



Histamine

Histamine: $C_5H_9N_3$,
4-(2-aminoethyl) imidazol
(or imidazol alkylamine)

The human food-borne disease is histamine poisoning caused by ingestion of large doses of preformed histamine in food.

Characteristics and sources of histamine

Main characteristics

Histamine, naturally present in the body, is a neurotransmitter heavily involved in inflammatory and allergic phenomena. It is synthesised by decarboxylation from histidine (an amino acid) and stored mainly in immune cells called mast cells, which release it when stimulated by the presence of a foreign molecule such as an allergen.

Histamine is one of the biogenic amines, compounds that are biologically active on the central nervous system, vascular system and in the stomach. With regard to food, non-volatile biogenic amines are derived from the decarboxylation of amino acids by bacterial and tissue enzymes. Most studies have focused on eight of them (four aliphatic amines: putrescine, cadaverine, spermidine, spermine; one heterocyclic amine: histamine; and three aromatic amines: phenylethylamine, tryptamine, tyramine). Some of these amines are diamines such as histamine, which will be degraded by diamine oxidases, and others are monoamines such as tyramine, which will be degraded by monoamine oxidases.

Sources of histamine

The formation of histamine in food depends on three key factors: the free L histidine content, the presence of bacteria able to synthesise histidine decarboxylase, and the conditions allowing their growth and the production of active enzymes (mainly temperature and pH).

Fish, whose flesh is rich in histidine, is the main food concerned by the formation of histamine. The main fish species associated with high amounts of histidine belong to the following families: *Scombridae* (tuna, mackerel, bonito), *Clupeidae* (sardine, herring), *Engraulidae* (anchovy), *Coryphaenidae* (dolphinfish), *Pomatomidae* (bluefish), *Scombrosidae*.

In fish, the main bacteria responsible for histamine formation are enterobacteria. The ability of mesophilic enterobacteria (*Enterobacter aerogenes*, *Klebsiella pneumoniae*, etc.) to produce histamine is well documented. The role of psychrotrophic bacteria in the production of histamine in refrigerated fishery products has been shown more recently. Strains of *Morganella morganii* isolated from tuna can produce high concentrations of histamine at temperatures of between 2 and 5°C. *Photobacterium phosphoreum* and *Pseudomonas fluorescens*, psychrotrophic bacteria naturally present in fish, are able to produce histamine at 5°C.

The formation of biogenic amines may also occur during the manufacture of fermented foods (cheese, alcoholic beverages, delicatessen meats and vegetables). The proteolytic activity during fermentation results in the release of histidine.

In dairy products, particularly cheese, but also in fermented beverages such as wine or cider, it appears to be gram-positive lactic-acid bacteria that are mainly involved in the production of histamine. Many species are able to decarboxylate histidine to histamine, but those most frequently cited in the literature are the lactobacilli, leuconostoc, enterococci and streptococci. For cheese, commensal flora in milk, especially enterobacteria, also appear to be involved in the production of histamine, as well as other biogenic amines (tyramine, cadaverine, etc.).

Transmission routes

Humans become infected by consuming foods containing high amounts of histamine (see dose-effect and dose-response relationships).

Human food-borne illness

Nature of the disease

The ingestion of high doses of histamine leads to the saturation of digestive enzymes catabolising histamine, and poisoning by intestinal absorption of unmetabolised histamine. The ingestion of lower doses of histamine in combination with other biogenic amines present in food can produce the same effect by competitive inhibition of histamine-degrading enzymes.

The main symptoms of histamine poisoning (or pseudo-food allergy syndrome) are related to the vasodilator effect of histamine. Dilation of blood capillaries causes haemoconcentration phenomena (Table 1).

Susceptible population group(s) ⁽¹⁾

There is great individual variability in the level of tolerance to histamine, which is explained by genetic predispositions concerning the activity of certain enzymes, gastrointestinal diseases or medical administration of enzyme inhibitors.

Individuals treated with isoniazid or other treatments interfering with histamine metabolism are more likely to develop histamine poisoning.

It has been estimated that 1% of the population is intolerant to histamine, 80% of whom are middle-aged.

Dose-effect ⁽²⁾ and dose-response ⁽³⁾ relationships

The threshold dose causing overload of the detoxification systems is very difficult to determine. It depends on many factors and individual variability. The European Food Safety Authority (EFSA) has examined a limited number of studies reporting dose-response relationships for food histamine in healthy volunteers and susceptible individuals. No adverse effects were observed in healthy volunteers exposed to a dose between 25 mg to 50 mg per person per meal. Much lower doses can cause poisoning in people intolerant to histamine.

On the basis of epidemiological data, it is accepted that histamine levels in fish below 50 mg/kg have no toxic effect. From 50 to 200 mg/kg, the fish presents a potential risk of toxicity. From 200 to 1,000 mg/kg, the fish has a probable risk of toxicity. Above 1,000 mg/kg, the fish is regarded as toxic and unsafe for consumption. A Danish study reported that in 80% of cases of histamine poisoning associated with fish, the products involved had levels greater than 500 mg/kg.

Cheeses that have been implicated in histamine poisoning had histamine levels greater than 850 mg/kg.

Data from outbreaks do not take into account the synergistic role played by other compounds than histamine (presence of other biogenic amines in the food), or the presence of inhibitors of detoxification enzymes (mainly alcohol and drugs) that enable the histamine to exercise its toxic effects.

Epidemiology

Histamine poisoning is monitored through the mandatory notification of foodborne outbreaks. Histamine poisoning is the leading cause of foodborne outbreaks associated with the consumption of fishery products in France. Since 1997, the number of reported outbreaks of histamine poisoning has varied from year to year but no downward trend has been observed. In France, between 2005 and 2009, 259 outbreaks of histamine poisoning were reported to the French Institute for Public Health Surveillance (InVS). The causal role of histamine was confirmed for 81 of these outbreaks (513 cases), which were overwhelmingly related to fish, and to tuna in particular (67/81).

In addition to the cases involving fish, cases of histamine poisoning associated with cheese (emmental, cheddar, gruyere) have also been identified. In 2006, an outbreak involving grated cheese containing histamine concentrations greater than 900 mg/kg was reported in Spain. These cases are mostly sporadic and rare considering the large-scale production of this type of cheese.

Role of foods

Main foods to consider

Among the fish species associated with a large amount of histidine, those belonging to the family *Scombridae* (tuna, mackerel) are the most common source of histamine poisoning (hence the term Scombroid Fish Poisoning). Hygiene and preservation practices of fish also determine contamination and multiplication of bacteria capable of synthesising histidine decarboxylase. Tuna caught in warm seas has an internal temperature at capture that is higher than that of other fish species and is also particularly sensitive to temperature fluctuations during handling.

In addition, fish with high amount of histidine which have undergone enzyme maturation treatment ⁽⁴⁾ in brine (e.g. salted anchovies, products based on salted anchovies, fish sauce) may have higher histamine levels.

The production of histamine in cheese concerns in particular those which have undergone a long ripening period (roquefort, gruyere, cheddar, gouda, edam, emmental). The wide variability in amine levels depends on many factors: biochemical characteristics, composition of the microbial flora in milk, and ferments added, as well as their dynamics during ripening (duration).

(1) Susceptible population group: people with a higher than average probability of developing symptoms of the disease, or severe forms of the disease, after exposure to a foodborne hazard [definition used in ANSES data sheets].

(2) Relationship between the dose (the quantity of microbial cells ingested during a meal) and the effect on an individual.

(3) For a given effect, the relationship between the dose and the response, i.e., the probability of this effect appearing in the population.

(4) Enzyme maturation: This is a long operation during which the fish acquires, in the presence of high salt concentrations, a characteristic flavour and texture under the action of endogenous (fish tissue and digestive) and bacterial enzymes.

Table 1. Characteristics of histamine poisoning

Mean incubation period	Target population	Main symptoms	Duration of symptoms	Duration of the contagious period (shedding)	Complications	Asymptomatic forms
1h (from a few minutes to a few hours)	The entire population All age groups combined	<u>First symptoms:</u> facio-cervical redness, skin rash, facial swelling, hot flushes, burning sensation in the throat, peppery taste in the mouth, itching, tingling of the skin, headache, heart palpitations, dizziness. <u>Secondary symptoms (gastrointestinal):</u> nausea, stomach pain, vomiting, diarrhoea.	3h (exceptionally several days in the most severe cases)	Not applicable	Anaphylactic shock	No

Using data from the scientific literature, survey results and consumption data from different Member States, EFSA's Panel on Biological Hazards (BIOHAZ) has issued the following conclusions on the food categories to consider with regard to histamine:

- based on the mean content of histamine, the food safety relevance of the considered food categories can be ranked in following decreasing order: salted anchovies, fish sauces, fermented vegetables, cheese, other fish and fishery products (fresh, frozen or canned unfermented fish) and fermented sausages;
- based on the consumer exposure, the food safety relevance of the considered food categories can be ranked in following decreasing order: fish and fishery products, fermented sausages, cheese, fish sauces and fermented vegetables. In the absence of consumption data, salted anchovies were not included in the exposure calculation.

Inactivation treatments in industrial environments

Histamine is a thermostable compound.

Monitoring in foods

In unfermented food products, the occurrence of biogenic amines is essentially the result of undesirable microbial activity. They can be indicators of fish or meat spoilage, since histamine, putrescine and cadaverine levels usually increase during the decomposition of these products.

Regulation (EC) No 2073/2005 as amended defines a safety criterion relating to histamine for two food categories:

- fishery products from fish species associated with a high amount of histidine ($n^{(5)}=9$, $c=2$, $m^{(6)}=100$ mg/kg, $M=200$ mg/kg);
- fishery products which have undergone enzyme maturation treatment in brine, manufactured from fish species associated with a high amount of histidine ($n=9$, $c=2$, $m=200$ mg/kg, $M=400$ mg/kg).

These limits apply to fish species from the following families: *Scombridae*, *Clupeidae*, *Engraulidae*, *Coryphaenidae*, *Pomatomidae*, *Scombresosidae*.

To date, there are no regulations applicable to other products, specifically cheese.

Various methods can be used to detect potentially high levels (TLC or thin layer chromatography, immuno-enzymatic techniques), and are considered as sorting methods. The method used in Regulation (EC) No 2073/2005 (currently undergoing standardisation) as amended is a high-performance liquid chromatography (HPLC) method, which allows a quantitative determination of biogenic amines.

Recommendations to operators

• Fishery products

Histamine is a thermostable compound that can persist in canned foods. The only effective means of prevention is to limit both contamination and microbial growth through the implementation of good hygiene practices: rapid evisceration and refrigeration (<2°C), compliance with the cold chain in particular for fish caught in warm seas, as is the case with tuna.

• Dairy products

Prevention also involves compliance with hygiene measures, control of the microbiological quality of milk intended for cheese production, selection of starter strains without histidine decarboxylase activity and compliance with the cold chain requirements for finished products.

Domestic hygiene

Recommendations to consumers

- Comply with hygiene rules and maintain the cold chain.

References and links

General references

- ANSES 2012. ANSES Opinion of 17 January 2012 on the request for scientific and technical support on the definition of fishery products which have undergone enzyme maturation to which a criterion for histamine applies.
<http://www.anses.fr/Documents/MIC2010sa0261.pdf>
- Bartholomew BA, Berry PR, Rodhouse JC, Gilbert RJ and Murray CK, 1987. Scombrototoxic fish poisoning in Britain: features of over 250 suspected incidents from 1976 to 1986. *Epidemiol. Infect.* 99, 775-782.
- Dalgaard P, Emborg J, Kjolby A, Sorensen N and Ballin N, 2008. Histamine and biogenic amines - formation and importance in seafood. In: *Improving seafood products for the consumer*. Borrensen T, ed. Woodhead Publishing Ltd., Cambridge, UK.
- EFSA Panel on Biological Hazards (BIOHAZ); Scientific Opinion on risk based control of biogenic amine formation in fermented foods. *EFSA Journal* 2011;9(10):2393.
<http://www.efsa.europa.eu/en/efsajournal/doc/2393.pdf>
- Emborg J, Dalgaard P and Ahrens P, 2006. *Morganella psychrotolerans* sp. nov., a histamine producing bacterium isolated from various seafoods. *Int. J. System. Evolut. Microbiol.* 56, 2473-2479.
- Linares DM, Martín MC, Ladero V, Alvarez MA, Fernández M, 2011. Biogenic amines in dairy products. *Critical Reviews in Food Science and Nutrition* 51, 7, 691-703.
- Maintz L and Novak N, 2007. Histamine and histamine intolerance. *American J. Clin. Nutr.* 85, 5, 1185-1196.

Useful links

- InVS : <http://www.invs.sante.fr/surveillance/tiac>
- National Reference Laboratory (NRL) for histamine: ANSES – Boulogne-sur-Mer Laboratory for Fishery Products.

(5) n: number of units in the sample; c: maximum number of results that can have values between m and M.

(6) m: concentration limit corresponding to a satisfactory quality; M: concentration limit corresponding to an unsatisfactory quality.