1-propene	No data
	3-MCPD 3-chloropropane-1,2-diol	Possible human carcinogen (group 2B)

those that involve the transcription factors, nuclear factor- $\kappa$ B and activator protein-1 (Stevens and Maier 2008).

Evidence for *in vivo* formation of acrolein adducts from ingested acrolein is still lacking. Therefore, the question whether acrolein is mutagenic after oral exposure should be clarified in further investigations. The International Agency for Research on Cancer (IARC 1995) classified acrolein concerning its carcinogenic potential in Group 3.

### Chloropropanols and chloroesters

Chloropropanols (Table 4) are foodborne contaminants that are formed during the thermal processing of various foodstuffs above usually 150 °C (Wenzl et al. 2007). The research group of Professor Jan Velisek in Velisek et al. 1978 at the Institute of Chemical Technology in Prague was the first to demonstrate that chloropropanols could be formed in hydrolyzed vegetable proteins (HVP) produced by hydrochloric acid hydrolysis of proteinaceous by-products from edible oil extraction such as soybean meal, rapeseed meal and maize gluten. It was shown that hydrochloric acid could react with residual glycerol and lipids associated with the proteinaceous materials to yield a range of chloropropanols and their isomers. Generally, 3-MCPD is the most widely

occurring chloropropanol in acid-HVPs together with lesser amounts of 2-MCPD, 1,3-DCP, 2,3-DCP and 3-chloropropan-1-ol.

The mechanism of 3-MCPD formation have been shown that it is formed from glycerol or acylglycerols and chloride ions in heat-processed foodstuffs that contain fat with low water activity. Although the overall levels of 3-MCPD in bakery products are relatively low, the high level of consumption of bread, and its additional formation from toasting, indicate that this staple food alone can be a significant dietary source of 3-MCPD (Breitling-Utzmann et al. 2003).

The toxic effects were noticed in kidneys of rats and mice. According to studies, MCPD has mutagenic activity *in vitro* (Robjohns et al. 2003) however negative results have been reported from a bone marrow micronucleus assay in rats (Fellows 2000). It has been observed that mutagenic activity seen *in vitro* was not expressed *in vivo* (Committee on Mutagenicity of Chemicals in Food 2000). No epidemiological or clinical studies in humans have been reported. The Scientific Committee on Food of the European Commission considered that a threshold-based approach for deriving a tolerable daily intake would be appropriate and determined a value of 2 µg of 3-MDCP/kg bw (The Scientific Committee on Food 2001). This value was confirmed as a provisional maximum tolerable daily intake by

**Table 5.** Recent studies of thermally processed food toxicants and their induced side effects.

Carcinogen/mutagen	Induced side effect	Reference
HAAs	The formation of high levels of DNA adducts and precancerous colon lesions in the A/J mice (A <sub>2</sub> C)	Kim et al. (2016)
Acrylamide	Induced of chronic colitis risk in the Fischer 344 rats (PhIP)	Nicken et al. (2016)
	Risk factor of prostate cancer, and genotypes related to HAA metabolic enzymes	Koda et al. (2017)
	Caused significant pathological changes in the kidney with acute tubular necrosis in the distal tubules in adult Wistar rats	Rajeh and Al-Dhaheeri (2017)
	Can cause dominant lethal mutations by mechanisms leading to impaired chromosome segregation during cell division in male F344/DuCrI rats	Recio et al. (2017)
	Decrease in meiotic spindle mass and an increase in chromosomal disruption in BALB/c mice	Aras et al. (2017)
	Induction of intracellular ROS generation, decreased mitochondrial membrane potential and GSH depletion in HepG2 cells	Chen et al. (2017)
	Induction of oxidative stress, reduction in the activities of superoxide dismutase and glutathione peroxidase, induction of a mitochondria-mediated intrinsic apoptotic pathway by loss of mitochondrial membrane potential, <i>bax/bcl-2</i> dysregulation, cytochrome c release, and activation of caspase-3 pathway in rat intestinal epithelioid cell line IEC-6	Jiang et al. (2018)
	Induction of oxidative stress characterized by significant increase in ROS, malondialdehyde levels and GSH consumption in rat PC12 cells	Pan et al. (2018)
	Induction of cytotoxicity through decreased cell viability and increased ROS production. AA exposure caused marked cell death in human retinal pigment epithelium cells, possibly through the caspase-3 dependent pathway	Albalawi et al. (2017)
	Induction of mitochondria-mediated cell apoptosis increased oxidative stress through ROS generation in R2C Leydig cells	Sun et al. (2018)
HMF	Induced cytotoxic, anti-proliferative, and apoptotic effects to A549 cells at 4.6 mM IC <sub>50</sub> dose in 24 h	Kacar et al. (2017)
Furan	Induced colon cancer in Chinese hamster V79 cells	Monien et al. (2012)
	Induced cytotoxic to Caco-2 cells	Zhao et al. (2017)
PAHs	Moderate depletion in the lymphoid cells and weak immunostaining of CD20 antigen of few lymphocytes appeared in the spleen in male Sprague Dawley rats	Alam, Zeid, and Imam (2017)
	Induction of liver injury in Male Wistar rats	Baş, Pandir, and Kalender (2016)
	Induced hepatotoxicity and hepatocarcinogenicity in the livers of Fischer 344 rats	Tryndyak et al. (2017)
	Induction of marked changes in miRNA expression, characterized by over-expression of hepatic miRNAs, miR-34a, miR-93, miR-200a, miR-200b, and miR-224, and downregulation of miR-375 in the livers of Fischer 344 rats	de Conti et al. (2016)
	Induced carcinogenicity in male F344/N Nctr rats in a 2-year gavage study	Von Tungeln et al. (2017)
	Decreased serum testosterone levels and increased levels of malondialdehyde; decreased significantly the enzymatic activity of testicular antioxidants, including GSH, superoxide dismutase, and catalase and induced histopathological alterations in the testis of Male Sprague-Dawley rats	El-Akabawy and El-Sherif (2016)
	Endocrinological defects and cellular degenerative changes in Male Wistar albino rats	Kara, Bas, and Pandir (2016)
	Induction of histological lesions, apoptosis, and senescence in the testes of rats, which were accompanied by shortened telomeres, reduced levels of telomerase reverse transcriptase protein, and increased expression of DNA damage response-related proteins in mouse spermatocyte-derived cells (BaP)	Ling et al. (2018)
	Induction of DNA damages through the AhR pathway in Hepa1c1c7, ARNT negative Bpr cells and AhR negative Tao cells (BaP)	Cui et al. (2017)
	Induced genotoxicity to MCL-5 and HepG2 cell lines (BaP)	Shah et al. (2016)
NAs	Induced toxicity to human fibrosarcoma HT1080 cells (BaP)	Matsumoto et al. (2017)
	Induction of ROS production and accumulation; DNA damage and genomic instability/ mutation in A549 and NC-H1975 cell lines (BaA, IP)	Bai et al. (2017)
	Increased levels of lipid peroxidation adducts, revealed morphologic features of cell damage and proliferation, indicating oxidative and toxic damage in liver's old male C57BL/6 mice	Pardo et al. (2018)
	Increased pathological developments and liver damage resulting in a decrease in liver function in female Kunming mice (NDMA)	Xiang et al. (2017)
	Induction of hepatic fibrosis in male Sprague-Dawley rats (NDMA)	Choi et al. (2017)
	Induction of hepatic fibrosis in Wistar strain male albino rats (NDMA)	Thirupathi et al. (2017)
	Glucose metabolism disorder and mitochondrial dysfunction (NDMA)	Liu et al. (2017)
	Induction of liver tumorigenesis in HEP-3B cells (NDEA)	Panchal et al. (2017)
	Induction of ROS generation and inflammation, damaging liver cells and inducing hepatocarcinogenesis in male Kunming mice (NDEA)	Qiu et al. (2017)
	Induction of infertility and hepatotoxicity in Male New Zealand rabbits	Sheweita et al. (2017)
Acrolein	Increased the gene expression of inflammatory and oxidative stress markers in culture of primary bronchial epithelial cells	Dwivedi et al. (2018)
	Induced apoptosis by in mouse Leydig cells	Gu et al. (2017)
	Induced cardiac dysfunction through transient receptor potential cation channel subfamily A activation and autonomic imbalance characterized by a shift toward parasympathetic modulation in Female C57BL/6 and TRPA1—/—mice	Kurhanewicz et al. (2017)
	Increased the aggregation of alpha-synuclein, suggesting that alpha-synuclein self-assembly, a key pathological phenomenon in human Parkinson disease in PC12 cells	Ambaw et al. (2018)

(continued)

Table 5. Continued.

Carcinogen/mutagen	Induced side effect	Reference
Chloropropanols and chloroesters	Induction of lipid accumulation in HepG2 cells through cAMP/PKA and AMPK signaling pathways via Gi/o-coupled receptor (1,3-DCP)	Lu et al. (2017)
	Decreased cell viability, induced apoptosis by means of the decrease of mitochondrial membrane potential and inflammation of BV-2 cells (1,3-DCP)	Xiao et al. (2018)
	The levels of serum aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase in male Sprague–Dawley rats were significantly increased as compared with those in normal rats (1,3-DCP)	Kim et al. (2016)
	Decreased body weight gain, increased relative kidney weights, induced anemia, and epithelial cell necrosis in epididymal ducts in male F344 and obese Zucker rats (3-MCPD)	Toyoda et al. (2017)
	Decreased of mitochondrial membrane potential and the impairment of mitochondrial oxidative phosphorylation system in human embryonic kidney HEK293FT cells	Peng et al. (2016)

the Joint FAO/WHO Expert Committee on Food Additives (JECFA 2007). The European Commission has set a regulatory limit for 3-MCPD (0.02 mg/kg) in HVP and soya sauce (The European Commission 2001). The International Agency for Research on Cancer classified 1,3-DCP and 3-MCPD (IARC 2013) as possible human carcinogens (Group 2B).

There are very few data on the metabolism of 2,3-DCP. In theory, 2,3-DCP could be metabolized to produce epichlorohydrin and that is the reason for genotoxicity and carcinogenicity structural alerts. Available *in vitro* mutagenicity data suggests that 2,3-DCP is genotoxic bacterial and mammalian cells (with and without metabolic activation) (Committee on Mutagenicity of Chemicals in Food 2004). The mutagenic and carcinogenic data for 1,3-DCP has been summarized by JECFA in 2001. JECFA came to conclusion that 1,3-DCP was hepatotoxic, induced a variety of tumors in differ organs in rats, and was genotoxic *in vitro*. The Committee on Mutagenicity of Chemicals in Food (2003) concluded that 1,3-DCP is not genotoxic *in vivo* in the tested tissues. Thus, Committee on Carcinogenicity of Chemicals in Food (2004) concluded the 1,3-DCP should be noticed as genotoxic carcinogen. It was also recommended to investigate carcinogenicity of 1,3-DCP *in vivo*. On these findings a tolerable daily intake of 1,3-DCP has not been set yet.

Recent attention has also been given to 3-MCDP esters, based on the discovery that refined vegetable oils in many harbor significant amounts of chloroesters. Due to the widespread use of processed vegetable oils in many different foods, exposure to MCPD may be higher than previously assessed, as the esters could hydrolyze *in vivo* due to the action of lipases and hence release free MCPD (Seefelder et al. 2008). The occurrence of chloroesters in food was first reported in HVP by Professor Velisek's group (Velisek et al. 1980). MCPD esters have also been detected in goat's milk, milk powders manufactured from cow's milk and human breast milk. Due to their structural similarity to mono- and diacylglycerols, MCPD-monoesters and DCP-diesteres represent potential substrates for lipases and can thus be converted into MCPD in the gastrointestinal tract.

### Food-related toxicants in microwave heating

There is only limited information about the formation of HAAs using microwave heating. Some studies found that

carboline types of HAAs were generated in chicken legs and duck breast in microwave cooking systems, while others demonstrated that HAAs were not formed during microwave cooking. Moreover, PhIP formation was compared between microwave processing and conductive heating methods that did not have equivalent heating ability. Thus, it is necessary to investigate the production of HAAs under microwave heating conditions systematically as these findings remain a controversy. In Fan et al. (2018) study, the formation of PhIP was comparable between these two heating methods. Microwave heating was found to produce PhIP in beef soup, but in smaller amounts ( $<0.1 \text{ ng} \cdot \text{mL}^{-1}$ ), compared with conductive heating ( $0.3 \text{ ng} \cdot \text{mL}^{-1}$ ). Thus, microwave heating may be a much safer cooking method in terms of less mutagenic PhIP formation.

Effect of different home-cooking methods on AA formation in pre-prepared croquettes was evaluated. Namely, the experiment showed that the mean AA content in all samples prepared in microwave conditions was significantly higher ( $420 \mu\text{g/kg}$ ) than that of roasting ( $360 \mu\text{g/kg}$ ), deep-frying ( $298 \mu\text{g/kg}$ ) or pan-frying ( $285 \mu\text{g/kg}$ ) ( $p < 0.05$ ). The manner in which heat is transmitted to a food appears to have a significant impact on the rate of AA formation. Among the domestic methods used, microwave treatment was more favorable for AA formation in products (Michalak et al. 2017). Yuan et al. (2007) investigated that higher AA level during microwaving and boiling of potato chips was obtained by microwaving heating method. Treatment of potato chips with microwave heating for 2.5–3.5 min in the range 550–750 W similarly resulted in acrylamide formation. The highest AA content was formed by 750 W microwave treatment as  $0.9 \pm 0.1 \text{ mg/kg}$ , which was significantly higher than that produced by traditional frying ( $180 \pm 1^\circ\text{C}$ ),  $0.7 \pm 0.1 \text{ mg/kg}$  ( $p < 0.05$ ). However, different experiment showed that microwave application prior to frying resulted in a marked reduction of AA level in the surface region, whereas a slight increase was noted for the core region. When the potato strips were subjected to frying after a microwave pre-cooking step, AA content in the whole potato strip was reduced by 36%, 41%, and 60% for frying at 150, 170, and  $190^\circ\text{C}$ , respectively, in comparison to the control (Erdogdu et al. 2007). Barutcu, Sahin, and Sumnu (2009) showed that microwave frying provided lower AA content and lighter color as compared to chicken parts fried



conventionally for 5 min for all types of flours. This reduction in AA level was the highest (34.5%) for rice flour containing batter.

HMF is food toxicant which usually occurs in honey and milk products. Application of microwave, ultrasound, and infrared heating of honey has been reported and claims have been made on the improved product quality. Microwave and infrared heating have gained popularity in food processing over conventional heating owing to their inherent advantage of rapidity and better-quality product. HMF is easily absorbed from food through the gastrointestinal tract and, upon being metabolized into different derivatives, is excreted *via* urine. In addition to exerting detrimental effects (mutagenic, genotoxic, organotoxic and enzyme inhibitory), HMF also provides antioxidative, anti-allergic, anti-inflammatory, anti-hypoxic, anti-sickling, and anti-hyperuricemic effects (Shapla et al. 2018). Bartakova et al. (2011) checked impact of HMF formation in microwave heating. Despite the honey having reached relatively high temperature levels (80–90 °C) at the highest power levels and the longest time periods, there was no gradual significant increase in HMF content which could be expected at conventional heating. The influence of different temperatures on HMF formation during the storage of UHT milk was studied by Cais-Sokolinska, Pikul and Dankow (2004). There were no significant differences in HMF concentration in milk stored at 4 and 8 °C, but storage at room temperature caused a two-fold increase in its amount when compared with freshly sterilized product. HMF concentration was strongly correlated with milk color changes.

Human exposure to furan occurs mainly through consume of coffee, canned foods and baby food. Recent studies have suggested that a simple approach to avoiding furan would be to heat infant foods in an open can while applying stirring. This would really result in a considerable evaporation of furan, if parents would adhere to this practice. The first studies regarding this phenomenon reported losses of 29–55% in vegetable purees during different warming procedures in microwave ovens (Santonicola and Mercogliano 2016).

Microwave heating has found application in reducing of PAHs content in food. The Kiralan, Erdogdu and Tekin's (2016) results, they demonstrated that the pre-microwave application led to 75% reduction of total PAHs content in olive pomace oil. This study highlighted the possibility of an alternative innovative strategy to apply in a process to suggest a simple solution for a significant industrial problem.

Another study found that that cooking of dried seafood products using indirect heating such as microwave cooking and steaming caused less increase in NDMA, as compared with direct heating such as a gas range (Lee et al. 2003).

## Summary

Cancer diseases are one of the most dangerous scourges of modern civilization. The occurrence of human cancer in a large percentage depends on environmental factors, which also includes diet. Evidence of the relationship between nutrition and cancer risk has been provided in a myriad of

experimental studies. Recent studies of side effects induced by thermally processed food toxicants were presented in Table 5. The strategies developed so far mitigate or eliminate formation of processed food toxicants and were studied in lab conditions but may not be suitable for commercial application. Therefore, further work is necessary to explore different possibilities studied in the laboratories on industrial conditions. It is important to note, that various food-related toxicants can be simultaneously formed during a single thermal process. Moreover, metabolism of food toxicants is also vital because of their danger to DNA structure, tissue and organ mutations. The xenobiotics, after being metabolized are thought to be even more toxic than the product itself. In this case, experiments at molecular level are needed to control the metabolism of carcinogens in human body. Nevertheless, reducing carcinogens in food products while protecting other quality aspects still remains a major challenge. Using microwave heating can be promising in the fight with forming thermal food toxicants during conventional food heat treatment, especially in food pretreatment.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Abbreviations

1,3-DCP	1,3-dichloropropene
2-MCPD	2-chloropropane-1,3-diol
2,3-DCP	2,3-dichloro-1-propene
3-MCPD	3-chloropropane-1,2-diol
AA	acrylamide
AzC	2-amino-9H-pyrido[2,3-b]indole
BaA	benz[a]anthracene
BaP	benzo[a]pyrene
BbF	benzo[b]fluoranthene
BghiP	benzo[g,h,i]perylene
BjF	benzo[j]fluoranthene
BkF	benzo[k]fluoranthene
Bw	body weight
CHR	chrysene, benzo[a]phenanthrene
DBaA	dibenz[ah]anthracene
Glu-P-1	2-amino-6-methylpyridine[1,2- $\alpha$ :3',2'-d]imidazole
Glu-P-2	2-aminodipyrido[1,2- $\alpha$ :3',2'-d]imidazole
GSH	glutathione
HAA	heterocyclic aromatic amines
HMF	5-hydroxymethylfurfural
IP	indeno[1,2,3-c,d]pyrene
IQ	2-amino-3-methylimidazo[4,5-f]quinolone
MeAzC	2-amino-3-methyl-9H-pyrido[2,3-b]indole
MeIQ	2-amino-3,4-dimethylimidazo[4,5-f]quinolone
NA	nitrosoamines
NDBA	N-nitrosodibutylamine
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NDPA	N-nitrosodipropylamine
NMOR	N-nitrosomorpholine
NPIP	N-nitrosopiperidine
NPYR	N-nitrosopyrrolidine
PAHs	polycyclic aromatic hydrocarbons
PAPS	3'-phosphoadenosine-5'-phosphosulphate
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
PUFAS	polyunsaturated fatty acids
ROS	Reactive Oxygen Species



SMF	5-sulfooxymethylfurfural
SULT	sulfotransferases
Trp-P-1	3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole
Trp-P-2	3-amino-1-methyl-5H-pyrido[4,3-b]indole

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