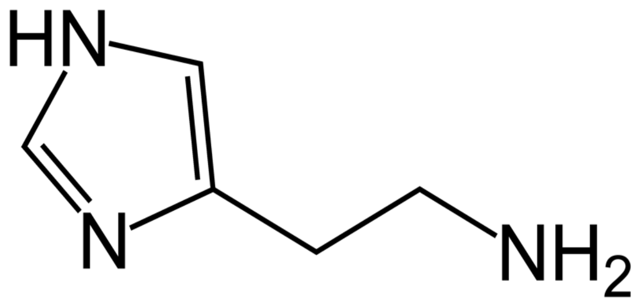
Histamine

Histamine: $C_5H_9N_3$

2-(1*H*-imidazol-5-yl)ethanamine

CAS No. 51-45-6



Semi-structural formula of histamine

The human foodborne illness known as histamine poisoning is caused by ingestion of histamine preformed in food by micro-organisms. When food poisoning occurs after eating scombroid fish, for example tuna, mackerel or bonito, it is called scombroid fish poisoning.

Characteristics and sources of histamine

Main microbiological characteristics

Histamine is a biogenic amine naturally occurring in the body. It is a neurotransmitter that interacts with four types of receptors present in smooth muscles, the stomach, the heart, nerve fibers, and immune and inflammatory cells. Histamine is involved in many physiological functions, as well as in inflammatory and allergic processes. It is synthesised in the body by enzymatic decarboxylation from histidine, and is mainly stored in immune cells called mast cells, which release it when activated by a pathogen or allergen.

Other biogenic amines such as putrescine, cadaverine, spermidine, spermine, tryptamine, tyramine and phenylethylamine may be found in food and cause similar effects to histamine, or potentiate effects when several of them are present.

Sources of histamine

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

The formation of histamine mainly occurs in fish whose flesh is rich in histidine, due to naturally present bacteria, particularly mesophilic enterobacteria, such as *Enterobacter aerogenes, Klebsiella pneumoniae, Morganella morganii*, *Serratia marcescens* and *Hafnia alvei*. *Morganella morganii* strains isolated from tuna can produce high concentrations of histamine at temperatures between 2°C and 5°C. Psychrotrophic bacteria such as *Photobacterium phosphoreum* and *Morganella psychrotolerans* present in refrigerated fishery products have also been shown to play a role. The lactic acid bacterial genus *Carnobacterium* and species *Clostridium perfringens* are also known to be implicated.

Histamine may also be formed during the manufacture of fermented foods, including cheese, alcoholic beverages, delicatessen meats and plant-based foods. Microbial proteolytic activity during fermentation releases histidine, which is a precursor of histamine. Lactic acid bacteria appear to be mainly involved in the production of histamine in dairy products, particularly cheese, fermented meat products and fermented beverages such as wine or cider. Many bacterial species are able to decarboxylate histidine to histamine, especially lactobacilli, leuconostocs, enterococci and streptococci. In the case of cheese, microbial communities in milk, particularly enterobacteria, appear to be involved in the production of histamine and other biogenic amines, such as tyramine and cadaverine. It should be noted, on the other hand, that certain micro-organisms in fermented products, such as *Lactobacillus casei, Arthrobacter* and *Brevibacterium* may feed on and break down histamine.

Transmission routes

Histamine poisoning in humans occurs following consumption of foods containing elevated amounts of histamine.

Human foodborne illness

Nature of the disease

Histamine-degrading enzymes in the body may become saturated when highly contaminated foods are ingested. The main symptoms of histamine poisoning – or pseudoallergic syndrome – relate to histamine's vasodilator effect (**Table 1**).

Table 1: Characteristics of the illness

Mean incubation period	Main symptoms	Duration of symptoms	Complications
1 hr (from a few minutes to a few hours)	Wide range of initial symptoms: redness of the face and neck, skin rash, swelling of the face, hot flushes, burning sensation in the throat, peppery taste in the mouth, skin itching, skin tingling or stinging, headache, heart palpitations, dizziness. Secondary symptoms, gastrointestinal in nature: nausea, stomach pain, vomiting, diarrhoea.	3 hr (exceptionally several days in the most severe cases)	Anaphylactic shock

Susceptible population group:[1] There is great individual variability in the level of tolerance to histamine, which is explained by genetic predispositions with regard to the activity of certain enzymes, gastrointestinal diseases or iatrogenic effects associated with medical administration of enzyme inhibitors.

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

Dose-effect[2] and dose-response[3] relationships

The threshold dose causing overload of the detoxification systems depends on multiple factors (individual variability). According to FAO/WHO, the histamine dose corresponding to a 10% probability of intoxication (BMDL[4]) is 50 mg in individuals intolerant to histamine.

This BMDL is supported by epidemiological data since no cases of intoxication associated with histamine levels below 50 $mg.kg^{-1}$ in fish have been reported. A Danish study reported that in 90% of cases of histamine poisoning associated with fish, the products involved had histamine levels greater than 500 $mg.kg^{-1}$. Most outbreaks are linked to levels greater than 1000 $mg.kg^{-1}$.

Cheeses implicated in histamine poisoning had histamine levels greater than 850 $mg.kg^{-1}$.

These data from clustered cases do not take into account the additive/synergistic role played by other biogenic amines or the presence of inhibitors of detoxification enzymes (mainly alcohol and drugs).

Epidemiology

Histamine poisoning is monitored through the mandatory notification of foodborne illness outbreaks. Between 2008 and 2019, 11 outbreaks of foodborne illness were confirmed on average each year, causing an average of 67 cases per year. Histamine poisoning is the leading cause of foodborne illness associated with the consumption of fish in France.

Between 2006 and 2015, the foods involved were mainly fish, causing 93% of outbreaks of histamine-induced foodborne illness (with 87% caused by tuna). Mixed dishes such as ravioli, moussaka and mixed salads, and cheeses such as Emmental were associated with 6% of these outbreaks.

Table 2: French epidemiological data on outbreaks of foodborne illness caused by histamine in France – updated March 2021

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Outbreaks of confirmed histamine-induced foodborne illness[1]												
Outbreaks (%[2])	17 (7%)	15 (7%)	4 (2%)	9 (4%)	13 (6%)	3 (2%)	7 (3%)	15 (5%)	11 (3%)	17 (6%)	11 (3%)	8 (2%)
Cases (%)	83 (3%)	71 (3%)	19 (1%)	32 (1%)	62 (3%)	10 (0%)	36 (1%)	135 (4%)	81 (2%)	136 (3%)	75 (2%)	41 (1%)
Outbreaks of suspected histamine-induced foodborne illness[3]												
Outbreaks (%)	34 (8%)	33 (7%)	23 (5%)	24 (4%)	28 (4%)	26 (3%)	25 (3%)	44 (5%)	31 (3%)	35 (4%)	23 (2%)	28 (3%)
Cases (%)	147 (3%)	137 (2%)	98 (2%)	106 (2%)	91 (1%)	144 (2%)	115 (2%)	190 (3%)	133 (2%)	148 (2%)	213 (3%)	181 (2%)

[1] Outbreaks in which histamine levels consistent with clinical signs were detected in the food consumed by sick individuals.
[2] % in relation to the total number of cases or outbreaks with specific agents.
[3] Outbreaks where histamine was not found or screened for. Histamine poisoning was then suspected from the mean incubation period and highly characteristic signs in sick individuals.

[1] 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 histamine ingested during a meal) and the effect on an individual.

[3] For a given effect, the relationship between dose and response, i.e. the probability of this effect occurring in the population.

[4] The BMDL is the lower bound of the 95% confidence interval for the benchmark dose (BMD). This is the dose corresponding to a specified level of response obtained by modelling the dose–response relationship from experimental or epidemiological data.

Role of food

Main foods to consider

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) and *Scombresocidae* (saury). Tuna and mackerel are the most common sources of histamine poisoning (hence the term scombroid fish poisoning). Good hygiene practices, especially during evisceration, and preservation conditions are major determinants of contamination and the growth 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 particularly sensitive to temperature fluctuations during handling. Enzyme maturation[5] in brine, e.g. for salted anchovies, products based on salted anchovies or fish sauce, can also result in high levels of histamine.

The production of histamine in cheeses is encouraged by long ripening periods (e.g. in Roquefort, Gruyère, Cheddar, Gouda, Edam and Emmental). Amine levels are highly variable and depend on many factors, including biochemical characteristics, the composition of microbial communities in milk and ferments, their dynamics during ripening and maturation duration.

Novel foods such as insects, which are known to have caused histamine poisoning in Asia, should be given special attention.

According to the European Food Safety Authority's (EFSA) Panel on Biological Hazards (BIOHAZ), the food categories to consider in terms of the health risk posed by histamine can be ranked in decreasing order by their average level of histamine: salted anchovies, fish sauce, fermented vegetables (e.g. sauerkraut), cheese, other fish and fishery products (e.g. fresh, frozen or tinned unfermented fish) and fermented sausages. Based on consumer exposure from consumption data provided by different Member States, this order can be changed to: fish and fishery products, fermented sausages, cheese, fish sauce 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, and its concentration in the main food categories to consider cannot be reduced by industrial heat treatments.

Controlling histamine should rely on maintaining specific conditions and applying a series of principles to prevent the formation of histamine in products high in histidine. One control method is to use common inactivation treatments to reduce the level of histamine-forming bacteria, including inhibition by chilling above or below 0°C.

Food biopreservation methods that use micro-organisms to inhibit the growth of histamine-producing bacteria can help control the formation of biogenic amines in fishery products.

Monitoring in food

The occurrence of biogenic amines in unfermented food products is essentially the result of undesirable microbial activity. Biogenic amines can be indicators of fish or meat spoilage as the levels of biogenic amines usually increase in decomposing fish and meat products.

Regulation (EC) No 2073/2005 as amended defines safety criteria regarding histamine for three food categories:

- fishery products from fish species associated with a high amount of histidine (n[8]= 9, c=2, m[9]= 100 mg.kg^{-1}, M=200 mg.kg^{-1});
- 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^{-1}, M=400 mg.kg^{-1}).
- fish sauce produced by fermentation of fishery products (n=1, c=0, m=M=400 mg.kg-1).

The limits for the first two categories apply to fish species from the following families: *Scombridae*, *Clupeidae*, *Engraulidae*, *Coryfenidae*, *Pomatomidae* and *Scombresocidae*.

Other foods are not subject to any regulations at this time.

Various analytical methods such as thin-layer chromatography and enzyme immunoassay methods can be used to detect high levels of histamine. The ISO 19343:2017 standard adopted in amended Regulation (EC) No 2073/2005 specifies a high performance liquid chromatography method for quantifying biogenic amines.

[5] Enzyme maturation is a long process undergone by fish during which it acquires, in the presence of high salt concentrations, a characteristic flavour and texture as a result of the action of endogenous enzymes in the tissue and digestive system of fish, as well as bacterial enzymes.

[6] D is the time required to divide by 10 the population of the microbiological hazard initially present.

[7] D_{10} is the dose (in kGy) needed to reduce a population to 10% of its initial value.

[8] n = number of units comprising the sample; c = maximum number of sample units giving values between m and M.

[9] m: concentration limit for satisfactory quality; M: concentration limit for unsatisfactory quality.

Recommendations to operators

Fishery products

Histamine is a thermostable compound that can persist in tinned foods. The only means of prevention is to limit both contamination and microbial growth through the implementation of good hygiene practices, such as rapid evisceration and chilling to below 2°C, and protecting the integrity of the cold chain.

This is particularly important for tuna, which is typically caught in warm seas.

Dairy products

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

Domestic hygiene

Recommendations to consumers

Consumers should comply with good hygiene practices and protect the integrity of the cold chain.

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. https://www.anses.fr/fr/system/files/MIC2010sa0261.pdf

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Dalgaard P, Emborg J, Kjolby A, Sorensen N & Ballin N, 2008. Histamine and biogenic amines - formation and importance in seafood. In: Improving seafood products for the consumer. Borrensen T, ed. Cambridge, UK, Woodhead Publishing Ltd.

EFSA Panel on Biological Hazards (BIOHAZ), 2011. Scientific Opinion on 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

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FAO/WHO, 2013. Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products. Meeting report. https://apps.who.int/iris/handle/10665/89216

Moniente, M, García-Gonzalo, D, Ontañón, I, Pagán, R & Botello-Morte, L. Histamine accumulation in dairy products: Microbial causes, techniques for the detection of histamine-producing microbiota, and potential solutions. Compr Rev Food Sci Food Saf. 2021; 20: 1481–1523. https://doi.org/10.1111/1541-4337.12704

Useful links

Santé Publique France: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-infectieuses-d-origine-alimentaire/toxi-infections-alimentaires-collectives

National Reference Laboratory (NRL) for histamine: ANSES – Laboratory for Food Safety in Boulogne-sur-Mer. https://www.anses.fr/fr/content/laboratoire-national-de-r%C3%A9f%C3%A9rence-histamine