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Review

A review on biogenic amines in food and feed: toxicological aspects, impact on health and control measures

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Abstract. Biogenic amines (BAs) represent a considerable toxicological risk in some food and feed products. They are formed under unhygienic conditions during storage and processing; therefore, an increase in the concentrations of those metabolites is related to putrefaction. Because BAs are thermostable, they remain in food and feed that have undergone heat treatment. There are several toxicological effects, especially caused by histamine, when high concentrations of BAs are ingested by humans, depending on the food itself and also on individual susceptibility and individual health status. The present paper reviews the main BAs in meat products, their use as spoilage indicators, the risk on human health and also the contamination of by-product meals. Furthermore, we highlight the state of art regarding impact of BAs on poultry, meat and eggs.

Additional keywords: bioactive amines, by-products, human health, meat, poultry, rendering.

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Introduction

Biogenic amines (BAs) are non-volatile low-molecular-weight nitrogenous organic bases, derived through decarboxylation of amino acids (Rêgo *et al*. 2014; Figueiredo *et al*. 2015). BAs (Fig. 1) can be found in almost all types of foods, feeds and beverages in different concentrations (Bover-Cid *et al*. 2014). Some susceptible products include cheese, fish, soy sauces, meat products, wine and beer (Silva and Glória 2002; Savvaidis and Ruiz-Capillas 2009; Gomes *et al*. 2014; Lee *et al*. 2015).

Biogenic amines can be both formed and degraded as a result of normal metabolic activities in humans, animals, plants and microorganisms (EFSA 2011). The main requirements for a considerable BA formation are the availability of free amino acids, the presence of decarboxylase-positive microorganisms and the conditions that allow bacterial growth (for instance, storage and fermentation), decarboxylase synthesis and decarboxylase activity. Hence, decarboxylase-positive microorganisms may be part of the microflora present in food or feed, which can be introduced by contamination before, during or after processing (ten Brink *et al*. 1990). BAs have important metabolic and physiological roles, such as the regulation of growth, control of blood pressure and neural transmission (Kalač 2014). Similarly, there is evidence that BA concentration increases as the hygienic quality of the products decreases (EFSA 2011).

Since BAs are formed by the action of living organisms (Ramos *et al*. 2014) present during food processing and storage, higher amounts of certain toxic amines may be found in foods due to poor-quality raw materials, microbial contamination and inappropriate conditions during storage (EFSA 2011). The presence of these amines in food is of interest, first, for toxicological reasons, because high concentrations of dietary BAs can be toxic for some consumers, depending on factors associated with the food itself (quantitative and qualitative), individual susceptibility and health status, which may differ due to genetic reasons or illness, and, second, for their role as quality indicators (Ruiz-Capillas and Jiménez-Colmenero 2004). People with respiratory disorder, heart problems or vitamin B_{12} deficiency are particularly sensitive. Individuals with stomach problems usually have lower intestinal oxidative activity and they are also an at-risk group (Cardozo *et al*. 2013).

The present review aims to provide an overlook on BAs in food and feed of animal origin, and also covers the impact of BAs on human health, discussing toxicological responses and some control measures.

Biogenic-amine production in animal-origin products and by-products

Meat and poultry

All foods with high content of proteins and free amino acids may provide suitable conditions for biochemical and microbial activity and, consequently, BA formation (Silla Santos 1996; Buňková *et al*. 2010). Additionally, the amount and type of amines in foods depend on the nature and origin of the substrate, considering that they can change during production, processing, fermentation and storage. Factors associated with raw materials, such as meat composition, pH and handling

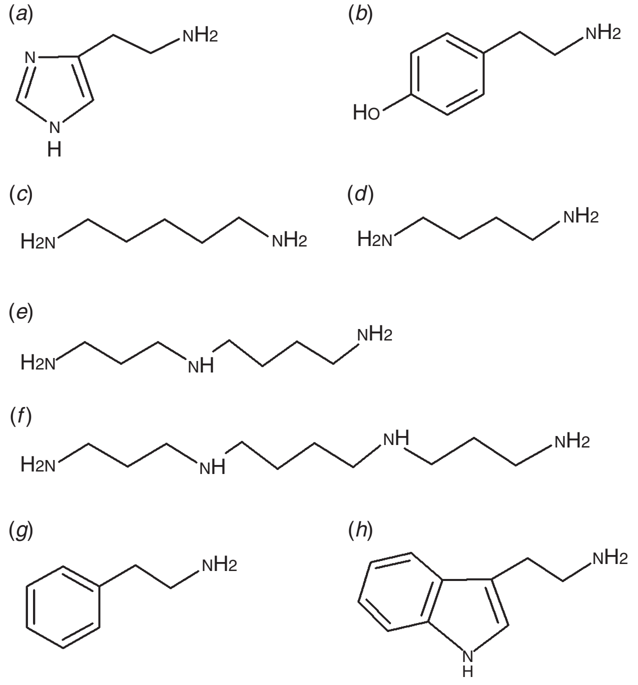

Fig. 1. (*a*) Histamine, (*b*) tyramine, (*c*) cadaverine, (*d*) putrescine, (*e*) spermidine, (*f*) spermine, (*g*) phenylethylamine and (*h*) tryptamine.

conditions are further influenced by the technological processes associated with the type of meat derivative (steak, roast, smoked, fermented and others) and storage conditions (Ruiz-Capillas and Jiménez-Colmenero 2004). The combined action of these factors mostly influences the final concentration of BAs, since it determines, directly or indirectly, the presence and the activity of substrates and enzymes (Ruiz-Capillas and Jiménez-Colmenero 2004).

Biogenic amines are resistant to heat treatment applied in food processing. Therefore, BAs have been considered as good indicators of freshness and spoilage, inferring the quality of fresh and processed food products, thus reflecting the raw-material quality and hygienic conditions during processing (Glória 2006; Hui 2006; Buňková *et al*. 2010).

So as to facilitate the evaluation and comparison of the BA concentration in food, the biogenic amine index (BAI) was established; it consists of the sum of concentrations of the BAs. BAI is more indicative of quality for fresh meat, tuna and cooked products, because fermented products vary more widely regarding manufacturing practices, use of starters, and certain processing steps. For example, some studies involving the analysis of beef and pork considered the amount of histamine (HIS), tyramine (TYM), putrescine (PUT) and cadaverine (CAD) to calculate the BAI, and, depending on the value, the meat can range from good quality to spoiled, as presented in Table 1 (Veciana-Nogués *et al*. 1997; Belitz *et al*. 2009).

The production of BAs has been associated with yeast and also with bacteria, either Gram-negative or Gram-positive (Alvarez and Moreno-Arribas 2014). The most important BAs found in food are HIS, TYM, PUT, CAD and phenylethylamine (PHE), which are produced by the decarboxylation of histidine,

Table 1. Biogenic amine index (BAI) of fresh meat and cooked products
Source: Ruiz-Capillas and Jiménez-Colmenero (2004); Belitz *et al*. (2009)

BAI	Characteristic
BAI < 5 mg/kg	Good-quality fresh meat
5 mg/kg < BAI < 20 mg/kg	Acceptable meat, but with initial spoilage signs
20 mg/kg < BAI < 50 mg/kg	Low-quality meat
BAI > 50 mg/kg	Spoiled meat

tyrosine, ornithine, lysine and phenylalanine respectively, and PUT, that can be formed through deamination of agmatine. Several bacterial groups associated with food spoilage and with a technological role are known to be able to decarboxylate amino acids and produce one or more BAs to a variable extent (Bover-Cid *et al*. 2014). These authors also discussed that although the ability to decarboxylate certain amino acids are a strain-dependent property, the ability to produce specific BAs is reported in some bacterial families or genera more often than in others. Enterobacteriaceae (including mesophilic and psychrotolerant *Morganella*, *Enterobacter*, *Hafnia*, *Proteus*, for example) and *Photobacterium phosphoreum* are the most prolific HIS-producing bacteria in fish substrate. Also, many enterobacterial strains isolated from meat and vegetables have been shown to produce diamines, PUT and CAD, and some particular strains have also been described as HIS producers, although less often and to a lesser extent than are the enterobacteria isolated from fish products.

It has been reported that red meat has more BAs than does white meat, probably due to the short fibres present in white meat, which are more susceptible to proteolysis (Vinci and Antonelli 2002). TYM and CAD were the main contributors to the total BA content in both red and white meat, although TYM concentration was much lower in white meat. Lázaro *et al*. (2013) also detected a higher TYM concentration (230.72 mg/kg) in commercial chicken breast, than that of any other BA, which ranged from 4.71 to 16.03 mg/kg.

During chicken meat storage at 4.0°C, a linear reduction in spermine (SPM) concentration was observed, while spermidine (SPD) concentration remained constant (Silva and Glória 2002). The authors reported that PUT, CAD, HIS and TYM concentrations were detected on the 15th day of storage. Another issue is the SPD : SPM index that allows detecting early stages of deterioration; therefore, its use is proposed during refrigerated storage of chicken meat.

Fresh beef, pork and chicken breast and leg were investigated during 1, 4, 7, 11 and 15 days of storage regarding the BA concentration (Min *et al*. 2007). As the storage period increased, the concentrations of PUT, CAD and TYM increased in all meat samples, except for TYM in beef.

Molognoni *et al*. (2018) tested a multi-purpose tool for food inspection, determining various BAs in meat products in 87 samples. These authors found concentrations of CAD, PUT, SPD, HIS, SPM and TYR respectively, ranging from non-quantified (NQ) to 124 mg/kg, NQ to 124 mg/kg, NQ to 229 mg/kg, NQ to 55 mg/kg, NQ to 261 mg/kg and NQ to 199 mg/kg.

Eggs

The lack of information on types and concentrations of amine contamination in eggs just after being laid and the changes and factors that may affect amine profile and concentrations in eggs are important subjects to new research (Oliveira *et al*. 2009). These changes may be used as an objective and reliable index of egg quality in order to better assess it. The presence of other amines besides SPM or SPD, such as PUT and agmatine, at concentrations higher than 1.0 mg/kg in the yolk could be used as a parameter of fresh-egg quality throughout storage (Oliveira *et al*. 2009). These same authors observed that fresh eggs (immediately after being laid) contain only SPD in yolk at low concentrations (<1.0 mg/kg). Therefore, the presence of other BAs in fresh eggs, or SPD levels higher than 1.0 mg/kg in yolk, may indicate that eggs are not fresh or that they have undergone microbial contamination.

Min *et al*. (2004) found high concentrations of CAD (67.60 ± 33.92 μg/g) in egg white of fertilised eggs, while CAD (64.37 ± 32.58 μg/g) and SPD (33.77 ± 0.75 μg/g) were detected in egg yolk. Also, commercial unfertilised eggs were analysed and almost no BAs were detected in egg white, whereas CAD (102.62 ± 6.49 μg/g) and SPM (32.57 ± 0.51 μg/g) were detected at a high concentration in yolk.

It was shown (Ramos *et al*. 2009) that ethanolamine, ethylamine, PUT, propylamine and CAD quantified in egg-yolk samples presented significant concentrations during shelf-life. However, the concentrations of the three first-mentioned BAs decreased with an increasing storage time (from 3 to 26 days), which may be attributed to the migration of BAs to albumen and also chemical changes.

The concentrations of BAs were evaluated by Figueiredo *et al*. (2013) in commercial eggs produced by layer hens, which were ~30 and 60 weeks old. These eggs were submitted to storage for 28 days (at room temperature or under refrigeration) and a chromatographic determination of bioactive BAs was performed. Figueiredo *et al*. (2013) detected only the presence of PHE in albumen, independently from the hen age or the storage condition, and SPD in egg yolk. They pointed out that PHE concentration in albumen increased significantly and reached levels above those considered toxic for this amine, despite the low levels of microbial contamination found in eggs stored at both temperatures. However, BA concentrations recorded in commercial eggs (Figueiredo *et al*. 2014) were considered low and would not be harmful to the consumer health. The highest values detected by these authors in egg yolk were 2.38 mg/kg (PUT) and 7.27 mg/kg (CAD), while, in the albumen, they reported PUT (1.95 mg/kg), CAD (2.83 mg/kg) and PHE (2.57 mg/kg).

Rêgo *et al*. (2014) evaluated bioactive amines and microbiological quality of pasteurised and refrigerated liquid whole eggs after 0, 7, 14 and 21 days of storage. They detected concentrations of PUT, CAD and TYM only in fertile liquid pasteurised egg; they observed that the storage contributed to the increase ($P < 0.05$) in the concentration of these amines. There was a high correlation between total coliform most probable number and CAD concentration, and a moderate correlation between the numbers of aerobic mesophilic microorganisms and TYM levels. PUT was detected from 14 days on, while the other BAs were detected only at 21 days. The values ranged from 9.1 (TYM) to 15.3 mg/kg (PUT). Rêgo *et al*. (2014) showed that egg deterioration in samples with a high BA concentration is associated with bacterial growth. Therefore, it is important to know the concentration of bioactive amines in liquid pasteurised egg, since amines are thermally stable, and their quantification as quality indicators implies the final product quality.

Recently, the quality of commercial eggs was evaluated by assessing bioactive amine concentrations (Assis *et al*. 2016). The results demonstrated the presence of PUT in all yolk and albumen samples, but at low concentrations. Other amines were also detected, although at a lower frequency, and SPM was found only in one albumen sample. It was concluded that commercial eggs are not a considerable source of polyamines and low concentrations of BA do not represent an important risk to consumer health.

By-products

By-products commonly used by the animal feed industry, such as meat and bone meal, blood meal, feather meal, poultry meal and fish meal, which have undergone some degree of spoilage, are generally considered rich sources of BAs (Smith *et al*. 2000).

One-third to one-half of each animal produced for meat, milk and eggs is not consumed by humans (Meeker 2009). The most important and valuable use for these animal by-products is as feed ingredients for livestock, poultry, aquaculture and companion animals. By-product is defined as a secondary product obtained during the processing of hides, skins, hair, feathers, hoofs, horns, feet, heads, bones, toe nails, blood, organs, glands, intestines, muscle and fat tissues, shells and whole carcasses (Meeker and Hamilton 2006). These raw materials are subjected to rendering processes, resulting in many valuable by-products such as meat and bone meal, meat meal, poultry meal, hydrolysed feather meal, blood meal, fish meal and animal fats (Meeker and Hamilton 2006).

The disposal of dead poultry in open fields is considered to be a serious problem for the poultry industry (Sander *et al*. 1996). As indicated by the previous authors, an increase in the BA concentrations in fermented poultry carcasses is a more sensitive or earlier sign of putrefaction. Therefore, these carcasses are not recommended as raw ingredient for poultry meal. Proteolysis, either autolytic or bacterial, may play a significant role in the release of free amino acids from tissue proteins, which offer a substrate for decarboxylases reactions (Shalaby 1996).

When used in feeds, animal by-products are valuable to balance amino acids in practical corn–soybean diets and their addition may not only reduce diet costs but may improve the growth response as well (Bermudez and Firman 1998; Firman 2006). Besides the high concentrations of amino acids, these meals are also excellent sources of energy, minerals and vitamins (Meeker and Hamilton 2006). However, fresh meat and similar materials are very susceptible to chemical and physical changes during storage or processing (Glória 2006). High concentrations of BAs may be present in processed meat meals, due to the action of microorganism enzymes that

Table 2. Biogenic amine concentration (mg/kg) in different by-product meals
Source: Barnes *et al*. (2001). n.d., not detected

By-product	Putrescine	Cadaverine	Histamine	Spermidine	Spermine
Meat and bone meal	57 (n.d.–286)	120 (n.d.–450)	21 (n.d.–208)	16 (n.d.–39)	31 (10–56)
Poultry meal	227 (84–390)	451 (140–879)	39 (28–95)	31 (19–53)	74 (55–96)
Fish meal	99 (12–537)	215 (64–557)	70 (8–1576)	31 (18–97)	27 (120–139)

decarboxylate free amino acids to their corresponding amines (den Brinker *et al*. 2003).

The production of BAs has been associated with some groups of microorganisms (EFSA 2011). For example, the production of PUT and CAD is frequently caused by enterobacteria, and TYM production is reported in the majority of enterococci. In this sense, animal by-products must be processed immediately after slaughter, so as to avoid microorganism growth and the potential production of BAs (den Brinker *et al*. 2003). By-product processing typically involves some form of heat and pressure treatment during a minimal amount of time that will inactivate microbial contaminants, thus preventing BA production (Bermudez and Firman 1998). However, heating alone may not be satisfactorily effective to fully eliminate bacterial contamination, which is more pronounced when previously heated products are inappropriately stored under uncontrolled temperatures or when they were subjected to low hygienic handling, affecting also the palatability attributes (Hui 2006; Kalač 2014).

It has been reported (Köse *et al*. 2003) that using stickwater meal for feeding animals can be more toxic than are meals produced from the fish solids, and care must be taken when using it. This is because HIS is mainly concentrated in the stickwater meal, extracted during processing; also this meal contains large amounts of organs and tissues parts, gills and heads of fish, which could lead to high bacterial counts. Interestingly, when fish samples were cooked and pressed, no bacterial growth was observed in the press-cake. However, when stickwater was used, bacterial growth was observed, indicating that recontamination occurred during drying, milling and handling, mainly from environment and equipment after cooking. Therefore, presence of higher concentrations of toxic BAs in food is undesirable and indicates the need for hygienic control procedures (EFSA 2011). Contamination of fish with HIS may be due to mishandling and bacterial production of HIS, a product from free histidine due to the action of bacterial HIS decarboxylase following time–temperature abuse (Hungerford 2010).

It has been highlighted (Jaw *et al*. 2012) that the most convenient explanation for high contents of HIS and other BAs found in fish meal and fish soluble concentrate samples (from <5.0 to 40–50 mg/100 g) would be the use of spoiled raw material and poor hygienic practices during production and packaging of fish meal, in combination with storage and transportation conditions, thus facilitating HIS formation. High histidine content in stored feedstuff and the presence of bacteria with high histidine decarboxylase activity, mainly *Enterobacteriaceae*, are the main factors affecting HIS concentration (Macan *et al*. 2006).

Table 3. Concentration range and median (mg/kg) of putrescine, cadaverine and histamine in different by-product meals
Source: den Brinker *et al*. (2003). n.d., not detected (limit of detection = 5 mg/kg); the ranges are concentrations (with the median concentrations in parentheses) of different biogenic amines

By-product	Putrescine	Cadaverine	Histamine
Fish meal	7–454 (102)	11–1340 (220)	n.d.–1620 (570)
Poultry meal	7–1340 (82)	n.d.–1350 (121)	n.d.–167 (19)
Meat meal	n.d.–695 (21)	n.d.–680 (29)	n.d.–258 (10)
Feather meal	5–267 (31)	n.d.–159 (42)	n.d.–90 (5)
Blood meal	n.d.–223 (13)	n.d.–280 (7)	n.d.–36 (4)

Progressive putrefaction of poultry carcasses, under common broiler-house conditions, produced tryptamine (TRY), PHE, PUT, CAD, HIS, TYM, SPD and SPM, which were detected even in fresh carcasses from broilers slaughtered at 28 days of age (Tamim and Doerr 2003). It was pointed out that final rendering product quality was reduced, such as a feed ingredient, and it was highly dependent on the observance of good management techniques, including rapid collection and processing of dead fowl; thus, raw material is vulnerable to bacterial deterioration when left at high temperatures for long periods prior rendering (den Brinker *et al*. 2003).

Aminogenic organisms that originate from animal parts (such as intestines, skin and fish gills) can spread to other sites, surfaces and equipment during handling of fresh, raw materials, at different steps such as degutting, filleting, slaughtering, cutting and mincing. These practices promote the increase of BAs during further processing and storage (EFSA 2011).

The presence of BAs in animal by-product meals has been reported in few papers (Barnes *et al*. 2001; den Brinker *et al*. 2003). In a study conducted at the University of Arkansas (Barnes *et al*. 2001), animal by-product meals used as feed ingredients were analysed for BAs over the course of a year and the average concentrations (and ranges, mg/kg) can be seen in Table 2. BA concentration in poultry meal is almost twice as high as that verified in fish meal, especially for PUT and CAD, while meat and bone meal has a BA concentration around one-third that of poultry meal for these same BAs. The authors concluded that since CAD can inhibit histidine degradation, thereby increasing tissue concentrations of this amino acid, it is suggested that both fish and poultry meal undergo more microbial degradation than does meat and bone meal.

Higher concentrations of BAs (Table 3) were found in five different animal-origin meals produced in Australia between 1994 and 1997 (den Brinker *et al*. 2003). These authors found a large variation in BA concentration among the meals, indicating that some products had undergone a severe microbial degradation.

The authors emphasised the importance of rendering animal by-products immediately after slaughter, particularly at high ambient temperatures, to avoid the production of high concentrations of BAs. Besides, the results indicated that further studies are required to determine the maximum limits for BAs in animal meals that will not impair animal production and food safety.

Impact on human health

High amounts of BAs may decrease food quality and produce several physiological symptoms, such as nausea, respiratory distress, headache, sweating, heart palpitations and hyper- or hypotension. The main symptoms associated with some BAs, such as HIS and TYM, when accompanied by alcohol and acetaldehyde, are nausea, headaches and respiratory disorders (Lee *et al*. 2015).

Polyamines participate in numerous physiological processes both favourable and damaging for human health (Kalač 2014). While polyamines play an important role in growth, BAs may be neuro- or vasoactive, as stated by Hui (2006). For instance, HIS increases vasopermeability and vasodilatation, causing urticaria, flushing, hypotension and headache. HIS also induces contraction of intestinal smooth muscle, causing abdominal cramps, diarrhoea and vomiting (Lehane and Olley 2000). It seems that polyamines do not trigger cancer, but accelerate tumour growth (Kalač 2014).

Some individuals are sensitive to BAs, resulting in symptoms resembling an allergic reaction (Guo *et al*. 2015). HIS poisoning can cause cutaneous (e.g. rash or inflammation), gastrointestinal (nausea, vomiting, diarrhoea), neurological (e.g. headache, burning or itching) or circulatory (hypotension) symptoms. According to Hui (2006), once formed in seafood, BAs are heat stable and will not be destroyed by cooking, baking or even canning.

Tyramine and PHE were claimed to cause certain migraines. However, migraine is a multifactorial problem that is not affected by only one dietary component but also by environmental, physiological and psychological factors (Bover-Cid *et al*. 2014). In cheese containing high levels of TYM, a ‘cheese reaction’ is observed, responsible for migraines, headaches and increased blood pressure symptoms (Savvaidis and Ruiz-Capillas 2009). There are limited outbreak reports due to the lack of official records (Bover-Cid *et al*. 2014).

Mammals, including humans, possess mechanisms of BA detoxification. However, the efficiency of detoxification varies considerably between different individuals and also according the toxic dose (ten Brink *et al*. 1990). These amines are not considered to be a serious risk for humans, as long as they are present in low concentrations and their metabolism is not blocked or genetically altered (Vidal-Carou *et al*. 1990). Under normal conditions, in healthy individuals, dietary BAs are metabolised very rapidly by specific enzymes, namely, monoamine (MAO) and diamine (DAO) oxidases (Prester 2011). Therefore, these enzymes in the intestinal mucosa rapidly detoxify BAs ingested with food. However, when this system fails to eliminate the high amounts of BAs ingested with certain spoiled or fermented foods (ten Brink *et al*. 1990), or if these enzymes are dysfunctional either genetically or due to the intake of inhibitors such as alcohol or certain antidepressant medications, BAs enter the systemic circulation and exert their toxic effect on different organs, causing serious human health problems (Alvarez and Moreno-Arribas 2014).

In individuals using MAO inhibitor antidepressants, the ingestion of 60 mg/kg of dietary TYM can cause migraine, while 100–250 mg/kg will produce a hypertensive crisis (Silla Santos 1996). Besides the genetic disposition or the physiological status, several environmental factors such as diet and medication can temporarily modify individual susceptibility (Bover-Cid *et al*. 2014).

Toxicological responses

It is generally very difficult to establish limits of toxicity of BAs in a given product, because their effects do not depend on their presence alone (type of amine and existing concentrations), but are also influenced by other compounds (modulating their effect) and by the specific efficiency of the detoxifying mechanisms in different individuals. Hence, the toxicity of BAs will depend on factors associated with the food itself (quantitative and qualitative) and also on factors associated with the consumer, such as individual susceptibility and state of health (Ruiz-Capillas and Jiménez-Colmenero 2004). There have been some studies on the *in vitro* toxicity and mutagenicity of BAs (Badolo *et al*. 1998), in which the effect has been analysed on the basis of the cytotoxicity of individual compounds (FAO/WHO 2012; Lee *et al*. 2015).

The toxicity of BAs to humans and chicks has received more attention than in other species. In the case of swine, for instance, after searching the literature, including the classical ‘Diseases of swine’ (Zimmerman *et al*. 2012), there is no association of BAs with any diseases. Since there are several similarities between swine and other monogastric species, especially humans, it can be suggested that more attention should be given to the damage caused by BAs to animal health.

The toxicological responses differ among species and they depend on the method of administration, and the toxicological effects. For instance, oral administration of HIS, alone or together with spoiled tuna, produced emesis in pigs (FAO/WHO 2012; Lee *et al*. 2015).

Humans

In humans and experimental animals, HIS is primarily metabolised by two enzymes, namely, diamine oxidase (DAO) and HIS-N-methyltransferase (HMT). DAO converts HIS into imidazole acetic acid, which can be conjugated with ribose before excretion. HMT converts HIS into methylhistamine, which is then converted by monoamine oxidase (MAO) into N-imidazole acetic acid. The ultimate end products of HIS metabolism are excreted in urine. In humans, DAO is expressed mainly in the intestinal tract, which limits the uptake of exogenous HIS into the circulatory system. However, HMT is widespread in human tissues, with the order of activity being liver > colon > spleen > lung > small intestine > stomach. Therefore, DAO is considered to be the major metabolic enzyme for ingested HIS, while HIS injected intravenously or intradermally is primarily metabolised by

HMT, which is very selective for HIS, while the substrates of DAO include other BAs such as CAD and PUT.

Dietary PUT, SPD and SPM participate in an array of important human physiological roles, including tumour growth (Kalac 2006; Dadáková *et al*. 2012). Beef, pork and meat products rank among the main dietary sources of SPM, with the usual concentration of SPM being 20–40 mg/kg. Extremely high concentrations of both SPD and SPM were determined in bovine, porcine and chicken livers. Very limited information is available on changes in polyamine concentration during meat and offal storage and processing. While PUT concentration increases as a result of bacterial activity during inappropriate storage and processing of animal-origin foods, SPD and SPM originate from raw materials (Kalac 2006).

Animal-origin foods are naturally rich in free amino acids and, therefore, they are susceptible to contamination by BAs. In fish and meat, BA concentration increases postmortem due to the high quantity of proteolytic enzymes present in the intestinal tract, combined with the rapid autolysis process (Cardozo *et al*. 2013).

Histamine in foods is not necessarily hazardous, because many foods contain small amounts of HIS, which is easily tolerated. A fairly efficient detoxification system exits in the intestinal tract to metabolise ingested HIS and HIS that may be formed by intestinal bacteria (Shalaby 1996).

Putrescine and CAD under heating are converted to pyrrolidine and piperidine respectively, from N-nitroso pyrrolidine and N-nitrosopiperidine. Therefore, technological food processes such as salting and smoking seem to induce nitrosamine formation, while cooking and frying enhance their formation, since raw materials were free from nitrosamines (Shalaby 1996).

Besides salting, other technological processes such as ripening, marinating and fermentation may increase BA formation. As an example, HIS formation in salted fish is probably due to the presence of halophilic or halotolerant microorganisms (Visciano *et al*. 2012).

Methylamine in fresh beef muscle is present at 2 mg/kg, while the other volatile aliphatic amines (dimethyl-, trimethyl-, ethyl-, diethyl- and isopropylamine) are detected only in trace amounts. The BAI values of fermented meat products are naturally higher; a limit of 500 mg/kg was proposed for salami. Other BAs include SPD (N-(3-aminopropyl)-1,4-butandiamine) and SPM (N,N-bis-(3-aminopropyl)-1,4-butandiamine), which are biogenetically formed from PUT and belong to the constituents of meat. The main compound is SPM, with a concentration in the range of 25–65 mg/kg (Belitz *et al*. 2009).

There are interesting differences for polyamines in different types of food. Red meat and meat products rank among the main dietary sources of SPM both in the UK (Bardócz 1995) and in Japan (Nishibori *et al*. 2007). Red meat contains SPM as the major component, while fish has more PUT than either SPD or SPM, and the polyamine composition of chicken meat is similar to that of red meat (Bardócz 1995).

The usual concentrations of PUT, SPD and SPM in fresh beef and pork are <2, <5 and 20–40 mg/kg respectively. During meat storage, PUT can be formed by bacterial activity, mainly of *Pseudomonas* and *Enterobacteriaceae*. Data on SPD and SPM changes during meat chill-storage are inconsistent; a slight decrease has been usually reported. Culinary processing of meat probably slightly decreases SPD and SPM concentrations (Paulsen and Bauer 2007). Very high concentrations of both SPD and SPM were found in bovine, porcine and chicken livers, ranking them among the richest sources of these polyamines (Krausová *et al*. 2006).

Foods with high polyamine concentrations should be avoided by patients with tumours (Kalač 2014). An increased intake and availability of dietary polyamines is advantageous during the periods of wound healing, post-operational recovery (except for tumours), liver regeneration, or compensatory growth of lungs or gut. It is urged to take into consideration the quantity of each consumed food item (Kalač 2014).

There is a positive correlation between the total concentrations of BAs and specific manufacturing processes (Lee *et al*. 2015). Processed products are more frequently contaminated at higher levels, although fresh and frozen fish may have HIS levels above 200 mg/kg (FAO/WHO 2012).

Assis (2014) reported low levels of polyamine in chicken breasts, as SPD and SPM at concentrations between 18.7–62.2 mg/kg and 49.1–64.9 mg/kg respectively in all samples. PUT, CAD, HIS and TYM were also detected, although in lower concentrations.

Brazilian legislation provides limits up to 100 mg of HIS for each kilogram of fish, in accordance with the recommendations of the scientific literature and the international standards. Since HIS is the only BA covered by Brazilian legislation (MAPA 2011), and by FAO/WHO (2012), much has to be investigated.

Although there is no specific legislation regarding the amine concentration in food and beverages, the presence and accumulation of amines is a matter of great importance (Gomes *et al*. 2014). According to Hui (2006), it is unknown whether the low concentrations (μg/kg) detected in food may represent any significant health risk to humans.

High concentrations of HIS were found in cooked tuna served in a Brazilian school (Takemoto *et al*. 2014). The concentration was 10 times more than the level allowed by the official legislation or Ministry of Agriculture. HIS outbreak associated with fish consumption is poorly elucidated in Brazil. By that time, this was the fourth known case and it occurred with grated tuna consumption containing edible oil and seasoned canned vegetable broth. The ingestion caused red spots around the mouth and face, besides swelling around the eyes. It was suggested that the outbreak originated from cross-contamination or storage under unsuitable temperature after meal preparation, because the intact sample from the same batch did not contain HIS.

Considering that both HIS and TYM at concentrations higher than 100 mg/kg, and PHE at concentrations >30 mg/kg, may cause adverse effects on human health (FDA 2012; Guidi and Gloria 2012); 48% of the samples could cause HIS poisoning, 61% could induce migraine headaches due to TYM and 31% could cause headache due to PHE. It has been pointed out that smoking and alcohol ingestion may also increase sensitivity to BAs by reducing the degradation capacity (EFSA 2011; FAO/WHO 2012).

A dose of 50 mg of HIS, which is the no-observed-adverse-effect level, is the level at which healthy individuals would not be expected to suffer any of the symptoms associated with scombrotoxin fish poisoning (SFP), such as peppery or metallic taste, oral numbness, headache, dizziness, palpitations, rapid and weak pulse (low blood pressure), difficulty in swallowing, and thirst (Hungerford 2010). In addition, no cumulative effect of consecutive meals containing fish was expected, because HIS is usually eliminated from the body within a few hours (FAO/WHO 2012).

The consumption of food containing large amounts of BAs can result in allergic reactions, characterised by difficulties in breathing, rash, vomiting and hypertension. Besides, BAs are also known as possible precursors of carcinogens such as N-nitrosamines (Cardozo *et al*. 2013).

Other studies that are believed to be helpful would be those that investigate the various factors that may enhance the sensitivity of the response to SFP in various populations. These would include investigation on genetic polymorphism in HIS toxico-dynamics and -kinetics, some physiological conditions such as menstruation, gastrointestinal tract diseases, medications, role of certain lifestyle practices such as smoking and alcohol consumption in altering BA metabolism, and age (FAO/WHO 2012).

Poultry

Fermentation of the amino acids such as histidine, ornithine, lysine, methionine, tyrosine, phenylalanine, tryptophan and arginine results in the production of HIS or SPD, PUT or SPD, CAD, SPD, TYM, PHE, TRY or serotonin, and agmatine or PUT or SPD respectively (Qaisrani *et al*. 2015). Likewise, the polyamine SPD is formed from the catabolism of amino acids including histidine, ornithine, methionine, and arginine, which may subsequently be converted into SPM. The same authors highlighted that although BAs are important for normal gut development, greater concentrations may cause gizzard erosion, mortality and a depressed growth rate in broilers. It was also observed (Tamim and Doerr 2003) that BAs have been found at high concentrations in animal by-product meals and have been associated with negative effects on animal performance. Previously, it was indicated (Bermudez and Firman 1998) that the BAs added to a corn–soybean meal diet with 10% of animal product, PHE (4.8 mg/kg), PUT (49 mg/kg), CAD (107 mg/kg) and HIS (131 mg/kg) are unlikely to produce deleterious effects on performance or the occurrence of lesions (gross pathology and histopathology) in broilers fed those diets. One year later, similar results were reported (Friday *et al*. 1999), even doubling the concentrations of the same BAs added in broiler diets. Only feed ingredients extremely high in these amines are likely to affect animal growth; it is suggested that an additive or synergistic action may be more important than the concentrations of any single amine or dietary amine load, and may better indicate the potential performance problems associated with dietary BAs (Barnes *et al*. 2001). The same authors pointed out that BAs have been implicated in a malabsorption syndrome in chickens characterised by a worst feed efficiency, proventriculus enlargement, decreased weight gain and increased carcass contamination from gastrointestinal tract caused by rupture during processing. In addition, it was observed that although gizzard erosion and ulceration syndrome in chickens are globally distributed and their subclinical form appears to be common in commercial poultry flocks, the condition is rarely mentioned in standard textbooks on poultry health, probably due in part to the lack of one definitive cause of the syndrome (Gjevre *et al*. 2013). Gjevre *et al*. (2013) identified congenital factors, starvation, nutritional deficiencies, toxic substances (such as BAs), infections, particle size of feeds, mashed or pelleted feeds, type of fibre, and microbial colonisation, as some predisposing factors that have been associated with these conditions in chickens.

It was evidenced that BAs including HIS may cause gizzard erosion in broilers (Barnes *et al*. 2001). Levels of HIS at 1 or 2 g/kg or the combination of histidine and CAD (1 g/kg each) reduced bodyweight and feed efficiency at 21 days of age (Macan *et al*. 2006). There was also an increase in the frequency and severity of gizzard erosion and proventriculus ulcers, which indicates that storage temperature is not among the main factors involved in HIS production in stored feedstuffs. It was concluded that stored feedstuff is a product of complex enzymatic activity, including microbial histidine decarboxylase, microbial and endogenous proteolytic enzymes and microbial diamine oxidases, in addition to pH value and oxygen availability.

The impact of protein fermentation on performance and gut health of modern broilers is becoming increasingly relevant in relation to the growing demand for cheaper sources of dietary protein that often have a low digestibility by poultry (Qaisrani *et al*. 2015).

A survey was conducted in Minas Gerais state, Brazil, so as to evaluate different polyamines and BAs in poultry carcasses. Poultry carcass samples were collected from five different regions of the state and none showed a difference in BAs. The values ranged from 3.0 to 4.3 mg/100 g SPD, 5.3 to 5.9 mg/100 g SPM and low concentrations of PUT, CAD, HIS and TYM were detected (<0.28, <1.15, <0.14, <0.25 mg/100 g respectively). Samples submitted to freezing or refrigeration and to federal or state inspection showed no difference among BA values comparing all five regions studied, presenting no risk to consumer health (Assis *et al*. 2015).

There are some possible benefits when BAs are administered orally. For instance, when chicks were fed increasing concentrations of dietary purified PUT (0%, 0.2%, 0.4%, 0.6%, 0.8%, 1.0%), it was verified that excess tissue PUT can be toxic to whole organisms, whereas small, orally administered doses of this metabolite can promote growth (Smith 1990). A similar study was conducted later with SPD when chicks fed diets containing 0.05% supplemental SPD had increased growth after only 1 day of feeding; it was concluded that the toxicity of polyamines increased with molecular weight and charge and, although some growth promotion is possible, the BA content of suspect feedstuffs should be determined with caution before feeding (Smith Mogridge and Sousadias 1996). Also, SPM was found to be more toxic to chicks than were other BAs, evaluated at the same concentrations as mentioned before in the diet (Sousadias and Smith 1995). Contrary, Girdhar Barta Santoyo and Smith (2006) showed that 0.3% of dietary PUT supplementation was beneficial to recover turkey poults from subclinical coccidiosis.

Control measures

Amino acid decarboxylation is the most common pathway of BA synthesis in foods, and aromatic amines may be formed by the action of living organisms (Shalaby 1996). BA concentrations depend on the combined influence of time and temperature; longer time and higher temperatures will lead to greater microbial growth and BA formation and other important factors can be involved, including pH, salt, oxygen availability and competition with other spoilage microorganisms (FAO/WHO 2012).

It has been reported that some BAs such as PUT, SPD and CAD increase with increasing storage time, while pH may increase after 8-day storage of meat at 4°C (Galgano *et al*. 2009). Other authors (Vidal-Carou *et al*. 1990) have reported amines increasing before the pH value increases in meat products. Vidal-Carou *et al*. (1990) evaluated HIS and TYM in pork under room and refrigerated temperatures and found that, at room temperature, both BAs presented higher concentrations, followed by a pH increase in both situations.

Formation of BAs in raw fresh materials generally happens as a consequence of product mishandling. Therefore, BA formation should be avoided by improving food-handling standards through preventive strategy from harvest (foods) or slaughtering (animal) to the consumer (EFSA 2011). Food and feed quality and safety management relying on hazard analysis and critical control points (HACCP) should be regarded as the primary approach to avoid BA risk (Hungerford 2010). Within the HACCP process, good hygienic practices (GHP) and good manufacturing practices (GMP), along with proper cleaning and disinfection procedures, should be carefully implemented from primary production. The objective of GMP in the rendering industry is primarily to prevent animal meals with low quality entering the animal food chain and to produce rendered animal products that are safe and suitable for their purpose. Most of the time, contamination routes are not well identified, which makes the implementation of efficient measures difficult to avoid contamination of raw material (EFSA 2011). As pointed out by the World Renderers Organisation (WRO 2013), renderers around the world operate according to varying degrees of regulation or codes of practice that are generally designed to address country-specific issues.

Many steps during slaughter and dressing procedures are prone to contaminate meat, e.g. hide/feather removal, evisceration, carcass washing, post-mortem inspection, trimming, and further handling in the cold chain (FAO/WHO 2005).

According to the Panel on Biological Hazards (EFSA 2011), the current control of the BA increase in food is based on the following two approaches: first, assurance and maintenance of hygienic quality of raw materials and production process; and, second, the implementation of specific conditions and production techniques so as to inhibit or eliminate microorganisms with aminogenic potential.

The most toxic and relevant BAs for food safety are HIS and TYM, while PUT and CAD potentiate these effects (Alvarez and Moreno-Arribas 2014). Moreover, these BAs are thermostable, not inactivated by thermal treatments used in food processing and preparation and, currently, as pointed out by Alvarez and Moreno-Arribas (2014), only prevention and monitoring strategies enable the control and formation of BAs in food during the production process and along the food chain. The process control should limit microbial cross-contamination in these conditions to as low as practicably achievable, and reflect the contribution in reducing meat-borne risks to human health (FAO/WHO 2005).

As reviewed by Kalač (2014), preservation methods such as gamma-irradiation, even at low doses, is effective in the suppression of PUT and typical BA formation, as compared with control variants, whereas SPD and SPM concentrations are affected in a limited extent only. This was reported for vacuum-packaged trout flesh and sea bream stored in ice. Even a higher efficacy was shown by high-pressure treatment of vacuum-packaged trout flesh.

Active packaging system of fresh meat formulated with essential oil of *R. officinalis* inhibits the growth of BAs and bacteria during storage time. The antibacterial and anti-BA action is due to the biological action of volatile components of *R. officinalis* extracted from the plant by hydrodistillation. The effect was perceived already in 2 days of storage, thus increasing shelf life of fresh meat (Sirocchi *et al*. 2013).

As indicated by FAO/WHO (2009), animal identification systems should begin at the primary-production level, so as to track the meat origin from farm to the abattoir and processor establishment. In this sense, animals should not be loaded for transport to the abattoir when (1) the degree of contamination of their external surface is likely to compromise hygienic slaughter and dressing, and suitable interventions such as washing or shearing are not available, (2) they may compromise the production of meat that is safe and suitable for human consumption, e.g. presence of specific disease conditions or recent administration of veterinary drugs; conditions causing animal stress may exist or arise that are likely to result in an adverse impact on meat safety.

Recently, it was reported that fermentation may be a strategy to minimise BAs in food (Guo *et al*. 2015). In the same way, radiation has also been successfully used (Cardozo *et al*. 2013). Risk-mitigation strategies mentioned include post-harvest chilling, gutting and gill removal, freezing and refrigerated storage, heating to inactivate HIS-producing bacteria, manipulating pH and increasing salt, modified atmosphere and vacuum packaging, high hydrostatic pressure, irradiation, food additives, using decarboxylase-free starter cultures for fermented fish and fishery products, BA degrading bacteria and enzymes, microbiological modelling to select safe storage times under particular conditions and sensory assessment for decomposition (FAO/WHO 2012). HIS formation and SFP can be easily controlled, because risk is best mitigated by applying basic GHP and HACCP system where it is feasible (FAO/WHO 2012).

Final considerations and conclusions

Biogenic amines are thermostable and are not inactivated by heat treatments used in food preparation. Currently, the only strategies for prevention and monitoring of raw materials and final products are considered to be evaluation of BA formation in food during the production process and along the food chain, in addition to cross-contamination control.

Although all protein-rich foods are also subject to conditions that allow microbial activity and BA synthesis, these compounds are considered indicators of bacterial decomposition or putrefaction of animal proteins. BA monitoring in raw materials and products along the food chain is important to assess the relevance of factors that induce their formation and concentration and the need to implement strategies to remediate their presence.

It is essential to broaden the studies on the conditions that potentiate BA synthesis, including the natural constituents of food and deterioration conditions. Additional toxicological studies are needed regarding the effects of high concentrations of BAs to animals when feeding meat and bone meals. Also, the effects on humans consuming meat products derived from these animals need to be elucidated.

There is still controversy about harmful potential of some BAs in the literature. Besides the need for more research on this topic, the current legislation in Brazil and abroad covers, in its normative scope, the maximum allowed concentration of only HIS in fish. Therefore, there is a need to add other BAs of interest in the quality control of several foods and by-products.

Conflicts of interest

The authors declare no conflicts of interest.

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