

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the prospection of chemical hazards of interest in food safety in Spain (2)

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Abstract

Throughout the food chain, various chemical hazards may be present, incorporated or produced, which may pose a risk to the consumer.

In 2018, the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) reviewed the most relevant chemical hazards for food safety in Spain, which had no specific regulation, identifying them and pointing out those foods or conditions which, *a priori*, could imply a greater risk for the consumer, to perform prospective studies, eventually. This new report addresses the following chemical hazards and matrixes: aluminium, antimony, chromium (VI), anthraquinones,

aflatoxins in hazelnuts, melamine, bisphenol A (BPA) analogues and *Aspergillus* mycotoxins (sterigmatocystin).

As in the previous report, the identification and characterisation, exposure assessment, recommendations and future considerations have been described for each of them.

On the other hand, it is essential to identify new hazards for which significant exposure may occur or to assess the risk arising from new or significantly increased exposure or susceptibility to a known hazard, not only for the eventual control of these emerging hazards but also to promote research and to improve consumer and scientific understanding.

Key words

Prospective, chemical hazards, aluminium, antimony, chromium (VI), anthraquinones, aflatoxins in hazelnuts, melamine, bisphenol A analogues, BPA, *Aspergillus* mycotoxins, sterigmatocystin.

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1. Introduction

Along the food chain, different chemical hazards may be present, incorporated or produced that could pose a risk to the consumer. Official control programmes seek to ensure the realization of risk-based controls of food safety hazards, but they only affect parameters with maximum limits set in certain foods. However, there are other hazards of interest in food safety for which there is no specific regulation, or there is, but only in certain foods, which can be the subject of prospecting programmes to obtain data that, in addition to protecting consumers from a specific hazard exposure, allow to perform a risk assessment. In addition, the identification of new hazards for which significant exposure may occur, or the risk assessment arising from new or significantly increased exposure or susceptibility to a known hazard is important, not only for the eventual control of these emerging hazards, but also to promote research and improve consumer and scientific community knowledge. In this regard, in 2018, the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) published a first report on the prospection of chemical hazards of interest to food safety in Spain (AESAN, 2018), in which the following were noted:

- Cylindrospermopsin (cyanobacteria toxin) in drinking water (not bottled).
- Chloropropanols and glycidol in baby food.
- Furan and derivatives in processed foods in general and baby foods in particular.
- Mineral oil hydrocarbons.
- Mycotoxins produced by fungi of the *Claviceps* genus in cereals and derived foods.
- *Alternaria* toxins in fruits, vegetables, cereals and tomatoes.
- *Fusarium* mycotoxins (enniatins, nivalenol) in cereals.
- Pyrrolizidine alkaloids in infant foods, food supplements, honey, pollen, tea, infusions and cereals.

In order to incorporate more hazards of interest to possible prospective studies, the Scientific Committee is requested to carry out a new review of the hazards of greatest interest in food safety in Spain that do not have a specific regulation, identifying them and pointing out those foods or conditions that, *a priori*, could imply a greater risk for the consumer.

2. Chemical hazards

The following chemical hazards and matrices have been considered:

- Aluminium.
- Antimony.
- Chromium (VI).
- Anthraquinones.
- Aflatoxins in hazelnuts.
- Melamine.
- Bisphenol A (BPA) analogues.
- Mycotoxins of *Aspergillus* (sterigmatocystin).

3. Aluminium

3.1 Hazard identification and characterisation

The report of the Scientific Committee of AESAN regarding the possible risk of dietary aluminium (Al) in 2009 describes extensively the dangers of dietary exposure to this metal, being this the main exposure route for the general population (AESAN, 2009).

It is poorly absorbed, and its bioaccumulation and persistence in the organism define its long-term toxicity. Its target organ is the brain (Exley, 1999), hence its relationship with neurodegenerative diseases, especially Alzheimer's disease. It also accumulates in the bones, increasing the possibility of fractures, especially in adolescents. According to the latest data from the European Food Safety Authority (EFSA) and the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO), Al is considered unlikely to be genotoxic and carcinogenic to humans.

EFSA established a LOAEL (Lowest Observed Adverse Effect Level) of 50 mg aluminium/kg body weight/day (range 50-100) and a NOAEL (No Observed Adverse Effect Level) of 10 mg aluminium/kg b.w./day (range 10-100), using neurotoxicity, testes toxicity, embryotoxicity and neurodevelopmental toxicity as endpoints (EFSA, 2008a).

WHO set a Provisional Tolerable Weekly Intake (PTWI) of 2 mg aluminium/kg b.w./week and EFSA indicates a Tolerable Weekly Intake (TWI) of 1 mg aluminium/kg b.w./week. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) used the study published by Poirier et al. (2011) as a basis for the evaluation, obtaining a NOAEL of 30 mg aluminium/kg b.w./day, applying an uncertainty factor of 100 (JECFA, 2011).

3.2 Exposure and risk assessment

In all the evaluations of the risk of intake of Al through food and/or additives carried out by both EFSA and WHO, this metal has been identified as a possible risk to health, mainly for the child population, as its intake exceeds the established reference values.

Most of Al intake comes from food, through different ways: food contaminated by its natural content of Al, water and industrialised foods with Al as a preservative and/or colourant (Crisponi et al., 2013) or by migration of materials in contact with food (AESAN, 2009).

EFSA estimated that adult exposure ranged from 0.2 to 1.5 mg aluminium/kg b.w./week and, for children, from 0.7 to 2.3 mg aluminium/kg b.w./week, concluding that the TWI of 1 mg aluminium/kg b.w./week is likely to be exceeded in a significant part of the European population (EFSA, 2008a).

3.2.1 Waters

The most bioavailable form of Al to be absorbed by the intestine is present in drinking water due to the use of Al sulphate as a flocculating agent in the treatment of water supplies. However, Al intake through drinking water is generally low. The maximum permitted Al contamination in drinking water is variable and dependent on the country, ranging from 0.03 to 0.2 mg/l of water (Matías et al., 2018). Al concentrations of 0.4 to 1 mg/l in drinking water have been detected in several cities (ATSDR, 2008).

The concentration of Al in natural waters is generally below 0.1 mg/l (ATSDR, 2008). The United States Environmental Protection Agency (EPA) has recommended a Secondary Maximum Conta-

minant Level (SMCL) of 0.05 to 0.2 mg/l for Al in drinking water (EPA, 2022). SMCL is not based on levels that can affect human or animal health, but on taste, smell, or colour. Also, the Food and Drug Administration (FDA) has set a limit for Al in bottled water of 0.2 mg/l (ATSDR, 2008).

3.2.2 Food

In 2008, the EFSA evaluated the dietary exposure of the European population to Al, resulting in 0.2-1.5 mg aluminium/kg b.w./week for the general population, up to 2.3 mg aluminium/kg b.w./week in children, exceeding the TWI and PTWI (EFSA, 2008a). In 2012, JECFA evaluated the exposure to this metal and also established that child population, a regular consumer of foods containing the highest amount of additives with Al, cereals and derivatives (bread, biscuits, cakes, etc.) could exceed the PTWI. Therefore, these two organisms have identified this metal as a possible health risk, mainly for child population, because its intake exceeds the established reference values (JECFA, 2012).

The daily intake of an adult is approximately 7 to 9 mg of Al per day through food.

3.2.3 Additives

In 2010, The European Commission proposed to re-evaluate all food additives that were allowed before 20th January 2009, setting 2018 as the deadline for food additives containing Al (EU, 2010a).

In 2013, EFSA assessed the exposure to Al from five aluminium-containing food additives (E-523, E-541 (i, ii), E-554, E-556 and E-559) in scenarios where all foods containing Al are consumed and at their maximum limits. In both scenarios, estimated intakes far exceeded PTWI and TWI (EFSA, 2013a).

Al compounds allowed in the manufacture of additives are regulated by Regulation (EU) No. 380/2012 amending Annex II to Regulation (EC) No. 1333/2008 as regards the conditions of use and the use levels for Al-containing food additives (EU, 2012a). In fact, additives containing Al are not allowed in infant formulas or processed cereal-based infant foods.

The EFSA Scientific Panel on Food Additives and Nutrient Sources Added to Food (ANS) issued a scientific opinion re-evaluating the safety of Al sulphates (E-520, E-521, E-522 and E-523) and sodium aluminium phosphate, acid (E-541) as food additives in 2018, concluding that these compounds are not of safety concern in the current authorised uses and use levels (EFSA, 2018).

3.2.4 Migration

The contribution of food cooked in Al utensils, Al foil used for wrapping, or beverage cans is virtually negligible (around 0.1 mg/day). The only exception is when cooking or storing food with high acidity or salinity in unprotected Al containers for long periods (EFSA, 2008a).

Commission Regulation (EU) 2016/1416 amending Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food (e.g. Al paper) sets an Al migration limit of 1 mg per kg of food (EU, 2016).

3.2.5 Population groups

Population groups most vulnerable to the toxic effects of Al are foetuses (metal passes through placenta), infants (metal is transferred into breast milk), and the child population in general, because they have a greater absorption capacity of this metal than the adult population.

3.3 Risk management strategies

The conclusions of the 2009 AESAN report (AESAN, 2009) were: 1) the scarcity of data on Al content in food in our country; 2) the need to carry out specific controls of Al levels in certain infant formulae; 3) carry out toxicity studies on Al-containing food additives in the adult population; and 4) availability of estimates of dietary exposure to Al in our country, including methods to identify its sources, intrinsic or added (additives, consequence of processing, migrations from storage containers, etc.), given the neurotoxic potential of this metal.

Little progress has been made so far in these areas.

Since the presence of Al in the natural environment cannot be reduced, it is possible to employ alternatives to its use in the manufacturing of additives and materials in contact with food. Thus, for waste water treatment, it has been suggested the use of vegetable coagulants, since treated water is one of the main routes of Al intake (Matías-Cervantes et al., 2018). Excessive use of Al associated with food additives should be effectively controlled (Ding et al., 2021).

EFSA also identified the following uncertainties and/or information gaps when assessing dietary exposure to Al (EFSA, 2008a):

- Lack of representative data of Al intake of the whole of Europe (data from Finland, United Kingdom, France and Spain).
- Strong variations between the different countries providing data and, within a country, differences between the types of surveys.
- Need for more data in the different population groups.
- Neither the individual Al compounds nor the specific sources contributing to the Al content of a specific food could be determined because the dietary studies and analytical methods used only determine the total Al content in foods.

Since the risk related to dietary exposure to Al cannot be excluded for certain consumer groups, further efforts should be made to reduce contamination and exposure.

The Council of Europe technical guide published in 2013 includes the following general recommendation: "Storage of acidic (e.g. fruit juices), alkaline (e.g. lye dough products) or salty, liquid foodstuffs in uncoated aluminium utensils should be limited in order to minimise release" (EDQM, 2013).

4. Antimony

4.1 Hazard identification and characterisation

Antimony (Sb) is a metalloid found in low levels in the environment, predominantly in its trivalent form (trihydroxyantimony ($\text{Sb}(\text{OH})_3$)), from both natural soil erosion and anthropogenic sources (EPA, 1979) (Mok and Wai, 1990).

Its absorption by the gastrointestinal tract is low (1-10 %) and depends on various factors such as the chemical form and solubility of the ingested Sb, age and diet. Several studies have evaluated factors that contribute to the body burden of Sb. A study on Norwegian women who were never pregnant found that increasing age (25 to 40 vs. 18 to 24 years), an omnivorous diet (compared to vegetarian diet), and smoking were associated with higher serum Sb levels (Fløtre et al., 2017). Sb is distributed throughout the body, being in the lungs, gastrointestinal tract, red blood cells, liver, kidneys, bones, spleen and thyroid where the highest levels are reached (Kirkland et al., 2007). Trivalent Sb is predominantly excreted in faeces, with smaller amounts in urine, and pentavalent Sb is excreted mainly in urine.

Sb trioxide is clastogenic *in vitro*, but not mutagenic, in gene mutation assays in bacteria and in cultured mammalian cells (ATSDR, 2019), although it is not expressed *in vivo* (Kuroda et al., 1991) (Gurnani et al., 1992). The International Agency Research on Cancer (IARC, 2015) has determined that Sb trioxide is possibly carcinogenic to humans (Group 2B) and Sb trisulfide is not classifiable as to human carcinogenicity (Group 3). The EPA has not evaluated Sb for carcinogenicity. The United States National Toxicology Program (US-NTP) established that Sb₂O₃ is a human carcinogen based on carcinogenicity tests in model organisms and the results of mechanical research (NTP, 2018). However, available data related to Sb carcinogenicity in humans are insufficient to assess the relationship between exposure to Sb₂O₃ and the risk of human cancer (Bolan et al., 2022).

Following a subchronic study of drinking water with potassium tartrate and Sb, a NOAEL of 6.0 mg antimony/kg b.w./day was proposed. Using this NOAEL and an uncertainty factor of 1000 (100 for intra-species and inter-species variation, and 10 for the use of a sub-chronic study), a Tolerable Daily Intake (TDI) of 0.006 mg antimony/kg b.w./day (or 0.36 mg Sb/person/day) was obtained (WHO, 2003a). Based on the above data and considering various exposures, a restriction of 0.04 mg antimony/kg food is applied. It should be noted that the migration limit could be exceeded at very high temperatures. This restriction would allow 10 % of TDI to be applied to food contact materials (ATSDR, 2019).

To date, no maximum limits have been set at State or Community level for the presence of Sb in food. A maximum admissible concentration of 5 µg/l for drinking water is established in the European Union (BOE, 2003). According to Commission Regulation (EU) No. 10/2011, manufacturers have to ensure that plastic containers do not transfer amounts of Sb above the specific migration limit value of 40 µg/kg, even if the food is to be cooked in the package (EU, 2011a). In the United States, while tap water is regulated by EPA, with a Maximum Contaminant Level (MCL) of 6 µg/l for drinking water (EPA, 2018), bottled water is considered a food product and therefore falls within the scope of FDA (2017) which has not specified a migration limit for Sb of PET (polyethylene terephthalate) packaging materials.

Following direct (inhalation or ingestion) or indirect (through food chain) exposure, Sb and Sb-derived compounds react with sulfhydryls in human tissue, causing cellular hypoxia by inhibiting enzymatic action and altering cellular ionic balance. All this would lead to metabolic malfunction and nervous system and vital organs impairment (Yang et al., 2015). Excessive ingestion of Sb by humans can cause nausea, diarrhoea, skin rashes, and respiratory disorders (Hua et al., 2021) (Bolan et al., 2022).

The main adverse effects occur in the heart (abnormal electrocardiogram readings), gastrointestinal tract (nausea, abdominal pain, vomiting, diarrhoea, anorexia), musculoskeletal system (myalgia, arthralgia), liver (alanine and aspartate aminotransferases increases), pancreas (increases in serum amylase levels) and nervous system (headache, dizziness) (Zaki et al., 1964) (Dancaster et al., 1966) (Sundar et al., 1998) (Thakur, 1998) (Palacios et al., 2001) (Andersen et al., 2005) (Lawn et al., 2006) (Neves et al., 2009).

The following toxicological data are available after oral exposure: acute, Minimal Risk Levels (MRLs) 1 mg antimony/kg b.w./day; NOAEL of 99 mg antimony/kg b.w./day (NTP, 1992); subchronic, MRL 0.0006 mg antimony/kg b.w./day; NOAEL of 0.064 mg antimony/kg b.w./day (Poon et al., 1998), with insufficient data for the derivation of a chronic MRL (ATSDR, 2019).

On the other hand, associations have been found between urine Sb levels and diabetes risk (data obtained from the 1999-2010 National Health and Nutrition Examination Survey, NHANES) (Menke et al., 2016), sleep problems and daytime sleepiness (data obtained from the 2005-2008 NHANES survey) (Scinicariello and Buser, 2016), autism and autism spectrum disorders (Saghazadeh and Rezaei, 2017).

In the mid-1990s, it was hypothesized that microbial growth in crib mattresses could generate stibnite from Sb trioxide in flame retardants. It was also hypothesised that stibnite could cause Sudden Infant Death Syndrome (SIDS) (Richardson, 1994).

4.2 Exposure and risk assessment

The general population may be exposed to Sb through ingestion of food and drinking water, inhalation of ambient air particles, or ingestion of contaminated soil or dust.

The uses of Sb are numerous. Shotyk et al. (2006) warned of the presence of Sb in significant concentrations in bottled water, relating them to the use of Sb as a catalyst in the production of PET bottles (Shotyk et al., 2006) (Shotyk and Krachler, 2007). This occurs especially under inadequate storage conditions, including exposure to sunlight and high temperatures (Westerhoff et al., 2007) (Bach et al., 2013) (Fan et al., 2014), being temperature the most influential factor in increasing Sb release (Greifenstein et al., 2013). In addition, regardless of the duration of ultraviolet exposure, the frequency of reuse (up to 27 times) was the main factor that linearly increases Sb leaching from PET bottles at all tested temperatures (Andra et al., 2012) (Filella, 2020).

For its part, Xu et al. (2021) studied the leaching and *in vivo* bioavailability of Sb in PET bottled beverages, especially when they are stored in poor conditions, finding that carbonated and protein-rich beverages exhibited a higher risk of exposure due to high leaching of Sb and the high bioavailability compared to other categories of beverages. The beverages considered were soft drinks, fruit juices, tea, sports drinks, protein drinks and coffee drinks. The Chronic Daily Intake (CDI) of Sb through these beverages was, in order: juice > soft drinks (including carbonated, sports and protein drinks) > tea > coffee, with values of 13.2, 9.30, 1.0 and 0.24 ng/kg b.w./day for children aged 2 to 18 years. For adults (≥ 19 years), the total CDI was, in order: tea > soft drinks > coffee > juice with values of 8.78, 4.63, 2.92 and 2.19 ng/kg b.w./day. Among all beverages, juices accounted for the largest contribution to Sb consumption in children (39.1 % of the total CDI), while tea accounted for

the largest contribution in adults (47.4 % of the total CDI). In addition to beverages, intake of other foods has been shown to be a significant route for human exposure to Sb (Chen et al., 2014) (Cao et al., 2016).

As for juices, Hansen et al. (2010) noted the possibility of Sb coming from a contaminated ingredient or from the production equipment and not only from PET.

Many studies have been published on the presence of Sb and the factors that influence PET bottles, although according to Filella (2020) their knowledge has not been deepened due to deficiencies in the design of the studies, such as the low number of samples, lack of statistical treatments, etc., which lead to poor conclusions and should be corrected in the future.

Total diet studies are also scarce. One of them, carried out in Catalonia in 2015, concluded that the population groups studied had daily intakes well below the toxicological safety level established by WHO, at 6 µg antimony/kg b.w./day. Bread, cereals and fruits were the foods that accounted for the most Sb (ACSA, 2015). Glorennec et al. (2016), found that diet represented more than 77 % of total Sb exposure in French children aged 3 to 6 years. For their part, Pearson and Ashmore (2020), when characterising the danger of Sb, observed that the group of babies were exposed to values that exceeded those estimated as healthy.

4.3 Risk management strategies

Experiments in risk management have been conducted at laboratory level regarding the reduction of Sb in contaminated soils, through the application of certain materials that adsorb the metalloid, decreasing its bioavailability in plants (Kumar et al., 2020) (Palansooriya et al., 2020), (Bolan et al., 2022), as well as the use of microbial communities that modify the toxicity and mobility of Sb compounds by redox processes (He et al., 2019) (Jeyasundar et al., 2021).

To reduce the risks associated with dietary exposure to Sb, it is necessary to conduct studies aimed at determining the transfer and bioavailability of Sb in different food matrices (Xu et al., 2021). In addition, it would be interesting to conduct chronic toxicity studies.

Regarding Sb leaching from PET bottles, different guidelines can be given to reduce this process such as, for example, washing the new bottles before first use, since contamination by this metalloid derives from the production process (Cheng et al., 2010), not storing the PET bottles in high temperature conditions (for example, car trunks) and non-reuse of bottles (Filella, 2020).

Follow-up studies are needed for infants and young children, especially since there is a chance of exposure from clothing and household items treated with flame retardants containing Sb.

5. Chromium (VI)

5.1 Hazard identification and characterisation

Chromium (Cr) is a metal present in nature, forming part of crocoite as lead chromate; it was isolated for the first time in 1798. The most frequently found form in nature is Cr (III), while the natural presence of Cr (VI) is rare as it is formed mainly in industrial processes (Klaassen, 2019). Cr (VI) has been identified as the most toxic form of chromium by rapidly crossing cell membranes and being reduced to Cr (III) causing toxic effects (Ahmed et al., 2013).

5.1.1 Toxicokinetic

Oral exposure to Cr (VI) occurs primarily through drinking water. However, environmental exposure to the compound is also relevant. Following oral exposure to Cr, its absorption in humans is low (<10 % of the ingested dose). However, for Cr (VI) the absorption is higher (2-10 %) than in the trivalent compound (0.5-2 %) (ATSDR, 2012). In both cases, Cr absorption is higher on fasting than on full stomach (O'Flaherty, 1996). Specifically, co-administration of Cr (VI) with orange juice has been shown to reduce oral absorption (Kerger et al., 1996). In addition, intestinal absorption appears to be hampered by contact with gastric juices both in humans and rats (De Flora et al., 1987).

Cr (VI) crosses the cell membrane easily through sulphate and phosphate transporters (ATSDR, 2012). Once it enters the cell, Cr (VI) is reduced to Cr (III) by ascorbic acid, glutathione or cysteine. Due to this process, free radicals are generated with formation of DNA adducts that appear to be responsible for the toxicity of Cr (VI) which will be detailed later (Reynolds et al., 2012) (Sun et al., 2015). After ingestion, there is also a metabolism reducing Cr (VI) to Cr (III) by saliva and to a greater extent by gastric juices (De Flora, 2000) (EFSA, 2014). Once Cr (VI) is absorbed and passed into the blood, it enters the erythrocyte where it may be retained. Cr compounds are distributed throughout the body with high levels in the liver, spleen, kidneys and bone marrow. Cr particles can be retained in the lungs for years (Klaassen, 2019).

Cr excretion occurs mostly in the urine. Cr (VI) elimination half-life is 35-40 hours (Sedman et al., 2006). Removal of Cr (VI) has been shown to be faster in the case of oral absorption versus other routes of exposure, clearly reflecting the transition to Cr (III) prior to gastrointestinal absorption (Coogan et al., 1991). However, it has been estimated that the total organism elimination of Cr (VI) is 22 days (WHO, 2000).

5.1.2 Toxic effects

By environmental exposure, Cr (VI) is corrosive and can cause chronic ulceration and perforation of the nasal septum, as well as ulceration in other areas of the skin, allergic contact dermatitis and asthma (Gibb et al., 2000a) (ATSDR, 2012). Accidental ingestion of high doses of Cr (VI) may result in acute renal failure characterised by proteinuria, haematuria and anuria, although kidney damage from chronic exposure to lower levels is not demonstrated (ATSDR, 2012). Following acute oral exposure to high doses of Cr (VI), respiratory, haematological, hepatic, renal and gastrointestinal tract effects occur, with doses between 4-360 mg chromium (VI)/kg b.w. being observed to be lethal (EFSA, 2014).

Repeated dose studies have reported different NOAELs, the lowest being 0.21 mg chromium (VI)/kg b.w./day, found in rats exposed for 2 years to this metal, which developed toxic effects at the hematic and hepatic levels, in addition to histiocytic cellular infiltrations in the mesenteric lymph nodes and duodenum (NTP, 2008). The organs most affected, according to these repeated oral dose studies of Cr (VI) are: blood system, liver, kidney and gastrointestinal tract (Kumar and Rana, 1982) (Kumar et al., 1985) (Vyskocil et al., 1993) (Chopra et al., 1996) (Acharya et al., 2001) (NTP, 2007, 2008). Changes in reproduction and development have also been observed in rats and mice to which the metal was administered orally, showing that Cr (VI) is capable of crossing the placental barrier and accumulating in the foetus (EFSA, 2014).

Carcinogenesis is one of the most studied effects of Cr. The relationship between environmental and occupational exposure to Cr (VI) and lung cancer has been demonstrated (Gibb et al., 2000b). In fact, Cr (VI) is classified in Group 1 by IARC as a human carcinogen for lung and even nasal and sinus cancer based on evidence of occupational exposure (IARC, 1990), while Cr (III) is classified in Group 3. On the other hand, the relationship between ingestion of drinking water contaminated with Cr (VI) and appearance of stomach cancer has been suggested (Sedman et al., 2006) (Smith and Steinmaus, 2009), although this effect is not fully confirmed in humans (IARC, 2012). In addition, due to these limited data in humans, a dose-response relationship could not be established so far.

Cr (VI) compounds have genotoxic effects, whereas Cr (III) compounds are usually non-genotoxic, probably due to their low ability to enter the cell (Klaassen, 2019). Cr (VI) has been found to enter the cell rapidly and is reduced to other chromium species, mainly Cr (III), which appears to be ultimately responsible for DNA damage. During this reduction process, different lesions such as Cr-DNA adducts, protein-DNA binding, Cr-DNA intrastrand cross-reactions, and oxidation of DNA bases can be generated (O'Brien et al., 2003) (Macfie et al., 2010). In addition, Cr (VI) has also been shown to be mutagenic in both bacterial and mammalian experimental models (O'Brien et al., 2003). Importantly, the genotoxic effects observed *in vivo* are discordant depending on the Cr (VI) route of administration, indicating that the reducing capacity of the gastrointestinal tract is a determining factor, as it can significantly reduce the absorption of Cr (VI) when administered orally (EFSA, 2014).

Cr (VI) can also react with other cellular components during its reduction process within the cell. Reactive oxygen species are generated that inhibit protein synthesis and stop DNA replication. Cr (VI) disrupts the p53 signalling pathway; alters ATM/ATR cell cycle control; induces apoptosis and interferes in DNA damage repair (Zhitkovich, 2005) (Salnikow and Zhitkovich, 2008). It can also react directly by activating cell signalling enzymes such as the Src kinase family, stimulating the signal cascade leading to repression of transcription of important cell-protective proteins (O'hara et al., 2003) (Nemec and Bachowsky, 2009) (Nemec et al., 2010).

5.2 Exposure and risk assessment

Despite the well-known occupational and environmental exposure to Cr, the 2014 EFSA report analysing data on chromium contents in food and drinking water, estimated that the greatest contribution to global exposure to Cr occurs orally, to which the inhalation of Cr compounds, such as those present in tobacco smoke should be added (EFSA, 2014).

It should be noted that the presence of Cr (VI) in drinking water is usually due to anthropogenic contamination. Thus, the natural Cr content in surface water is 1-10 µg/l. However, although the usual content in drinking water is less than 2 µg/l, in heavily contaminated waters this concentration can increase up to 120 µg/l (WHO, 2003b).

The above-mentioned EFSA report collected the analysis of 88 water samples in which a lower limit of 0.2 µg/l and an upper limit of 1.9 µg/l were determined for tap water. For bottled water, the values ranged from 0.3 µg/l to 3.4 µg/l (EFSA, 2014). The panel assumed that all the Cr present in the analysed water came from Cr (VI) for two reasons: the ratio of Cr (VI)/total was 0.97, and, in addition, the water for human consumption is usually treated with oxidizing agents in its purification process,

which would favour the presence of Cr (VI) over Cr (III). This report concludes that there is concern about the average intake of Cr (VI) through drinking water for infants. Experts established the lowest BMDL₁₀ (Benchmark Dose Lower Confidence Limit) level for diffuse epithelial hyperplasia in female mice and the lowest BMDL₀₅ level for blood toxicity in male rats as reference points for the evaluation of non-cancer effects in a 2-year chronic toxicity study. Margins of Exposure (MOE) indicate that there is no concern for non-cancer effects considering the current exposure to Cr (VI) through drinking water. For carcinogenic effects, the lowest BMDL₁₀ level for the combination of adenomas and carcinomas in mouse small intestine was selected as a reference point. Thus, calculated MOE indicated low concern regarding Cr (VI) exposure through drinking water for all age groups except infants (0-1 years). In this sense, it has been considered that the highest exposures to Cr (VI) through any type of drinking water occur in the younger populations (0-3 years), so there could be a risk in children of other age groups in addition to infants. For all these reasons, the report indicates that further data on the Cr content in water would be necessary to improve this estimate. Finally, other forms of ingestion of Cr (VI) should also be considered, such as consumption of certain foods that use water for their preparation, like coffee, infusions, soups, powdered milk or dehydrated fruit juices. In the worst-case scenario, where there would be no reduction of Cr (VI) to Cr (III), it was estimated that exposure to the metal could double relative to drinking water consumption alone (EFSA, 2014).

To date, there is no statutory maximum level of food content for Cr (VI). As for Europe, there exists a parametric level of 50 µg Cr/l for the total Cr content in water intended for human consumption (EU, 1998) and a maximum limit of 50 µg/l for the total Cr content in natural mineral water (EU, 2003). Currently, this value of the presence of Cr in water is under evaluation by the WHO, so a parametric value of 25 µg/l has recently been established for which there is a compliance deadline until 2036 (EU, 2020).

On the other hand, the presence of Cr (III) in food is common, and a TDI of 0.3 mg/kg b.w./day has been established. In the case of Cr (VI), it has not been possible to establish a safe level of intake due to its demonstrated association with cancer (EFSA, 2014). Although there is a great lack of data on the presence of Cr (VI) in food, experts have indicated that the presence of Cr (VI) in food could contribute substantially to its exposure, and should be considered.

5.3 Future considerations

It is important to highlight the lack of Cr (VI) content data in both food and drinking water. As with food, it seems that the absorption of this metal is favoured during fasting, so its presence in food hinders its own absorption. So far, the biggest concern for Cr (VI) exposure appears to be through drinking water, particularly in the 0-1 age group. However, the scarcity of data prevents a correct risk assessment, so controls on the content of Cr (VI) in both water and food should be carried out.

6. Anthraquinones

6.1 Hazard identification and characterisation

Anthraquinone ($C_{14}H_8O_2$; 208.216 g/mol; CAS: 84-65-1; EC: 201-549-0, 9,10-anthraquinone, ATQ) is an aromatic organic compound with a 9,10-dioxoanthracene ring (ECHA, 2022a) (Figure 1). ATQ belongs to a very heterogeneous family of chemical compounds called generically anthraquinones, since its polyhydroxylated structure allows multiple zones and types of substitution ($-CH_3$, $-CH_2OH$, $-CHO$, $-COOH$). In fact, there may be some confusion in the scientific literature, but the term ATQ only refers to the isomer 9,10-anthraquinone where positions 9 and 10 of the central ring of the anthracene molecule have been oxidised to carbonyl groups. Some of the most studied anthraquinones are those derived from hydroxyanthracene, such as aloe-emodin, chrysophanol and rhein among others, present in rhubarb and in aloe vera plant (IARC, 2018). This document focuses on ATQ and not on its hydroxylated derivatives.

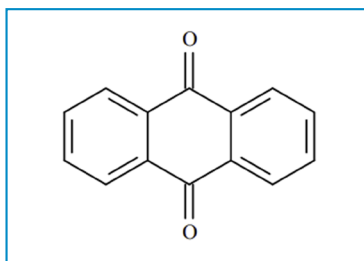


Figure 1. Chemical structure of anthraquinone (9,10-dioxoanthracene, ATQ). **Source:** (ECHA, 2022a).

ATQ presents different pathways of formation. In the exogenous pathway, anthraquinones are formed from the oxidation of Polycyclic Aromatic Hydrocarbons (PAHs) generated by the incomplete combustion of organic material. Generically, oxidised forms of PAHs (oxy-PAHs) are called anthraquinones. ATQ is the quinone derived from anthracene and is therefore also considered an environmental pollutant. The toxicology of PAHs is already established and maximum levels (2 $\mu\text{g}/\text{kg}$ benzo[a]pyrene, and 12 $\mu\text{g}/\text{kg}$ for the sum of the four main PAHs) in food are legislated (IARC 1987) (EFSA 2008b).

In the endogenous pathway, ATQ can be naturally generated by the metabolic activity of different organisms. Anthraquinones are secondary metabolites present in the bark and root of many plant families such as *Polygonaceae*, *Rhamnaceae*, *Rubiaceae*, *Fabaceae*, *Xanthorrhoeaceae*, *Leguminosae* and *Liliaceae*. Anthraquinones are mostly present as glycosides, since this structure gives them greater solubility and reduces their chemical reactivity towards other organic compounds. The main sugars involved are rhamnose and glucose, which are usually bound at positions C-6 and C-8. The glycone forms are converted to the corresponding aglycone by the action of β -glycosidases or through oxidative reactions. ATQ is found in the rhizome and root of certain plants (e.g., *Rheum palmatum* L. and *Rheum officinale* Baillon) at levels of 2.2 to 6.0 % (EFSA, 2020a). The aloe vera plant (*Aloe* spp.) contains different anthraquinones, mainly located on the outside of the leaf pulp

(Rahman et al., 2017). ATQ is removed from aloe vera products prior to commercial use by different methods such as maceration, reflux with heat application, microwave assisted extraction, among others (Zhao et al., 2011). This extraction also eliminates other substituted anthraquinones such as physcion, chrysophanol, aloe-emodin and rhein. Anthraquinones are also natural constituents in fungi (*Aspergillus* sp., *Eurotium* sp., *Emericella* sp., *Fusarium* sp., *Penicillium* sp., *Mycosphaerella* sp., *Microsporium* sp., etc.), bacteria (*Streptomyces* sp.), lichens and insects of the *Coccidae* family.

Some therapeutic applications have been described for certain natural anthraquinones based on their antioxidant, estrogenic, vasodilator, laxative and diuretic activity, as well as antiosteoporotic, anti-inflammatory, antidiabetic, antiviral, neuroprotective and antimicrobial (Duval et al., 2016). That is why anthraquinones, and mainly their hydroxylated derivatives, can be found in a wide variety of dietary supplements, traditional Chinese pharmacological preparations, and medications (Malik and Muller, 2016). However, toxicity problems have arisen in recent decades, including hepatotoxicity (Wu et al., 2018), nephrotoxicity (NTP, 2001), cardiotoxicity (Malik and Muller, 2016), carcinogenicity (Doi et al., 2005), and severe diarrhoea (Pelletier et al., 2000). These risks should be evaluated before using anthraquinone-containing supplements as chronic therapeutic treatments (Guo and Mei, 2016).

Anthraquinones have a multitude of industrial uses. One of the main applications is as a natural pigment widely used in the textile industry as it is a very stable molecule to washing and heat (Yu, 2002) (IARC, 2018). It is also used as an additive in the alkaline processing of paper pulp or as an electrolyte in flow batteries that provide long-term electrical storage. Specifically, ATQ is used as an accelerator for the separation of lignin and cellulose in the preparation of cellulose fibres. ATQ is a powerful bird repellent, so it is used in the formulation of pesticides, insecticides and fungicides. However, in the European Union it is not allowed for use either as pesticide or in food contact materials (EU, 2009).

6.1.1 Toxicokinetic

The possible routes of exposure to ATQ are oral, dermal and inhalatory. In ¹⁴C-ATQ oral administration experiments in rats, ATQ is rapidly and efficiently absorbed in the aglycone form (>99.8 %), being distributed to all organs and tissues of the body, although it may partially concentrate in adipose tissue (NTP, 2005). No bioaccumulation processes have been described in any particular tissue. 96 hours after intake, 95 % of the ATQ is metabolised and eliminated through the bile in the faeces and urine. Half-life of ATQ in plasma is 10-12 hours. The possibility of transformation of the hydroxylated derivatives of anthraquinones with each other, for example, between aloe-emodin and rhein has recently been demonstrated (Wang et al., 2021). The main metabolic pathways of anthraquinones are hydrolysis, glucuronidation, and sulfation, and secondarily methylation and demethylation, hydroxylation and dehydroxylation, oxidation/reduction (hydrogenation), acetylation, and esterification by intestinal microbiota and liver metabolic enzymes. In the liver, ATQ undergoes hydroxylation in its aromatic ring by the action of the enzymes cytochrome P450 (CYP1A2 and CYP2B1) and, subsequently, conjugation with glucuronic acid and sulphate takes place to be excreted (Doi et al., 2005). ATQ metabolites are primarily 2-hydroxy-anthraquinone (CAS 605-32-3) and secondarily 1-hy-

droxy-anthraquinone, together with other minority conjugates (IARC, 2018). 2-hydroxy-anthraquinone is also a natural metabolite found in certain plants such as *Rubia tinctorum*, *Primula hedyotidea* and *Galium odoratum*.

6.1.2 Mechanism of action

Although the carcinogenic effects of ATQ have not yet been fully elucidated, its toxicity is considered to be equivalent to the compound from which it is derived, anthracene (Shukla et al., 2017). Toxicity was assessed in female F344 rats under subchronic dietary exposure conditions (Dodd et al., 2013). Microscopic changes were observed in the liver (mild centrilobular hypertrophy), spleen (proliferation and pigmentation of mild haematopoietic cells) and kidneys (minimal hyaline drops). A NOAEL of 31.3 mg anthraquinone/kg b.w./day was established based on the absence of hepatic histopathology. Chronic oral exposure in B6C3F mice found an increased incidence of adenoma and hepatic carcinoma (single or combined), regardless of sex, in the groups exposed between 265-235 mg anthraquinone/kg b.w./day (NTP, 2005).

In 2013, the IARC classified ATQ as a possible carcinogen (Group 2B) in humans, being liver and kidneys the main target organs (IARC, 2013). The IARC indicated that the toxicological results on bacterial mutagenesis and genotoxicity collected in the scientific literature and available to that date were contradictory. The main drawback found in the risk assessment was that some of the studies did not declare the purity of the starting compound, where 9-nitroanthracene could appear as an excipient at 0.09 % levels. However, 2-hydroxy-anthraquinone has shown relevant bacterial mutagenic and genotoxic activity. Based on this, IARC indicates that there is sufficient experimental evidence in animals to establish the probable carcinogenicity of ATQ in humans. Direct evidence on carcinogenicity in humans is still incomplete, and is limited to workers exposed during the manufacture of ATQ as a dye who are also simultaneously exposed to other chemicals.

6.1.3 Legislative maximum levels

According to Commission Decision 2007/565/EC, the use of ATQ as a biocidal product has been banned in the European Union since 22 August 2008 (EU, 2007). Commission Regulation (EU) No. 1146/2014 on Maximum Residue Limits (MRLs) sets the default value of 0.01 mg/kg for citrus fruits, pome fruits, stone fruits and other fruits, fresh and frozen vegetables, aromatic plants, fresh legumes, mushrooms and cereals, and 0.02 mg/kg for nuts, oil seeds and fruits, tea and herbal teas (EU, 2014). In 2012, EFSA indicates that toxicological information is insufficient to establish a maximum limit that can provide sufficient protection to the consumer and therefore recommends maintaining the established value of 0.01 mg/kg. Regulation (EU) No. 1146/2014 considers that certain organic foods could have levels higher than 0.01 mg/kg of ATQ (EFSA, 2012, 2019) (EU, 2014). Subsequently, this Regulation confirmed the MRL for ATQ at the detection limit of 0.01 mg/kg, although for certain food groups (spices, tea leaves and herbal infusions) the MRL is allowed to be extended to 0.02 mg/kg due to analytical limitations (EU, 2014).

Different quantitative methods have been described for the determination of ATQ in foods, based primarily on liquid chromatography with mass spectrometry detection (HPLC-MS/MS), fluorescen-

ce or diodes, gas-mass chromatography, and capillary electrophoresis and chromatography in supercritical fluids (Schneiderman et al., 1987) (De Santis and Moresi, 2007) (Shi et al., 2007) (Dongxiu et al., 2009) (Malik et al., 2010) (Stodůlková et al., 2010) (Supe, 2011) (Shi et al., 2014) (Aichner and Ganzera, 2015) (Duval et al., 2016) (Feng et al., 2017) (Kitano et al., 2018) (Huang et al., 2019) (Shi et al., 2019). The possible interference of caffeine and theobromine in the determination of ATQ in coffee and tea has been observed (Diaz-Galiano et al., 2021).

6.2 Exposure and risk assessment

The presence of ATQ in food has been mainly associated with environmental contamination, but it is also proposed that it can be generated during processing, although the details of the mechanism and the variables that affect its presence in food are unknown (DG-SANTE, 2017). In addition to combustion gases, external contamination during plants cultivation and processing (for example, teas, herbs, spices) by bacteria or insects that can biosynthesize it, irrigation water, as well as the use of fertilizers formulated with ATQ must also be considered as possible routes of environmental contamination. On the other hand, it is known that different plant families, such as *Polygonaceae*, *Rhamnaceae*, *Rubiaceae*, *Fabaceae*, *Liliaceae*, *Xanthorrhoeaceae* and *Leguminosae*, can naturally produce ATQ as a secondary metabolite (Shukla et al., 2017). Even so, the risk assessment of the presence of ATQ in food has been mostly treated as an environmental contaminant. In this case, external contamination may occur unintentionally as:

- Environmental pollutant derived from the oxidative thermal degradation of persistent organic pollutants from agricultural machinery.
- Residues in food from non-EU countries due to the use of poultry repellents, pesticides and biocides not allowed in the European Union.
- Migration from packaging material as it is a residue in the production of paper and cardboard. Levels of 196.1 ng were determined in pizza crust indicating a 3.96 % migration of ATQ from the carton (Louch, 2008). The BfR (2013) estimated that migration from a pizza carton packaging would be 0.04 mg anthraquinone/kg pizza, exceeding the maximum allowable limit.
- As a colour enhancer in teas (De Liberto and Werner, 2016) (IARC, 2018) (Wang et al., 2018).

In 2012, ATQ was detected for the first time at above legal limit level in foods (teas and herbal infusions) from third countries (outside the European Union). The EFSA report on pesticide residues in the European Union indicates that ATQ was detected in 6 out of 124 foodstuff from the European Union, and in 14 out of 102 foodstuff from outside the European Union (EFSA, 2019). On the other hand, from March 2018 to March 2022 (5 years), 20 alerts have been reported in the RASFF (Rapid Alert System for Food and Feed) in several countries of the European Union (Spain, Germany, Finland, Poland, the Netherlands and Belgium) relating to the presence of ATQ in food, with 3 in 2020, 10 in 2021 and 7 in 2022 which have motivated the retention of the product at the border. The foods involved are mostly yerba mate from Argentina and teas from China, and to a lesser extent spices (cardamom, paprika) from India and Vietnam, and foods made in European Union countries such as mate tea from the Netherlands. The concentration of ATQ in these notifications ranged from 15 to 360 µg/kg (RASFF, 2022).

The formation of ATQ during the processing of different foods has been studied since it was first detected in black tea. Anggraini et al. (2020) evaluated the presence of ATQ at each stage of the green and black tea manufacturing process. For green tea, ATQ was present on the untreated leaf and concentration increased until the start of the drying step. In the case of black tea, the ATQ content increased significantly in the first drying stage, while it decreased in the final stage. Researchers suggest that the presence of ATQ is mainly due to the smoke emitted by the wood fire used to drive the processing machinery, and to a lesser extent by endogenous formation as a result of the temperature applied during drying. Similar results were found by Wang et al. (2018) where initial ATQ levels decreased between 63.0 and 82.9 % during black tea processing. The authors suggest that the presence of ATQ in tea leaves comes mostly from external deposition by environmental contamination. The presence of ATQ in tea beverage is related to the leaf levels and has a low solubility (1.35 mg/l at 25 °C), where only 1.6-13.7 % of the ATQ would pass to the infusion.

Zastrow et al. (2019) studied the content of ATQ along with that of several PAHs (anthracene and the sum of the content of four PAHs) in smoked Frankfurt-style sausages. The lowest ATQ content (<LOQ, Limit of Quantification; LOQ= 1 µg/kg) was obtained when friction generated smoke was used, and the highest level (3.2 µg/kg) under high smoke density conditions and at prolonged smoking time. However, no direct correlation could be established between ATQ and PAHs content in the food. The researchers highlight the greater volatility of ATQ and anthracene with respect to the rest of PAHs that make them more sensitive to variations in the temperature and ventilation used in smoking.

Liang et al. (2021) investigated the molecular mechanisms involved in the accumulation of medically active ingredients, such as anthraquinones, during post-harvest processing of rhubarb. Anthraquinone levels in rhubarb are related to the response to stress episodes in the plant, and they evidenced that a similar physiological process that occurred during drying that would explain the higher levels of anthraquinone in smoked rhubarb versus shade drying. Smoke drying generated an environment of strong abiotic stress (high temperature and high concentration of CO₂) that was more conducive to ATQ accumulation through activation of metabolic pathways of biosynthesis.

A pioneering study addresses the chemical pathway of formation of ATQ in food as a result of processing (Zamora and Hidalgo, 2021). ATQ can be generated from cycloaddition reactions between hydroquinone and 2-alkenal. In the specific case of tea, the presence of ATQ above the maximum limit would be justified by the reaction between hydroquinone and the unsaturated aldehyde crotonaldehyde (C₄H₆O) during the drying process of tea leaves (60 °C/72 hours). This research concludes that the presence of ATQ in food should also be considered as a process contaminant when generated naturally during heat treatment, in addition to being a residue of environmental contamination.

6.3 Recommendations

ATQ may be present in food either by environmental contamination, when generated or incorporated during processing, or by migration from the packaging (e.g. paper and cardboard). Although the carcinogenic effects of ATQ in humans are not yet fully elucidated, toxicity is considered to be

equivalent to anthracene. The side effects are reinforced because the main metabolite, 2-hydroxy-anthraquinone, is a carcinogen. The IARC indicates that there is sufficient experimental evidence in animals to establish the probable carcinogenicity of ATQ in humans (Group 2B). Although the presence of ATQ as a pesticide is not expected, other possible routes of contamination have been identified in recent years that may increase the risk to the consumer.

It is recommended to incorporate ATQ analysis into collaborative studies of chemical agents on dried and/or smoked foods in general, and particularly those that come from plant extracts (e.g., teas, herbal extracts for infusion). The determination of ATQ could be extended to other oxidised forms of PAHs since the assessment of the presence of ATQ should not be considered in isolation. In line with DG-SANTE, the presence of ATQ should be assessed together with the presence of the most frequent PAHs residues (DG-SANTE, 2017). Thus, the simultaneous analysis of ATQ with PAHs will help to discern whether the origin of the presence of ATQ is related to an illegal use as a pesticide.

7. Aflatoxins in hazelnuts

7.1 Hazard identification and characterisation

A new EFSA report on “Risk assessment of aflatoxins in food” was published in 2020. Information regarding hazard identification and characterisation is extensively reviewed in that report (EFSA, 2020b).

Briefly, aflatoxins B1, B2, G1 and G2 (AFB1, AFB2, AFG1 and AFG2) are mycotoxins produced primarily by toxigenic strains of the fungi *Aspergillus flavus* and *Aspergillus parasiticus*. The most frequently found aflatoxin in contaminated food samples is AFB1 and the other three are generally not found in the absence of AFB1.

In short-term studies (7 to 90 days), AFB1 shows multiple negative effects in rodents, including inhibition of normal growth, liver and kidney damage, as well as sustained alterations in the intestinal microbiota. AFB1 is a genotoxic and carcinogenic substance. There is evidence of genotoxic effects in pregnant mice, foetuses and young animals. Unlike AFB1, there are fewer studies available on the genotoxicity of other aflatoxins. Epidemiological studies reported since 2006 reinforce evidence that exposure to aflatoxins is associated with a risk of developing hepatocellular carcinoma, with an increased risk for people infected with hepatitis B (HBV) and C (HCV) viruses.

The Panel on Contaminants in the Food Chain (CONTAM) of EFSA considered that the hepatic carcinogenicity of aflatoxins remains the key effect for risk assessment. In view of the genotoxic properties, the CONTAM Panel considered that it was not appropriate to establish an IDT, and instead selected a BMDL₁₀ of 0.4 µg/kg aflatoxin B1 b.w./day for the incidence of hepatocellular carcinoma in male rats after AFB1 exposure for use in a Margin of Exposure (MOE) approach.

7.2 Exposure and risk assessment

In 2007, EFSA issued a report assessing the risk associated with an increase in the current maximum limit for aflatoxins (2 µg aflatoxin B1/kg and 4 µg total aflatoxins/kg). The contamination data provided by the Member States showed a median, mean, 95th percentile and maximum of 0-0.16,

0.85-0.95, 3.00 and 200 µg/kg for AFB₁, respectively, and 0-0.30, 1.50-1.70, 6.20 and 200 µg/kg for total aflatoxins, respectively. The percentage of samples below the Limit of Detection (LOD) was 70.3 %, that of samples above 8 µg/kg AFB₁ was 1.7 % and that of samples above 10 µg/kg total aflatoxins was 2.9 %, demonstrating the wide range of variability (EFSA, 2007).

For the specific case of Spain, a total aflatoxin exposure of 0.825-1.907 ng/kg b.w./day was theoretically determined (based on the proposed new limits, 10 µg total aflatoxins/kg, in force today). The contribution of hazelnut consumption to this intake was <0.1 %, with maize and oilseeds being the main route of exposure. In that exposure calculation, it was considered that the contamination values would in no case exceed the legal limits. It was concluded that the modification of the maximum level for total aflatoxins in force at that time from 4 to 10 µg/kg would allow for a 2.7 % increase in compliant batches and would result in an increase in the average levels of total aflatoxin contamination from 0.31-0.53 to 0.57-0.78 µg/kg (EFSA, 2007).

MOE based on BMDL₁₀ in animals indicated a possible concern regarding aflatoxin intake in all regions of the European Union. However, BMDL₁₀ and BMDL₁ values calculated based on human study data from sensitive (male only) populations having a high prevalence of HBV infection suggest that humans may be less sensitive than mice used to derive BMDL₁₀ in animals (EFSA, 2007).

However, recently, Ebrahimi et al. (2022) performed a review of the results of the presence of aflatoxins in nuts published in recent years, and reported an average level of 17.33 µg of total aflatoxins/kg and 10.54 µg of aflatoxin B₁/kg in hazelnuts. In Turkey, Keskin and Gürsoy (2019) investigated the presence of aflatoxins in hazelnut, toasted hazelnut and hazelnut cream samples, with incidences of 30, 14 and 45 %, respectively, and contamination levels of 2.11-10.03, 0.1-4.04 and 0.2-6.02 µg/kg, respectively. In addition, Demirhan and Demirhan (2022) found 50 % positive samples, with averages between 0.21 and 1.03 µg/kg in hazelnut cream. Gallo et al. (2021) analysed the results obtained between 2017-2020 by an official control laboratory located in southern Italy, concluding that 4.5 % of the samples of batches imported from countries outside the European Union exceeded the maximum limit, of which 13.3 % corresponded to hazelnuts, being only exceeded by pistachios (52 %). 5.6 % of the hazelnut samples analysed were non-compliant.

In recent years, hazelnuts and their derivatives have been the fourth product that has motivated the highest number of notifications in the RASFF related to aflatoxins, after peanuts, pistachios and dried figs. In general, the number of annual notifications is between 30 and 50. Since 2016, when most notifications were due to hazelnuts imported from Turkey, the percentage has been decreasing, with only 4 in 2021. Instead, there has been an increase in notifications due to new countries of origin, mostly Azerbaijan (as of 2017) and Georgia (as of 2019) (RASFF, 2022).

7.3 Risk management strategies

Conventional strategies for the prevention of mycotoxin production/contamination require pre- and post-harvest approaches. In pre-harvest, they deal with the control of fungal contamination in the field, while in post-harvest, they focus on processing and storage. However, traditional strategies do not appear to be sufficient, the presence of aflatoxins is unavoidable under certain environmental conditions and requires additional processing for decontamination.

In addition to prevention systems based on sampling, analysis and discrimination of contaminated batches, in recent years there has been intense research and patented physical decontamination technologies based on high-speed colour sorting, spectroscopic techniques, and hyperspectral image analysis methods to remove contaminated hazelnuts from each batch (Kalkan et al., 2011) (Wu et al., 2018).

In conclusion, the current reality seems to demonstrate the frequent presence of aflatoxins both in hazelnuts and in pistachios and peanuts. The management of this risk currently relies on the sampling and analysis of batches entering the European Union, either by the competent authority, by the traders of raw materials, or by each individual processing industry. However, the limitations of any sampling method applied on large batches have been highlighted, given the heterogeneous distribution of aflatoxins in the different fruits that compose them. Thus, a prospective food level study available to the consumer is therefore necessary to assess the risk.

8. Melamine

8.1 Hazard identification and characterisation

Melamine (2,4,6-triamino-1,3,5-triazine, CAS 108-78-1, $C_3H_6N_6$) is a nitrogenous organic compound used as an additive in the synthesis of melamine-formaldehyde polymers employed in the manufacture of laminates, coatings, and moulded polymers such as tableware and cookware (Figure 2). In addition, melamine is used in the manufacture of flame-retardant materials, adhesives, paints and fertilisers. Melamine and its methylated derivatives are used in the coatings of food cans and containers, so the possible residual migration of the monomer to the food must be controlled. Melamine is used in the manufacture of adhesives, paper and cardboard resistant to moisture. Initial migration of melamine may be due to the residual monomer in the polymer, while subsequent migration may result from the polymer decomposition (Li et al., 2019). Melamine is produced from urea, cyanic acid and ammonia, with cyanuric acid, ammelide and ammeline as intermediates. Melamine is also a degradation product of cyromazine which is used as a pesticide (acaricide and insecticide) and an antiparasitic (ectoparasiticide), and has maximum limits established in Regulation (EU) No. 37/2010 (EU, 2010b).

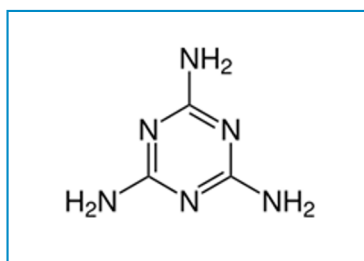


Figure 2. Chemical structure of melamine (CAS 108-78-1). **Source:** (ECHA, 2022b).

Due to its high nitrogen content, melamine was fraudulently used between the 1950s and 1960s as a source of non-protein nitrogen in ruminant feeding, but evidence of severe renal failure limited its

use. In 2004, kidney damage problems in dogs caused by the presence of melamine in animal feed were detected in South Asian countries. In 2008, the so-called milk powder crisis from China contaminated with melamin took place. This food fraud caused kidney stones and acute kidney damage in infants and young children. Analysis of kidney stones indicated that most of these uroliths were composed of melamine cyanurate (MCA) which is the complex between melamine and cyanuric acid (Weng et al., 2016). Depending on the purification process, melamine may contain by-products of related structure, particularly cyanuric acid, ammelide and ammeline. There is sufficient evidence to confirm that the combination of melamine and cyanuric acid increases the nephrotoxicity of both compounds separately (Li and Chow, 2017). The European Commission established in Decision 2008/798/EC (EU, 2008) a maximum limit of 2.5 mg melamine/kg food and banned products imported from China containing milk or dairy products.

Melamine has a high absorption rate (>90 %) in the gastrointestinal tract. The half-life of the compound ranges from 2.7 to 4.9 hours in rats and approximately 4 hours in pigs. The metabolism of melamine in rats is very limited and is mostly eliminated through the urine in its original form. The inherent toxicity of the melamine molecule is considered to be very low and the main adverse health consequences are due to its ability to form crystals, which are the main cause of kidney damage. The kidneys are the main target organ of damage to melamine exposure. Histological evaluation of kidneys of dogs that have ingested food contaminated with melamine reveals the presence of uroliths and lymphoblastic interstitial nephritis. In rats, melamine and cyanuric acid cause degeneration of the proximal tubule and its necrosis, as well as nuclear pyknosis, mitochondrial vesicles, and cellular inflammation. In addition to damage to proximal tube cells, blockage of distal tubules and presence of crystals in the bladder was observed (Melnick et al., 1984) (Baynes et al., 2008) (Zhu et al., 2009) (Xie et al., 2010) (Chen et al., 2014) (Guan and Deng, 2016) (Li and Chow, 2017). Although toxicokinetic studies in animals show that most of the melamine ingested is excreted, low concentrations of melamine have been detected in the edible tissues of animals, milk and eggs of farm animals (Sun et al., 2011) (Yang et al., 2011) (Tkachenko et al., 2015). The transfer rate in any of the above cases is less than 3.2 % of the ingested melamine. Melamine may also affect organs other than the kidney, as abnormalities in sperm functionality and effects on hippocampal synaptic plasticity and behaviour have been described in rats (Zhang et al., 2011) (Yan et al., 2012). Pharmacokinetic studies in animal models established a Lethal Dose (LD₅₀) of 3161 mg melamine/kg b.w. A NOEL of 63 mg melamine/kg b.w./day has been established for urinary stone formation based on assays in rats and applying an uncertainty factor of 100 (WHO, 2008).

In 2008, melamine-associated nephrotoxicity was also described in young children (6-18 months) who consumed melamine-adulterated infant milk. The main clinical manifestation was urolith formation, increased proteinuria, and chronic nephritis leading to severe renal damage (Wen et al., 2010, 2016). Other evidence suggests that beyond its renal effects, melamine may also act as an endocrine disruptor and neurotoxin (Tian et al., 2016) (Bolden et al., 2017).

In 2010, EFSA adopted a scientific opinion related to the presence of melamine in human and animal feed, where the main risk to dietary exposure to melamine is the formation of crystals in the urinary tract and kidney damage. Melamine is not considered as a mutagenic substance for humans,

but as a possible carcinogen (Group 2B) due to sufficient evidence in experimental animals, since the increase in stones was also associated with a higher incidence of transitional cell carcinoma in the urinary bladder (IARC, 2019). A Tolerable Daily Intake (TDI) of 0.2 mg melamine/kg b.w./day was established from a BMDL₁₀ of 0.74 mg melamine/kg b.w./day for a 10 % increase in the incidence of nephrolithiasis. It is very important to note that co-exposure to melamine and cyanuric acid in all laboratory animal trials showed higher nephrotoxicity, specifically nephrolithiasis, compared to melamine or cyanuric acid alone. Based on this evidence, EFSA recommends the simultaneous determination of the presence of melamine and its structural analogues in food and feed. However, there is insufficient evidence whether ammelide and ammeline can form crystals with melamine (EFSA, 2010).

The European Commission established a Specific Migration Limit (SML) of 0.5 mg/kg, assuming a maximum consumption of 1 kg of exposed food. This SML served as a criterion for evaluating the suitability of substances as food contact material. Regulation (EU) No. 594/2012 amending Regulation (EC) No. 1881/2006 introduces a new section 7 setting the maximum melamine content in foodstuffs (EU, 2012b). The maximum levels are 1.0 mg/kg in infant formulae and follow-on formulae and 2.5 mg/kg in any other foodstuff. In 2013, Regulation (EU) No. 107/2013 amended Annex I to Directive 2002/32/EC as regards maximum levels of melamine in canned pet food as the migration in high moisture food was higher than in dry food, setting it at 2.5 mg/kg in feed over a moisture content of 12 % (EU, 2013).

Melamine is determined by HPLC-MS/MS with an LOD of 0.09 ng/ml, being the reference method (EFSA, 2010). Among the most efficient screening techniques in terms of sensitivity levels, fluorescence spectroscopy, infrared spectroscopy and ELISA techniques can be highlighted, since it does not require pre-treatment of the sample and the analysis time is between 1 and 5 minutes (Rovina and Siddiquee, 2015).

8.2 Exposure and risk assessment

Beyond intentional exposure due to adulteration fraud, unintentional exposure due to the migration of melamine from food contact materials containing melanin-formaldehyde plastics, container liners, paper, cardboard and adhesive material may also occur. The rate of migration of melamine depends on the temperature, acidity, contact time and type of simulant used, as well as the quality of the product. The risk is increased when the food has an acidic pH and when is microwave heated (EFSA, 2010).

Melamine is an authorised substance in the manufacture of thermoset plastic materials in contact with food. Regulation (EU) No. 284/2011 amends the SML of melamine and formaldehyde in plastic materials in contact with food of Chinese origin, limiting them from the previous 30 mg/kg to 15 mg/kg. The Regulation lays down specific conditions and detailed procedures for the import of polyamide and melamine plastic kitchenware originating in or consigned from the People's Republic of China and the Hong Kong Special Administrative Region (EU, 2011b, 2015).

In this context, possible sources of exposure to melamine are through: (i) tableware made from melamine derivatives, (ii) canned food with an inner lining of the container containing melamine,

(iii) adhesives and other food packaging, and (iv) water from the industrial manufacture of these chemicals.

A recent study has evaluated dietary exposure pathways of melamine in the United States population through the association between dietary intake and melamine concentration in the urine of subjects (Melough et al., 2020). The research concludes that dietary habits that include consumption of processed meats, whole grains, and possibly other plant-based foods may be important sources of exposure to melamine in the American population. Researchers argue that the use of the pesticide cyromazine can cause contamination of plant-based foods with melamine, since this pesticide is metabolised into melamine through a dealkylation reaction in plants and animals. However, an important limitation of this research is that exposure resulting from the migration of materials in contact with food such as packaging and cooking utensils was not considered.

Melamine is also an environmental pollutant as it is present in air, dust, soil, sewage sludge and sediment. Since melamine is stable to degradation, is not metabolised by animals and is rapidly excreted, it is likely to be present in food of plant origin. This fact may explain why rice consumption was associated with the presence of melamine in the urine of citizens in different regions of China. Melamine was detected in more than 85 % of urine samples with a mean concentration of 2.524 µg/g (Shi et al., 2020).

A TDI of 8100 ng melamine/kg b.w./day based on stone formation in rodent bladder (Wu and Zhang, 2013), and 3150 ng melamine/kg b.w./day based on renal lesions derived from a combined melamine: cyanuric acid (63:50) feed in rats (Choi et al., 2010) has been estimated. Since melamine and cyanuric acid have been shown to have a strong synergistic effect on urolithiasis (Jacob et al., 2011), the TDI of 3150 ng melamine/kg b.w./day appears to be the best option to limit the associated risk of exposure to melamine. EFSA estimated exposure to melamine in the average adult population at 7.97 µg melamine/kg b.w./day. In the worst-case scenario (>P95), the exposure does not exceed 11 µg melamine/kg b.w./day, being well below the TDI of 0.2 mg melamine/kg b.w./day (EFSA, 2010). The main contributors to the exposure are milk, water, vegetables and cereals, but it is due to the higher consumption of these food categories than to the high presence of melamine in them. Other studies have calculated the Estimated Daily Intake (EDI) based on melamine concentration in food, while the information available on human internal exposure is very limited. Melamine EDI for infants were between 1 and 2 orders of magnitude below the TDI (Zhu and Kannan, 2019). However, EFSA concluded that the cumulative theoretical exposure due to the use of melamine-formaldehyde plastic tableware is more than 7-fold higher than TDI in the 3 age groups studied (infants, young children and adults), although it is approximately 3-fold higher in a 1.5-year-old child compared to that of a 6-month-old infant and that of an adult, which are similar (EFSA, 2010).

Commission Recommendation (EU) 2019/794 on a coordinated control plan to establish the presence of certain substances migrating from materials and articles intended to come into contact with food indicates that, plastic tableware and kitchen utensils, including non-conventional plastic cooking utensils and tableware, such as reusable coffee cups using additives in plastic derived from natural sources such as bamboo, should be sampled in relation to the presence of melamine and formaldehyde (EU, 2019).

However, in recent years the Member States of the European Union have found that it is being placed on the market an increasing number food contact materials and articles made from plastic and to which bamboo or other “natural” substances are added. An example of this is kitchen or tableware, such as reusable plates, bowls, and coffee glasses. In parallel, the RASFF system has notified 141 alerts since 2021 of the presence of melamine in contact materials made with bamboo fibres. It has been found that in certain cases the migration levels of melamine and formaldehyde exceed the SML of 2.5 and 15 mg/kg respectively, as laid down in Commission Regulation (EU) No. 10/2011, leading to the withdrawal of the product from the market. AESAN evaluated the presence of melamine in packaged beverages where levels were all lower than the LOQ (0.5 mg/kg), and therefore lower than the limit set at 2.5 mg/kg (Bustos et al., 2015).

8.3 Recommendations

Increased use of thermosetting plastics partially made with melamine-formaldehyde polymers for use in tableware, containers and utensils may increase the risk associated with the presence of melamine and its structural analogues. As co-exposure to melamine and cyanuric acid has shown a greater nephrotoxic effect compared to melamine alone, the joint evaluation of melamine and its structural analogues, mainly cyanuric acid, is recommended. Child population may be the most vulnerable population group with higher exposure rates than adult population.

9. Bisphenol A analogues (BPA)

9.1 Hazard identification and characterisation

In recent years, the use of bisphenol A (BPA) has been regulated in different countries given its known effect as an endocrine disruptor. Law 7/2022 on waste and contaminated soils for a circular economy prohibits the use of BPA in packaging (BOE, 2022). Thus, this compound is being gradually replaced by other bisphenolic compounds in industrial applications. Structural analogues of BPA, such as bisphenol S (BPS), bisphenol P (BPP), bisphenol F (BPF), bisphenol B (BPB), bisphenol E (BPE) and bisphenol AF (BPAF) (Figure 3) are being used as alternatives to BPA in the production of resins that are used in food contact materials. However, these compounds exhibit endocrine disrupting activity similar to or even superior to BPA, demonstrated in numerous experimental works (Andújar et al., 2019). Likewise, BPA analogues have been shown to exhibit cytotoxicity, genotoxicity, reproductive toxicity, and neurotoxicity in laboratory studies (Chen et al., 2016).

Overall, studies on the occurrence of bisphenol analogues in environmental compartments, consumer products and foodstuffs clearly demonstrate that analogues other than BPA are present in the environment and that humans are exposed through multiple routes, being food the most important. Although BPA is generally the most dominant bisphenol in different matrices, some analogues approximate or exceed BPA in concentrations in some food samples, probably reflecting a shift from BPA to other substitutes in food-contact materials. Although the number of studies is increasing current scientific knowledge, it is apparently insufficient.

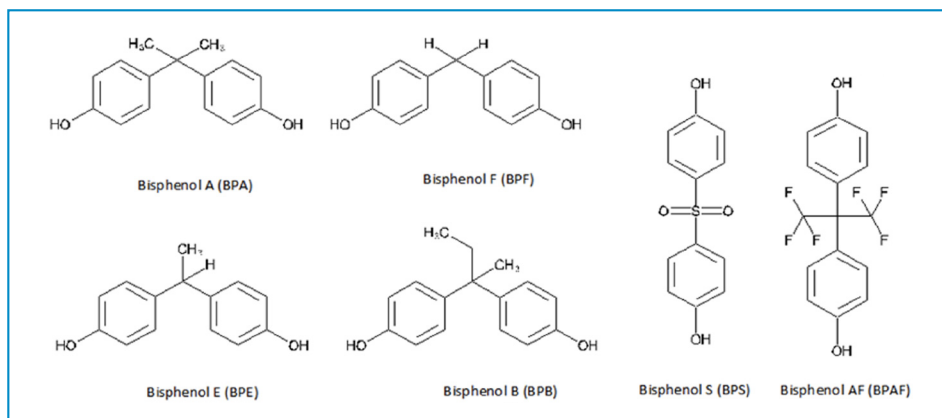


Figure 3. Chemical structure of bisphenol A analogues. **Source:** (Andújar et al., 2019).

At the global level, the regulation of BPA has been strengthened, while the regulation of widely used analogues such as BPS and BPF is insufficient. The increased use of BPS has attracted the attention of the scientific community and regulatory agencies such as the European Chemicals Agency (ECHA), and has been included in the EU's Community Rolling Action Plan (CoRAP) since 2014 as a substance suspected of endocrine disrupting activity. BPS is currently authorised under Regulation (EU) No. 10/2011 for use as a monomer in plastic materials in contact with food with a SML of 0.05 mg/kg food (EU, 2011a). The European Commission requested EFSA to assess the impact on the current authorisation of BPS in plastic food contact materials of recent studies submitted by BPS registrants in response to the ECHA Decision on the evaluation of substances under Regulation (EC) No. 1907/2006 (EU, 2006). These studies included an Extended One-Generation Reproductive Toxicity Study (EOGRTS), with developmental neurotoxicity cohorts (Developmental Neurotoxicity Study, DNT) and Developmental Immunotoxicity Study (DIT) (OECD Test Guidelines, TG 443), and a Toxicokinetic Study (TK) (OECD TG 417) in rats. The lowest EOGRTS NOAEL was identified for developmental neurotoxicity and developmental immunotoxicity at the lowest tested BPS dose of 20 mg/kg b.w./day. The mean dose of 60 mg bisphenol S/kg b.w./day was the NOAEL for overall systemic toxicity, while developmental neurotoxicity, fertility and reproductive performance were not affected even with the high tested dose of 180 mg bisphenol S/kg b.w./day. EFSA recommends the collection of data on the use of BPS in plastic present in food contact materials and on its occurrence and migration to food in the context of its possible use as an alternative to BPA (EFSA, 2020c).

With regard to BPF, it has been considered as a "substance requiring regulation" by the International Chemical Secretariat (ChemSec). Lee et al. (2022) conducted recently a long-term toxicity study (90-day repeat-dose toxicity test), genotoxicity, and BPF pharmacokinetic studies in rats. The authors determined a NOAEL of 2 mg bisphenol F/kg b.w./day for male animals and 5 mg bisphenol F/kg b.w./day for females, and a NOEL (No Observed Effect Level) of 2 mg bisphenol F/kg b.w./day for male rats and 1 mg bisphenol F/kg b.w./day for females, with the target organ being the small intestine.

9.2 Exposure and risk assessment

Since the main route of exposure to bisphenol is food, EFSA has reassessed the risk of the presence of BPA in food (EFSA, 2021). In its BPA re-evaluation draft, the expert panel has established a new TDI of 0.04 ng bisphenol A/kg b.w./day. When comparing the new TDI with estimates of consumer exposure to BPA through their diet, EFSA concludes that those with medium and high exposure to BPA in all age groups exceed the new TDI, indicating potential health problems. However, despite its proven presence in food and its increasing use, no assessment of dietary exposure to BPA analogues by official bodies has been carried out. There are different studies that demonstrate the presence of these endocrine disruptors in foods frequently consumed in different countries, mainly BPS and BPF.

In the United States, BPF was found to be the most abundant BPA analogue present in various foods, including beverages, dairy, fats and oils, fish and seafood, meats, cereals, fruits and vegetables (Liao and Kannan, 2013). The average of the concentrations of BPA and BPF in United States foods were 3 and 0.93 ng/g wet weight, respectively. Canned foods were found to contain higher concentrations of individual and total bisphenols than foods sold in glass, paper, or plastic containers.

Liao and Kannan (2014), in a study conducted in China, determined the presence of 8 bisphenols in 13 food categories. The most frequently found bisphenols were BPA and BPF, which were detected at mean value concentrations of 4.94 ng/g and 2.50 ng/g fresh weight, respectively. The highest overall concentration (sum of 8 bisphenols) was found in canned products (27.0 ng/g), followed by fish and shellfish (16.5 ng/g) and beverages (15.6 ng/g). In contrast, the lowest overall concentration was found in milk and dairy products, cooking oils and eggs (2-3 ng/g). Higher total concentration levels were detected in canned food (56.9 ng/g) than in food in glass (0.43 ng/g), paper (11.9 ng/g) or plastic (6.40 ng/g) containers.

Other studies have shown the presence of BPA analogues in canned vegetables, fruits and soft drinks (Gallart-Ayala et al., 2011), as well as in honey (Cesen et al., 2016), fish (Sadeghi et al., 2016) and mustard (Zoller et al., 2016). BPF has been found in white mustard seeds at levels of mg/kg, being a natural reaction product that is formed during its preparation. Mustard is one of the most widely used condiments worldwide and, according to some authors, is the main source of BPF in humans, in Europe and probably worldwide (Zoller et al., 2016). In addition, BPF and BPS have been detected in dairy products, meat, vegetables and cereals (Liao and Kannan, 2013).

In studies analysing food in different European countries, BPA remains the most frequently detected bisphenol in the food analysed. Other bisphenols frequently detected in Europe were BPF, BPS and BPB (Gallart-Ayala, 2011) (Cacho et al., 2012) (Grumetto et al., 2013) (Alabi et al., 2014) (Regueiro and Wenzl, 2015) (Gallo et al., 2017) (Cirillo et al., 2019) (González et al., 2020). In a recent study analysing the presence of BPA and analogues in foods frequently consumed by the Spanish child population (Gálvez-Ontiveros et al., 2021), a total of 52 % of the samples showed detectable concentrations of bisphenols. BPA was the most frequently detected bisphenol in ultra-processed foods (mean= 43.28 ng/g). BPS was the second most frequently detected bisphenol in food samples (26.5 %). BPE was found in 4.1 % of food samples. However, BPF, BPAF, BPB and BPP were not found

in any of the samples analysed. The highest value of bisphenol was found in processed foods, in canned tuna samples, with a mean value of 409 ng/g BPA and 187.8 ng/g BPS. A particular concern is that canned tuna food is one of the most consumed fish products (Russo et al., 2019). In addition, the bioaccessibility of bisphenol is higher in canned fish and seafood than in other food matrices with values ranging from 80 to 99 % (Cunha et al., 2017). These results are consistent with other studies showing higher concentrations of individual and total bisphenols in canned foods than in foods sold in glass, paper, or plastic containers (Liao and Kannan, 2013).

9.3 Exposure assessment

The population groups most vulnerable to the toxic effects of BPA analogues are pregnant women and children in early postnatal life (infants and young children). This is not surprising, since it is during these periods (especially early pregnancy) that all organs (brain, liver, muscles, skeleton) are formed and that certain mechanisms of endocrine regulation are not mature. Several lines of evidence show that many childhood and adult diseases, including cardiovascular diseases, obesity, and metabolic disorders including type 2 diabetes, certain reproductive cancers, and neurodevelopmental diseases may be a consequence of exposure to endocrine disruptors during pregnancy. Although there are fewer data on childhood, various studies in animal and epidemiological models show that exposure to these compounds can produce greater adverse effects at this stage of life (Demeneix and Slama, 2019).

9.4 Risk management strategies

Taking into account the latest EFSA report on the health effects of BPA and the restrictions on its use that are occurring in different countries, it is necessary to look for safe alternatives. The current use of BPA analogues such as BPS and BPF should be controlled as different *in vitro*, *in vivo* and human studies show that they have endocrine disrupting effect similar to BPA. At the global level, BPA regulation has been strengthened, while the regulation of its analogues is insufficient.

Although the number of papers is increasing, current scientific knowledge is apparently insufficient to elucidate food sources of bisphenol analogues at the national or global level. A comprehensive assessment of dietary exposure to these compounds is necessary, particularly to BPS and BPF as their use is high and their presence in European foods has been demonstrated. It is recommended that it be analysed in food, especially in canned food and, in the case of BPF, in mustard, where its levels have been found to be higher.

10. Sterigmatocystin

10.1 Hazard identification and characterisation

Sterigmatocystin (STE) was first isolated in 1954 from *Aspergillus versicolor* cultures. Today it is known to be a mycotoxin produced by several species of fungi belonging to the genera *Aspergillus*, *Bipolaris*, *Botryotrichum*, *Humicola* and *Penicillium*, although the main producers are the *A. flavus*, *A. parasiticus* and *A. nidulans*, common polluting fungi of corn, rice and feed (Wagacha and Muthomi, 2008) (Rank et al., 2011) (Gruber-Dorninger et al., 2017).

STE shares its biosynthetic pathway with aflatoxins. In particular, STE acts as a biogenic precursor of aflatoxin B1 (AFB1) and aflatoxin G1 (AFG1). In aflatoxigenic fungal species such as *A. flavus* and *A. parasiticus*, where STE quickly becomes the direct precursor of AFB1 and AFG1, STE rarely accumulates. However, substrates colonized by *A. nidulans* and *A. versicolor* may contain high amounts of STE (Yabe and Nakajima, 2004).

In *in vivo* studies, STE is able to induce toxic effects in several animal species, such as mice, rats, monkeys, chickens, ruminants and fish, varying the effect according to the species, route and frequency of administration. The LD₅₀ obtained after exposure to STE ranged from 5 µg/egg in 5-day-old chicken embryos to 166 mg/kg b.w. in rats orally exposed to mycotoxin (Purchase and van der Watt, 1969). Several studies indicate that liver and kidneys are the main target organs of acute toxicity (Sreemannarayana et al., 1988). Exposure to STE has also been shown to induce oxidative stress-related deterioration in liver and kidneys of rats (Sivakumar et al., 2001) (Dubravka et al., 2019).

Liu et al. (2012) also observed an alteration of normal immune function following exposure to STE, providing data on how the immunotoxicity of STE contributes to its carcinogenesis. It is also related to a reduced immune response and impaired balance of the adaptive immune system, as well as the induction of oxidative stress, apoptosis, mitochondrial dysfunction and activation of specific pathways.

Accordingly, in light of animal studies conducted to date and human cancer cases analysed, STE has been classified as possibly carcinogenic to humans (Group 2B) by the IARC (1987).

Despite evidence of its carcinogenicity, there are only limited data on the detection of STE in human blood or urine available in the literature. Some epidemiological studies show possible associations between exposure to STE and the risk of developing cancers such as gastric, liver, and lung cancer (Lou et al., 1995) (Huang et al., 2004). STE-DNA and STE adducts were also used as biomarkers in blood and urine samples, respectively, from patients with liver or stomach cancer (Tian et al., 1995) (Cao et al., 2018).

The HPLC-MS/MS technique allows the detection with high sensitivity of STE in food, with a LOD in the range of 0.05-0.15 µg/kg for cereals and nuts, and 0.005-0.01 µg/kg for beer (Versilovskis et al., 2007) (Versilovskis et al., 2009).

The maximum levels of STE are not regulated within the European Union. Prior to their entry to the European Union, the Czech Republic and Slovakia had established STE limits of 5 µg/kg for some cereals and milk (FAO, 2004) (Stroka et al., 2004).

Due to the lack of official STE control programmes, there are no reliable assessments of human and animal food exposure, nor are safe levels known in food (EFSA, 2013). JECFA is currently working on a safety assessment of STE proposed by the *Codex* Committee on Contaminants in Food (FAO/WHO, 2015).

10.1.1 Presence in food

STE concentrations in grains and grain products range from a few µg/kg to more than mg/kg. Higher STE concentrations (in the range of 3.8 to 4.3 mg/kg) were detected by Takahashi et al. (1984) in brown rice grains stored in a warehouse for 2 or 3 years after harvest. Among the mycotoxins

studied, STE was the most frequently detected mycotoxin in 180 samples of Italian rice by Bertuzzi et al. (2019), with detected levels in the range of 0.16 to 8.34 µg/kg, which vary according to the variety of rice. In Japanese cereals and foods harvested between 2016 and 2018, Yoshinari et al. (2019) demonstrated the presence of STE in 19.9 % of all samples, with concentrations mainly between 0.05 and 0.5 µg/kg. It was also found that coffee was contaminated by STE. García-Moraleja et al. (2015) demonstrated the occurrence of STE in different coffee beverages with an incidence of 16 % and concentrations ranging from 7.65 to 63.19 µg/kg. In cheeses, contamination occurs particularly on the surface, following fungal deterioration during ripening and storage.

For feed, levels of 0.68-2.25 µg sterigmatocystin/kg were found in 14 feed samples (Biancardi and Dall 'Asta, 2015). STE contamination was detected in silage and feed from a commercial maize mill in Burkina Faso (Warth et al., 2012) (Panasiuk et al., 2019). However, there are insufficient data to assess the rate of transfer of STE to milk or other animal products, such as meat and eggs, when animals are exposed to contaminated food (EFSA, 2013b).

Therefore, in light of all this and in accordance with the definition of “emerging mycotoxins” as “mycotoxins, which are not routinely determined or regulated by law; however, evidence of their incidence is rapidly increasing”, there is increasing awareness of the importance of establishing a better risk assessment for this mycotoxin and it may be correct to consider STE as an emerging mycotoxin that needs further investigation in order not to underestimate the potential risk associated with its exposure.

10.2 Prevention of food contamination by STE

Conventional action plans use pre- and post-harvest physical, chemical and biological strategies to reduce mycotoxigenic fungi growth and biosynthesis of mycotoxins in food products (Kabak et al., 2006).

Since the use of natural preservatives to control fungal growth and mycotoxin production is of collective interest, a growing number of studies have been conducted in recent years to try to counteract the adverse effects associated with mycotoxin exposure with natural substances (Krihnaswamy et al., 2010) (Fernández-Blanco et al., 2016) (Hu et al., 2017).

Likewise, the results revealed that cheese samples inoculated with fungi and 250 ppm of propolis had a significant effect on the decrease of STE production and, concentrations of 500 and 1000 ppm, had a significant inhibitory effect on mould growth (Aly and Elewa, 2007). Onion and garlic essential oils also demonstrated significant antifungal activity on *A. versicolor* mycelial growth and antimycotoxin activity on STE production, both individually and in mixtures (Kocic-Tanackov et al., 2012).

Conclusions of the Scientific Committee

This review covers a number of chemical substances which may pose a risk to human health and which are considered emergent in the absence of concrete evidence of their danger and specific regulation on their content in foods. The aim of this review is to provide a starting point for possible prospective studies, with an emphasis on identifying foods that may be of particular importance in relation to the considered hazards. Hence, this report does not conduct a comprehensive risk

assessment of these compounds. It does include specific information on the description of the identification and characterisation of each of the hazards reviewed, the exposure assessment, as well as a number of recommendations for risk management, and future considerations on the possibilities of control in the food chain, which may help to improve the knowledge of these hazards among consumers and other relevant sectors.

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