Chemical Hazards in Foods

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Abstract This extensive chapter focuses on chemical hazards that have increased dramatically because of the economic development in various sectors including agriculture, food processing, industry and transport. Chemical hazards in food chain pose a wide range of health risks varying from irritation to chronic diseases and cancer. Moreover, exposure to a combination of chemical hazards may be associated with additive, antagonistic, and synergistic interactions. Thus it is necessary to monitor their concentrations in food and reduce exposure to consumers. The well compiled chapter includes occurrence, detection, legislation, toxicity and risk assessment of a variety of chemicals of both natural and man-made origin.

Keywords Chemical hazards · Chemical contaminants · Food

Introduction

Food safety is a global concern and major issue for both manufacturers and consumers. Many toxic chemicals including natural occurring toxins, food additives, pesticides, adulterants, process contaminants, environmental contaminants, food contact materials, veterinary drugs, and others can be found in foods and feeds and may pose a risk to human and animal health. Among these chemical hazards, mycotoxins are of greatest concern in terms of human health as well as economics. While pesticides are important to control pests and diseases caused by pathogens and parasites, they can harm human and animal health when accumulate in agricultural products. Several chemical contaminants including acrylamide, furan, 3-MCPD, glycidyl fatty acid esters (GE), and polycyclic aromatic hydrocarbons (PAHs) can also be formed in food by cooking or other food processing methods. Acrylamide can form

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as a by-product during the heating of starchy food products like potato and bread to above 120 °C. 3-monochloropropane-1-2 diol (3-MCPD) and GE are other process contaminants that form during the refinement of edible oils and fats. The current knowledge on several chemical hazards that have been natural or man-made origin are discussed in this chapter.

Mycotoxins

Mycotoxins occur in agricultural products mainly the result of the activity of three genera: *Aspergillus*, *Penicillium* and *Fusarium* (Pitt et al. 2000). Fungi from genera *Fusarium* are mainly active in the field, while both *Aspergillus* and *Penicillium* species are considered the more likely storage fungi. Mycotoxins have been associated with severe toxic effects to animals and humans, from allergic responses to cancer and death, depending on a number of factors including intake levels, duration of exposure, toxin species, mechanisms of action, metabolism and defence mechanisms. The most dangerous and frequently found mycotoxins in nature are aflatoxins (AFs), ochratoxin A (OTA), trichothecenes (T-2/HT-2 toxin and deoxynivalenol (DON)) and fumonisins (FUMs) (Kabak et al. 2006). The chemical structures of frequently detected mycotoxins are illustrated in Fig. 1. The Scientific Commission of the European Community have regulated maximum limits (MLs) for certain mycotoxins including naturally occurring AFs, aflatoxin M_1 (AFM$_1$), OTA, FUMs (fumonisin B_1 (FB$_1$) + fumonisin B_2 (FB$_2$)), DON, zearalenone (ZEA) and patulin in foodstuffs due to their health hazards to human (European Commission 2006). Mycotoxins have been evaluated for their carcinogenic potential by International Agency for Research on Cancer (IARC) (IARC 1993). The carcinogenic potential of some mycotoxins have been shown in Table 1.

Aflatoxins

AFs are produced primarily by three species of toxigenic Aspergilli, *A. flavus*, *A. parasiticus* and rarely *A. nomius*. Fungal contamination and subsequently AFs synthesise can occur in commodities in the field, at harvest, during post-harvest and in storage. The main factors that affect the formation of AFs are temperature and humidity (EFSA 2004). Both *A. flavus* and *A. parasiticus* can grow at temperatures ranging from 10 to 43 °C, with an optimum temperature of 32–33 °C. However, AFs can be synthesised at 12–40 °C (Koehler et al. 1985).

AFs can be found a wide range of commodities (Table 2) including peanuts, tree nuts (hazelnuts, pistachios, almonds, walnuts, Brazil nuts), spices (*Capsicums* spp.), dried fruits (figs, raisins) and a range of cereals (especially maize). Although AFs contamination is generally considered to be a problem in tropical/subtropical regions of Africa, Asia and Latin America, it can also be produced in temperate countries of Europe and North America (EFSA 2004).
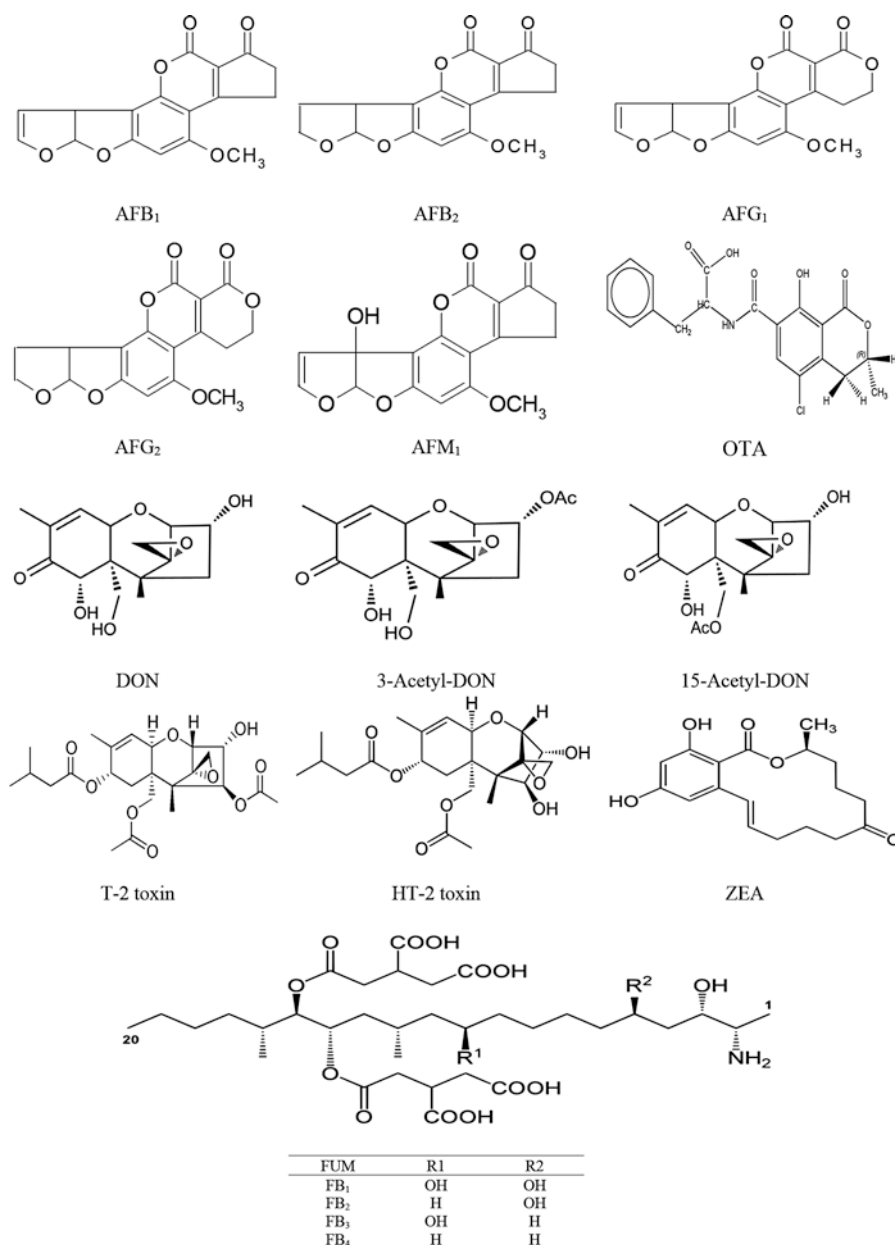
Fig. 1 Chemical structures of mycotoxins

Table 1 Mycotoxins classified by IARC

Mycotoxin	IARC Group	Evaluation
AFB_1 and naturally occurring AFs	Group 1	Human carcinogen
Aflatoxin M_1	Group 2B	Possibly carcinogenic to humans
Ochratoxin A	Group 2B	Possibly carcinogenic to humans
Fumonisin B_1	Group 2B	Possibly carcinogenic to humans
Sterigmatocystin	Group 2B	Possibly carcinogenic to humans
Deoxynivalenol	Group 3	It is not classifiable as to its carcinogenicity to humans
Zearalenone	Group 3	It is not classifiable as to its carcinogenicity to humans
Patulin	Group 3	It is not classifiable as to its carcinogenicity to humans

Table 2 Major mycotoxins, associated moulds and product of primary concern

Mycotoxin	Principal producing moulds	Product of primary concern
Aflatoxins	*Aspergillus flavus, A. parasiticus, A. nomius*	Peanuts, tree nuts (hazelnuts, pistachios, almonds etc.), figs, raisins, *Capsicums*, maize, cocoa beans
Ochratoxin A	*Aspergillus ochraceus, A. carbonarius, Penicillium verrucosum.*	Cereals (wheat, rice, etc.) and cereal-based products, *Capsicums*, raisins, figs, coffee and cocoa beans, wine and beer
Fumonisin B_1	*Fusarium moniliforme, F. proliferatum*	Maize and maize-based products
Deoxynivalenol	*Fusarium graminearum, F. culmorum*	Cereals (especially wheat, rice and barley) and cereal-based products
T-2/HT-2 toxin	*Fusarium sporotrichioides, F. equisetiiculmorum, F. poae*	Cereals and cereal-based products
Zearalenone	*Fusarium graminearum, F. culmorum, F. equiseti, F. sporotrichioides*	Maize and maize-based products
Moniliformin	*Fusarium moniliforme, F. oxysporum, F. fujikuroi*	Cereals and cereal-based products
Patulin	*Penicillium expansum, P. patulum, Aspergillus clavatus, Byssochlamys fulva*	Apple juice/concentrate

AFs occur in several chemical forms, approximately 19 different toxic derivatives of AFs have been reported. The four main naturally produced AFs (Fig. 1) are AFB_1, aflatoxin B_2 (AFB_2), aflatoxin G_1 (AFG_1) and aflatoxin G_2 (AFG_2). "B" and "G" refer to the blue and green fluorescent colours produced by these compounds under ultraviolet (UV) light on thin-layer chromatography plates, while subscript numbers 1 and 2 indicating major and minor compounds respectively. Following ingestion, AFB_1 is metabolized in the liver through the cytochrome P450 enzyme

system to various metabolites, including the endo- and exo-epoxides of AFB_1, the hydroxyl-metabolites AFM_1, aflatoxins M_2 and M_4, and aflatoxins P_1 and Q_1, as well as conjugated metabolites (McLean and Dutton 1995). The carcinogenicity of AFB_1 arises from its interaction with the DNA-guanine moiety to produce to the aflatoxin-N7-guanine adduct, whereas the acute toxicity of AFB_1 is believed to stem from interaction between the dihydrodiol and protein amino groups to produce Schiff base adducts (Pitt et al. 2000).

AFM_1, the 4-hydroxy metabolite of AFB_1, is the predominant metabolite of AFB_1 in milk. When lactating animals such as cows, goats and humans are fed with feedstuffs contaminated with AFB_1, this metabolite can be transferred to milk as AFM_1 in the range of 0.3–6.3% (Choudhary et al. 1998).

AFs are major class of mycotoxins produced by *Aspergillus* species which are both acutely and chronically toxic to various animal species, including humans, causing acute liver damage, liver cirrhosis, tumour induction and teratogenesis (Pitt 2000). AFs were first discovered in 1960s as a result of deaths of thousands of turkeys in the UK and this was referred to as "turkey × disease". Investigation led to the fact that outbreaks were associated with groundnut meal infected with *A. flavus* and contaminated by a compound which fluoresced blue under UV light (Moss 2002).

Exposure to AFs at high levels can led to acute human aflatoxicosis leading to jaundice, oedema, GI haemorrhage, and ultimately, death (Shephard 2008a). There have been reported several outbreaks of acute toxicity of AFs to humans, but not rarely. One of the most serious outbreak of aflatoxicosis occurred in the region of western India in 1974, leading to 397 recognized cases and 106 deaths. The outbreak was traced to consumption of maize heavily contaminated with AFs ranged between 6.25 and 15.6 mg kg^{-1}. Daily consumption of toxin by some of the patients was calculated to be 2–6 mg of AFs for several weeks (Krishnamachari et al. 1975). Other documented fatal human aflatoxicosis outbreaks have been reported in Kenya in 1981: 20 cases and 12 reported deaths (Ngindu et al. 1982); and Malaysia in 1988: 13 deaths (Lye et al. 1995). One of the largest outbreak of aflatoxicosis have happened in the eastern and central districts of Kenya in 2004 where 317 people were ill and 215 died, following the consumption of contaminated maize (up to 8 mg kg^{-1} AFs). More recently, a similar outbreak in the eastern districts of Kenya during 2005 resulted in 75 cases, with 32 deaths (Shephard 2008b).

Two human diseases, Kwashiorkor and Reye's syndromes may also associate with the ingestion of AFs-contaminated food. Kwashiorkor, a disease of children in Northern Africa, is usually attributed to nutritional deficiencies, but may also be related to AFs intake (Hendrickse et al. 1982). Similarly, Reye's syndrome, which is characterized by acute encephalopathy and fatty degeneration of the viscera has been linked to AFs because this mycotoxin has been detected in the organs of affected children in Thailand, Australia and New Zealand (Becroft and Webster 1972). AFs have been linked to hepatocellular carcinoma and classified as human carcinogens (IARC 1993).

Ochratoxin A

OTA is produced primarily by *Penicillium verrucosum*, *Aspergillus ochraceus* and *Aspergillus carbonarius* (EFSA 2006). While *P. verrucosum* is the main producer in cereals and cereal products for OTA in cooler regions of Northern Europe (Olsen et al. 2003) and Canada (JECFA 2001), *A. ochraceus* grows at moderate temperatures and it can infect a wide range of stored commodities including coffee beans, cocoa, cereals and edible nuts (EFSA 2006). *A. carbonarius* grows at high temperatures and is associated with maturing fruits, especially grapes (JECFA 2001).

Invasion with toxigenic species of *Aspergillus* and *Penicillium* has been reported worldwide and subsequently OTA can be found as a natural contaminant in cereals (wheat, maize, oat, millet, rye, barley and rice) cereal-based products, pulses, dried figs, raisins, wine, grape juice, beer, coffee beans, cocoa, as well as nuts (Table 2).

OTA has been reported to be carcinogenic (group 2B), teratogenic, immunotoxic, genotoxic and possibly neurotoxic to experimental animals (European Commission 2002). It is also a well-known nephrotoxic agent and has been associated with fatal human kidney disease, and with an increased incidence of tumours of the upper urinary effect (JECFA 2001).

Fumonisins

FUMs are produced primarily by *Fusarium moniliforme* and *Fusarium proliferatum*. These species cause *Fusarium* kernel rot of maize, an important disease in hot climates. As *F. moniliforme* and *F. proliferatum* grow over a wide range of temperature but only at relatively high water activities (above about 0.9), FUMs are formed in maize only before harvest or during the early stage of drying. Other FUMs producing species are *F. napiforme*, *F. anthophilum*, *F. dlamini* and *F. nygamai* (Musser and Plattner 1997).

FUMs can also be found in sorghum, asparagus, rice and mung beans. It has been also detected in several processed products such as beer, bread, breakfast cereals, chilli pickles, corn flakes, curry paste, maize muffin, maize pops cereals, maize starch, maize-based infant cereals, noodles (Arranz et al. 2004).

FUMs are characterized by a 19-20 carbon amino-polyhydroxyalkyl chain which is diesterified with propane-1,2,3-tricarboxylic acid. The first FUMs identified were FB_1 and FB_2 from cultures of *F. moniliforme* MRC 826, an isolate from South African maize (Gelderblom et al. 1988). The 28 FUMs analogs that have been characterized since 1988 can be separated into four main groups, identified as the fumonisin A, B, C, and P series (JECFA 2001). FB_1 has an empirical formula of $C_{34}H_{59}NO_{15}$ with a molecular weight of 721.838, and a melting point of 103–105 °C (Scott 1993).

FB_1 is the causative agent in the incidence of neurotoxic syndrome equine leukoencephalomalacia (ELEM) (Gelderblom et al. 1996). The ELEM, also known as "crazy horse disease" characterized by liquefactive necrotic lesions in the white

matter of the cerebral hemispheres of horses and other equine species. FB_1 also causes pulmonary oedema syndrome and hydrothorax in pigs (Ross et al. 1990); and it is also hepatotoxic and carcinogenic in rats (Gelderblom et al. 1988, 1991, 1996). The liver and kidney are the main target organs of FB_1 in mice and rats (Gelderblom et al. 1991). The FB_1-induced changes to cellular membranes, specifically those related to fatty acid changes in the major membrane phospholipid, and the altered fatty acid content of the hepatocytes are likely to be key events in explaining the cytotoxic effects and altered growth responses induced by FUMs in primary hepatocytes (Gelderblom et al. 1996).

FB_1 is not genotoxic and mutagenic (Gelderblom and Snyman 1991). There is some evidence *in vitro* for developmental toxicity, but except for chicken no teratogenic effects were reported in either *in vitro* or *in vivo* studies (SCF 2000). Other toxic effects of FB_1 such as neurotoxic and immunotoxic have also been reported (Stockmann-Juvala 2007).

Trichothecenes

Trichothecenes are a very large family of naturally occurring sesquiterpenoid metabolites produced by a number of fungal genera including *Fusarium*, *Stachybotrys*, *Myrothecium*, *Trichoderma*, *Cephalosporium*, *Verticimonosporium* and others. Although the number of trichothecenes runs into hundreds, only a few of them have been shown to be agriculturally important. Among Fusaria, *F. poae*, *F. sporotrichioides*, *F. moniliforme*, *F. culmorum* and *F. graminearum* are the most common trichothecene producers (Bennet and Klich 2003).

The trichothecene mycotoxins are non-volatile, low-molecular-weight (MW 250–500). The trichothecenes are colourless, mostly crystalline solids (European Commission 2003). All trichothecenes contain an olefinic bond at 9, 10 and an epoxide group at C-12, 13, characterized as 12, 13-epoxytrichothecene, and classified mainly as types A, B, C and D (Ciegler 1978) The most common type A trichothecenes are T-2 toxin, HT-2 toxin, neosolaniol, monoacetoxyscirpenol and diacetoxyscirpenol produced by mainly *F. sporotrichioides* and *F. poae*, while common type B trichothecenes include DON, and its 3-acetyl and 15-acetyl derivatives (3-AcDON and 15-AcDON, respectively), nivalenol (NIV) and fusarenon-X produced principally by *F. graminearum* and *F. culmorum* (Placinta et al. 1999). The type C trichothecenes are crotocin and crotocol (Ciegler 1978), while macrocyclic trichothences (type D) include satratoxins, verrucarins and roridins and produced by the members of the genus *Myrothecium* and *Stachybotrys* (Sudakin 2003).

Trichothecenes mainly occur in cereal grains such as wheat, barley, maize, oats, rice, soya beans and in derived products such as breakfast cereals, bread and beer. These compounds are also seldom detected in other food commodities including sorghum, potatoes, bananas, mustard seed, groundnuts, mangoes and sunflower seed. According to European Commission reports (2003), type B trichothecenes such as DON (57% of tested grain samples), 15-AcDON (20%), NIV (16%), fusarenon-X

(10%) and 3-AcDON (8%) are more frequent in European grain samples than type A trichothences. While T-2 toxin is the most common type A trichothecene (20% of tested samples), other toxins including HT-2 (14%), T-2 triol (6%), diacetoxyscirpenol (4%), monoacetoxyscirpenol (1%) and neosolaniol (1%) are less common.

T-2 Toxin and HT-2 Toxin

T-2 toxin and HT-2 toxin (type A trichothecenes) are produced by certain *Fusarium* species, especially *F. sporotrichioides*, *F. poae*, *F. equiseti* and *F. acuminatum* (JECFA 2001). T-2 and HT-2 toxins often occur together rarely in grains such as maize, wheat, barley, oats and rye as wells as in some cereal-based products including malt, beer and bread (SCF 2001a). Among type A trichothecenes, T-2 and HT-2 toxins were found to be two most frequent contaminants of cereal grains (3490 samples) from EU Member States. The frequency of occurrence of T-2 toxin and HT-2 toxin was 28% and 24% for maize, 21% and 12% for wheat (and wheat flour), 21% and 17% for rye (and rye flour), 16% and 41% for oats, and 3% and 5% for barley, respectively. The mean concentrations of T-2 toxin in positive samples were ranged from 3 to 255 μg kg^{-1} in maize, 2–160 μg kg^{-1} in wheat (and wheat flour), 10–193 μg kg^{-1} in rye (and rye flour), 10–550 μg kg^{-1} in oats, and 1.7–280 μg kg^{-1} in barley. The mean value of HT-2 toxin contamination has been reported to range from 3 to 120 μg kg^{-1} in maize, 3.3–50 μg kg^{-1} in wheat (and wheat flour), 10–70 μg kg^{-1} in rye (and rye flour), 10–1150 μg kg^{-1} in oats, and 1.7–287 μg kg^{-1} in barley (European Commission 2003). T-2 toxin and its metabolites may also be found in trace amount in animal products.

T-2 toxin can inhibit DNA, RNA and protein synthesis both *in vitro* and *in vivo* (Shinozuka et al. 2001). This compound also induces apoptosis both *in vitro* (at 10 ng ml^{-1} levels in HL-60 human promyelocytic leukemia cells and at 0.2 g ml^{-1} in mouse thymocytes) (Ueno et al. 1995; Shinozuka et al. 2001) and *in vivo* (at 10 mg kg^{-1} b.w. in intestinal crypt epithelial cells, and thymic and splenic lymphocytes in mice) (Li et al. 1997) in various organs. Moreover, T-2 toxin could inhibit the mitochondrial electron transport system, with succinic dehydrogenase as one site of action (Khachatourians 1990).

T-2 toxin is about 10 times more toxic than DON (Ueno et al. 1973). Acute effects of T-2 toxin occur after oral exposure to 0.06–10 mg kg^{-1} body weight (b.w.) in various species. The effects include non-specific symptoms like weight loss or poor weight gain, feed refusal or reduced feed intake, dermatitis, vomiting, diarrhoea, haemorrhages and necrosis of the epithelium of stomach and intestine, bone marrow, spleen, testis and ovary (SCF 2001a).

T-2 and HT-2 toxins have been associated with alimentary toxic aleukia (ATA) in humans. During World War II, a very severe human disease occurred in the former Soviet Union, particularly population in Orenburg. The disease, known as ATA is believed to be related to ingestion of over-wintered grains infected with *F. poae* and *F. sporotrichioides* that were milled into flour and made into bread. The most severe outbreak of the disease was in 1944, but outbreaks have also been reported in 1952,

1953, and 1955 particularly in people consuming over-wintered wheat (SCF 2001a). In an outbreak of toxicosis in China, 97 out of 165 persons fell ill who had consumed rice infected with *F. heterosporum* and *F. graminearum*. The level of T-2 toxin in these mould rice was up to 420 µg kg⁻¹. The symptoms were nausea, dizziness, vomiting, chills, abdominal distension, abdominal pain, thoracic stuffiness and diarrhea (Wang et al. 1993).

The FAO/WHO Joint Expert Committee on Food Additives (JECFA) proposed a provisional maximum daily intake (PMTDI) of 60 ng kg⁻¹ b.w. per day for T-2 and HT-2 toxins, alone or in combination, using a safety factor 500 (JECFA 2001). A temporary TDI (t-TDI) of 0.06 µg kg⁻¹ b.w. for the sum of T-2 and HT-2 toxins was set by the SCF of the European Commission (SCF 2001a). No regulations exist for T-2 and HT-2 toxins but EU plans regulatory limits for these mycotoxins in cereals and cereal products.

Deoxynivalenol

DON also known as vomitoxin belongs to the type B trichothecenes and is produced principally by *F. graminearum* (teleomorph *Gibberella zeae*) and *F. culmorum*. Both species are important plant pathogens, causing FHB in wheat and *Gibberella* ear rot in maize (JECFA 2001).

DON has been found as a natural contaminant in various cereal crops such as wheat, buckwheat, maize, barley, oats, rye, rice, sorghum and triticale. It has also been detected in processed cereal products including malt, beer, bread and breakfast cereals etc. In contaminated cereals 3-AcDON and 15-AcDON can in significant amounts (10–20%) occur concomitantly with DON (SCF 2000). Data were available for samples of 11,022 grains from EU Member States. DON was found to be the most frequent trichothecene in cereal grains such as wheat (and wheat flour) (6358 samples, 61% positive), maize (520 samples, 89% positive), barley (781 samples, 47% positive), rye (and rye flour) (271 samples, 41% positive), and oats (595 samples, 33% positive). The concentrations of DON in positive samples ranged from 2 to 50,000 µg kg⁻¹ in wheat (and wheat flour), 7–8850 µg kg⁻¹ in maize, 1.7–619 µg kg⁻¹ in barley, 2–5004 µg kg⁻¹ in oats and 2–595 µg kg⁻¹ in rye (and rye flour). The frequency of occurrence of 3-AcDON and 15Ac-DON was 8% and 20% positive, with ranging from 1.7 µg kg⁻¹ to 520 µg kg⁻¹ and from 1.7 µg kg⁻¹ to 1320 µg kg⁻¹, respectively (European Commission 2003). The transfer of DON from animal feed to meat and other animal products appears to be extremely small.

DON (12, 13-epoxy-3, 4,15-trihydroxytrichotec-9-en-8-one) has a molecular weight of 296.32 with the empirical formula of $C_{15}H_{20}O_6$ and a melting point of 131–135 °C. DON contains one primary and two secondary hydroxyl groups and is soluble in water and polar solvents such as methanol and acetonitrile.

DON may induce several detrimental health effects after acute, short-term, or long-term administration. The exposure to DON at low concentrations can result in a reduction in food consumption (anorexia), while higher doses induce vomiting (emesis). Although it has been suggested that chronic toxic effects of 15-AcDON

are similar to those of DON, 15-AcDON had twice the acute oral toxicity of DON. Acute doses of both DON (60–1000 mg kg⁻¹) and 15-AcDON (40–160 mg kg⁻¹) result in a variety of toxic signs ranging from necrosis of the gastrointestinal tract, bone marrow, lymphoid tissues, and focal lesions in kidney and cardiac tissue. The kidney of the mice appears to be 5–10 times more sensitive to 15-AcDON than DON, whereas the hearth was more sensitive to DON than 15-AcDON (Forsell et al. 1987).

Food Additives and Flavourings (FAF)

FAF are a variety of organic chemicals that are incorporated deliberately or by accident into the food during production/processing, which cannot normally be consumed as food (Deshpande 2002; Inetianbor et al. 2015; Martins et al. 2019). According to the Food and Drug Administration (FDA), food additives are any substance, the intended utilize of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise effecting the features of any foodstuff (FDA 1993). Direct food additives are substances which are deliberately supplemented to food for a specific aim, while indirect ones are the substances to which foods are exposed throughout manufacturing, processing, packing or storage, and found in foods at trace amounts (Al-Shammari et al. 2014; Pressman et al. 2017). FAF are used for various purposes (Deshpande 2002; Shibamoto and Bjeldanes 2009; Pressman et al. 2017). These are:

- Assisting in technological processes in the production of processed foods
- Preventing microbiological deterioration
- Increasing durability
- Maintain and protecting nutritive value and
- Making food attractive to consumers by improving and correcting sensory properties such as colour, appearance, taste, texture, and flavour.

Some FAF have been used in foods since ancient times. For example; vinegar and salt in the production of pickles, salting in bacon or fish, or sulphur dioxide in wines (Shibamoto and Bjeldanes 2009). Food additives used in the production of foodstuffs are toxic as dose-dependent (Ergun 2015). However, they do not have harmful effects on human health if they are used in accordance with the specified acceptable daily intake (ADI) values in the results of scientific research (Inetianbor et al. 2015).

Today, more than 100,000 chemical agents are used for various purposes and this number is increasing every year. Human health and the environment have been damaged by the mistakes made in the years when the chemicals were used intensively and relatively uncontrolled. As a result, fear and reaction to the use of chemicals in societies have emerged. However, toxicological investigations and the development of risk management practices for chemicals have enabled the use of safe chemicals. Today, drug, cosmetics, pesticides, chemicals used in industry, as well as the effects of FAF on human health are examined in detail, and the use of

unacceptably risky ones is not permitted. The developed international rules aim to prevent human health from being harmed by chemical use. In this process, countries do not make evaluation on their own related to chemicals. International organizations determine the rules of safe use. Food additives and its fragmentation are the most effectively controlled group of chemicals. The products must be absolutely nontoxic in the amounts used (Ergun 2015; Inetianbor et al. 2015).

The use of additives in foods is regulated by organizations responsible for food, medicine and health protection in most countries. Although regulations vary from country to country, they are all compatible with toxicological and technological applications (Ergun 2015). Each food additive has an internationally recognized number. In the European Community, the substances which are allowed to be used are given the E-code (number), which is the first letter of the word European. The E-code means that an additive is suitable for use in foods (Inetianbor et al. 2015; Shukla et al. 2017).

The quantity and type of food additives used must be approved by health institutions. On this area, the United States FDA is a very important organisation. On the other hand, they should not conceal processing and production defects, deceive the consumer and reduce the nutritional value of food. The use of food additives has been prohibited or restricted in certain foodstuffs because of the potential adverse effects on human health, sometimes because of the lack of technological necessity or misleading the consumer. The effects of food additives on health are only appear due to the fact that they are added to foods in very high doses, or as a result of one-way feeding for a long time (Ergun 2015).

Foodstuffs present in the market include distinct kinds and amounts of food additives, which may cause some health problems in humans (Inetianbor et al. 2015). The health problems of food additives on human beings can occur immediately, or if there is persistent exposure or accumulation in the body, they may have long-term detrimental effects. Acute adverse effects may occur in the form of headaches, energy reduction, allergic reactions and mental, behavioural or immune-related changes (Pandey and Upadhyay 2012). Synthetic preservatives and artificial colorants can exacerbate the symptoms of attention deficit and hyperactivity disorder. Moreover, food additives can also cause the reduction of nutritional value of foods. In this case, it may lead to subclinical malnutrition in people who are not adequate and balanced nutrition (Inetianbor et al. 2015).

Food Colours

Synthetic and natural food colours (from vegetables, minerals, or animals) include colour adjuncts, colour stabilizers, colour protective, colour retention agents, etc. Most food colours do not add any nutritional value to the food, but they provide to the food the appearance that consumers want (Pandey and Upadhyay 2012; Shukla et al. 2017). Red, blue and yellow colour pigments used in the production of foodstuffs and derived from natural sources belong to polyphenols and carotenoid family (Shukla et al. 2017). They are usually used in ripe olives, potatoes, candies, pastries,

sauces and syrups (Shibamoto and Bjeldanes 2009). Artificial dyes are one of the most frequently used contaminants in foods. The exposure to food colourants may results in a reduction in the learning ability of experimental animals (Aljaff et al. 2013).

Tartrazine is a monoazo dye that can be used as an additive in food products (Deshpande 2002). However, high amounts of tartrazine intake may cause various health problems in humans. Especially, it may have genotoxic effects against human lymphocytes and can also be straightly linked to DNA. Moreover, it may cause adverse effects on neurobehavioral parameters and may also lead to learning and memory deficiency (Inetianbor et al. 2015). Tartrazine can also create allergic problems, tissue swelling, hyperactivity, urticaria (hives), asthma, purpura, and itching in sensible persons (Deshpande 2002; Omaye 2004; Shibamoto and Bjeldanes 2009). Because of these toxic effects, it is of great importance to audit the concentration of tartrazine added in foodstuffs.

Curcumin is another colourant, which may cause iron deficiency in sensitive patients or mild nausea and diarrhoea when taken in high amounts (Inetianbor et al. 2015).

Annatto extract (bixin-based and norbixin-based, E160b), a carotenoid, is a native colouring substance acquired from the orange coloured external layer of the seeds of the tropical tree *Bixa orellana* L. (Deshpande 2002). It is allowed to use in certain products such as margarine, cheeses, appetizing snack products, coated nuts, extruded products and flavoured cereals, except for spices (Scotter 2009). However, it has been reported that annatto is the cause of rare food-related allergies in sensitive individuals. This dye can also cause anaphylactic shock and intestinal syndrome (Inetianbor et al. 2015).

Preservatives

Food preservatives are the class of food additives that may prevent, delay or inhibit the growth of food-spoilage microorganisms and pathogens (Al-Shammari et al. 2014). Preservatives can be divided into two groups: Class I (naturals such as salt and honey) and Class II (synthetics such as calcium propionate, sodium nitrite, sulphites and disodium EDTA) (Inetianbor et al. 2015). The effects of antimicrobial agents depend on type of food, storage conditions, target microorganism and its count, type and concentration of preservative, storage temperature and time, pH and buffering capacity of food. Among these substances sodium nitrite, sorbates, benzoates, propionates and sulphites are the most commonly used preservatives in food industry in the world (Shibamoto and Bjeldanes 2009; Inetianbor et al. 2015).

Nitrites and nitrates are considered to be a controversial additive (Al-Shammari et al. 2014). They are used especially in the production of meat and fish products since it prevents the development of *Clostridium botulinum* which is responsible for the production of *botulinum* neurotoxin. However, the use of these compounds may increase carcinogenic nitrosamine formation, especially in acidic mediums. It can

be induced tumours in a variety of organs such as liver, respiratory tract, kidney, oesophagus, stomach, and pancreas. Nitrosamines can cause not only carcinogens but also mutagenic effects (Omaye 2004). In individuals exposed to excessive nitrate exposure, nitrate changes its structure by binding to haemoglobin and causes a change in the so-called methaemoglobin which results in the skin turning blue (Omaye 2004; Inetianbor et al. 2015). Moreover, high levels of nitrate or nitrite exposure may increase the incidence of tumours of the brain tumours, leukaemia, nose and throat in children. It has been reported that high nitrate exposure induces the increased incidence of sudden infant death syndrome, risen risk of heart and nervous system imperfections (Inetianbor et al. 2015).

Benzoic acid has long been used as the antimicrobial agent in the food industry, especially in the production of carbonated and other drinks, fruit salads, jam and jellies, canned foods, mincemeat, margarine, assorted desserts, relishes, pies, and soy sauce. In these foods, its sodium salt is generally used. The sodium salt of benzoic acid is lesser toxic than the acid form. Adverse effects in experimental animals may occur in the form of the allergies (skin rashes and asthma), weight loss, diarrhoea, internal bleeding, destruction of the inner membranes, liver and kidney-related problems, hypersensitivity, brain damage and paralysis resulting in death (Shibamoto and Bjeldanes 2009; Pandey and Upadhyay 2012).

Sorbic acid, propionic acid and their salts are used primarily to inhibit mould and yeast (Deshpande 2002; Shibamoto and Bjeldanes 2009). Sorbates and propionates, the safest antimicrobials used to increase the shelf life of foods, are generally non-toxic at the permitted concentrations, and have no adverse effects even at high concentrations. In contrast, sorbate-containing pharmaceuticals or cosmetics may cause allergic reactions by damaging mucous layers and skin at high concentrations. Moreover, 6 g of sodium propionate taken by daily diet shows local antihistaminic effect in adults (Deshpande 2002). The JECFA has established an ADI of 0–25 mg kg^{-1} b.w. for sorbic acid and 0–5 mg kg^{-1} b.w. for benzoic acid (JECFA 1996).

Sulphur dioxide (gas form) and its salts (sodium sulphite, potassium sulphite, and potassium metabisulphite) are among the oldest antimicrobials used in foods and beverages. The usage of sulphide in foods such as meats and fish was constricted or prohibited in the USA because it destructs the vitamin B_1. In contrast, they are commonly used in fruit and vegetable drying and wine production. It may cause some adverse effects such as inflammation of polyuria, visceral organ atrophy, irritates bronchial tubes, bone marrow atrophy, limited growth, and spectacle eyes in experimental animals at high doses (Deshpande 2002; Inetianbor et al. 2015).

Antioxidants

Antioxidants are substances added to oil and fat containing foods to protect peroxidation or oxidative rancidity and thus maintain their integrity, palatability, and shelf life (Pandey and Upadhyay 2012; Inetianbor et al. 2015; Shukla et al. 2017). They

are divided into two groups; natural or synthetic. As the first group is a relatively weak antioxidant characters, synthetic antioxidants are often used in the production of foods (Shibamoto and Bjeldanes 2009). Antioxidants are also divided into three groups according to their effect types: Anti-browning agent, Antioxidant and Antioxidant synergist (Pandey and Upadhyay 2012). Most important antioxidants are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, tertiary-butylhydroquinone, thiodipropionic acid, and dilauryl thiodipropionate (Inetianbor et al. 2015; Shukla et al. 2017).

BHT and BHA, which are synthetic phenolic compounds, are widely used in the production of several foods such as margarine, oils, crisps and cheese due to their antioxidant characteristics (Deshpande 2002; Pandey and Upadhyay 2012). When taken in high doses, they cause adverse effects such as chronic allergic reactions, malformations and damage to the metabolic system in experimental animals (Shibamoto and Bjeldanes 2009). Moreover, BHA and BHT are suspected to have a detrimental effect on the lung, liver and kidney and most significantly increase the risk of cancer. These antioxidants can have a carcinogenic (stomach) and cytotoxic effect when taken in high doses (Inetianbor et al. 2015).

Propyl gallate is the most effective antioxidant among various gallates and is commonly used in a wide variety of foods such as vegetable oils and butter (Omaye 2004). When exposure to 1% or higher doses of dietary propyl gallate of experimental animals, it causes a decrease in weight gain, delayed growth, anaemia, and kidney damage. It can induce kidney damage in rats and cause 40% death in the first month following consumption (Deshpande 2002; Shibamoto and Bjeldanes 2009).

Emulsifiers and Stabilizers

Emulsifiers are substances used to obtain fixed liquid mixtures, to stabilize gas-in-liquid and gas-in-solid mixtures (Inetianbor et al. 2015). They also support stability, extend shelf life, and audit rancidity reactions, viscosity, and texture. About three-fourths of the emulsifiers used in the world are mono- and diacyl glycerides and their derivatives (Martins et al. 2019). Stabilizers improve and stabilize the tissue of foods, emulsions, suspensions, and foams. Moreover, they prevent the formation of crystals, and decrease the stickiness of icing in baked products. The most commonly used stabilizers are gum arabic, agar-agar, alginates, casein, carrageenan, carboxymethyl cellulose and its sodium salts, starch and derivatives, xanthan, guar and pectin (Inetianbor et al. 2015; Martins et al. 2019).

Acidity Regulators

pH regulators control the pH of the food. They affect the odour, flavour, viscosity, texture and, primarily shelf life by straight influencing on the oxidation/enzymatic reactions and prevention growth of microorganisms. pH agents are acids, alkaline

chemicals, conjugated salts and buffers (Inetianbor et al. 2015). They can be used alone or in combination with buffers such as salts of the phosphates, lactates and citrates. The most common acidity regulators are acetic, citric, malic, benzoic and formic acid (Martins et al. 2019).

Succinic acid has been reported to be used as a pH regulator and also flavouring and neutralizing agent in foods. However, it can be moderately toxic to the skin, in particular, can also cause eye irritation (Deshpande 2002).

Sweeteners

Sweeteners are used to condense the sweetness and keep the energy value of the food (calories) low (Inetianbor et al. 2015). These sweeteners, which are alternative to sugar, are artificial and have no nutritive values. Sweeteners such as fructose, isomalt, sugar alcohols, and maltodextrin have fewer calories than sugars, but are never calorie free. Sweeteners are chemically evaluated in five different categories; peptides, sulphonamides (acesulfame, cyclamates and saccharin), low-calorie sweeteners, chlorosaccharides and polyols (Martins et al. 2019).

Artificial sweeteners such as saccharin, aspartame, sucralose and acesulfame K may cause health problems when taken in high quantities (Inetianbor et al. 2015). Saccharin is a non-nutritive artificial sweetener that is 300–500 times sweeter than saccharides (Omaye 2004; Shibamoto and Bjeldanes 2009). Saccharin with very low toxicity may cause allergic reactions such as a headache, breathing difficulty, skin rashes, diarrhoea, and bladder tumours (Deshpande 2002). It is also thought to cause this sweetener irritability and muscle dysfunction.

Aspartame, one of the controversial sweeteners found in products such as cheese, chocolate, citrus, fatty foods, ice creams, wines and beers, is one of the substances that induce migraines. Symptoms related to complaints from foods containing aspartame include headache, giddiness, mood swings, arthrosis soreness, inexplicable depression, spew or nausea, abdominal spasm and cramping, diarrhoea, memory problems, and weariness (Inetianbor et al. 2015).

Flavour Enhancers

Flavour enhancers are substances which impart characteristic flavours when added to foods and beverages, and enhance the flavours of the other substance by acting synergistically (Deshpande 2002; Shibamoto and Bjeldanes 2009). Natural flavourings are not abundant and they cause high costs. For this reason, flavourings obtained by chemical means, which are known as nature identical, are used in the production of foods (Shukla et al. 2017). Some of the flavourings can cause dizziness and palpitations (Ergun 2015).

Monosodium glutamate (MSG), sodium salt of glutamic acid, is one of the most intensively used and controversial flavour enhancers (Deshpande 2002). MSG is generally produced by a natural fermentation process in industry (Al-Shammari et al. 2014). It is accountable for the fifth basic taste known as Umami (Deshpande 2002). Although MSG is generally known as a safe additive, some studies with young mice have been found to cause brain damage (Omaye 2004). In addition, some individuals may usually have symptoms similar to heart attacks and a feeling of pressure in the upper body when consuming foods containing high amounts of MSG. The use of MSG supplements has been banned in baby foods (Inetianbor et al. 2015).

Myristicin has been reported to induce several health problems such as headache, nausea, abdominal pain, hypotension and dizziness. Allyl isothiocyanate is an important flavouring that can be used in foods and gives the food a mustard and horseradish flavour. It may cause epithelial hyperplasia and stomach ulcers in the liver (in dogs) and may also induce mitotic activity and toxicity in experimental animals in high concentrations. Cinnamyl-2-aminobenzoate is one of the most used synthetic flavourings in drinks, confectioneries, puddings, gums, and bakery products. It gives food an aroma of grapes or cherries. The National Cancer Institute has reported that it causes cancer in experimental animals when taken at 15,000 μg kg^{-1} or greater with a diet (Deshpande 2002).

Acrylamide

Acrylamide (AA) is an industrial chemical which is odourless, colourless and crystalline at room temperature (Jin et al. 2013). This organic compound is highly soluble in water and polar solvents, and has a low molecular weight (71.08) vinyl compound (Besaratinia and Pfeifer 2007; Zamani et al. 2017). However, it is usually not-soluble in carbon tetrachloride which is a non-polar (EFSA 2015). The molecular formula of AA is $CH_2=CH-CO-NH_2$ (C_3H_5NO) (Chen et al. 2012; Shibamoto and Bjeldanes 2009). Synonyms are 2-propenamide, acrylic amide and ethylene carboxamide (EFSA 2015). It has a boiling point of 125 °C and a thaw point of 84.5 °C with a density of 1.27 g ml^{-1} at 25 °C (Gaikwad et al. 2016; Zamani et al. 2017).

There are two forms of AA, monomeric and polymeric. Monomer form is form found in foods (Arusoglu 2015). It is highly reactive in the air and can quickly polymerize. Namely, monomers can bind together and then form new polymers of AA (polyacrylamide) with new properties (Besaratinia and Pfeifer 2007). Nowadays, that polyacrylamide compound is widely used compound for different goals (flocculants, coagulant, sealants, soil stabilizers, binders and additives/adhesives/fixatives) in different industries. It is generally used for drinking water, sewage and wastewater treatment, construction of dams and roadways, soap making, recovery of enriched oil, and in paper and pulp industry. In addition, it has recently been used in chromatography and electrophoresis applications such as protein separation and

purification (Arusoglu 2015; Shibamoto and Bjeldanes 2009). Furthermore, cigarette (especially in smoke) contains AA (1–2 μg/cigarette) (Claeys et al. 2016). It can also be found in high amounts (up to several milligram per kilogram) in commonly consumed everyday foods and is a proven carcinogen (Besaratinia and Pfeifer 2007; Bongers et al. 2012).

AA is absent in the raw materials but, is formed during processing of some foods at high temperature (Gaikwad et al. 2016). The AA formation were first determined in the raw materials of plant origin which was subjected to high-temperature heat treatment in 2002 (Halford et al. 2012; Claeys et al. 2016). An increase in public health concern for AA has been observed following the provocative disclosure of the presence of AA in certain foods (such as in cooked, fried, toasting, roasted and baked high carbohydrate foods) prepared at temperatures above 120 °C and widely consumed throughout the world (Chen et al. 2012; EFSA 2015; Besaratinia and Pfeifer 2007). The formation, quantities, and toxicity of AA in foods have attracted the attention of many government agencies and national authorities because of this public concern and the potential risk to public health (Chen et al. 2012; Claeys et al. 2016).

AA is formed during Maillard reactions. During these reactions, especially the asparagine reacts with reducing sugars (glucose and fructose) during heating processes at temperatures higher than 120 °C (Bongers et al. 2012; Jin et al. 2013; Claeys et al. 2016; Zamani et al. 2017). On the other hand, the combination of the temperature and heating period to which the foodstuffs are exposed upon the formation of AA are very important (EFSA 2015). When the temperature is increased to 180 °C, AA formation reaches the highest level (Arusoglu 2015). The temperature at which AA begins to form in a food depends on the moisture content of that food. Less than 20 μg kg^{-1} AA is formed, when cooking process is applied to the wet potatoes at 120 °C under pressure. However, about 10,000 μg kg^{-1} AA occurs when dry potato powder is heating (EFSA 2015). AA is usually not found in large amounts in boiled foods, but can be found in significant amounts, especially in foods produced by deep frying or frying/roasting (Kopanska et al. 2017). Not only the temperature, cooking time and moisture content but also the method of cooking, immersion in different solutions (NaCl, CaCl$_2$, citric acid) before the heat treatment, pH, frying oil, water activity, type of food (presence and concentration of precursor molecules such as asparagine and reducing sugars), affect also the formation and amount of AA (EFSA 2015; Gaikwad et al. 2016). This is the cause of differences in the AA content of the same foods produced by different companies, and even among the batches of the same brand of food (Bongers et al. 2012).

AA may also be composed of 3-amino-propionamide (beta-alanine amide, $C_3H_8N_2O$) which is present in different amounts in various potato varieties (Zyzak et al. 2003; Jin et al. 2013). This compound is a potent precursor compound in the formation of AA and forms as a transient intermediate during the thermal degradation of asparagine (Jin et al. 2013). There are also AA formation routes that do not require asparagine. AA can be composed of acrolein (it turns into acrylic acid with the oxidation reaction) and acrylic acid (reacts with ammonium) in foods containing lipid under high temperatures (Shibamoto and Bjeldanes 2009; Kopanska et al. 2017), or it can also occur from gluten (Halford et al. 2012).

According to each country's tradition and unique food preparation methods, the amount of AA in food may be different (Zamani et al. 2017). AA has been detected in several foods such as potato products, chips, French fries and roasted corn flakes, coffee (brewed or not brewed, coffee substitutes etc.) and bakery products (pastry, biscuits, bread, rolls etc.) (Bongers et al. 2012; EFSA 2015). In addition, humans are exposed to AA indirectly by food packaging containing polyacrylamide (Zamani et al. 2017). Amount of AA in some raw and processed food products is given in Table 3.

According to WHO, daily intake of AA is 0.3–2.0 µg kg^{-1} b.w. It is estimated that daily intake of AA in children (infants, toddlers and other children) is 2–3 times higher than in adults (Besaratinia and Pfeifer 2007; EFSA 2015). This is due to the fact that children have a higher calorie intake than adults, and a higher feeding rate with AA-rich foodstuffs such as French fried potatoes and soft breads (Halford et al. 2012; Gaikwad et al. 2016; Zamani et al. 2017). The presence of soft bread with low AA content in the products on this list may be surprising, however, too much bread is consumed in Europe and especially in Turkey, and this is normally increasing the concentration of the exposure to AA (Halford et al. 2012; Arusoglu 2015). Other foods that cause total AA exposure of children and adolescents are breakfast cereals, pastry, biscuits, crackers, crisp bread, rolls and other products based on cereals. All of these food groups together with coffee are the basic contributors for adults, elderly and very elderly (EFSA 2015). The mean intakes of AA for men and woman are 0.36 µg kg^{-1} per day and 0.33 µg kg^{-1} per day, respectively. The highest intake of AA in males occurs between the ages of 16 and 30. Whereas, 13-old boys and girls intake less amount of AA then adult (0.52 µg kg^{-1} per day and 0.49 µg kg^{-1} per day, respectively) (Zamani et al. 2017).

Parameters Influencing the Formation of AA

The main agent of AA-forming is free asparagine amount. Asparagine is an amino acid that can be found in very different concentration range, depending on the type of plant and year of harvest (Shibamoto and Bjeldanes 2009; Halford et al. 2012). Especially asparagine combined with glucose and fructose is very significant agent in the AA formation (EFSA 2015). When the level of reducing sugar is high, the formation of the AA increases accordingly, whereas when the sugar levels are low, the formation of the AA is proportional to the amounts of the precursor amino acids (Halford et al. 2012). A significant decrease in AA concentrations can be achieved by controlling glucose and fructose amounts in potato varieties (Biedermann-Brem et al. 2003; EFSA 2015). In addition to choosing the right variety, crop varieties such as potato cultivar with low-reducing sugars (manipulation of the metabolic regulator) and/or free asparagine can be obtained through hybridization, genetic modification and other genetic techniques such as the identification of quantitative traits (Noti et al. 2003; Halford et al. 2012; EFSA 2015). At the same time, the ratio of fructose to glucose affects AA concentration of fried potato strips. Increased

Table 3 Amount of AA in some raw and processed food products (Besaratinia and Pfeifer 2007; Arusoglu 2015; EFSA 2015)

Category of food	Foodstuff	Mean concentration (μg kg⁻¹)	Maximum concentration (μg kg⁻¹)
Cereals/cereal-based products	Cereal-based products	343	7834
	Raw/boiled cereals and pasta	15	47
	Processed cereals/pasta (toasted, fried, grilled) Soft bread Gingerbread	123 42 1000	820 – –
	Bread and rolls	446	3436
	Pastry and biscuits	350	7834
	Cereals for breakfast (crispy)	96	1346
	Pizza	33	763
Fish and other seafood	Breaded, fried, baked foods	25	233
Meat and offal products	Coated, cooked, fried foods Flaked meat *Adana kebap*	19 57 127	313 63 250
Milk and dairy products		6	36
Nuts and oil seeds		84	1925
Legumes		51	320
Roots and tubers of plant	Roots and tubers of plant	477	5312
	Potato purees (mashed or boiled)	16	69
	Baked potato	169	1270
	Potato crisps (chips/french fries)	110	5312
Stimulants/other analogues		509	7300
	Coffee (Roasted/brewed/ non-brewed) Coffee powder Turkish coffee	13 200 25	1291 230 266
	Coffee extracts	1100	4948
	Coffee substitutes	845	7300
	Products of cocoa	220	909
	Roasted green tea	306	660
Sugars and honey		24	112

Table 3 (continued)

Category of food	Foodstuff	Mean concentration (µg kg⁻¹)	Maximum concentration (µg kg⁻¹)
Vegetables	Raw, boiled and canned vegetables	4	25
	Toasted, baked, fried or grilled vegetables	59	202
Fruits	Dried or fried fruits	131	770
Other processed products	Alcoholic beverages (beer, gin, wine)	7	46
	Baby food (canned, jarred, dry powder)	16	121
	Baby food (cereal-based, biscuits etc.)	73	1217
	Dried food	121	1184
	Chocolate Powder	75	100

fructose ratios support the formation of AA (Mestdagh et al. 2008). On the other hand, proper storage circumstances are also important in the formation of AA (Noti et al. 2003). The storage of potatoes has seasonal effects on the amount of AA (Powers et al. 2013; EFSA 2015).

Temperature is one of the important factors in the formation and degradation of AA. The effect of food processing on the formation of AA and their reduction strategies are given in the following:

- The main factors affecting the AA levels in coffee as well as in potato and cereal products are time and roasting degrees. In the production of French fries, the increase of temperature may increase the amount of AA more pronounced than the rising of duration at the constant temperature frying process. Oil frying temperature above 170–175 °C may produce high amounts of AA in the final product. Even the highest temperature and the longest processing time in the convection oven contains less AA than the fried potato patties prepared in the stove (215 °C for 6.5 min). Because of AA generally occurs towards the end of the frying process, the temperature is very important towards the end of process. Dropping to the temperature 140–145 °C towards the end of the process reduces AA formation to significant levels (EFSA 2015).
- The type of vegetable oil used in the frying process also affects the level of AA. For example, sweet potatoes fried in palm olein contain less concentration of AA than fried in soya bean oil. Moreover, the most effective way to reduce the amount of AA in frying is by immersion in the citric acid solution (1 g L⁻¹). This process reduces AA by about 77% (EFSA 2015).
- Peeling of potato causes a decrease in AA level in the production of chips. Because reducing sugars can be found at higher level near the peel. In addition, sliced potatoes are usually washed with water at ambient temperature before frying. During the washing process, significant levels of the primary AA precursors

in the potato is away with water, thereby reducing the production of AA in fried slices (Gaikwad et al. 2016).

- The formation of AA is higher in the crust of the food than in the interior; therefore, reducing the surface area of the food can reduce AA in baked products (Gaikwad et al. 2016).
- The addition of a food-grade colouring agent in the production of frozen French fries may result in a reduction in AA level. Because, the dark coloured product is requested by the consumers, however, it increases the formation of AA. With the addition of food-grade colouring agent, both the desired colour is obtained and the formation of AA can be reduced (Gaikwad et al. 2016).
- Some amino acids (e.g., glycine, taurine, lysine, and cysteine) and organic acids (acetic acid, ascorbic acid, citric acid, monosodium citrate, sodium citrate, lactic acid) can suppress to the formation of AA in potato products (Jin et al. 2013; Gaikwad et al. 2016). Especially, glycine can reduce the formation of AA by up to 50%, but may create unwanted odour (Arusoglu 2015). It has been stated that application of a small amount of citric acid before cooking and/or frying can greatly reduce the formation of acrylamide in fried and baked potato fries (Jung et al. 2003).
- The reduction of asparagine levels using asparaginase enzyme prior to the heat treatment of food was successfully used in some food products such as cereal-based products. However, it is not a process that can be applied to all foods because it is ineffective to some products or causes unacceptable changes in the product. This enzyme hydrolyses asparagine to aspartic acid (EFSA 2015). It has been reported that asparaginase can reduce acrylamide formation by 80% in fried potatoes (Mahajan et al. 2012).
- The adding of ammonium carbonate and bicarbonate to foods may result in high amounts of AA formation (EFSA 2015).
- The prolongation of the fermentation time in the production of fermented products leads to some decrease in the amount of AA. This is because; yeast is the use of free asparagine in metabolism. On the other hand, AA is often found in the bread crust, while the AA is not found in the bread (Arusoglu 2015). AA formation in French fries may be adequately reduced by lactic acid fermentation of the potatoes before deep-frying (Baardseth et al. 2006).
- The flour type and toasting time may also affect the formation of AA. After toasting, higher amounts of AA forms in bread made from potato flour than wheat, rye or multi-grain flour (EFSA 2015).

Toxicological Evaluation

Its low molecular weight and high water solubility allow the AA to readily pass through different biological membranes. The chemical structure and the ability to undergo metabolic transformation of AA allows it to react easily with various cellular targets (Besaratinia and Pfeifer 2007). Toxicological studies on AA are per-

formed in rats, mice, monkeys, cats, and dogs using different doses and exposure routes (oral, intravenous etc.). Oral LD_{50} values of AA for rats, mice and rabbits are >150 mg kg^{-1} b.w., 107 mg kg^{-1} b.w. and 150–180 mg kg^{-1} b.w., respectively (EFSA 2015).

AA has genotoxic, neurotoxic, reproductive toxic and immunotoxic effects (Gaikwad et al. 2016). AA has been classified as Group 2A (probable carcinogen) by IARC, and as a Category 2 carcinogen and mutagen by the European Union (IARC 1994; Halford et al. 2012). AA has a structure similar to vinyl carbamate and acrylonitrile, known to be carcinogenic. However, multiple tumours may develop in animals when taken in large amounts through potable water. AA may also increase the risk in some types of cancer such as kidney and breast cancer especially after menopause (Zamani et al. 2017).

AA is a strong and effective lethal neurotoxic matter. The toxic effect of AA on both human occupational exposure and animals is neurotoxicity. For example, during the construction of the railway tunnel, Swedish workers had signs of deterioration in nerve function. It has been observed that it was due to a private gel called "Rhoca Gel", which contains AA used against water leaks in the tunnel wall (Kopanska et al. 2017; Zamani et al. 2017).

AA may damage DNA at a dose of 10, 20 and 30 mg kg^{-1}. There is insufficient evidence for the effect of AA on reproductive toxicity in humans. However, it has been demonstrated that the adverse effects of AA on male reproductive parameters including reduced sperm counts in rats with a No Observed Adverse Effect Level (NOAEL) of 2 mg kg^{-1} per day (EFSA 2015).

Recently, AA has been stated to induce oxidative stress (Kopanska et al. 2017; Zamani et al. 2017). AA may cause formation of reactive oxygen species by affecting cellular redox chain. AA and glycidamide may interact with the group of nucleophiles in cells. Oxidative stress is an important step in the induction of various types of cell death types such as apoptosis which stated as blobbing of membranes, shrinkage of cells, and DNA fragmentation It has also an immunotoxic effect, and may reduce the final body weight, spleen and thymus weights, and lymphocyte count in experimental animals (Zamani et al. 2017).

The intake of AA may rise the rate of lung and skin adenoma and carcinoma in mice, and may also stimulate scrotal mesotheliomas, thyroid gland adenomas and/or mammary gland tumours. It can stimulate adenocarcinomas, central nervous system tumours, clitoral gland adenomas and oral papillomas, tumour risk of the uterus, colon and clitoral gland in rats (Besaratinia and Pfeifer 2007; Chen et al. 2012).

The half-life of AA is between 2.4 and 7.0 h according to the toxicokinetic researches in humans. More than 60% of AA can be excreted from the body with the urine which is the major route of excretion (Besaratinia and Pfeifer 2007; Zamani et al. 2017). Only 4% of AA with stool is discarded after 7 days (EFSA 2015). AA is often metabolized by conjugation with glutathione. It can be also metabolised by epoxidation by cytochrome P450 2E1 (CYP2E1) into an epoxy derivative (glycidamide), which is widely distributed into tissues (Bongers et al. 2012; Kopanska et al. 2017). This metabolite is more reactive than AA, the parent compound against DNA and proteins (Besaratinia and Pfeifer 2007). After recruitment into the human

body, the AA and its metabolite, primarily conjugated with glutathione, and then converted to by-products of mercapturic acid, which are excreted in urine (Zamani et al. 2017). Mercapturic acid is an important compound and is the major metabolite of AA and glycidamide. Urinary excretion levels of these metabolites are used as biomarkers of AA exposure. The formation of glycidamide is important because it represents the pathway underlying the genotoxicity and carcinogenicity of AA (EFSA 2015).

Furan

Furan (C_4H_4O) is an uncoloured chemical that is associated with the flavour character of foodstuffs (particularly undesirable flavour) (Nerín et al. 2016; Santonicola and Mercogliano 2016). It is a mini cyclic ether with high volatility which molecular weight is 68.07 g mol^{-1}, and it starts to boil at 31.04 °C. Furan and its derivatives such as methylfuran were first detected in thermal treated foodstuffs (food and beverages) about 50–60 years ago. Only furan may occur in foods or may occur together with derivatives (Knutsen et al. 2017). In 2004, FDA released a notification on the presence of furan and its derivatives (2-methylfuran, 2-alkylfuran, 2-ethylfuran, 2-pentylfuran, 2,5-dimethylfuran, 2-butylfuran, 2,3-benzofuran) in many of the heat-treated foodstuffs such as canned and jarred foods (Fromberg et al. 2014; Santonicola and Mercogliano 2016). Furan and its derivatives has also been detected in tobacco (Xu et al. 2017), industrial wastes and exhaust gas from diesel and gasoline engines (Bas et al. 2016; Knutsen et al. 2017).

Furan compounds resulting from heat treatment and dioxin-like furan compounds (polychlorinated dibenzo-furans, PCDF) are different from each other. In both, however, the main compound is furan and used as a solvent for rosin and polishes. In addition, it is used in the preparation of organic compounds and pharmaceuticals (Vranová and Ciesarová 2009). Dioxin and dioxin-like furan are highly chemically stable organochlorine compounds and are considered among the major food contaminants arising from environmental pollution (Ergun 2015).

People are generally exposed to furan or its derivatives formed by thermal applications via hot-air dried, baked, fried, grilled and roasted foodstuffs. Various factors such as temperature and time used in production, pH, water activity, storage temperature and duration, the amino acid to sugar ratio, oxygen, presence of metals, presence/absence of inhibitors and activators can affect furan formation and amounts in foodstuffs (Nie et al. 2013; Santonicola and Mercogliano 2016). Among these, processing temperature and time, pH and the amino acid to reducing sugar ratio play important role in the formation of furan (Knutsen et al. 2017).

Furan and its derivatives are among the Maillard reaction products that occur during processes such as heating and browning (Bogdanova et al. 2018). Their formation by Maillard reactions depends on activators such as amino acids and sugars (Santonicola and Mercogliano 2016). Pasteurization applications applied to foods cause lower furan formation than sterilization applications (Knutsen et al. 2017).

Similarly, higher levels of furan may occur in frying than in baking. In productions performed industrially, furan amounts in foods rise with rising temperature, especially, up to 200 °C (Nie et al. 2013). However, when the process temperature overruns 200 °C, the amount of the furan may vary without depending on the temperatures (Santonicola and Mercogliano 2016). Fromberg et al. (2014) stated that there were no differences with regard to furan amounts between French fries fried at 160 °C and 175 °C. However, they reported that an important rise in the amount of furan when the frying temperature rose to 190 °C and more browning on the surfaces of potato chips. The researchers also determined that the colour increased from the brown to darker as it continued to toasting in the making of toasted bread, and with the browning increased, it rose of the furan amount in the product.

pH can affect the amount of furan at temperatures above 110 °C. For example, in a study performed by Nie et al. (2013) at pH 7.00 (30 min and at 150 °C), it was stated that a much higher amount of furan was formed than pH 9.4 and 4.2. However, at the same pH, as the temperature increases the amount of furan increases significantly. For example, when the temperature rises from 120 to 150 °C at pH 7.0, the amount of furan increases from 34 to 304 ng mL^{-1}.

The main mechanisms for formation of furan and its derivatives can be originated from (i) thermal degradations of reducing sugars and Maillard browning reactions in the presence of reducing sugars and amino acids; (ii) disruption of some amino acids due to heat treatment; (iii) thermal lipid oxidation of unsaturated fatty acids or triglycerides; (iv) the thermal oxidation of some compounds such as carotenoids; (v) the decomposition of ascorbic acid foods; and (vi) heating of unsaturated aldehydes (Vranová and Ciesarová 2009; Fromberg et al. 2014).

As mentioned above, the main source of the furans in foodstuffs is the deterioration of carbohydrates (glucose, fructose or lactose) found in high amounts in the food due to heat treatment (Fromberg et al. 2014; Santonicola and Mercogliano 2016). According to FDA, carbohydrates and amino acid mixtures or alanine, serine, cysteine, casein, ascorbic acid, unsaturated/polyunsaturated fatty acids are multiple precursor compounds affect the presence and amount of furan in foods (Vranová and Ciesarová 2009; Nerín et al. 2016). Furan may also occur as a result of interaction with some non-precursor substances such as starch (Knutsen et al. 2017).

Furan may occur if amino acids such as serine, cysteine are subject to heat treatment without the need for any other source. However, furan is not form if alanine, threonine and aspartic acid are alone. In addition to the heat treatment, reducing sugar, serine or cysteine is required for the formation of furan from these amino acids. In the roasting process applied to the foods that do not contain amino acids, the furan mainly consists of intact sugars (Vranová and Ciesarová 2009; Knutsen et al. 2017). The presence of alanine, threonine or serine can support the formation of furan, which can result from both sugars and amino acids. The parent furan may be composed of pentose sugars such as ribose (Santonicola and Mercogliano 2016).

Ascorbic acid is also effective in furan formation. The ascorbic acid present in the food is first oxidized to dehydroascorbic acid, followed by hydrolysis to produce 2,3-diketogulonic acid. This compound is first converted to aldotetrose and then to

furan. Nevertheless, ascorbic acid does not undergo oxidation under non-oxidative conditions and 2,3-diketogulonic acid is not produced. Instead, it undergoes hydrolysis followed by decarboxylation, and then furan can form by following the ribose pathway (Vranová and Ciesarová 2009). Moreover, ascorbic acid alone causes a certain amount of furan formation, while less furan is formed when it is subjected to heat treatment with other substances (glycine, serine, erythrose or linoleic) in the mixture (Santonicola and Mercogliano 2016).

Mono-unsaturated acids such as oleic acid are specified not to form furans. The furan is composed of unsaturated fatty acids and, as the degree of unsaturation increases, furan formation increases (Santonicola and Mercogliano 2016). On the other hand, antioxidants such as tocopherol acetate can greatly reduce furan formation (70%) (Vranová and Ciesarová 2009). Ionized radiation of apple and orange juices causes furan formation (Fan 2005).

Not only industrial products, but also home-made cooked foods may contain furan (Vranová and Ciesarová 2009; Fromberg et al. 2014). It has been detected in coffee (47–5982 µg kg^{-1}), canned foods (1–105 µg kg^{-1}), baby food (4–224 µg kg^{-1}) and breakfast cereals (2–387 µg kg^{-1}) (Nerín et al. 2016; Santonicola and Mercogliano 2016). Furan has also been determined in soups, fruits and dried fruit products such as raisin, plum and banana, cereal based products, snack foods, cooked chicken, sodium caseinate, hazelnut, fruit and vegetable juices, tin containing meat and pasta, plum beverage, soy protein, rapeseed protein and caramel (Vranová and Ciesarová 2009; Fromberg et al. 2014). In a recent study, furan was detected in 100% of beer samples collected from different supermarkets in Riga, Latvia, with the levels ranging from 1.4 to 32.5 µg kg^{-1} (Bogdanova et al. 2018). However, furan was not occurred in some of foodstuffs produced in home such as omelette, pancakes, fruit compotes, cakes and cookies do not include furan (Fromberg et al. 2014).

However, the amount of toxic furan formed by heat treatment in foodstuffs is far below the amounts that can cause harmful effects in humans (Vranová and Ciesarová 2009). Furan content can be considerably reduced in some foods such as foods applied heating or cooking process. But, approximately 50% of the furan may remain in the product (Fromberg et al. 2014). For example, furan can be volatilizing by stirring during heating of canned or jarred foodstuffs in an open stove. Up to 85% reduction can be achieved in open container by stirring a time of 5.5 h in boiling water (Santonicola and Mercogliano 2016). On the other hand, volatilization of furans during thermal processes highly depends on the contents of foodstuff. For example, lipophilic substances such as fats cause furan to be retention considerably (Fromberg et al. 2014).

Furan has been classified as a possible carcinogen (group 2B) (IARC 1995) and can induce a dosage-dependent increment in hepatocellular adenomas and carcinomas in both rat and mice. Furan was added to the list of carcinogens in tobacco (Xu et al. 2017).

Furan causes tumour-inducing effect in experimental animals. The most striking effect is the induction of hepatic cholangiocarcinomas (Vranová and Ciesarová 2009). Furan causes ATP loss resulting in activation of cytotoxic enzymes including

endonucleases. Furan can also trigger gene mutations, chromosome deflections and sister chromatid alterations in mammalian cells, chromosomal aberrations in bone marrow cells in mice, and formation of liver tumours in infant male mice (Knutsen et al. 2017). In addition, furan can cause severe histopathological changes in rats (Bas et al. 2016), detrimental impacts in the pancreas and adrenal cortex (Karacaoglu et al. 2012), and also reduce the albumin amount by causing liver dysfunction (Bas et al. 2016). Furan also has a moderate nephrotoxic effect in rodents when administered orally. On the other hand, it induces histological alters in testes, prostate gland and seminal vesicles in rats (Knutsen et al. 2017).

No limitation on the amount of furan present in foods has been specified so far and, still not also covered by European Union Regulation (Knutsen et al. 2017). As furan causes a carcinogenic effect, the amounts in foods should be kept as low as possible. Depending on the food consumed, children between the ages of 4 and 6 receive an average of 1.5 μg furan per day, and adults 27 μg (Santonicola and Mercogliano 2016). Because of their low polarity, furan and its derivatives are rapidly and intensely absorbed from the intestine and lung both in the human body and in experimental animals to an extent of at least 80%, and then quickly metabolized with cytochrome P450 2E1 (CYP2E1) enzymes (Knutsen et al. 2017; Bogdanova et al. 2018). It then goes to various organs through which it can accumulate or act through biological membranes. While the accumulation in the liver and kidneys increases due to repeated furan doses, less accumulation may be in the stomach, blood and lungs (Santonicola and Mercogliano 2016; Knutsen et al. 2017).

3-MCPD and Glycidyl Fatty Acid Esters

Glycerol-based process contaminants are found in vegetable oils, fats and some processed foods that raise potential health concerns for people who consume high amount of these products. 3-Monochloropropane-1,2-diol (3-MCPD), 2-monochloropropane-1,3-diol (2-MCPD) and their fatty acid esters are process contaminants and may found in vegetable oils, mainly in palm oil, and numerous heated foods (EFSA 2013). They are among non-volatile chloropropanols, was discovered by Velísek et al. (1978) in the late 1970s in the composition of acid-hydrolysed vegetable protein (acid-HVP) used for savoury flavour-enhancing food ingredient such as soya (EFSA 2016).

Glycidyl fatty acid esters (GE) are food processing contaminants and they are formed during the physical refining process of vegetable oils and fats at high temperatures (over 200 °C), i.e. in the deodorization step. GE are hydrolysed in glycidol in the gastrointestinal tract (EFSA 2016).

Free 3-MCPD or free 2-MCPD can be occur when foods that contain both fat and salt are exposed to high temperatures during production. The fatty acid esters of 3- and 2-MCPD are formed during the refining of vegetable oils and fats either from acylglycerols (Freudenstein et al. 2013) or from triacylglycerol (Destaillats et al. 2012). The formation and level of 3-MCPD esters depend on the level of acylglyc-
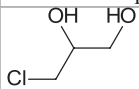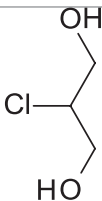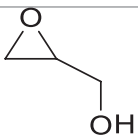
erols (tri-, di- and monoacylglycerols), the concentration of chlorine, pH, the deodorization temperature and time (EFSA 2013).

GE are formed mainly from diacetylglycerol during the deodorization step of physical refining of oils (in excess of 200 °C). The highest levels of GE, as well as 3-MCPD and 2-MCPD were detected in palm oil, which can have a high diacetylg-lycerol (4–12%) content (EFSA 2016).

Chemical Characteristics

3- and 2-MCPD belong to the group of chloropropanols which are chlorinated derivatives of glycerol. While the chlorine atom is in position 3 in 3-MCPD, it is in position 2 in 2-MCPD molecule. Glycidol has not only glycerol as chloropropanols but also an epoxide structure. GE are substances consisting of glycidol esterified with a fatty acid (BfR 2016). The chemical and physical properties of 3-MCPD, 2-MCPD and glycidol compounds are shown in Table 4. It has been also reported that fatty acid esters of 3- and 2-MCPD, and glycidol have similar properties, with slightly lower melting points (Hamlet et al. 2011).

Table 4 Chemical and physical properties of 3- and 2-MCPD, and glycidol

Parameter	3-MCPD	2-MCPD	Glycidol
Name	3-monochloropropane-1,2-diol	3-monochloropropane-1,3-diol	Glycidol
IUPAC systematic name	3-chloropropane-1,2-diol	2-chloropropane-1,3-diol	oxiranylmethanol
CAS Number	96-24-2	497-04-1	556-52-5
Empirical formula	$C_3H_7ClO_2$	$C_3H_7ClO_2$	$C_3H_6O_2$
Molecular weight (g mol^{-1})	110.5	110.5	74.08
Density (g ml^{-1})	1.32	1.32	1.12
Melting point	−40 °C	−40 °C	−45 °C
Boiling point	213 °C (at 760 mmHg)	213 °C (at 760 mmHg)	167 °C (at 760 mmHg)
Solubility	Soluble in water, alcohol and ether	Soluble in water, alcohol and ether	Soluble in water, alcohol and ether
Colour	Colourless or pale yellow	Colourless or pale yellow	Colourless
Chemical structure			

Since glycidol has only one hydroxyl group, it can form monoesters. However, 3- and 2-MCPD can each form monoesters and diesters with fatty acids under high temperatures during the refining of vegetable oils and fats. Lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid are known the major esterifying fatty acids (EFSA 2016).

Analytical Methods

There are several analytical methods for the determination of chlorinated propanols and their esters in refined oils, fats and numerous foods. The analytical methods used for chloropropanols have been largely described by Hamlet et al. (2011). The determination of 3- and 2-MCPD is usually carried out by gas chromatography-mass spectrometry (GC-MS) methods. To enhance volatility and mass detector response, derivatisation step is needed. The derivatisation reagents have been applied including heptafluorobutyrylimidazole (HFBI), *N*,*O*-bis(trimethylsily) trifluoroacetamide (BSTFA), heptafluorobutyric anhydride (HFBA) or more recently using of phenylboronic acid (PBA) (Platinga et al. 1991). The limit of quantifications (LOQs) for free 3-MCPD and 2-MCPD are up to levels of 15 µg kg^{-1} and 10 µg kg^{-1}, respectively. However, currently there is no available method for the determination of free glycidol substance.

Methods for analysing ester-bound 3- and 2-MCPD and glycidol are commonly based on two different approaches, direct and indirect analysis. The indirect methods for esters of 3- and 2-MCPD and glycidol in processed foods are well characterised in various foods, using t-butyl methyl ether, t-butyl methyl ether/hexane or diethyl ether/hexane as extraction solvents. Three methods adopted by the American Oil Chemists' Society (AOCS) have been developed for quantification of fatty acid esters of 3- and 2-MCPD and glycidol, and show LOQs in the range 15–30 µg kg^{-1} (EFSA 2016).

Occurrence Data

A number of studies have been conducted on the levels of 3-MCPD, 2-MCPD, glycidol and their esters in vegetable oils and fats within the last two decades. The results of these studies are summarised in Table 5.

In 2006, a comprehensive report on the risks for human health related to the presence of 3- and 2-MCPD, and their fatty acid esters, and GE in food has been published by EFSA. In this exposure assessment, 7175 occurrence data on 3- and 2-MCPD and glycidol in soy sauce, HVP and similar products (702 data points), oils and fats (4754 data points), and various foods including infant formula, cereal-based products and potato crisps (1719 data points) have been evaluated. Within the categories of oils and fats, palm oils/fats had the highest concentrations of 3-MCPD

Table 5 Content of 3-MCPD, 2-MCPD, glycidol and their esters in vegetable oils and fats

Substance	Food	No. of samples	Incidence n (%)	Range (min-max), µg kg^{-1}	Reference
3-MCPD	Cold pressed/ refined safflower oils	11	5 (45.5)	<100–3218	WeißHaar (2008)
Free 3-MCPD	Virgin seed oils	9	–	<9–12	Zelinková et al. (2006)
	Refined seed oils	5	–	<3–<9	Zelinková et al. (2006)
	Virgin olive oils	4	–	<3–<9	Zelinková et al. (2006)
	Refined olive oils	5	–	<9	Zelinková et al. (2006)
Bound 3-MCPD	Virgin seed oils	9	–	<100–337	Zelinková et al. (2006)
	Refined seed oils	5	–	<300–1234	Zelinková et al. (2006)
	Virgin olive oils	4	–	<100–<300	Zelinková et al. (2006)
	Refined olive oils	5	–	<300–2462	Zelinková et al. (2006)
	Edible oils	27	3 (11)	260–300	Jedrkiewicz et al. (2016)
	Margarines	5	5 (100)	1300–7300	Jedrkiewicz et al. (2016)
	Fish oils	5	5 (100)	1500–5500	Jedrkiewicz et al. (2016)
	Soybean oil	5	–	<100–500	Kuhlmann (2011)
	Rapeseed oil	5	–	<100–1000	Kuhlmann (2011)
	Sunflower oil	5	–	100–2100	Kuhlmann (2011)
	Palm oil	20	–	1100–10,000	Kuhlmann (2011)
	Vegetable oil fat mixes	11	11 (100)	897–2435	Seefelder et al. (2008)
Bound 2-MCPD	Edible oils	27	3 (11)	180–230	Jedrkiewicz et al. (2016)
	Margarines	5	5 (100)	630–1700	Jedrkiewicz et al. (2016)
	Soybean oil	5	–	<LOQ[a]–100	Kuhlmann (2011)
	Rapeseed oil	5	–	<LOQ–300	Kuhlmann (2011)

<div align="right">(continued)</div>

Table 5 (continued)

Substance	Food	No. of samples	Incidence n (%)	Range (min-max), µg kg^{-1}	Reference
	Sunflower oil	5	–	<LOQ–300	Kuhlmann (2011)
	Palm oil	20	–	200–5900	Kuhlmann (2011)
Bound glycidol	Soybean oil	5	–	<100–600	Kuhlmann (2011)
	Rapeseed oil	5	–	<100–300	Kuhlmann (2011)
	Sunflower oil	5	–	<100–400	Kuhlmann (2011)
	Palm oil	20	–	300–18,000	Kuhlmann (2011)

[a]*LOQ* limit of quantification

(from esters), 2-MCPD (from esters) and glycidol (from esters), with the middle bound (MB) levels of 2912 µg kg^{-1}, 1565 µg kg^{-1} and 3955 µg kg^{-1}, respectively. The MB levels of 3-MCPD, 2-MCPD and glycidol from esters in vegetable fats/oils varied from 48 µg kg^{-1} to 608 µg kg^{-1}, 86–270 µg kg^{-1} and 15–650 µg kg^{-1}, respectively. With regard to margarine and similar products, the MB levels were 181–668 µg kg^{-1} for 3-MCPD from esters, 80–236 µg kg^{-1} for 2-MCPD from esters, and 114–582 µg kg^{-1} for glycidol from esters (EFSA 2016).

According to that report, potato crisps, hot surface cooked pastries, shortcrusts and cookies had the highest levels of 3- and 2-MCPD and glycidol from esters among the food groups other than fats and oils. The MB levels were varied from 154 to 247 µg kg^{-1} for total 3-MCPD, from 79 to 135 µg kg^{-1} for total 2-MCPD, and from 110 to 149 µg kg^{-1} for glycidol from esters in these products.

There are also several studies focusing on the occurrence of chlorinated propanols in baby formula in the scientific literature. Zelinková et al. (2009) analysed a total of 14 infant and baby food products for the presence of free and bound 3-MCPD. While the authors were not detected free 3-MCPD in any of the samples, the levels of bound 3-MCPD in baby foods ranged from 62 to 588 µg kg^{-1}. EFSA (2016) reported the mean levels of 3-MCPD, 2-MCPD and bound glycidol in infant formulas (powder) of 108, 44 and 87 µg kg^{-1}. In a recent study, Arisseto et al. (2017) found 3-MCPD and GE in 37.5% (15 out of 40 samples) and 42.5% (17 out of 40 samples) of infant formula available in the Brazilian market up to levels of 600 µg kg^{-1} and 750 µg kg^{-1}, respectively. In another study conducted in the United States, infant formulas containing palm/palm olein contained bound 3-MCPD and glycidol at levels from 21 µg kg^{-1} to 920 µg kg^{-1}, and from <LOQ to 400 µg kg^{-1}, respectively. However, palm/palm olein-free infant formulas contained bound 3-MCPD and glycidol in the range of 72–160 µg kg^{-1}, and 5–150 µg kg^{-1}, respectively (Leigh and MacMahon 2017).

Toxicological Evaluation

The main target organ is kidney and 3-MCPD can induce nephropathy, renal tubular hyperplasia and adenomas in the chronic exposure. This compound has been classified by IARC as a "possible human carcinogen (group 2B)" (IARC 2012). In 2001, the European Union Scientific Committee on Food (SCF) set a tolerable daily intake (TDI) of 2 µg kg^{-1} b.w. (SCF 2001b). However, a TDI of 0.8 µg kg^{-1} per day for 3-MCPD and its fatty acid esters has been established by EFSA CONTAM Panel (EFSA 2006). It is important to note that no-health based guidance value for 2-MCPD has been established due to the lack of sufficient toxicological data.

The toxicological effect of GE has not been fully elucidated yet and there is no data in vivo. On the other hand, it is stated that GE has been demolished by up to 100% as a result of digestion process in humans and turned into glycidol. There is strong evidence that glycidol is a genotoxic compound as a result of *in vitro* and *in vivo* studies. Glycidol was also classified by IARC as "probable human carcinogen (group 2A)" (IARC 2000).

Legislation

Commission Regulation (EC) No. 1881/2006 sets maximum levels (MLs) for certain contaminants in foodstuffs (European Commission 2006), which has been amended and replaced with new regulation to revise legal limits for 3-MCPD and GE. In the European Union (EU), maximum level (ML) of 20 µg kg^{-1} 3-MCPD has been established for HVP and soy sauce for liquid products containing 40% dry matter, corresponding to a maximum of 50 µg kg^{-1} in the dry matter. With regard to GE expressed as glycidol, the EU has set a ML of 1000 µg kg^{-1} for vegetable oils and fats, and 500 µg kg^{-1} for vegetable oils and fats destined for the production of baby food or processed cereal-based food for infants and young children. The Commission has also established ML of 50 µg kg^{-1} (as from July 1, 2019) for GE (expressed as glycidol) in the infant formula, follow-on formula and foods for special medical purposes intended for infants and young children (powder form), while the legal limit of 6 µg kg^{-1} (as from July 1, 2019) for liquid form (European Commission 2018).

Polycyclic Aromatic Hydrocarbons

While, PAHs are a very large family of organic compounds that consist of about ten thousand individual chemical substances, a few of which occur in considerable amounts in the environment and foodstuffs. They are composed of two or more fused aromatic rings and do not contain heteroatoms. When the PAHs have contain

up to four fused benzene rings, called as "light PAHs". The PAHs containing more than four benzene rings are known as "heavy PAHs", which are more stable and more toxic than light ones (Wenzl et al. 2006).

PAHs are formed primarily by incomplete burning of carbon-containing organic materials, such as coal, crude oil, gas, wood, garbage or tobacco, and also formed during various industrial processes such as in the cracking of petroleum, or in inter-nal–combustion engines in vehicles. Humans are exposed to PAHs through different routes, mainly via intake of food, inhaled air and drinking water. Food can be con-taminated with PAHs that are present in soil, air or water, and mostly by industrial food processing methods and home food preparation applications. The main source of contamination of meat and dairy products with PAHs is heat processing, such as grilling, roasting, drying and smoking processes (EFSA 2008).

Chemical Characteristics

PAHs are stable, fat-soluble, high boiling and melting points and low vapour pres-sure (EFSA 2008) Some chemical, physical and carcinogenic properties of the 16 PAHs (15 EU priority PAHs + 1) are summarised in Table 6. The chemical struc-tures of 16 PAHs are illustrated in Fig. 2.

Occurrence Data

A large number of studies have been performed for the determination of PAHs in various foods. The results of these studies conducted on the last decade are sum-marised in Tables 7 and 8. As can be seen in Table 7, the incidence of PAH4 in vegetable oils are quite high. The levels of PAHs in vegetable oils were ranging from 0.1 µg kg^{-1} to 7.5 µg kg^{-1}, 0.01–6.9 µg kg^{-1}, 0.3–8.6 µg kg^{-1} and 0.5–13.1 µg kg^{-1} for BaP, BaA, BbFA and CHR, respectively. The highest concentration of BaP (7.5 µg kg^{-1}) was detected in maize oil originating from Brazil. For oils and fats, the legal limits were set at 2 µg BaP and 10 µg PAH4 per kg product, respectively (European Commission 2011).

While there are large differences in the individual PAHs content of various con-sumer products (Table 8), high concentrations of PAHs have been reported in bar-becued/grilled and smoked products.

The individual concentrations of BaP, BaA, BbFA and CHR in grilled/barbecued and smoked samples (meat, chicken or fish samples) are up to levels of 17.5 µg kg^{-1}, 36.5 µg kg^{-1}, 13.8 µg kg^{-1}, and 27.8 µg kg^{-1}, respectively. In EFSA report, results of 9714 food samples in 33 food categories on the occurrence of one or more of the 16 PAHs submitted by the 18 European countries were evaluated. Data for the full set of PAH15 were reported for 1375 food samples. According to results, 31.8% of the samples did not contain any PAH analysed above the limit of detection. The

Table 6 Chemical, physical and carcinogenic properties of 16 PAHs

PAH	Abbreviation	CAS Number	Emperical formula	Molecular weight ($g\ mol^{-1}$)	Melting point (°C)	IARC group
Benzo[a]anthracene	BaA	56-55-3	$C_{18}H_{12}$	228.3	160.7	2A
Benzo[b]fluoranthene	BbFA	205-99-2	$C_{20}H_{12}$	252.3	168.3	2B
Benzo[j]fluoranthene	BjFA	205-82-3	$C_{20}H_{12}$	252.3	165.4	2B
Benzo[k]fluoranthene	BkFA	207-08-9	$C_{20}H_{12}$	252.3	215.7	2B
Benzo[c]fluorene	BcFL	205-12-9	$C_{17}H_{12}$	216.3	126.5	3
Benzo[ghi]perylene	BghiP	191-24-2	$C_{22}H_{12}$	276.3	278.3	3
Benzo[a]pyrene	BaP	50-32-8	$C_{20}H_{12}$	252.3	178.1	2A
Chrysene	CHR	218-01-9	$C_{18}H_{12}$	228.3	253.8	3
Cyclopenta[cd]pyrene	CPP	27208-37-3	$C_{18}H_{10}$	226.3	170.0	3
Dibenz[a,h]anthracene	DBahA	53-70-3	$C_{22}H_{14}$	278.3	266.6	2A
Dibenzo[a,e]pyrene	DBaeP	192-65-4	$C_{24}H_{14}$	302.3	232.0	2B
Dibenzo[a,h]pyrene	DBahP	189-64-0	$C_{24}H_{14}$	302.3	317.0	2B
Dibenzo[a,i]pyrene	DBaiP	189-55-9	$C_{24}H_{14}$	302.3	282.0	2B
Dibenzo[a,l]pyrene	DBalP	191-30-0	$C_{24}H_{14}$	302.3	162.4	2B
Indeno[$1,2,3-cd$]pyrene	IP	193-39-5	$C_{22}H_{12}$	276.3	163.6	2B
5-methylchrysene	MCH	3697-24-3	$C_{19}H_{14}$	242.3	117.1	2B

incidence of individual PAH15 in 1375 food products ranged from 3.6% to 77.8%. CHR was the most prevalent PAH in food products, followed by BaA (70.3%), BbFA (63.1%), benzo[ghi]perylene (56.4%), and BaP (54.9%). The mean concentration of BaP in all food products was 0.8 μg kg^{-1}. However, BaP was detected in 100% of barbecued meat samples, with a mean level of 1.92 μg kg^{-1}. In this EFSA report, the median dietary exposure of BaP across European countries was calculated both for mean and high dietary consumers and varied between 3.9 ng kg^{-1} b.w. day^{-1} and 6.5 ng kg^{-1} b.w. day^{-1}, respectively. The median dietary exposure to PAH4 was calculated as 19.5 ng kg^{-1} b.w. day^{-1} for mean consumers, and 34.5 ng kg^{-1} b.w. day^{-1} for high consumers. It has been also concluded that estimates intakes of BaP and PAH4, based on available exposure data, were of low concern for human health (Margin of Exposure (MoE) >10,000) (EFSA 2008).

Benzo[a]anthracene   Benzo[b]fluoranthene   Benzo[j]fluoranthene

Benzo[k]fluoranthene   Benzo[ghi]perylene   Benzo[a]pyrene

Chrysene   Cyclopenta[cd]pyrene   Dibenz[a,h]anthracene

Dibenzo[a,e]pyrene   Dibenzo[a,h]pyrene   Dibenzo[a,i]pyrene

Dibenzo[a,l]pyrene   Indeno[1,2,3-cd]pyrene   5-methylchrysene

Benzo[c]fluorene
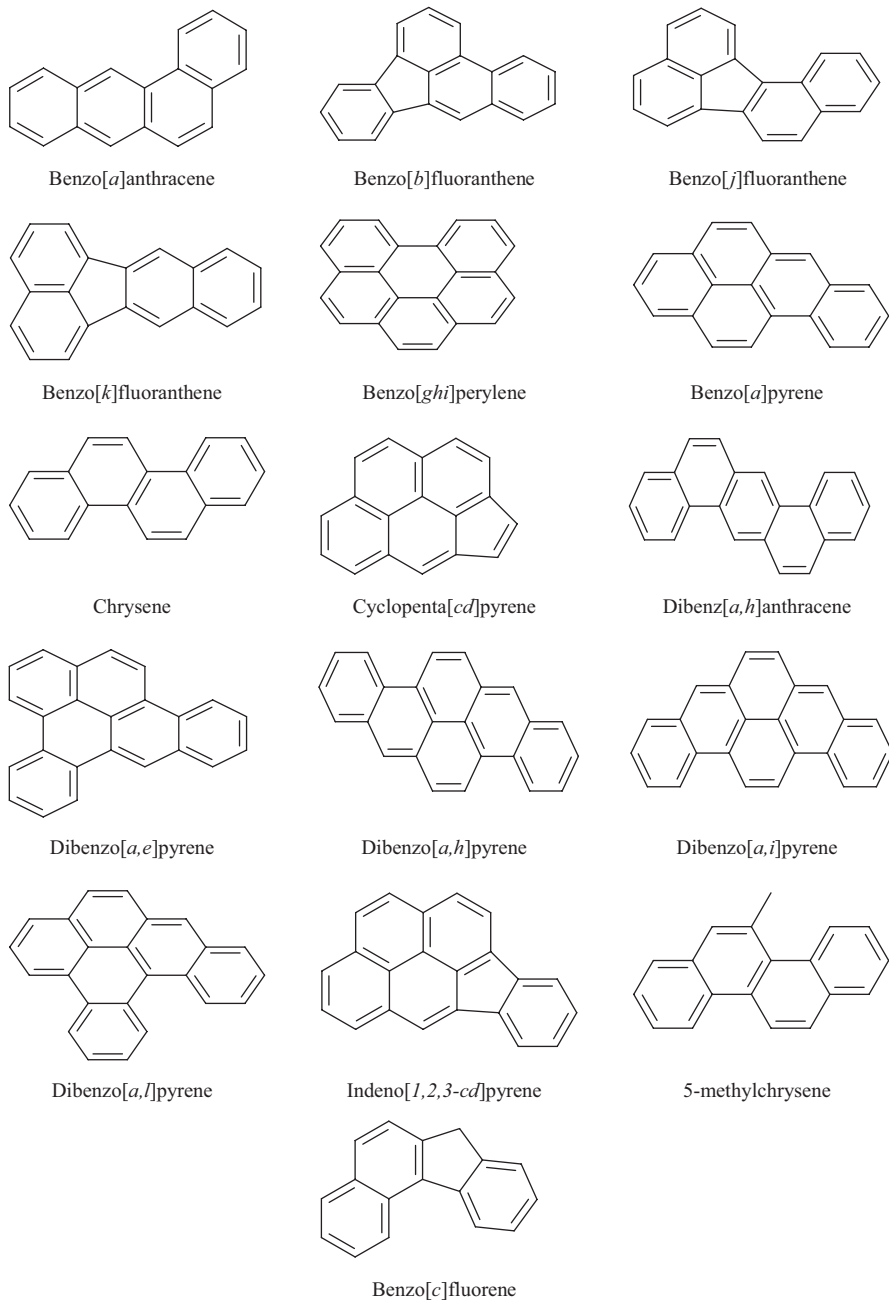
Fig. 2 Chemical structures of PAHs16

Table 7 Occurrence and levels of PAH4 in vegetable oils

Food	Country	BaP[a] Incidence/No. of samples	Range (min–max), µg kg⁻¹	BaA[b] Incidence/No. of samples	Range (min–max), µg kg⁻¹	BbFA[c] Incidence/No. of samples	Range (min–max), µg kg⁻¹	CHR[d] Incidence/No. of samples	Range (min–max), µg kg⁻¹	Reference
Blended oil	Iran	13/13	0.9–3.7	–	–	–	–	–	–	Yousefi et al. (2018)
Canola oil	Brazil	NR[e]/23	<0.1–6.3	NR/23	<0.1–4.7	NR/23	<0.1–4.8	NR/23	<0.1–7.9	Molle et al. (2017)
Cottonseed oil	China	5/5	0.2–6.3	5/5	0.3–6.4	5/5	1.5–7.9	5/5	1.1–8.1	Shi et al. (2016)
Frying oil	Iran	14/14	0.9–5.2	–	–	–	–	–	–	Yousefi et al. (2018)
Maize oil	China	12/12	0.4–1.6	12/12	0.7–2.1	12/12	0.9–2.6	12/12	1.1–3.7	Shi et al. (2016)
Maize oil	Brazil	26/26	0.3–7.5	26/26	0.4–6.7	26/26	0.6–5.4	26/26	1.1–13.1	Molle et al. (2017)
Maize oil	Iran	6/6	0.9–5.0	–	–	–	–	–	–	Yousefi et al. (2018)
Olive oil	China	8/8	1.3–0.9	8/8	0.01–1.0	8/8	0.4–1.2	8/8	0.8–1.9	Shi et al. (2016)
Peanut oil	China	10/10	0.7–4.7	10/10	0.7–6.9	10/10	0.3–8.6	10/10	0.6–8.6	Shi et al. (2016)
Rapeseed oil	China	10/10	1.1–2.2	10/10	0.3–2.4	10/10	1.8–3.1	10/10	0.5–3.0	Shi et al. (2016)
Sesame oil	China	10/10	0.1–2.6	10/10	0.1–2.7	10/10	0.5–4.9	10/10	0.8–4.5	Shi et al. (2016)
Soybean oil	China	15/15	0.4–1.5	15/15	0.4–2.5	15/15	1.1–2.8	15/15	1.1–3.6	Shi et al. (2016)

(continued)

Table 7 (continued)

Food	Country	BaP[a]		BaA[b]		BbFA[c]		CHR[d]		Reference
		Incidence/No. of samples	Range (min–max), µg kg⁻¹	Incidence/No. of samples	Range (min–max), µg kg⁻¹	Incidence/No. of samples	Range (min–max), µg kg⁻¹	Incidence/No. of samples	Range (min–max), µg kg⁻¹	
Sunflower oil	China	10/10	0.7–1.7	10/10	0.6–1.1	10/10	1.4–2.9	10/10	1.0–2.2	Shi et al. (2016)
Sunflower oil	Brazil	26/26	0.3–6.3	NR/26	<0.2–3.4	26/26	0.3–2.5	NR/26	<0.3–6.4	Molle et al. (2017)
Sunflower oil	Iran	5/5	0.9–1.1	–	–	–	–	–	–	Yousefi et al. (2018)

[a]BaP: Benzo[a]pyrene
[b]BaA: Benzo[a]anthracene
[c]BbFA: Benzo[b]fluoranthene
[d]CHR: Chrysene
[e]*NR* not reported

Table 8 Occurrence and levels of PAH4 in various food products

Food	Country	BaP[a]		BaA[b]		BbFA[c]		CHR[d]		Reference
		Incidence/ No. of samples	Range (min–max), μg kg⁻¹	Incidence/ No. of samples	Range (min–max), μg kg⁻¹	Incidence/ No. of samples	Range (min–max), μg kg⁻¹	Incidence/ No. of samples	Range (min–max), μg kg⁻¹	
Basil	India	25/25	0.85–2.9	NR/25	<0.09–3.1	25/25	1.6–9.3	25/25	1.6–9.7	Rozentāle et al. (2018a)
Thyme	Poland/ China	25/25	1.3–5.7	25/25	0.81–7.6	25/25	1.8–11.5	25/25	2.95–18.2	Rozentāle et al. (2018a)
Oregano	Turkey	NR[e]/25	<0.05–1.6	NR/25	<0.09–2.7	NR/25	<0.04–1.5	NR/25	<0.09–8.4	Rozentāle et al. (2018a)
Black tea	Argentina	27/27	0.2–92.5	27/27	0.2–62.8	27/27	0.1–67.6	27/27	2.5–109.1	Londoño et al. (2015)
Green tea	Argentina	14/14	0.4–61.3	14/14	0.7–74.4	14/14	0.2–66.6	14/14	4.6–153.7	Londoño et al. (2015)
Bread	Turkey	20/20	0.11–0.25	20/20	0.01–0.09	11/20	<0.01–0.08	20/20	0.01–0.11	Kacmaz (2016)
Breakfast cereals	Turkey	20/20	0.09–0.30	20/20	0.03–0.23	10/20	<0.01–0.14	20/20	0.03–0.25	Kacmaz (2016)
Mixed vegetables in olive oil	Italy	0/4	<0.01	3/4	0.07–0.14	4/4	0.07–0.11	4/4	0.18–0.30	Samnino (2016)
Mushrooms in sunflower oil	Italy	5/5	0.08–0.10	5/5	0.15–0.29	5/5	0.16–0.27	5/5	0.35–0.51	Samnino (2016)
Mayonnaise	Italy	6/6	0.04–0.10	6/6	0.08–0.26	6/6	0.09–0.16	6/6	0.14–0.44	Samnino (2016)
Soybean	Brazil	1/39	3.49	3/39	0.5–58.8	2/39	1.4–18.5	30/39	0.9–103.9	Garcia et al. (2017)

(continued)

Table 8 (continued)

Food	Country	BaP[a]		BaA[b]		BbFA[c]		CHR[d]		Reference
		Incidence/ No. of samples	Range (min–max), μg kg^{-1}	Incidence/ No. of samples	Range (min–max), μg kg^{-1}	Incidence/ No. of samples	Range (min–max), μg kg^{-1}	Incidence/ No. of samples	Range (min–max), μg kg^{-1}	
Milk powders	Uruguay	NR/44	<0.001–11.5	NR/44	<0.005–4.1	NR/44	<0.001–2.7	NR/44	<0.004–8.7	Londoño et al. (2017)
Milk powders	Argentina/ Brazil	28/31	0.01–0.57	30/31	0.02–2.46	25/31	0.07–1.49	24/31	0.19–5.88	Londoño et al. (2013)
Barbecued beef	Denmark	29/91	<0.3–17.5	–	–	–	–	–	–	Duedahl-Olesen et al. (2015)
Barbecued pork	Denmark	16/54	<0.3–8.4	–	–	–	–	–	–	Duedahl-Olesen et al. (2015)
Barbecued chicken	Denmark	3/30	<0.3–0.6	–	–	–	–	–	–	Duedahl-Olesen et al. (2015)
Canned/ smoked fishes	Poland	NR/60	<0.18–4.8	NR/60	<0.18–36.5	NR/60	<0.18–3.9	NR/60	<0.18–27.8	Zachara et al. (2017)
Chicken fillets	Poland	NR/15	<0.18–2.3	NR/15	<0.18–1.2	NR/15	<0.18–3.2	NR/15	<0.18–2.7	Zachara et al. (2017)
Grilled meat	Malaysia	NR/162	<0.03–12.5	–	–	NR/162	<0.03–13.8	–	–	Farhadian et al. (2010)
Grilled meat (gas grilled)	Iran	80/80	0.28–5.0	NR/80	<0.15–4.3	NR/80	<0.15–1.0	NR/80	<0.15–4.3	Gorji et al. (2016)

		Incidence/ No. of samples	Range (min-max), µg kg⁻¹	Incidence/ No. of samples	Range (min-max), µg kg⁻¹	Incidence/ No. of samples	Range (min-max), µg kg⁻¹	Incidence/ No. of samples	Range (min-max), µg kg⁻¹	
Grilled meat (choarcoal grilled)	Iran	80/80	0.45–5.8	NR/80	<0.15–5.2	NR/80	<0.15–5.2	NR/80	<0.15–4.1	Gorji et al. (2016)
Pork hams	Poland	NR/25	<0.18–2.7	NR/25	<0.18–10.2	NR/25	<0.18–4.1	NR/25	<0.18–9.6	Zachara et al. (2017)
Sausages	Poland	NR/20	<0.18–6.2	20/20	0.81–15.0	NR/20	<0.18–5.2	NR/20	<0.18–12.4	Zachara et al. (2017)
Smoked meat products	Latvia	NR/128	<0.05–6.0	NR/128	0.05–14.2	NR/128	<0.05–4.6	NR/128	0.1–14.5	Rozentāle et al. (2018b)

[a]BaP: Benzo[a]pyrene
[b]BaA: Benzo[a]anthracene
[c]BbFA: Benzo[b]fluoranthene
[d]CHR: Chrysene
[e]NR not reported

Toxicological Evaluation

In long-term studies, PAHs caused kidney and liver damage, and cataracts, jaundice and skin tumours. Among, PAHs, benzo[*a*]pyrene (BaP) is the most common PAH, which could be used as a marker of exposure. However, BaP constitutes only 1–20% of the total concentration of carcinogenic PAHs (Wenzl et al. 2006). BaP is also considered as a human mutagen (EU Category M2) and a human reprotoxic compound (EU Category M2) (BfR 2009). The SCF concluded that 15 PAHs, namely benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, benzo[*a*]pyrene, chrysene, cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*] pyrene, dibenzo[*a,l*]pyrene, indeno[*1,2,3-cd*]pyrene and 5-methylchrysene caused mutagenicity/genotoxicity in somatic cells in experimental animals *in vivo*. There is also strong evidence from *in vivo* data that these PAHs with the exception of benzo[*ghi*]perylene have carcinogenic effects in experimental animals (EFSA 2008). In addition, benzo[*c*]fluorene is also identified as a priority PAHs by JECFA.

Legislation

Specific ML of BaP and sum of BaP, benz(a)anthracene, benzo(b)fluoranthene and chrysene were set by EU for foodstuffs containing oils and fats, smoked foods and foods where environmental pollution might cause high levels of contamination. While the legislative limit of BaP varies from 1 µg kg^{-1} for foods for infants and young children to 10 µg kg^{-1} for *Bivalve molluscs*, the ML of sum of BaP, benz(a) anthracene, benzo(b)fluoranthene and chrysene in various foods of between 1 µg kg^{-1} (for foods for infants and young children) and 35 µg kg^{-1} (for Bivalve molluscs) (European Commission 2011).

Chlorinated Organic Compounds

Chlorinated organic compounds are divided into three groups: polychlorobiphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs, dioxin), polychlorinated dibenzofurans (PCDFs, furan) (Ergun 2015; González et al. 2019). PCBs are a general name used to express different chlorinated derivatives of biphenyl and consist of a very heterogeneous group of chemicals. PCBs with very low solubility in water are heat stable, non-flammable, and do not break down easily (Shibamoto and Bjeldanes 2009). However, they may be oxidized to dibenzo dioxin and dibenzo furans under specific conditions (Ayaz and Yurttagul 2008).

PCBs are materials commonly used in as coolants and lubricants in transformers and capacitors, and as hydraulic fluids and heat exchange fluids in electrical/elec-

tronic equipment (Arvanitoyannis et al. 2014; Thompson and Darwish 2019). In addition, they are also used in plasticizers and paints (Shibamoto and Bjeldanes 2009). They can be transmitted to food in various ways and large amounts. PCBs were detected frequently in fishes and seafood caught at high concentrations in large lakes (Shibamoto and Bjeldanes 2009; Arvanitoyannis et al. 2014). They are also found in organic and conventional meat, oils, milk and cheese (González et al. 2019).

More than 90% of PCBs are absorbed from the gastrointestinal tract, and accumulated mostly in adipose tissue in the skin, adrenal glands, and aorta. The amount of PCBs in the adipose tissue decreases more slowly than in the blood. It is usually excreted with faeces from the body. Via urinary excretion is in low amounts but, human milk excretion is very low compared to urine (Shibamoto and Bjeldanes 2009).

PCBs may cause acute and chronic effects in various animals (Omaye 2004; Thompson and Darwish 2019). They have carcinogenic, teratogenic and neurotoxic effects (Thompson and Darwish 2019). It leads to progress rather than initiating cancer formation. In addition, they can cause harmful effects by entering the phase of metabolic enzymes such as oxidases, reductases and conjugates. The most important effects in humans are stubborn acnes in the head and chest skin (Ayaz and Yurttagul 2008). Moreover, they may cause a number of problems in language delay, mental and motor development in humans (Thompson and Darwish 2019).

Dioxin is a highly chemically stable organochlorine compound and is considered one of the major food contaminant arising from environmental pollution (Ergun 2015). Dioxin is a toxic substance that has attracted the attention of the world after the incident known as "Seveso Disaster". In most of the chemicals (chlorophenols, phenoxyacid herbicides, chlorinated biphenyls and aromatic hydrocarbons) commonly used in industry, dioxin is present as impurity (Ayaz and Yurttagul 2008).

Dioxin sources can be listed as follows:

- Dioxin can be transmitted to the environment from the paper manufacturing industry. Especially, the chlorination stage in the bleaching units of the paper industry leads to the formation of dioxins,
- It can be produced as a by-product during the production of chlorophenols used as herbicides, fungicides, insecticides and bactericides,
- It can be found in most of the pharmaceuticals that we use frequently in our daily lives,
- Plastics, which constitute a significant part of local wastes such as polyvinyl chloride, also cause PCDD formation,
- It may occur in exhaust gases of automobiles using leaded fuel, and
- It may occur during the burning of wood and also formed by burning chlorine-based chemical compounds with hydrocarbons (Ayaz and Yurttagul 2008; Shibamoto and Bjeldanes 2009).

Dioxin can be taken from food, beverages, respiration and/or skin to the human body (Ayaz and Yurttagul 2008). The most important cause of dioxin exposure of humans is their diets (Shibamoto and Bjeldanes 2009). People are exposed to dioxin in particular with animal foods (Ergun 2015) such as milk and dairy products, fish and meat (Deshpande 2002; Shibamoto and Bjeldanes 2009).

Even small amounts of dioxin, which can be found in foods (fish and seafood), air, soil and water, can adversely affect human health (Arvanitoyannis et al. 2014). Dioxin containing 1–3 chlorine atoms is considered to be the lowest toxic effect, while chlorine containing dioxin at 2,3,7,8 (tetrachlorodibenzodioxin, TCDD) is considered to be the most toxic (Omaye 2004; Ayaz and Yurttagul 2008). That dioxin is one of the most potent teratogens known (Deshpande 2002). On the other hand, TCDD has been reported to be a more potent carcinogen than AFB_1 in studies done in female rats. The toxic effect of dioxins, and in particular TCDD, can vary from live to alive (Shibamoto and Bjeldanes 2009). However, health problems generally caused by dioxin include loss of appetite, changes in pigmentation in the skin, liver disorders, psychological abnormalities, neurological problems, high blood pressure, increased blood lipid and cholesterol levels. In addition, there are reports about the occurrence of congenital disorders such as reproductive disorders, palate cleft and defective kidney formation and the formation of soft tissue cancers (Ayaz and Yurttagul 2008).

Heavy Metals

Heavy metals (HMs) are used for metals with a specific gravity greater than 4.0 g/cm³ (Raikwar et al. 2008) and as having an atomic number over 20 (El-Kady and Abdel-Wahhab 2018). HMs are not formed as organic pollutants, they are naturally present in the earth's crust (El-Kady and Abdel-Wahhab 2018). Living all organisms need trace amounts of HMs to sustain various physiological functions. These HMs are cobalt (Co), iron (Fe), copper (Cu), manganese (Mn), molybdenum (Mo), vanadium (V), strontium (Sr), and zinc (Zn). There are also metals that are not necessary for metabolism. The most important ones are cadmium (Cd), mercury (Hg), lead (Pb), arsenic (As), Uranium (U), aluminum (Al) and tin (Sn) (Shibamoto and Bjeldanes 2009; Nfon et al. 2009).

HMs are one of the oldest toxic substances known since ancient times (Deshpande 2002). People are exposed to HMs in different ways, such as inhalation, and ingestion of foods or beverages (Iheanacho et al. 2017; Hejna et al. 2018). Volcanic eruptions, continental weathering, forest fires and mining-related operations are important sources of HMs (El-Kady and Abdel-Wahhab 2018). Depending on the developing technology, as well as sewage, agricultural chemicals (pesticides, fertilizers), domestic and untreated industrial effluents, the contamination of HMs is increasing and the residues and wastes of the related industries pollute the environment, plants, human and foods (Jan et al. 2015). Since they do not degradable and have high water soluble properties, they remain in the environment for a long time. HM pollution is increasing day by day in worldwide, especially in developing countries (Tasrina et al. 2015) As a result, certain amounts of toxic HMs in foods can exceed allowable limits.

HMs, which are dangerous, can be exceedingly poisonous even in low exposure doses and can be transmitted to foods (El-Kady and Abdel-Wahhab 2018).

Especially, foods can be exposed to metallic contamination at various stages of the production (such as harvest, handling, processing storage etc) and consumption chain. In the breeding and harvesting stage, contamination may occur from the soil, air, water and agricultural activities (pesticides, fertilizers), and in the processing stage from metal equipment and packaging materials (canned, plastic) (Deshpande 2002; Ayaz and Yurttagul 2008). Pollution of surface waters and groundwater by industrial wastes is another important cause of the HMs that people and animals are exposed (Deshpande 2002). Raw materials type and quality, distance of the raw material to the roadside, additives, soil eating and inadvertent contamination can affect dietary intake of HMs (Hejna et al. 2018). An important amount of heavy metals can be transferred to the edible parts of plants grown in heavy metal-rich soils (Tasrina et al. 2015).

HMs can cause cancer, kidney damage, endocrine disruption, cardiovascular, renal and immunological problems, nervous system damage and even death at very high concentrations in humans (Hejna et al. 2018; Edelstein and Ben-Hur 2018). IARC has included some heavy metals in the group of substances that can be carcinogenic to humans (Hejna et al. 2018). Factors affecting the toxicity of metals; metabolic interactions of metals, formation of metal-protein complexes, and routes of exposure, chemical form or type of HM (Deshpande 2002), as well as the age, gender, lifestyle, genetics and nutritional status of the exposed individuals (Hejna et al. 2018). Especially infants, children and adolescents are more susceptible to heavy metal-borne infections than adults. Today, to avoid heavy metal poisoning, some arrangements have been made in many countries about the maximum amounts of heavy metals that can be found in foods and beverages (Edelstein and Ben-Hur 2018).

An important part of the HMs gets strongly attached to the blood cells and tissues. Then, they are slowly excreted from the body via in the urine and lesser extent via gastrointestinal tract (Dorne et al. 2011). Therefore, they accumulate in some organs such as blood, liver, kidney, and hair (Deshpande 2002; Hejna et al. 2018). Some of the heavy metals which are more dangerous to human and animals are summarised below:

Arsenic

Arsenic, an inherently comprising and, distributed metal ubiquitous in the environment is present in low amounts in foods (Jan et al. 2015). Arsenic is contaminated to the environment from volcanic explosions, mining activities, steel production and coal and fossil fuels, as well as agricultural activities such as the use of pesticides (El-Kady and Abdel-Wahhab 2018). People can be exposed to arsenic from soil, water, air and food (Jan et al. 2015).

Both various organic and inorganic form of arsenic may be found in foods and environment. Organic arsenic can accumulate in fish and sea products such as shellfish, oysters, mussels and shrimp in high amounts (Shibamoto and Bjeldanes 2009).

While a small amount (10%) of arsenic found in fish and seafood is inorganic, most of the arsenic (almost 90%) in all other foods such as rice is inorganic (Dorne et al. 2011; El-Kady and Abdel-Wahhab 2018). The amount of arsenic in plants may vary depending on various factors such as soil content, water contamination, air pollution and/or fertilizer use (Ayaz and Yurttagul 2008).

Arsenic is readily absorbed from the foodstuffs in the GI system and transferred to all organs and tissues. It accumulates mostly on the skin, hair and nails. In a lesser proportion accumulates in the bones and muscles (Deshpande 2002).

Unlike mercury and lead, inorganic arsenic and its compounds are more toxic for humans than their organic forms (Deshpande 2002; Dorne et al. 2011). Intake of high amounts of arsenic can cause acute intoxication, and accordingly nausea, muscle weakness, vomiting, edema neurotoxic problems, and severe diarrhoea may occur (Shibamoto and Bjeldanes 2009; Edelstein and Ben-Hur 2018). Loss of appetite, weight loss, gastrointestinal disorders, liver enlargement, anemia, reduction of white blood cells, peripheral neuritis, hyperkeratosis and skin melanosis can occur in chronic intoxications (Deshpande 2002). Moreover, arsenic may lead to gastrointestinal problems and also skin, liver, and kidney cancers by affecting numerous organs (Jan et al. 2015).

Cadmium

Cadmium is a naturally found and widely distributed heavy metal in the environment. It is widely used in technological processes and form as most by-products. For these reason, cadmium can be found in soil, air, water, vegetation, tobacco, dust and food sources (Shibamoto and Bjeldanes 2009). Foods contain mostly inorganic salts of cadmium (Deshpande 2002). Moreover, cadmium can be found in the aquatic environments due to industrial and agrochemical wastes (El-Kady and Abdel-Wahhab 2018).

Cadmium can be found in several foods with a wide range of contamination levels (Deshpande 2002). A 30% of the daily intake of cadmium is provided from animal foods, while 70% is provided from herbal sources such as especially vegetables (El-Kady and Abdel-Wahhab 2018). Vegetarian people who consume foods such as cereals, nuts, oilseeds and pulses in high amounts may be exposure up to 5.4 mg kg^{-1} b.w. per week to cadmium (Dorne et al. 2011). Genetic factors, age and nutritional factors affect the absorption of cadmium taken with foods (Deshpande 2002). Significant amounts of cadmium may accumulate in shellfish and some animals' kidneys. It can be transmitted to herbal foods by irrigation water (Ayaz and Yurttagul 2008). Other sources of cadmium contamination include cadmium-containing food machinery and equipment, zinc galvanized equipment, glass, porcelain, rechargeable batteries, anticorrosion agents (Deshpande 2002; El-Kady and Abdel-Wahhab 2018).

Cadmium has been classified as group 1 (human carcinogen) (Deshpande 2002). Dietary high amounts of cadmium increase the risk of various cancers such as lung

cancer in humans (Hejna et al. 2018). It has toxic effects on the cardiovascular and skeletal system (Gomiero 2018). It causes slow and irreversible liver and kidney damages, dermal irritation, ulcer, inactivation of some enzymes in humans (Dorne et al. 2011; Hejna et al. 2018). Chronic intoxications occur in the form of growth retardation, reproductive disorders (Ayaz and Yurttagul 2008) and osteoporosis (Gomiero 2018). The high amounts of cadmium intake may also lead to *itai*, a bone disease that can lead to death (Raikwar et al. 2008).

Lead

Lead is one of the most plenty natural metals in the world because of it can be easily separated from the ore. It has been widely used for a variety of purpose in the industry in mining, smelting, refining, battery manufacturing, and so on (Dafaelseed et al. 2007; Jan et al. 2015). Thus, it can be found in air, water, soil and food (Raikwar et al. 2008).

One of the sources of lead contamination is tetraethyl lead, which is added to increase the octane rating to gasoline (Deshpande 2002; Jan et al. 2015). Half of the lead in the exhaust gas released from the vehicles spreads on both sides of the highways. As a result of this, lead content increases in plants growing in soil and in this soil. On the other hand, lead values are reduced when the distance away from the highway, and also as the soil depth increase (Ayaz and Yurttagul 2008).

People can be exposed to lead contamination from a wide variety of sources (Jan et al. 2015). The most important sources of non-industrial contamination are foods (more than 90%) and water (Shibamoto and Bjeldanes 2009). The amount in water may vary depending on the source of the lead. The use of lead-containing pipes and tanks in water distribution, especially if the water is soft and acidic, leads to an increase in lead content in water. This is because the acid in the water dissolves the lead in the pipes and therefore increases the concentration. Another important source of lead contamination is the glaze in ceramic containers. The amount of lead in acidic foods stored in such containers may increase (Ayaz and Yurttagul 2008). Other sources of contamination are lead used for soldering, canned food, lead-containing substances used to hunt animals such as birds and rabbits, leaded crystal cups, bottles and containers, storage batteries, insecticides, and newspaper which used for food packaging purposes (Deshpande 2002).

Foods with the highest lead content are usually shellfish. There is less lead in milk, fruits, vegetables, cereal products, potatoes, fish, meat, and tap water (Deshpande 2002; Dorne et al. 2011). Most of lead remains in the roots of plants (El-Kady and Abdel-Wahhab 2018). However, children can also be exposed to significant amounts of lead, especially from paints in dust, soil and toys in the house (Dorne et al. 2011). Lead is more easily absorbed in children (approx. 40%) than adults (approx. 10%) (Deshpande 2002).

There are several factors affecting the absorption of lead from the gastrointestinal tract (Shibamoto and Bjeldanes 2009). Absorbed lead acts as calcium in the

body and accumulates in various organs (Raikwar et al. 2008). 95% of the absorbed lead is distributed in hard tissue (bones, teeth, hair, and nails), 2% in blood and 3% in soft tissues in the liver, kidneys, aorta, muscle and brain (Deshpande 2002; Shibamoto and Bjeldanes 2009).

Organic form of lead is more dangerous than the inorganic one (Ayaz and Yurttagul 2008). One of the clinical symptoms of lead poisoning in the body is the interaction with some enzyme systems which are necessary for biosynthesis, and which lead to anaemia (El-Kady and Abdel-Wahhab 2018). Acute lead exposure may cause health problems such as loss of appetency, headache, hypertension, kidney failure, abdominal ache, lassitude, sleeplessness, arthritis, hallucinations and vertigo. Chronic intoxications may result in mental insufficiency, birth faults, allergy, weight losses, hyperactivity, paralysis, brawn weakness, brain damage, kidney detriments and even deaths (Jan et al. 2015). Lead can also induce anorexia, dyspepsia, constipation, paroxysmal abdominal pain and colic attack (Deshpande 2002). Intake to high amounts of lead in pregnant women may lead problems such as miscarriage, stillbirth, preterm delivery, low birth weight (Iheanacho et al. 2017).

Mercury

Mercury is mainly used in various activities such as thermometer, battery, fluorescent lamp, dye and fungicide production. In addition, it is used as amalgams in dental preparations (Deshpande 2002; Jan et al. 2015).

Mercury can be found in meat products, plants and especially in fish and other seafood (Shibamoto and Bjeldanes 2009). This is due to the fact that more than 3/4 of the total mercury in fish is in the form of methyl mercury produced by microorganisms in the sea. Especially in fishes such as swordfish, tuna, whale, shark and dolphin, mercury level can reach to 6 µg g^{-1}. Plants absorb only a limited amount of mercury with their roots even in soils contaminated with high levels of mercury. While mercury cannot be detected in potatoes, beans, olive oil and rice, in some cereal and cereal-based foods can be found up to 0.57 µg g^{-1} (El-Kady and Abdel-Wahhab 2018). The majority of the mercury found in plants is due to surface contamination with the atmosphere and to a lesser extent from the soil (Ayaz and Yurttagul 2008). The reason for the high content of mercury in the soil is the intensive use of pesticides and fungicides which include high amounts of mercury in their compositions (El-Kady and Abdel-Wahhab 2018).

Mercury has three different chemical forms: (i) elemental (metallic, HgO), (ii) organic (phenyl mercuric salts and alkyl mercuric compounds) and (iii) inorganic (monovalent and divalent). These chemical forms of mercury have its own toxicity and have negative impacts on health. The toxicity of mercury can vary related to chemical forms and its distribution in the human body. Because of its lipophilic properties, the organic mercury form readily absorbed after ingestion is more dangerous than the other two forms on health (Deshpande 2002; Jan et al. 2015). Organic mercury (methyl mercury) causes adverse effects on the central nervous

system, and these affects are caused by the accumulation of mercury in the motor regions of brain and central nervous system (Jan et al. 2015).

Foods can include both organic and inorganic forms. Inorganic forms are mercury chloride (HgCl), mercury bromide (HgBr) and mercury oxide (HgO), and organic forms methyl mercury (El-Kady and Abdel-Wahhab 2018). Inorganic mercury compounds, which have a half-life of about 40 days, damage the gastrointestinal tract, liver and kidneys when taken with food (Shibamoto and Bjeldanes 2009; Jan et al. 2015). They cause acute kidney failure and neurotoxicity in humans (Hejna et al. 2018). Moreover, acute inorganic mercury poisoning may cause gastrointestinal discomfort, abdominal pain, nausea, vomiting and bloody diarrhoea (Shibamoto and Bjeldanes 2009). Consumption of marine products containing high amounts of mercury (MeHg) during pregnancy causes the birth of children with neurological problems (El-Kady and Abdel-Wahhab 2018). On the other hand, in humans consuming high amounts of mercury-containing fish and crustaceans, a disease called *Minamata* occurs. *Minamata* is mercury poisoning that occurs in the form of decreased appetite, weakness, blindness, stagnation, inaction (Raikwar et al. 2008). Methyl mercury, one of the six most dangerous toxic chemicals in the environment, is neurotoxic for the adult and fetus because it accumulates in the brain (Deshpande 2002).

Conclusions

People are routinely exposed to many chemicals including naturally occurring substances, unapproved food additives and adulterants, agrochemicals, food processing contaminants, migration from food packaging materials and environmental/industrial pollutants. Some of these chemical hazards are not only toxic but also remain in the environment for a long time, and building up to high levels in the food chain and accumulate in the body tissue.

The strict regulations for certain chemical hazards have been established by the national governments and international bodies such as European Commission and Codex Alimentarius. It is recommended to monitor chemical hazards in food chain routinely and the preventive actions must be conducted in order to reduce exposure to chemical substances. However, the risk assessment of chemical hazards in the food chain is a non-static process and it needs to be flexible without long consistency. It should be needed forthcoming analyses including the assessment of multiple substance–exposure scenarios.

References

Aljaff P, Rasheed BO, Omer TA (2013) A comparison between natural and synthetic food flavoring extracts using infrared spectra and optical activity. IOSR J Appl Phys 5(3):1–6

Al-Shammari E, Bano R, Khan S, Shankity I (2014) The effect of preservatives and flavour additive on the production of oxygen-free radicals by isolated human neutrophils. Int J Nutr Food Sci 3(3):210–215

Arisseto AP, Silva WC, Scaranelo GR, Vicente E (2017) 3-MCPD and glycidyl esters in infant formulas from the Brazilian market: occurrence and risk assessment. Food Control 77:76–81

Arranz I, Baeyens WRG, Van Der Weken G, De Saeger S, Van Peteghem C (2004) Review: HPLC determination of fumonisin mycotoxins. Crit Rev Food Sci Nutr 44:195–203

Arusoglu G (2015) Acrylamide formation and its effects on human health. Acad Food 13:61–71. (In Turkish)

Arvanitoyannis IS, Kotsanopoulos KV, Papadopoulou A (2014) Rapid detection of chemical hazards (toxins, dioxins, and PCBs) in seafood. Crit Rev Food Sci Nutr 54:1473–1528

Ayaz A, Yurttagul M (2008) Toxic elements in foods. II. Hacettepe. University Faculty of Health Sciences Department of Nutrition and Dietetics, Klasmat Printing, Ankara, p 37. (In Turkish)

Baardseth P, Blom H, Skrede G, Mydland LT, Skrede A, Slinde E (2006) Lactic acid fermentation reduces acrylamide formation and other maillard reactions in French Fries. J Food Sci 71:28–33

Bas H, Pandır D, Kalender S (2016) Furan-induced hepatotoxic and hematologic changes in diabetic rats: the protective role of lycopene. Arh Hig Rada Toksikol 67:194–203

Becroft DMO, Webster DR (1972) Aflatoxins and Reye's disease. Br Med J 4:117

Bennet JW, Klich M (2003) Mycotoxins. Clin Microbiol Rev 16:497–516

Besaratinia A, Pfeifer GP (2007) A review of mechanisms of acrylamide carcinogenicity. Carcinogenesis 28:519–528

BfR (Bundesinstitut für Risikobewertung) (2009) PAHs in consumer products must be reduced as much as possible. Updated BfR Expert Opinion No. 025/2009. Available from https://www.bfr.bund.de. Accessed 30 Jan 2019

BfR (Bundesinstitut für Risikobewertung) (2016) Frequently asked questions regarding the contamination of foods with 3-MCPD, 2-MCPD and glycidyl fatty acid esters. Available from https://www.bfr.bund.de. Accessed 21 Jan 2019

Biedermann-Brem S, Noti A, Grob K, Imhof D, Bazzocco D, Pfefferle A (2003) How much reducing sugar may potatoes contain to avoid excessive Acr formation during roasting and baking. Eur Food Res Technol 217:369–373

Bogdanova E, Rozentale I, Pugajeva I, Emecheta EE, Bartkevics V (2018) Occurrence and risk assessment of mycotoxins, acrylamide, and furan in Latvian beer. Food Add Contam Part B 11:126–137

Bongers ML, Hogervorst JG, Schouten LJ, Goldbohm RA, Schouten HC, van den Brandt PA (2012) Dietary Acr intake and the risk of lymphatic malignancies: the Netherlands cohort study on diet and cancer. PLoS One 7(6):e38016

Chen Y-H, Xia E-Q, Xu X-R, Ling W-H, Li S, Wu S, Deng G-F, Zou Z-F, Zhou J, Li H-B (2012) Evaluation of Acr in food from China by a LC/MS/MS Method. Int J Environ Res Public Health 9:4150–4158

Choudhary PL, Sharma RS, Borkhateria VN (1998) Carry-over of aflatoxin B₁ from feed as aflatoxin M₁ in milk of Indian cows. Milchwissenschaft 53:513–515

Ciegler A (1978) Trichothecenes: occurrence and toxicoses. J Food Prot 4:399–403

Claeys W, Meulenaer B, Huyghebaert A, Scippo M-L, Hoet P, Matthys C (2016) Reassessment of the Acr risk: Belgium as a case-study. Food Control 59:628–635

Dafaelseed MS, Eltayeb MM, Hassan AB, Babiker EE (2007) Heavy metals and pesticides residue in commercial fresh vegetables in Sudan. In: Ahmed A (ed) Science, technology and sustainability in the Middle East and North Africa. Section VI. Inderscience Enterprises Limited, Geneva, pp 347–354

Deshpande SS (2002) Handbook of food toxicology. CRC Press, New York, p 920

Destaillats F, Craft BD, Dubois M, Nagy K (2012) Glycidyl esters in refined palm (*Elaeis guineensis*) oil and related fractions. Part I: formation mechanism. Food Chem 131:1391–1398

Dorne JL, Kass GE, Bordajandi LR, Amzal B, Bertelsen U, Castoldi AF, Heppner C, Eskola M, Fabiansson S, Ferrari P, Scaravelli E, Dogliotti E, Fuerst P, Boobis AR, Verger P (2011) Human risk assessment of heavy metals: principles and applications. Met Ions Life Sci 8:27–60

Duedahl-Olesen L, Aaslyng M, Meinert L, Christensen T, Jensen AH (2015) Polycyclic aromatic hydrocarbons (PAH) in Danish barbecued meat. Food Control 57:169–176

Edelstein M, Ben-Hur M (2018) Heavy metals and metalloids: sources, risks and strategies to reduce their accumulation in horticultural crops. Sci Hortic 234:431–444

EFSA (European Food Safety Authority) (2004) Opinion on the scientific panel on contaminants in the food chain on a request from the commission related to aflatoxin B_1 as undesirable substance in animal feed. EFSA J 39:1–27

EFSA (European Food Safety Authority) (2006) Opinion of the scientific panel on contaminants in the food chain on a request from the commission related to ochratoxin A in food. Question No EFSA-Q-2005-154. EFSA J 365:1–56

EFSA (European Food Safety Authority) (2008) Polycyclic aromatic hydrocarbons in food. Scientific opinion of the panel on contaminants in the food chain. Question No EFSA-Q-2007-136. EFSA J 724:1–114

EFSA (European Food Safety Authority) (2013) Analysis of occurrence of 3-monochloropropane-1,2-diol (3-MCPD) in food in Europe in the years 2009-2011 and preliminary exposure assessment. EFSA J 11(9):3381

EFSA (European Food Safety Authority) (2015) Scientific opinion on Acr in food EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA J 13(6):4104

EFSA (European Food Safety Authority) (2016) Risks for human health related to the presence of 3- and 2-monochloropropanediol (MCPD), and their fatty acid esters, and glycidyl fatty acid esters in food. EFSA J 14(5):4426

El-Kady AA, Abdel-Wahhab MA (2018) Occurrence of trace metals in foodstuffs and their health impact. Trends Food Sci Technol 75:36–45

Ergun B (2015) Toxicology, food safety and environmental health. Anadolu University Publication, Eskisehir, p 253. (In Turkish)

European Commission (2002) EC No 472/2002 of 12 March 2002 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs. Off J Eur Union L75:18–20

European Commission (2003) Reports on tasks for scientific co-operation in Task 3.2.10. Collection of occurrence data of *Fusarium* toxins in food and assessment of dietary intake by the population of EU Member States. Directorate-General Health and Consumer Protection, Brussels

European Commission (2006) Commission regulation (EC) No 401/2006 of 23 February 2006 laying down the methods of sampling and analysis for the official control of the levels of mycotoxins in foodstuffs. Off J Eur Union L70:12–34

European Commission (2011) Commission Regulation (EU) No 835/2011 of 19 August 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in foodstuffs. Off J Eur Union L 215:4

European Commission (2018) Commission Regulation (EU) 2018/290 of 26 February 2018 amending Regulation (EC) No 1881/2006 as regards maximum levels of glycidyl fatty acid esters in vegetable oils and fats, infant formula, follow-on formula and foods for special medical purposes intended for infants and young children. Off J Eur Union L55:27–29

Fan X (2005) Impact of ionizing radiation and thermal treatments on furan levels in fruit juice. J Food Sci 70:409–414

Farhadian A, Jinap S, Abas F, Sakar ZI (2010) Determination of polycyclic aromatic hydrocarbons in grilled meat. Food Control 21:606–610

FDA (Food and Drug Administration) (1993) Toxicological principles for the safety assessment of direct food additives and color additives used in food. Redbook II, Draft Guidance. US FDA, Center for Food Safety and Applied Nutrition, College Park. Subchapter II-definitions

Forsell JH, Jensen R, Tai J-H, Witt M, Lin WS, Pestka JJ (1987) Comparison of acute toxicities of deoxynivalenol (vomitoxin) and 15-acetyldeoxynivalenol in the B6C3F$_1$ mouse. Food Chem Toxicol 25:155–162

Freudenstein A, Weking J, Matthäus B (2013) Influence of precursors on the formation of 3-MCPD and glycidiyl esters in a model oil under simulated deodorization conditions. Eur J Lipid Sci Technol 115:286–294

Fromberg A, Mariotti MS, Pedreschi F, Fagt S, Granby K (2014) Furan and alkylated furans in heat processed food, including home cooked products. Czech J Food Sci 32(5):443–448

Gaikwad KY, Athmaselvi KA, Sarathchandra G (2016) Acr in potato chips, its formation, reduction and identification: a review. Int Res J Eng Technol 3:50–61

Garcia LP, Gomes FML, Tfouni S, Vicente E, Savi GD, Santos K, Scussel VM (2017) Polyclic aromatic hydrocarbons in commercial brands of dry whole soybeans for direct human consumption. Food Addit Contam Part B 10:15–20

Gelderblom WCA, Snyman SD (1991) Mutagenicity of potential carcinogenic mycotoxins produced by *Fusarium moniliforme*. Mycotoxin Res 7:46–52

Gelderblom WCA, Jaskiewicz K, Marasas WFO, Thiel PG, Horak RM, Vleggaar R, Kriek NPJ (1988) Fumonisins-novel mycotoxins with cancer-promoting activity produced by *Fusarium moniliforme*. Appl Environ Microbiol 54:1806–1811

Gelderblom WCA, Jaskiewicz K, Marasas WFO, Thiel PG (1991) Toxicity and carcinogenicity of the *Fusarium moniliforme* metabolite, fumonisin B$_1$ in rats. Carcinogenesis 12:1247–1251

Gelderblom WCA, Smuths CM, Abel S, Snyman SD, Caewood ME, Van der Westhuizen L, Swanevelder S (1996) Effect of fumonisin B$_1$ on protein and lipid synthesis in primary rat hepatocytes. Food Chem Toxicol 34:361–369

Gomiero T (2018) Food quality assessment in organic vs. conventional agricultural produce: findings and issues. Appl Soil Ecol 123:714–728

González N, Marquès M, Nadal M, Domingo JL (2019) Occurrence of environmental pollutants in foodstuffs: a review of organic vs. conventional food. Food Chem Toxicol 125:370–375

Gorji ME, Ahmadkhaniha R, Moazzen M, Yunesian M, Azari A, Rastkari N (2016) Polycyclic aromatic hydrocarbons in Iranian kebaps. Food Control 60:57–63

Halford NG, Curtis TY, Muttucumaru N, Postles J, Elmore JS, Mottram DS (2012) The acrylamide problem: a plant and agronomic science issue. J Exp Bot 63:2841–2851

Hamlet CG, Asuncion L, Velisek J, Dolezal M, Zelinková Z, Crews C (2011) Formation and occurrence of esters of 3-chloropropane-1,2-diol (3-CPD) in foods: what we know and what we assume. Eur J Lipid Sci Technol 113:279–303

Hejna M, Gottardo D, Baldi A, Dell'Orto V, Cheli F, Zaninelli M, Rossi L (2018) Review: nutritional ecology of heavy metals. Animal 12:2156–2170

Hendrickse RG, Coulter JBS, Lamplugh SM, Macfarlane SBJ, Williams TE, Omer MIA, Suliman GI (1982) Aflatoxins and kwashiorkor: a study in Sudanese children. Br Med J 285:843–846

IARC (International Agency for Research on Cancer) (1993) Some naturally occurring substances, food items and constituents, heterocyclic aromatic amines and mycotoxins, vol 56. World Health Organization, Lyon. 489p

IARC (International Agency for Research on Cancer) (1994) Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum 60:374–389

IARC (International Agency for Research on Cancer) (1995) Working group on the evaluation of carcinogenic risks to humans, Furan. IARC Monogr Eval Carcinog Risks Hum 63:393–407

IARC (International Agency for Research on Cancer) (2000) Some industrial chemicals. IARC Monogr Eval Carcinog Risks Hum 77:469–486

IARC (International Agency for Research on Cancer) (2012) 3-monochloro-1,2-propanediol. In: IARC Monographs, some chemicals present in industrial and consumer products, food and drinking-water, vol 101. IARC, Lyon, pp 349–374

Iheanacho EU, Ndulaka JC, Onuh CF (2017) Environmental pollution and heavy metals. Eur J Biotechnol Biosci 5:73–78

Inetianbor JE, Yakubu JM, Ezeonu SC (2015) Effects of food additives and preservatives on man - a review. Asian J Sci Technol 6:1118–1135

Jan AT, Azam M, Siddiqui K, Ali A, Choi I, Haq QMR (2015) Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants. Int J Mol Sci 16:29592–29630

JECFA (Joint FAO/WHO Expert Committee on Food Additives) (1996) Evaluation of certain food additives and contaminants: forty-sixth report of the joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 868. WHO, Geneva

JECFA (Joint FAO/WHO Expert Committee on Food Additives) (2001) Fifty-sixth meeting, 6-15 February. WHO, Geneva

Jedrkiewicz R, Glowacz A, Gromadzka J, Namiesnik J (2016) Determination of 3-MCPD and 2-MCPD esters in edible oils, fish oils and lipid fractions of margarines available on Polish market. Food Control 59:487–492

Jin C, Wu X, Zhang Y (2013) Relationship between antioxidants and Acr formation: a review. Food Res Int 51:611–620

Jung MY, Choi DS, Ju JW (2003) A novel technique for limitation of acrylamide formation in fried and baked corn chips and in French Fries. J Food Sci 68:1287–1290

Kabak B, Dobson ADW, Var I (2006) Strategies to prevent mycotoxin contamination of food and animal feed: a review. Crit Rev Food Sci Nutr 46:593–619

Kacmaz S (2016) Polycyclic aromatic hydrocarbons in cereal products on the Turkish market. Food Addit Contam Part B 9:191–197

Karacaoglu E, Selmanoglu G, Kılıc A (2012) Histopathological effects of the food contaminant furan on some endocrine glands of prepubertal male rats. Turk J Med Sci 42:1207–1213

Khachatourians GG (1990) Metabolic effects of trichothecene T-2 toxin. Can J Physiol Pharmacol 68:1004–1008

Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, Cottrill B, Dinovi M, Edler L, Grasl-Kraupp B, Hogstrand C, Hoogenboom L, Nebbia CS, Oswald IP, Petersen A, Rose M, Roudot AC, Schwerdtle T, Vleminckx C, Vollmer G, Chipman K, Meulenaer BD, Dinovi M, Mennes W, Schlatter J, Schrenk D, Baert K, Dujardin B, Wallace H (2017) Risks for public health related to the presence of furan and methylfurans in food. EFSA J 15(10):5005

Koehler PE, Beuchat LR, Chinnan MS (1985) Influence of temperature and water activity on afla-toxin production by *Aspergillus flavus* in cowpea seeds and meal. J Food Prot 48:1040–1043

Kopanska M, Czech J, Zagata P, Dobrek L, Thor P, Formicki G (2017) Effect of the different doses of Acr on acetylocholinoesterase activity, thiol groups, malondialdehyde concentrations in hypothalamus and selected muscles of mice. J Physiol Pharmacol 68:565–571

Krishnamachari KAVR, Bhat RVN, Agarajon V, Tilek TBG (1975) Hepatitis due to aflatoxicosis. Lancet 305:10631–11063

Kuhlmann J (2011) Determination of bound 2,3-epoxy-1-propanol (glycidol) and bound mono-chloropropanediol (MCPD) in refined oils. Eur J Lipid Sci Technol 113:335–344

Leigh J, Macmahon S (2017) Occurrence of 3-monochloropropanediol esters and glycidyl esters in commercial infant formulas in the United States. Food Addit Contam Part A 34:356–370

Li G, Shinozuka J, Uetsuka K, Nakayama H, Doi K (1997) T-2 toxin-induced apoptosis in intesti-nal crypt epithelial cells of mice. Exp Toxicol Pathol 49:447–450

Londoño VAG, Garcia LP, Scussel VM, Resnik S (2013) Polycyclic aromatic hydrocarbons in milk powders marketed in Argentina and Brazil. Food Addit Contam Part A 30:1573–1580

Londoño VAG, Reynoso CM, Resnik S (2015) Polycyclic aromatic hydrocarbons (PAHs) survey on tea (*Camellia sinensis*) commercialized in Argentina. Food Control 50:31–37

Londoño VAG, Reynoso CM, Resnik S (2017) Polycyclic aromatic hydrocarbons in milk powders marketed in Uruguay. Food Addit Contam Part B 10:284–291

Lye MS, Ghazali AA, Mohan J, Alwin N, Nair RC (1995) An outbreak of acute hepatic encepha-lopathy due to severe aflatoxicosis in Malaysia. Am J Trop Med Hyg 53:68–72

Mahajan RV, Saran S, Kameswaran K, Kumar V, Saxena RK (2012) Efficient production of L-asparaginase from *Bacillus licheniformis* with low-glutaminase activity: optimization, scale up and acrylamide degradation studies. Bioresour Technol 125:11–16

Martins FCOL, Sentanin MA, De Souza D (2019) Analytical methods in food additives determination: compounds with functional applications. Food Chem 272:732–750

McLean M, Dutton MF (1995) Cellular interactions and metabolism of aflatoxin: an update. Pharmacol Ther 65:163–192

Mestdagh F, De Wilde T, Castelein P, Németh O, Van Peteghem C, De Meulenaer B (2008) Impact of the reducing sugars on the relationship between acrylamide and maillard browning in French fries. Eur Food Res Technol 227:69–76

Molle DRD, Abballe C, Gomes FML, Furlani RPZ, Tfouni SAV (2017) Polycyclic aromatic hydrocarbons in canola, sunflower and corn oils and estimated daily intake. Food Control 81:96–100

Moss MO (2002) Mycotoxin review-1. *Aspergillus* and *Penicillium*. Mycologist 16:116–119

Musser SM, Plattner RD (1997) Fumonisin composition in cultures of *Fusarium moniliforme*, *Fusarium proliferatum*, and *Fusarium nygami*. J Agric Food Chem 45:1169–1173

Nerín C, Aznar M, Carrizo D (2016) Food contamination during food process. Trends Food Sci Technol 48:63–68

Nfon E, Cousins IT, Jarvinen O, Mukherjee AB, Verta M, Broman D (2009) Trophodynamics of mercury and other trace elements in a pelagic food chain from the Baltic Sea. Sci Total Environ 407:6267–6274

Ngindu A, Kenya PR, Ocheng DM, Omondi TN, Ngare W, Gatei D, Johnson BK, Ngira JA, Nandwa H, Jansen AJ, Kaviti JN, Siongok TA (1982) Outbreak of acute hepatitis caused by aflatoxin poisoning in Kenya. Lancet 319:1346–1348

Nie S, Huang J, Hu J, Zhang Y, Wang S, Li C, Marcone M, Xie M (2013) Effect of pH, temperature and heating time on the formation of furan in sugar–glycine model systems. Food Sci Human Wellness 2:87–92

Noti A, Biedermann-Brem S, Biedermann M, Grob K, Albisser P, Realini P (2003) Storage of potatoes at low temperatures should be avoided to prevent increased Acr formation during frying or roasting. Mitt Lebensmittelunters Hyg 94:167–180

Olsen M, Jonsson N, Magan N, Banks J, Fanelli C, Rizzo A, Haikara A, Dobson A, Frisvad J, Holmes S, Olkku J, Persson SJ, Börjesson T (2003) Prevention of ochratoxin A in cereals. In: Advances in food mycology. Advances in experimental medicine and biology, vol 571. Springer, Boston. Final report to project OTA PREV-QLK1-CT-1999-00433 from 1 February 2000 to 31 October 2003

Omaye ST (2004) Food and nutritional toxicology. CRC Press, Boca Raton, pp 254–265

Pandey RM, Upadhyay SK (2012) Food additive. In: El-Samragy Y (ed) Food additive. InTech, Rijeka, pp 1–30. https://doi.org/10.5772/34455. ISBN: 978-953-51-0067-6. Available from http://www.intechopen.com/books/food-additive/food-additive

Pitt JI (2000) Toxigenic fungi: which are important? Med Mycol 38:17–22

Pitt JI, Basilico JC, Abarca ML, Lopez C (2000) Mycotoxins and toxigenic fungi. Med Mycol 38:41–46

Placinta CM, D'Mello JPF, Macdonald AMC (1999) A review of worldwide contamination of cereal grains and animal feed with *Fusarium* mycotoxins. Anim Feed Sci Technol 78:21–37

Platinga WJ, Van Toorn WG, Van der Stegen GHD (1991) Determination of 3-chloropropane-1,2-diol in liquid hydrolysed vegetable proteins by capillary gas chromatography with Same ionization detection. J Chromatogr 555:311–314

Powers SJ, Mottram DS, Curtis A, Halford NG (2013) Acrylamide concentrations in potato crisps in Europe from 2002 to 2011. Food Addit Contam Part A 30:1493–1500

Pressman P, Clemens R, Hayes W, Reddy C (2017) Food additive safety: a review of toxicologic and regulatory issues. Toxic Res App 1:1–22

Raikwar MK, Kumar P, Singh M, Singh A (2008) Toxic effect of heavy metals in livestock health. Vet World 1:28–30

Ross PF, Nelson PE, Richard JL, Osweiler GD, Rice LG, Plattner RD, Wilson TM (1990) Production of fumonisins by *Fusarium moniliforme* and *Fusarium proliferatum* isolates associated with equine leukoencephalomalacia and a pulmonary oedema syndrome in swine. Appl Environ Microbiol 56:3225–3226

Rozentāle I, Lun AY, Zacs D, Bartkevics V (2018a) The occurrence of polycyclic aromatic hydrocarbons in dried herbs and spices. Food Control 83:45–53

Rozentāle I, Stumpe-Vīksna I, Začs D, Siksna I, Melngaile A (2018b) Assessment of dietary exposure to polycyclic aromatic hydrocarbons from smoked meat products produced in Latvia. Food Control 54:16–22

Sannino A (2016) Polycyclic aromatic hydrocarbons in Italian preserved food products in oil. Food Addit Contam Part B 9:98–105

Santonicola S, Mercogliano R (2016) Occurrence and production of furan in commercial foods. Ital J Food Sci 28:155–177

SCF (Scientific Committee on Food) (2000) Opinion of the Scientific Committee on Food on *Fusarium* toxins, Part 3: Fumonisin B_1 (FB_1). SCF/CS/CNTM/MYC/24 FINAL. SCF, Brussel

SCF (Scientific Committee on Food) (2001a) Opinion of the Scientific Committee on Food on *Fusarium* toxins, part 5: T-2 toxin and HT-2 toxin, European Commission SCF/CS/CNTM/MYC/25 Rev 6 final. SCF, Belgium

SCF (Scientific Committee on Food) (2001b) Opinion on 3-monochloro-propane-1,2-diol (3-MCPD), updating the SCF opinion of 1994 adopted on 30 May 2001. European Commission, Brussels. Available from http://ec.europa.eu/food/fs/sc/scf/out91_en.pdf

Scott PM (1993) Fumonisins. Int J Food Microbiol 18:257–270

Scotter M (2009) The chemistry and analysis of annatto food colouring: a review. Food Addit Contam 26:1123–1145

Seefelder W, Varga N, Studer A, Williamson G, Scanlan FP, Stadler RH (2008) Esters of 3-chloro-1,2-propanediol (3-MCPD) in vegetable oils: significance in the formation of 3-MCPD. Food Addit Contam 25:391–400

Shephard GS (2008a) Impact of mycotoxins on human health in developing countries. Food Addit Contam 25:146–151

Shephard GS (2008b) Risk assessment of aflatoxins in food in Africa. Food Addit Contam 25:1246–1256

Shi L-K, Zhang D-D, Liu Y-L (2016) Incidence and survey of polycyclic aromatic hydrocarbons in edible vegetable oils in China. Food Control 62:165–170

Shibamoto T, Bjeldanes L (2009) Introduction to food toxicology. Food Science and Technology international series, 2nd edn. Elsevier, London, p 309

Shinozuka J, Suziki H, Tsutsui S, Nakayama H, Doi K (2001) T-2 toxin-induced apoptosis and c-fos mRNA expression in con A-stimulated mouse thymocyte primary cultures. J Toxicol Pathol 14:247–251

Shukla P, Sharma A, Sharma S (2017) Food additives from an organic chemistry perspective. MOJ Bioorg Org Chem 1(3):70–79

Stockmann-Juvala H (2007) Neuro- and immunotoxic effects of fumonisin B_1 in cells. Academic Dissertation, Faculty of Pharmacy of the University of Helsinki, 75p, Helsinki

Sudakin DL (2003) Trichothecenes in the environment: relevance to human health. Toxicol Lett 143:97–107

Tasrina RC, Rowshon A, Mustafizur AMR, Rafiqul I, Ali MP (2015) Heavy metals contamination in vegetables and its growing soil. Environ Anal Chem 2:1–6

Thompson LA, Darwish WS (2019) Environmental chemical contaminants in food: review of a global problem. J Toxicol 6:1–14

Ueno Y, Sato N, Ishii K, Sakai K, Tsunoda H, Enomoto M (1973) Biological and chemical detection of trichothecene mycotoxins of *Fusarium* species. Appl Microbiol 25:699–704

Ueno Y, Umemori K, Nilimi E, Tanuma S, Nagata S, Sugamata M, Ihara T, Sekijima M, Kawai K, Ueno I, Tashiro F (1995) Induction of apoptosis by T-2 toxin and other natural toxins in HL-60 human promyelotic leukemia cells. Nat Toxins 3:129–137

Velísek J, Davídek J, Hajslová J, Kubelka V, Janícek G, Mankova B (1978) Chlorohydrins in protein hydrolysates. Z Lebensm Unters Forsch 167:241–244

Vranová J, Ciesarová Z (2009) Furan in food – a review. Czech J Food Sci 27:1–10

Wang ZG, Feng JN, Tong Z (1993) Human toxicosis caused by mouldy rice contaminated with *Fusarium* and T-2 toxin. Biomed Environ Sci 6:65–70

WeißHaar R (2008) Determination of total 3-chloropropane-1,2-diol (3-MCPD) in edible oils by cleavage of MCPD esters with sodium methoxide. Eur J Lipid Sci Technol 110:183–186

Wenzl T, Simon R, Kleiner J, Anklam E (2006) Analytical methods for polycyclic aromatic hydrocarbons (PAHs) in food and the environment needed for new food regulation in the European Union. Trends Anal Chem 25:716–725

Xu A, Fan Z, Chen Z, Zhou Y, Liu S, Huang S, Xu X, Long C, Wang W, Zhu J, Li X, Xu C (2017) Simultaneous determination of furan and vinyl acetate in vapor phase of mainstream cigarette smoke by GC-MS. An Acad Bras Cienc 89:383–389

Yousefi M, Shemshadi G, Khorshidian N, Ghasemzadeh-Mohammadi V, Fakhri Y, Hosseini H, Khaneghah AM (2018) Polycyclic aromatic hydrocarbons (PAHs) content of edible vegetable oils in Iran: a risk assessment study. Food Chem Toxicol 118:480–489

Zachara A, Galkowska D, Juszczak L (2017) Contamination of smoked meat and fish products from Polish market with polycyclic aromatic hydrocarbons. Food Control 80:45–51

Zamani E, Shokrzadeh M, Fallah M, Shaki F (2017) A review of acrylamide toxicity and its mechanism. Pharm Biomed Res 3:1–7

Zelinková Z, Svejkovská B, Velíšek J, Doležal M (2006) Fatty acid esters of 3-chloropropane-1,2-diol in edible oils. Food Addit Contam 23:1290–1298

Zelinková Z, Doležal M, Velíšek J (2009) Occurrence of 3-chloropropane-1,2-diol fatty acid esters in infant and baby foods. Eur Food Res Technol 228:571–578

Zyzak DV, Sanders RA, Stojanovic M, Tallmadge DH, Eberhart BL, Ewald DK, Gruber DC, Morsch TR, Strothers MA, Rizzi GP, Villagran MD (2003) Acrylamide formation mechanism in heated foods. J Agric Food Chem 51:4782–4787