# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## Discussion paper on histamine in cheese

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### Introduction

1. Histamine poisoning is a well-established phenomenon that often arises from the consumption of food, particularly fish, which has high levels of histamine as a result of bacterial spoilage. Histamine can also be present as a consequence of fermentation in foods such as cheese or sausage, with reports of high levels of histamine in cheese becoming increasingly common. While there is specific legislation regarding histamine levels in fish, there is currently no legislation covering histamine levels in other foods. Therefore, when responding to incidents and enquiries involving cheese, the Food Standards Agency (FSA) gives advice based on case reports of histamine poisoning in the literature, and on the European Commission's (EC) action level for histamine in fish (200mg/kg), this level is a useful starting point as the portion sizes for fish and cheese are relatively comparable.

2. In recent years, the FSA has also begun to include an acute reference dose (ARfD) for histamine that was established by the European Food Safety Authority's (EFSA) Panel on Biological Hazards (BIOHAZ) (EFSA, 2011). Typically, when providing advice, the FSA models various consumption scenarios and compares them to the ARfD to establish the level of risk to the consumer. When performing this modelling, the FSA takes into account the type of cheese involved, likely consumers and the expected quantity to be consumed. Particular attention is paid to whether the product is likely to be consumed by children, as FSA incident data suggest that children may be particularly sensitive to high levels of histamine.

3. This discussion paper provides background information on the issue of histamine in food as well as details of the approach currently taken by the FSA when advising on incidents involving high levels of histamine in cheese, of some of the complicating factors such as potentiation by other biogenic amines, and on the EFSA opinion on biogenic amines in fermented foods.

### Background

4. Biogenic amines, such as histamine, are nitrogenous organic bases of low molecular weight. They may be classified as heterocyclic, aliphatic or aromatic according to their chemical structure, and divided into monoamines or diamines

depending on the number of amine groups present. Histamine is classified as a heterocyclic diamine (EFSA, 2011). See Figure 1 for the structures of some biologically and toxicologically important biogenic amines.

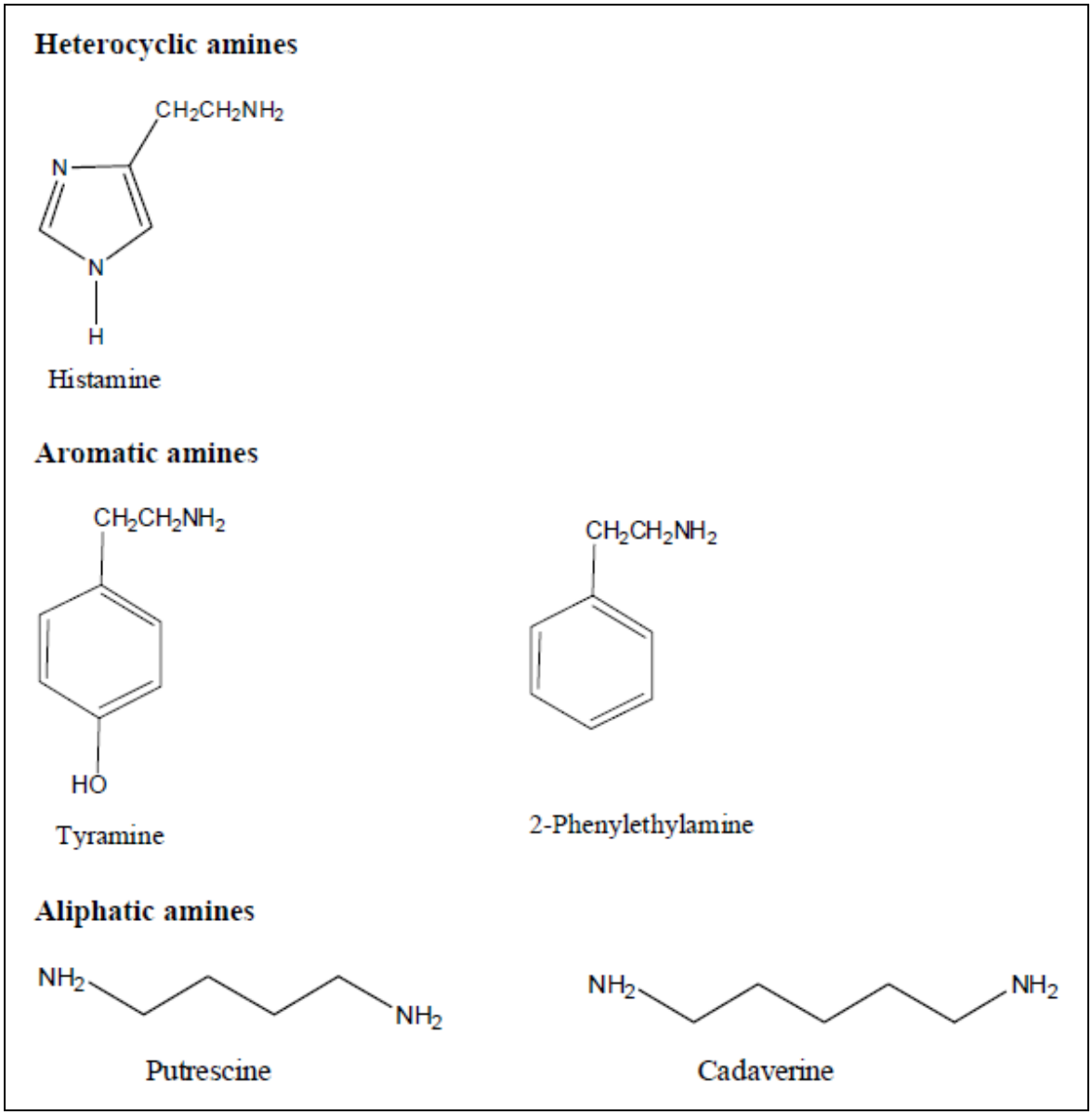


Figure 1. Structures of the biogenic amines histamine, tyramine, 2-phenylethylamine, putrescine, and cadaverine (reproduced from EFSA, 2011)

5. Biogenic amines occur naturally in humans and are involved in a number of important physiological processes. Histamine acts as both a local hormone and a neurotransmitter. It is involved in synaptic transmission, blood pressure control, gastric acid secretion, allergic reactions, immune responses, and cell growth and differentiation (EFSA, 2011). Histamine exerts these effects by binding to receptors ($H_1$ – $H_4$) that are present on the membranes of target cells found throughout the body, most notably in the respiratory, cardiovascular, gastrointestinal, haematological, and immunological systems (Lehane and Olley, 1999).

**Biogenic amines in food**

6. In food, biogenic amines are typically formed by the bacterial decarboxylation of amino acids. The primary biogenic amines present in food are histamine, tyramine, putrescine, cadaverine, and phenylethylamine; these are formed from the decarboxylation of histidine, tyrosine, ornithine, lysine, and phenylalanine, respectively. Biogenic amines are thermo-stable and are not inactivated by heat treatments used in food processing or preparation (EFSA, 2011).

7. Biogenic amine formation in food is highly dependent on several factors. The most important of these factors are the availability of free amino acids, the presence of bacteria that are able to synthesise amino acid decarboxylases (histidine decarboxylase in the case of histamine), and conditions that favour the growth of these bacteria, and support the synthesis and activity of amino acid decarboxylases (EFSA, 2011 and Stratton, Hutkins and Taylor, 1991).

8. The conditions needed to encourage histamine formation in food largely depend on the strain of decarboxylase-producing bacteria that is present, and therefore may vary considerably. In general, the biogenic amine formation rate increases with temperature and is minimised at low temperatures due to the inhibition of bacterial growth, and a reduction in proteolytic and decarboxylase activities. The optimum temperature for biogenic amine formation has been reported to be between 20 and 37°C. While storage at low temperatures (<20°C) should reduce biogenic amine formation, some strains of bacteria have been found to actively contribute to biogenic amine accumulation at high rates during storage below 5°C (EFSA, 2011).

9. Other influential factors include pH, salt content and the availability of oxygen. A low pH can inhibit bacterial growth but can also stimulate bacteria to produce decarboxylases as part of their defence mechanism against the acidity. A high salt content can inhibit the activity of the decarboxylases produced by some strains of bacteria but enhance the activity of those produced by some other strains. Similarly, the availability of oxygen can reduce the production of biogenic amines by some bacterial strains or encourage their production by others (EFSA, 2011).

10. Cases of histamine poisoning typically occur following the consumption of spoiled or bacterially contaminated fresh, frozen, or smoked fish, or canned fish products (EFSA, 2011). In these cases, spoilage may not necessarily be organoleptically evident (Stratton, Hutkins and Taylor, 1991). Histamine formation in fish and fish products is related to the histidine content of the fish; therefore, fish of the Scombridae family, such as tuna and mackerel, which contain abundant amounts of histidine, are frequently implicated in cases of fish-related histamine poisoning. The main bacteria responsible for histamine formation in fish are members of the Enterobacteriaceae family; these bacteria may have been present in the marine environment or introduced during food handling. Prolonged storage of fish at ‘abuse temperatures’ (temperatures above which the fish should be stored) can significantly increase histamine production (Lehane and Olley, 1999).

11. The Microbiological Criteria Regulation (EC) 2073/2005 contains criteria relating to histamine in fishery products. These regulations stipulate that the critical levels of histamine are different according to whether the products have undergone

enzyme maturation treatment in brine or not. For the enzyme matured products, the critical concentration of histamine is 200 mg/kg, and for simple fish products is 100 mg/kg, based on the average of nine samples. Of the nine samples no two can be higher than 100 mg/kg (and 200 mg/kg) but none can be higher than 200 mg/kg (or 400 mg/kg for enzyme matured products) (EC, 2005; Hungerford, 2010).

12. After fish, cheese (particularly ripening cheese) is the next most commonly implicated food item associated with histamine poisoning (EFSA, 2011; Stratton, Hutkins and Taylor 1991). The formation of histamine in cheese, and some other fermented foods, is a simultaneous consequence of fermentation by lactic acid bacteria rather than spoilage due to bacterial contamination. Microorganisms that have been associated with histamine production in fermented foods include strains of *Oenococcus oeni*, *Pediococcus parvalus*, *Pediococcus damnosus*, *Leuconostoc* species, *Tetragenococcus* species, *Lactobacillus saerimneri* 30a, *Lactobacillus hilgardii*, *Lactobacillus buchnerii*, and *Lactobacillus curvatus*. It has been suggested that the activity of bacterial histidine decarboxylases can continue even after bacterial autolysis (EFSA, 2011).

13. The characteristics of some types of cheese can make them more susceptible to the accumulation of high concentrations of histamine. These characteristics include, but are not limited to, long maturation periods and the use of unpasteurised milk, acid curds, or starter cultures that contain microorganisms known to produce histamine. It is important to note that these characteristics do not always result in high histamine concentrations and may be desirable characteristics of the cheese; this makes it particularly difficult to determine the specific conditions that result in high histamine concentrations, and to establish procedures that could prevent high concentrations. Annex A contains tabulated information from the literature and monitoring programmes on the levels of histamine in different types of cheese.

14. Another factor that complicates the issue of histamine in food is the occurrence of bacterial “hotspots” where formation rates may be elevated; these result in an uneven distribution of histamine throughout the food and may distort analytical results by indicating that a very high level of histamine is present. Hotspots are a well-recognised issue in fish that mean that histamine concentrations may vary considerably between fish in the same batch and even in different parts of the same portion of fish. Currently, it is not clear whether hotspots also occur in cheese, but it is something that must be taken into consideration when assessing analytical results.

### *Current testing methods*

15. Presently, high-performance liquid chromatography (HPLC)-based methods are the only methods which reliably and with high sensitivity can simultaneously quantify concentrations of all biogenic amines in fermented food, therefore, are most suitable for analysis of fermented foods. Currently, there is insufficient information in order to recommend detailed monitoring schemes and methods. Monitoring of biogenic amine concentrations in fermented food during the production process could be used as one of the parameters for the process hygiene assessment. Monitoring of raw materials and products at multiple points along the food chain is necessary to evaluate the relevance of various factors contributing to biogenic amine formation and accumulation in fermented foods (EFSA, 2011).

16. The FSA have been informed, anecdotally, that some of the larger cheese manufacturers and supermarket chains have set rejection limits of 500 mg/kg for histamine in cheese. The implementation of limits or monitoring such as this is less likely to be undertaken by smaller cheese manufacturers as testing for histamine is relatively expensive. It is anticipated that more details on histamine rejection limits and monitoring practices in the industry will be available at a later date.

## Histamine in the body

### *Metabolism*

17. Dietary amines are able to cross the intestinal epithelium passively; however, a barrier in the intestinal mucosa that is formed of amine oxidases prevents them from doing so, and thus limits their access to their sites of action. In healthy individuals, metabolism of dietary biogenic amines by these amine oxidases is normally a rapid process (Fogel, Lewinski and Jochem, 2007).

18. The major histamine metabolising enzymes are diamine oxidase (DAO) (also known as histaminase) and histamine *N*-methyltransferase (HNMT); the products of both inactivation pathways do not possess the same physiological properties as histamine (Taylor, 1987).

19. DAO is the body's first barrier against dietary histamine. It is primarily located in the small intestine, where it is continuously produced by intestinal epithelial cells and secreted into the lumen from plasma membrane-associated vesicular structures. DAO metabolises histamine in the extracellular space by oxidative deamination to form imidazole acetaldehyde, this is then metabolised by aldehyde dehydrogenase to form imidazole acetic acid (Wankte, 2015; EFSA, 2011; Maintz and Novak, 2007). DAO is also found in the liver, kidneys, white blood cells, and the placenta. In pregnant women, blood levels of DAO are 100-300 fold higher than those in non-pregnant women (Wantke. 2015).

20. HNMT is the body's second line of defence against dietary histamine: when histamine is absorbed despite the efforts of intestinal DAO, it is transported to the liver where HNMT degrades it. HNMT is a cytosolic protein that metabolises histamine in the intracellular space by ring methylation to form N-methylimidazole acetic acid via N-methylhistamine and N-methylimidazole acetaldehyde. HNMT is widely expressed throughout the body, with high expression reported in the kidneys, lymph nodes, eyes and lungs as well as the liver. Due to its widespread expression, it has been proposed that the main function of HNMT is to degrade endogenous histamine (Wantke, 2015; EFSA, 2011). The plasma membrane-associated organic cation transporters OCT-2 and OCT-3 have been suggested to facilitate the metabolism of histamine by HNMT (Fogel, Lewinski and Jochem, 2007).

### *Toxicology*

21. DAO and HNMT are generally sufficiently active to metabolise the levels of histamine that are normally present in the diet (Taylor, 1987). However, consumption of food or beverages containing particularly high concentrations of histamine,

especially in the presence of factors that increase an individual's sensitivity to histamine, may overwhelm these pathways and result in histamine poisoning (see paragraphs 35-44) (EFSA, 2011).

22. The incubation period for histamine poisoning ranges from a few minutes to several hours; the symptoms generally only last for a few hours and can be treated with antihistamines if necessary (EFSA, 2011). The symptoms of poisoning relate to histamine's physiological effects: it can cause the dilatation of peripheral blood vessels, capillaries and arteries which can induce hypotension, flushing and headache; the contraction of smooth muscle resulting in abdominal cramps, diarrhoea and vomiting if this occurs in the gastrointestinal tract; and it can stimulate sensory and motor neurons causing the pain and itching associated with urticarial lesions (Stratton, Hutkins and Taylor, 1991). Other symptoms can include nasal secretion, bronchospasm, asthma, tachycardia, extrasystoles, oedema of the eyelids and pruritus (EFSA, 2011). A review of 258 suspected cases of histamine poisoning (following the consumption of spoiled fish), that occurred in Britain from 1976-1986, noted that the most consistently reported symptoms were rash, diarrhoea, flushing, and headache (Bartholomew *et al*., 1987).

23. Putrescine and cadaverine have been identified as potentiators of histamine toxicity. These biogenic amines are capable of inhibiting both the intestinal and extra-intestinal metabolism of histamine, resulting in a greater proportion of dietary histamine crossing the intestinal mucosal barrier and circulating around the body, and a decreased rate of inactivation at extra-intestinal sites. There is currently insufficient information to determine the concentrations of putrescine and cadaverine that potentiate the effects of histamine (EFSA, 2011). Ultimately, histamine potentiation by putrescine and/or cadaverine may not be a significant factor when very high levels of histamine are ingested; however, the presence of these biogenic amines may be the reason that histamine ingestion via food appears to be more toxic than ingestion via an aqueous liquid (i.e. under experimental conditions) (Taylor, 1987; Stratton, Hutkins and Taylor, 1991).

24. It is difficult to make an estimate of the occurrence of histamine poisoning as the disease is thought to be greatly underreported due to its relatively mild nature, and as there is significant potential for misdiagnosis as food allergy (Stratton, Hutkins and Taylor, 1991). However, reports to the FSA of incidents involving histamine in cheese are becoming increasingly common (see Annex B). This may be due to an increase in the consumption of cheese with high levels of histamine, a general increase in the levels of histamine in cheese, or an increase in awareness of the symptoms of histamine poisoning.

25. Concerns have been raised by industry that efforts to reduce the salt content of cheese could lead to increased bacterial growth and therefore increased levels of histamine formation. Currently, the evidence surrounding salt content and histamine formation is contradictory, and the EFSA stated that it can be assumed that the effect of salt either inhibiting or stimulating biogenic amine production is dependent on the strain of histamine-producing bacteria (EFSA, 2011).

*Volunteer studies*

26. Motil and Scrimshaw (1979) investigated the role of histamine as a causative factor in scombroid poisoning by dosing healthy volunteers, in a randomised double-blind fashion, with graded doses of histamine in grapefruit juice or tuna sandwiches. A total of eight healthy adults with no history of allergies took part. During the first phase of the investigation, 4 of the subjects received grapefruit juice with or without histamine at increasing doses (25, 50, 100, 150, and 180 mg) on random alternate days for 10 days. Once the safety of these histamine doses was established, all 8 subjects were given 100 g of high-quality tuna (as a sandwich) with or without the same graded doses of histamine for another 10 days. Clinical symptoms and vital signs were recorded daily. During the first phase, symptoms were reported on 10/20 histamine days compared to 5/20 control days[1]. Complaints were variable and included headache, facial flushing, warmth, vertigo, nausea and palpitations. The complaints were generally mild, except in one subject who experienced noticeable facial flushing and severe headache at 180 mg histamine. During the second phase, complaints were recorded on 14/40 histamine days and 8/40 control days. The complaints included throbbing headaches, warmth, facial flushing, vertigo and nausea. Headache and facial flushing (alone or in combination) were most consistently noted at higher doses; 4 out of 8 subjects experienced mild to severe headache and flushing at doses ≥ 100 mg. Symptoms generally subsided without treatment within one hour of onset (Motil and Scrimshaw, 1979).

27. Lüthy and Schlatter (1983) conducted a randomised, double-blind, placebo-controlled study to assess the effect of 25 mg histamine, 25 mg tyramine and 5 mg phenylethylamine in apple juice (200 ml) on 25 healthy volunteers and 2 migraine patients. No statistically significant effect was found with histamine and tyramine, but phenylethylamine produced symptoms like headache, dizziness and discomfort in some volunteers. In a second experiment the effect of four different wines (200 ml (originally reported as 2 dl)) that contained several naturally-occurring biogenic amines in various amounts (histamine = not detected - 21 ppm; tyramine = 1 - 23 ppm; phenylethylamine = not detected - 6 ppm; putrescine = 2 - 55 ppm ) on 20 volunteers was recorded. The percentage of volunteers experiencing symptoms was of the same order of magnitude as the first experiment. No correlation was found to exist between the occurrence of symptoms and the concentration of biogenic amines in the wine samples (Lüthy and Schlatter, 1983).

28. Clifford, Walker and Wright (1989) reported the results of a single-blind study in 7 healthy volunteers investigating the association between the histamine content of mackerel and incidence of scombroid poisoning. The volunteers consumed 50 g of fresh mackerel (control) that contained total histamine levels of 0.43-0.9, 150, or 300 mg, or 50 g of deliberately spoiled mackerel that contained 45-57, 150, or 300 mg. The objective parameters of pulse rate, skin temperature and peak expiratory flow rate were recorded for 6 hours following ingestion, and subjective parameters (i.e. symptoms) were measured for 24 hours after ingestion. No significant effects were observed; however, headaches, flushing and oral tingling were reported frequently following doses of 300 mg histamine from both control and spoiled mackerel (Clifford, Walker and Wright, 1989). It is inferred that each of the 7 subjects received each dose of both the control and spoiled mackerel; however, it has not been made

[1] There were a total of 20 days of histamine exposure (5 days for each of the 4 subjects) and 20 days of no histamine exposure or control days (5 days x 4 subjects). In the second phase, there were 40 days of histamine exposure (5 days x 8 subjects) and 40 control days (5 days x 8 subjects).

clear in which order this was carried out, or whether there was a washout period between the doses.

29. van Gelderen *et al*. (1992) studied the effect of histamine administered in samples of fish to 8 healthy volunteers in a randomised, double-blind fashion. The subjects were administered 0, 45 or 90 mg of histamine in samples of spoiled herring paste, or 90 mg of histamine deliberately added to samples of fresh herring paste, for breakfast. The experiment took place on 4 separate days (one for each fish sample), with all ingestions at an interval of at least 2 days. The subjects were observed for 6 hours after breakfast. Special attention was paid to clinical symptoms, blood pressure, and electrocardiogram (ECG). Two of the subjects showed effects (facial flushing, headache) that could be attributed to the ingestion of histamine at doses of 90 mg (both volunteers reacted after the 90 mg spoiled fish samples and one also reacted after the fresh fish sample). No significant changes were observed in blood pressure or ECG (van Gelderen *et al*. 1992).

30. Kanny *et al*. (1993) studied the effects of ingested histamine in 8 healthy volunteers and 25 patients with chronic urticaria (of at least 6 weeks duration). A 120 mg dose of histamine was instilled into the duodenum of each subject. This dose was well-tolerated by the healthy volunteers with the only reported symptom being facial flushing within 10 minutes of instillation. Of the 25 subjects with chronic urticaria, instillation produced symptoms in 21 patients. Early onset symptoms developing during the first hour after instillation included urticaria, acceleration in heart rate (HR) (of 8 beats per minute), a drop in blood pressure (BP) (of at least 10 mm/Hg in systolic and diastolic pressures), facial flushing, pruritus, headache, gastrointestinal disturbances (bloating, cramps, nausea or epigastric burning), and respiratory manifestations (rhinitis or cough). Cardiovascular symptoms and flushing developed within a few minutes following instillation but were transient and lasted no more than 15 minutes. Late-onset symptoms developing between 1 and 12 hours after instillation included urticaria, pruritus, headache, gastrointestinal disturbances (bloating or abdominal pain), and asthma attack (in 1 subject) (Kanny *et al*., 1993).

31. Following on from their 1993 study, Kanny *et al*. (1996) noted clinical symptoms whilst performing a study to examine the structural changes in the duodenal mucosa induced by ingested histamine in patients with chronic urticaria. Seven subjects suffering from chronic urticaria received 120 mg of histamine via a duodenal instillation whilst undergoing duodenal-jejunal endoscopy with concurrent mucosal biopsy. Throughout the procedure, blood pressure was monitored and symptoms were noted. Four subjects developed symptoms within 1 hour after histamine instillation; these symptoms included urticaria, headache, acceleration of HR (greater than 8 beats per minutes), and a drop in systolic and diastolic BP (of 10 mm/Hg). One subject developed diarrhoea 4 hours later (Kanny *et al*., 1996).

32. Menne *et al*. (2001) performed a double-blind, placebo-controlled oral histamine provocation test on 40 patients with suspected histamine intolerance, in order to investigate the applicability of the study design in determining histamine intolerance. Patients were challenged with samples of sparkling wine (200ml) containing either negligible amounts of histamine (<0.02 mg/L and <0.004 mg per sample) or 20 mg/L (4 mg histamine per sample). The patients received the samples on two consecutive days, and had their BP and HR measured at 15 and 30 minutes

after ingestion. In addition to this, the patients completed a symptom diary on each test day. Of the 40 patients, 12 demonstrated clear symptoms following provocation with histamine but not placebo; the most frequent complaints included dizziness, headache, nausea, furred tongue and itching. The BP and HR of the 12 patients who developed symptoms did not differ significantly (Menne *et al*., 2001).

33. Wöhrl *et al*. (2004) conducted a randomised, double-blind, placebo-controlled cross-over study in 10 healthy female volunteers to assess the effects of oral provocation with liquid histamine. The volunteers were hospitalised and challenged on two consecutive days with placebo (peppermint tea) or 75 mg of pure histamine (dissolved in peppermint tea). Objective parameters (heart rate, blood pressure, skin temperature and peak flow rate) as well as clinical symptoms were recorded from baseline for 24 hours. The volunteers received a histamine-free diet, which was also low in allergen, for 24 hours before hospitalisation and throughout the whole observation period. After histamine challenge, 5/10 subjects showed no reaction. One volunteer experienced tachycardia and mild hypotension after 20 minutes post-ingestion, and sneezing, itching of the nose and rhinitis after 60 minutes. Four volunteers experienced delayed symptoms that started 3 to 24 hours post-ingestion; these symptoms included diarrhoea, flatulence, headache, pruritus and ocular symptoms (itching, erythema and oedema). There was no significant difference in any of the objective parameters between histamine and placebo challenge. The authors concluded that a single oral dose of 75 mg of pure histamine could provoke immediate or delayed symptoms in 50% of healthy volunteers (Wöhrl *et al*., 2004).

34. Table 1 below shows the dose-response relationship of histamine in humans following oral administration as provided in EFSA (2011). After assessing the results of the available volunteer studies, a no observed adverse effect level (NOAEL) of approximately 50 mg per healthy volunteer per meal, and a lowest observed adverse effect level (LOAEL) of 75 mg per healthy volunteer per meal can be established.

Table 1. Dose-response relationship of histamine in humans after oral administration (reproduced from EFSA, 2011)

| Administration | Histamine (Ingested) | Symptoms | No. of subjects showing symptoms/ total no. of subjects | Reference |
|---|---|---|---|---|
| *Solid foods* | | | | |
| Tuna | 25 mg | No symptoms | 0/8 healthy volunteers | Motil and Scrimshaw, 1979 |
| Herring paste | 45 mg | No effect level | 0/8 healthy volunteers | van Gelderen *et al*., 1992 |
| Tuna | 50 mg | No symptoms | 0/8 healthy volunteers | Motil and Scrimshaw, 1979 |
| Herring paste | 90 mg | Warm face, flushing, headache | 2/8 healthy volunteers | van Gelderen *et al*., 1992 |
| Tuna | 100 mg | Mild headache, flushing | 1/8 healthy volunteers | Motil and Scrimshaw, 1979 |
| Tuna | 150 mg | Mild headache, flushing | 2/8 healthy volunteers | Motil and Scrimshaw, 1979 |
| Tuna | 180 mg | Mild to severe headache, flushing | 4/8 healthy volunteers | Motil and Scrimshaw, 1979 |
| Mackerel | 300 mg | Headache, flushing, oral tingling (no significant effects) | Not indicated/7 healthy volunteers | Clifford *et al*., 1989 |
| *Non-alcoholic drinks* | | | | |
| Apple juice | 25 mg | No statistically significant effects | Not indicated/25 healthy volunteers and 2 migraine patients | Lüthy and Schlatter, 1983 |
| Grapefruit juice | 25 mg | No significant effect | 0/4 healthy volunteers | Motil and Scrimshaw, 1979 |
| Grapefruit juice | 50 mg | No significant effect | 0/4 healthy volunteers | Motil and Scrimshaw, 1979 |
| Peppermint tea | 75 mg | Diarrhoea, headache, sneezing, flatulence | 5/10 healthy females | Wöhrl *et al*., 2004 |
| Grapefruit juice | 100 mg | Mild headache, flushing | 2/4 healthy volunteers | Motil and Scrimshaw, 1979 |
| Grapefruit juice | 150 mg | Mild headache, flushing | 2/4 healthy volunteers | Motil and Scrimshaw, 1979 |
| Grapefruit juice | 180 mg | Severe headache, flushing | 1/4 healthy volunteers | Motil and Scrimshaw, 1979 |
| *Alcoholic drinks* | | | | |
| Wine | 0.12-4.2mg | No statistically significant effects | Not indicated/20 healthy volunteers | Lüthy and Schlatter, 1983 |
| Wine | 100 mg | No effects | 0/2 healthy volunteers | Lüthy and Schlatter, 1983 |
| Sparkling wine | 4 mg | Dizziness, headache, nausea, itching | 12/40 patients with histamine intolerance | Menne *et al*., 2001 |
| *Digestive histamine challenge* | | | | |
| Instillation into the duodenum | 120 mg | No symptoms | 0/8 healthy volunteers | Kanny *et al*., 1993 |
| Instillation into the duodenum | 120 mg | Urticaria, headache, accelerated HR, drop in BP, nausea, diarrhoea | 26/32 patients with chronic urticaria | Kanny *et al*., 1993; 1996 |

### *Factors that increase sensitivity to histamine*

35. Several factors can increase sensitivity to histamine and increase the likelihood of poisoning occurring at high histamine concentrations; some of these factors may even be sufficient to result in poisoning at concentrations of histamine that would not normally cause toxicity in healthy individuals. The most significant of these factors is genetic or acquired impairment of metabolic enzyme activity.

36. Genetic impairment of DAO or HNMT activity can be a result of functional polymorphisms in the DAO or HNMT genes that cause decreased enzyme activity or reduced production of the enzymes; several such polymorphisms have been associated with inflammatory and gastrointestinal diseases. The HNMT gene shows 8 single nucleotide polymorphisms (SNPs), of which one causes an amino acid substitution that results in a variant which expresses lower enzyme activity and is more frequently found among asthmatics. An SNP located in the DAO gene has been shown to code for an altered protein that has been associated with the severity of ulcerative colitis (Fogel, Lewinski and Jochem, 2007). A variety of other SNPs in the DAO gene have been associated with diseases such as food allergy, gluten-sensitive enteropathy, Crohn's disease, and colon adenoma (Maintz and Novak, 2006). Individuals with these diseases may be more sensitive to dietary histamine because of the decreased levels or lower activity of oxidases in the intestinal lumen compared to healthy individuals (EFSA, 2011).

37. It has been shown that in patients with food allergy[2], average intestinal DAO activity was significantly lower than in healthy individuals (EFSA citing Raithel *et al*., 1999). Patients suffering from histamine intolerance also exhibit impaired histamine degradation due to either decreased DAO levels or reduced activity (Wantke, 2015). In these patients, even a small amount of histamine ingested with food may cause adverse health effects (EFSA, 2011), therefore it is recommended that sufferers follow a diet that is low in or free from histamine by avoiding foods known to be rich in histamine. It is also recommended that sufferers avoid consumption of foods known or believed to contain compounds that cause the release of endogenous histamine (known as 'histamine liberators') such as egg whites, nuts and fish (Maintz and Novak, 2007). A study in French sufferers of histamine intolerance estimated that 1% of the population has the disease, 80% of those being women who were approximately 40 years old (Jarisch, 2015; Maintz and Novak, 2007).

38. Physiological status can also modify sensitivity to histamine. In women, a premenstrual decrease in the activity of B-type monoamine oxidase (MAO) may increase sensitivity to histamine (Bardócz, 1995). However, the physiological increase in DAO production reported in pregnant woman may decrease sensitivity to histamine and would explain the remissions of food intolerance that are frequently observed during pregnancy (Wantke, 2015; Mainz and Novak, 2007).

39. Individuals with chronic urticaria, atopic eczema, respiratory and coronary problems, or those suffering from hypertension or vitamin B12 deficiency are particularly at risk because of their sensitivity to lower doses of biogenic amines

[2] Defined in the EFSA opinion as an immune-mediated hypersensitivity to ingested allergens.

(EFSA, 2011 citing Borysiewicz and Krikler, 1981; Russell and Maretić, 1986; Taylor *et al*., 1989; Bardócz, 1995; Maintz *et al*., 2006; Maintz and Novak, 2007).

40. Acquired enzyme impairment may be transient and reversible. DAO is a sensitive enzyme that is inhibited by various substances including alcohol, its degradation product acetaldehyde, and a variety of drugs (EFSA, 2011; Wantke, 2015). Drugs that have been associated with the inhibition of DAO activity include the MAO and DAO inhibitors that are used to treat stress, depression, Alzheimer's and Parkinson's disease, as well as painkillers, anti-hypertensive drugs, mucolytics, antibiotics (including the anti-tuberculosis agent isoniazid), and agents that reduce gut motility (e.g. acetylcysteine, clavulanic acid, metoclopramide, verapamil, cephalospirones, etc.) (EFSA, 2011). Table 2 contains a more comprehensive list of drugs that are known to inhibit diamine oxidase or to release endogenous histamine (adapted from Maintz and Novak, 2007).

Table 2. Drugs that inhibit diamine oxidase or cause the release of endogenous histamine (adapted from Maintz and Novak, 2007)

| **Substance class** | **Agent/s** |
|---|---|
| Contrast media | *(none provided by Maintz and Novak)* |
| Muscle relaxants | Pancuronium, alcuronium, D-tubocurarine |
| Narcotics | Thiopental |
| Analgesics | Morphine, pethidine, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, metamizole |
| Local anaesthetics | Prilocaine |
| Antihypotonics | Dobutamine |
| Antihypertensives | Verapamil, alprenolol, dihydralazine |
| Antiarrhythmics | Propafenone |
| Diuretics | Amiloride |
| Drugs influencing gut motility | Metoclopramide |
| Antibiotics | Cefuroxime, cefotiam, isoniazid, pentamidin, clavulanic acid, chloroquine |
| Mucolytics | Acetylcysteine, ambroxol |
| Broncholytics | Aminophylline |
| H2-receptor antagonists | Cimetidine |
| Cytostatics | Cyclophosphamide |
| Antidepressants | Amitriptyline |

41. The anti-tuberculosis agent isoniazid is a well-known example of a drug that interacts with histamine, there are several case reports in the literature documenting this interaction. Uragoda and Kottegoda (1977) analysed 21 cases of patients who were being treated with isoniazid and had developed histamine poisoning after consuming skipjack tuna. The authors found that the symptoms of poisoning varied between patients, as did the length of time that symptoms took to appear (Uragoda and Hottegoda, 1977). Uragoda and Lodha (1979) reported the case of a 51 year old man with tuberculosis who was being treated with 300 mg of isoniazid daily and suffered from histamine intoxication after consuming a meal consisting of 'very

strong' Cheshire cheese approximately 6 hours after taking his daily dose. The patient suffered from nausea, flushing, palpitations and frontal headache shortly after starting the meal, his symptoms had ceased by the following morning. Uragoda and Lodha proposed that, despite the gap between the dose of isoniazid and the meal, the patient's serum isoniazid concentration had remained sufficiently high to inhibit DAO (Uragoda and Lodha, 1979).

42. In terms of measures that are taken to advise patients about this food-drug interaction, the current recommendations in the patient information leaflets (PIL) for isoniazid state that '*Isoniazid may interact with foods containing histamine (e.g. tuna fish) or tyramine (e.g. cheese, red wine). These foods should be avoided if you are receiving isoniazid.*' (Medicines and Healthcare Products Regulatory Agency (MHRA), 2015) and '*If you take isoniazid … concurrently with cheese or fish, you may experience redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or light-headedness*' (World Health Organization (WHO), 2011).

43. Russell and Maretić reported the case of 35 people who had suffered from histamine poisoning following consumption of marlin at a 'fish fry'. When analysing the symptoms, they observed an association between the severity of clinical manifestations and the consumption of alcohol (Russell and Maretić, 1986).

44. Current FSA incident data, provided in Annex B, indicate that young children are particularly sensitive to dietary histamine. The incidents reported to the FSA often involve children aged approximately 5 years old, who had consumed cheddar type cheeses in the form of a meal (e.g. lasagne or macaroni cheese) whilst at nursery or school. Some of these incidents have also involved adults (e.g. nursery staff) who have reported similar but milder symptoms after consuming or handling the implicated cheese. While the exact reason that young children are more sensitive to histamine is not clear, it has been proposed that their lower body weight may be a significant factor. However, the incident data may be misleading due to the fact that reports of histamine poisoning are more likely to be made if multiple individuals are affected at the same time (i.e. a class of children).

## Key points from the EFSA scientific opinion

45. The EFSA BIOHAZ Panel's 'Scientific opinion on risk-based control of biogenic amine formation in fermented foods' (Annex C) provides a comprehensive overview of the issue of biogenic amines in a variety of fermented foods including cheese. The opinion identifies histamine and tyramine as the most toxic biogenic amines and as being particularly relevant for food safety. Much of the subject matter (e.g. formation of amines, metabolism and toxicology) has already been discussed above. Below is an explanation of the acute reference dose (ARfD) that was set by the panel, and a summary of their key conclusions and recommendations.

### *Acute reference dose*

46. The BIOHAZ Panel stated the critical endpoint in acute histamine intoxication is an allergy-like reaction comprising symptoms like headache, flushing, itching and

urticaria. Results from the limited number of volunteer studies suggested a potential NOAEL of 50 mg of histamine for the symptoms headache and flushing, but this was based on limited number of individuals: 66 healthy and 74 sensitive. Some healthy individuals did not show symptoms at concentrations up to 6 times higher than the NOAEL (300 mg), and in some sensitive individuals, no negative effects were observed at concentrations up to 2.4 times higher than the NOAEL (125 mg). Therefore, it was assumed that the NOAEL may already be a conservative approach and no factor for intra-species variation was necessary. The Panel did not take into account the information on outbreak data, as the actual amount of histamine ingested leading to acute effects is often unknown and several other factors such as potentiation of acute effects by other biogenic amines, alcohol or medication could not be excluded (EFSA, 2011).

47. The limited published information available led the Panel to suggest a potential ARfD of 50 mg of histamine per healthy person per meal. The Panel noted that this level may be occasionally exceeded by consumption of one or more food items containing high amounts of histamine during the same meal (e.g. cheese and wine), and warned that, in patients with histamine intolerance, even small amounts of histamine in ingested food may cause adverse health effects, so only levels below detectable limits could be considered as safe (EFSA, 2011).

***EFSA's conclusions and recommendations***

48. The BIOHAZ Panel concluded that the present knowledge and toxicity data on histamine alone and in combination with other biogenic amines is limited, but that the fermentation of food provides the conditions necessary for intensive microbial activity and therefore the potential for histamine formation. The Panel also concluded that biogenic amine formation in fermented foods is a complex process affected by multiple factors and their interactions; hence, risk mitigation options based on these factors/interactions must be considered as general principles and cannot be ranked individually. The suggested mitigation options include minimising the occurrence of biogenic amine-producing microorganisms through ensuring good hygienic status of the raw material and, where possible, additional microbial controls; ensuring that microorganisms intended to be used as starter cultures be confirmed as not producing biogenic amines and able to outgrow autochthonous microbiota under conditions of production and storage; and that all aspects of fermented food processing, distribution and storage should be adjusted and balanced in each particular product to avoid or minimise potential enhancing effects on biogenic amine formation and to enable dominance of starter cultures where used (EFSA, 2011).

49. The BIOHAZ Panel recommended that further research is needed on: the toxicity and associated concentrations of histamine in different foods, as well as related potentiating effects of putrescine and cadaverine, in particular concerning food involved in outbreaks and sporadic cases; the consumption data of fermented foods, especially cheese; the production process-based control measures for biogenic amines in fermented food including monitoring and verification aspects and the development of challenge tests; the evaluation of the need for and, if/where necessary, development of process hygiene criteria for histamine in fermented foods, as well as food safety criteria for histamine in fermented foods other than fish. Also, validation of methods for biogenic amine analysis is recommended for all

relevant food types including standardisation and harmonisation of procedures, external quality assessment and availability of certified reference materials (EFSA, 2011).

## Current FSA approach to incidents involving histamine

50. The current FSA approach to all incidents involving histamine (including those in fish) is often initially based on the figures presented in Table 3 below (adapted from Bartholomew *et al*., 1987). Using these figures allows a qualitative risk assessment to be performed when detailed information about an incident is not available, or a full risk assessment is not necessarily required (e.g. if the advice is being provided retrospectively).

Table 3. Concentrations of histamine in food and corresponding levels of toxicity (adapted from Bartholomew *et al*., 1987)

| Histamine concentration (mg/kg) | Health effects |
|---|---|
| <50 | Safe for consumption (for most individuals) |
| 50-200 | Possibly toxic |
| 200-1000 | Probably toxic |
| >1000 | Toxic |

51. If further information becomes available, a full risk assessment can be performed with an exposure assessment using data from the National Diet and Nutrition Survey (NDNS) rolling programme, or based on a portion size approach where survey data are not available. When responding to incidents involving high levels of histamine in cheese, the FSA generally consider NDNS data alongside various portion sizes to account for differences in the consumption of different types of cheese, this approach is discussed below in paragraphs 55 - 60.

52. Once the exposure assessment has been completed, the results can be compared to the EFSA ARfD (50 mg per meal). As the ARfD applies to adults, and there is no comparable reference dose in toddlers and children, then it should be scaled for bodyweight when these age groups have been included in the exposure assessment. To scale the reference dose, it is divided by the EFSA default adult bodyweight, currently 70 kg, and multiplied by the current average bodyweight of the corresponding age group (taken from the NDNS). If necessary, the results of the exposure assessment can also be compared to the LOAEL (75 mg) (from Wöhrl, 2004), which can be scaled for bodyweight in the same way. See Table 4 below for scaled ARfDs and LOAELS for toddlers (1.5 - 3 years) and children (4 - 10 years). If teenagers (11 - 18 years) have been included in the exposure assessment, their exposure results can be compared to the adult ARfD and LOAEL as their average

bodyweight (59.2 kg) is considerably higher than those of toddlers and children, and thus more comparable to the adult doses.

Table 4. Scaled ARfDs and LOAELs for toddlers (1.5 - 3 years) and children (4 - 10 years) based on the EFSA adult ARfD of 50 mg per meal (EFSA, 2011), and an adult LOAEL of 75 mg per meal (Wöhrl, 2004)

| Age group | Average bodyweight (kg) | Scaled ARfD (mg/meal) | Scaled LOAEL (mg/meal) |
|---|---|---|---|
| Toddlers (1.5 - 3 years)[a] | 14.6 | 10.4 | 15.6 |
| Children (4 - 10 years)[a] | 27.1 | 19.4 | 29.0 |

[a] Average bodyweights taken from years 1- 4 of the NDNS rolling programme (Bates *et al*., 2014)

53. Where multiple analytical results are provided, as is often the case with fish and fish products, risk assessments are performed using the mean histamine concentration and the highest reported histamine concentration. The mean concentration is calculated using *all* available analytical results, including those that do not breach regulatory limits, as this provides a more realistic idea of the concentration across a batch. If results are reported for multiple batches, risk assessments can be performed separately for each batch.

54. Once the risk assessment has been completed, it will be passed on to relevant colleagues in the appropriate FSA policy team so that they can implement risk management procedures (i.e. a product withdrawal or recall if necessary). If advice is being provided following an incident that has included reports of illness, then the risk assessment can be used to confirm whether histamine was the cause of the illness, and to determine what actions need to be taken regarding any remaining batches or product that may also be affected.

### *Exposure scenarios*

55. According to FSA incident data the type of cheese that is most often implicated in incidents is hard, Cheddar-type cheese. For this reason, the exposure scenarios detailed below focus on consumption of this or similar types of cheese. Table 5 includes acute consumption data, on a grams per meal basis for easy comparison with the ARfDs and LOAELs, for hard, Cheddar-type cheeses for toddlers (1.5 - 3 years), children (4 - 10 years), teenagers (11 - 18 years) and adults (19+ years) from years 1 – 4 of the NDNS rolling programme (Bates *et al*., 2014).

Table 5. Acute consumption of hard Cheddar-type cheeses (in grams/person/meal) for UK population groups (Bates *et al*., 2014)

| Age Group | Number of consumers | Mean (g/meal) | 97.5th percentile (g/meal) | Maximum (g/meal) |
|---|---|---|---|---|
| Toddlers (1.5 - 3 years) | 231 | 26 | 60 | 146 |
| Children (4 - 10 years) | 449 | 34 | 90 | 200 |
| Teenagers (11 - 18 years) | 499 | 45 | 112 | 180 |
| Adults (19+ years) | 1191 | 51 | 123 | 240 |

56. When completing an exposure assessment for histamine in cheese, various recommended or suggested portion sizes may be taken into consideration alongside the NDNS consumption data; this approach can help to account for differences in the consumption of more specialist or artisan cheeses.

57. For adults, the recommended portion size for hard cheese is 30 g (British Nutrition Foundation (BNF), 2014). According to the FSA portion size book, the approximate portion sizes for a cheeseboard, a cheese sandwich and a ploughman's lunch are 20, 45 and 120 g of cheese respectively (FSA, 2002). These portion sizes, along with the NDNS consumption data, can be used to calculate the minimum concentration of histamine (mg per kg of cheese) that is required for an adult to reach the ARfD and the LOAEL for each different portion (see Table 6).

58. As comparable portion sizes are not available for toddlers and children, approximate portion sizes can be estimated by extrapolation from adult portion sizes and NDNS data. The NDNS data indicate that mean toddler and child consumption values are approximately 50 and 67% those of the adult consumption values respectively. Based on these ratios, a variety of portion sizes can be established for toddlers and children by calculating 50% and 67% of the adult portions. As with adults, these portion sizes and the NDNS consumption data can be used to calculate the minimum concentration of histamine (mg per kg of cheese) that is required for toddlers and children to reach their scaled ARfDs and the LOAELs for each different portion type (see Table 7 for toddlers (1.5 - 3 years) and Table 8 for children (4 - 10 years)).

59. The NDNS data indicate that teenager consumption values of hard cheese are similar to those for the adults; therefore the same portion sizes are used for both age groups (see Table 6).

Table 6. Minimum concentrations of histamine (mg/kg) in different portion sizes of cheese required to reach the ARfD (50 mg/meal) and LOAEL (75 mg/meal) (Wöhrl, 2004). These portion sizes apply to teenagers (11 - 18 years) and adults (19+ years).

| **Portion type** | | **Portion size (g/meal)** | **Minimum concentration of histamine required to reach ARfD (mg/kg)** | **Minimum concentration of histamine required to reach LOAEL (mg/kg)** |
|---|---|---|---|---|
| Cheeseboard[a] | | 20 | 2500 | 3750 |
| Recommended[b] | | 30 | 1667 | 2500 |
| Sandwich[a] | | 45 | 1111 | 1667 |
| Ploughman's[a] | | 120 | 417 | 625 |
| NDNS mean[c] | Teenager | 45 | 1111 | 1667 |
| | Adult | 51 | 980 | 1471 |
| NDNS 97.5$^{th}$ percentile[c] | Teenager | 112 | 446 | 670 |
| | Adult | 123 | 407 | 610 |
| NDNS maximum[c] | Teenager | 180 | 278 | 417 |
| | Adult | 240 | 208 | 313 |

[a] Portion sizes taken from the Food Standards Agency portion size book (FSA, 2002)
[b] Portion size as recommended by the British Nutrition Foundation (BNF, 2014)
[c] Data from years 1-4 of the National Diet and Nutrition Survey rolling programme (Bates *et al*., 2014)

Table 7. Minimum concentrations of histamine (mg/kg) in different portion sizes of cheese required to reach the scaled toddler (1.5-3 years) ARfD (10.4 mg/meal) and LOAEL (15.6 mg/meal).

| Portion type | Portion size (g/meal) | Minimum concentration of histamine required to reach ARfD (mg/kg) | Minimum concentration of histamine required to reach LOAEL (mg/kg) |
|---|---|---|---|
| Cheeseboard[a] | 10 | 1040 | 1560 |
| Recommended[b] | 15 | 693 | 1040 |
| Sandwich[a] | 23 | 452 | 678 |
| Ploughman's[a] | 60 | 173 | 260 |
| NDNS mean[c] | 26 | 400 | 600 |
| NDNS 97.5$^{th}$ percentile[c] | 60 | 173 | 260 |
| NDNS maximum[c] | 146 | 71 | 107 |

[a] 50% of the adult portion sizes taken from the Food Standards Agency portion size book (FSA, 2002)
[b] 50% of the portion size recommended for adults by the British Nutrition Foundation (BNF, 2014)
[c] Data from years 1-4 of the National Diet and Nutrition Survey rolling programme (Bates et al., 2014)

Table 8. Minimum concentrations of histamine (mg/kg) in different portion sizes of cheese required to reach the scaled child (4 - 10 years) ARfD (19.4 mg/meal) and LOAEL (29 mg/meal).

| Portion type | Portion size (g/meal) | Minimum concentration of histamine required to reach ARfD (mg/kg) | Minimum concentration of histamine required to reach LOAEL (mg/kg) |
|---|---|---|---|
| Cheeseboard[a] | 13 | 1492 | 2231 |
| Recommended[b] | 20 | 970 | 1450 |
| Sandwich[a] | 30 | 647 | 967 |
| Ploughman's[a] | 80 | 243 | 363 |
| NDNS mean[c] | 34 | 571 | 853 |
| NDNS 97.5$^{th}$ percentile[c] | 90 | 216 | 322 |
| NDNS maximum[c] | 200 | 97 | 145 |

[a] 67% of the adult portion sizes taken from the Food Standards Agency portion size book (FSA, 2002)
[b] 67% of the portion size recommended for adults by the British Nutrition Foundation (BNF, 2014)
[c] Data from years 1-4 of the National Diet and Nutrition Survey rolling programme (Bates et al., 2014)

60. The data in Tables 6-8 indicate that, as a worst case scenario, histamine concentrations in the range of 70-280 mg/kg would result in exposure to the ARfDs at the maximum consumption levels of hard cheese reported in the NDNS for the age groups toddler, children, teenagers and adults; concentrations in the range of 100-420 mg/kg would result in exposure to the LOAELS at the maximum reported consumption values. It is anticipated that calculating the concentrations of histamine required for various age groups to reach their respective ARfDs and LOAELs in different exposure scenarios, can inform the setting of an 'action' level for histamine in cheese. This 'action' level could act as a guide to be used by the FSA and local authorities to determine when action might need to be taken following the results of histamine sampling. Although this level would be useful, it is likely that for the time being a case-by-case approach would still be required.

**Summary and discussion**

61. Histamine is a heterocyclic diamine that occurs naturally in humans and is involved in a number of important physiological processes. Histamine, along with other biogenic amines, may be present in cheese and other fermented foods as a

result of fermentation by lactic acid bacteria. The bacteria use amino acid decarboxylase enzymes to produce biogenic amines from free amino acids. In order for biogenic amine formation to occur, conditions must favour bacterial growth, and support the synthesis and activity of the bacterial amino acid decarboxylases. These conditions vary depending on the strain of lactic acid bacteria but generally involve temperature, salt content, pH, and oxygen availability.

62. The characteristics of some types of cheese can make them more susceptible to the accumulation of high concentrations of histamine. These characteristics include, but are not limited to, long maturation periods and the use of unpasteurised milk, acid curds, or starter cultures that contain microorganisms known to produce histamine. It is important to note that these characteristics do not always result in high histamine concentrations and may be desirable characteristics of the cheese; this makes it particularly difficult to determine the specific conditions that result in high histamine concentrations, and to establish procedures that could prevent high concentrations.

63. Presently, high-performance liquid chromatography-based methods are the only methods which reliably and with high sensitivity can simultaneously quantify concentrations of all biogenic amines in fermented food. However, there is currently insufficient information in order to recommend detailed monitoring schemes and methods. Monitoring of biogenic amine concentrations during the production process, and of raw materials and products at multiple points along the food chain, could be used as parameters for the process hygiene assessment.

64. Dietary histamine is rapidly metabolised by the enzymes diamine oxidase and histamine N-methyltransferase. These are normally sufficiently able to deal with the level of histamine present in the diet but can potentially be overwhelmed following the consumption of food with particularly high concentrations of histamine. The symptoms of histamine poisoning are related to its physiological effects; therefore common symptoms include rash, diarrhoea, headache, flushing, itching and urticaria. Data from the available volunteer studies indicate a potential no observed adverse effect level of approximately 50 mg per healthy volunteer per meal, and a lowest observed adverse effect level of 75 mg per healthy volunteer per meal.

65. The presence of certain factors can increase the sensitivity of the consumer to histamine. One of the most significant sensitising factors is the inhibition of diamine oxidase through the use of certain medications, consumption of alcohol, or the concomitant consumption of potentiating biogenic amines such as putrescine and cadaverine. Some genetic and physiological factors can also increase sensitivity to histamine by causing decreased diamine oxidase production or activity. These factors include certain inflammatory and gastrointestinal diseases such as food allergy and ulcerative colitis. Age may also be a sensitising factor as FSA incident data suggest that young children may be more sensitive to histamine than adults.

66. It is difficult to make an estimate of the occurrence of histamine poisoning as the disease is thought to be greatly underreported due to its relatively mild nature, and as there is significant potential for misdiagnosis as food allergy. However, reports to the FSA of incidents involving histamine in cheese are becoming increasingly common. This may be due to an increase in the consumption of cheese

with high levels of histamine, or an increase in awareness of the symptoms of histamine poisoning.

67. After reviewing the available data, the EFSA BIOHAZ Panel suggested an acute reference dose of 50 mg per meal per healthy adult. The Panel noted that this level may be occasionally exceeded by consumption of one or more food items containing high amounts of histamine during the same meal, and warned that, in patients with histamine intolerance only levels below detectable limits could be considered as safe. The Panel stated that there were insufficient data to determine the concentrations of putrescine and cadaverine that potentiate histamine poisoning.

68. The BIOHAZ Panel concluded that the present knowledge and toxicity data on histamine alone and in combination with other biogenic amines are limited, and that biogenic amine formation in fermented foods is a complex process affected by multiple factors and their interactions. Suggested risk mitigation options include ensuring good hygiene status to minimising the occurrence of biogenic amine-producing microorganisms; ensuring that microorganisms intended to be used as starter cultures do not produce biogenic amines and are able to outgrow autochthonous microbiota under the conditions of production and storage; and that all aspects of fermented food processing, distribution and storage should be adjusted to avoid or minimise potential enhancing effects on biogenic amine formation.

69. The BIOHAZ Panel recommended that further research is needed on: the toxicity and associated concentrations of histamine in different foods, as well as related potentiating effects of putrescine and cadaverine; the consumption of cheese; the production process-based control measures for biogenic amines in fermented food; the evaluation of the need for and, if/where necessary, development of process hygiene criteria for histamine in fermented foods, as well as food safety criteria for histamine in fermented foods other than fish. Also, validation of methods for biogenic amine analysis is recommended for all relevant food types including standardisation and harmonisation of procedures, external quality assessment and availability of certified reference materials.

70. As there are currently no regulatory limits for histamine in cheese, the FSA provides advice regarding such incidents on a pragmatic risk assessment basis. Therefore, the current FSA approach to handling incidents involving histamine in cheese includes an initial qualitative assessment based on the reported concentrations, followed by a more detailed risk assessment with a comprehensive exposure assessment if necessary. When it comes to cheese, the exposure assessment may consider various portion sizes to account for differences in the consumption of different types of cheese. The results of the exposure assessment are compared to the EFSA acute reference dose and a lowest observed adverse effect level, which may be scaled to account for the different bodyweights of non-adult age groups if needed. Once completed, the risk assessments are passed to FSA Policy teams who decide which risk management actions are appropriate.

<u>Questions on which the views of the Committee are sought</u>

71. Members are invited to comment on the information provided in this paper and to consider the following questions.

i). Do Members have any comments on the acute reference dose of 50 mg per meal established by the EFSA BIOHAZ Panel?

ii). Do Members have any comments on the approach currently being taken by the FSA when performing risk assessments for histamine in cheese?

iii). Do Members have any further comments?

**Secretariat**

**June 2015**

**Abbreviations**

ARfD – Acute reference dose

BIOHAZ – EFSA Panel on Biological Hazards

BNF – British Nutrition Foundation

BP – Blood pressure

DAO – Diamine oxidase

EC – European Commission

ECG - Electrocardiogram

EFSA – European Food Safety Authority

FSA – Food Standards Agency

g – grams

HNMT – Histamine N-methyltransferase

HR – Heart rate

LOAEL – Lowest observed adverse effect level

MAO – Monoamine oxidase

mg – milligrams

mg/kg – milligrams per kilogram

mg/L – milligrams per litre

MHRA – Medicines and Healthcare products Regulatory Agency

NDNS – National Diet and Nutrition Survey

NOAEL – No observed adverse effect level

PIL – Patient information leaflet

ppm – parts per million

SNP – Single nucleotide polymorphism

WHO – World Health Organization

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# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## Discussion paper on high histamine levels in cheese

1. Annex A contains tabulated information on the levels of histamine in different types of cheese. The data are separated into results from monitoring/occurrence data (Tables 1 and 2), results from case reports of histamine poisoning in the literature (Table 3), and results from experimental work that has been reported in the literature (Table 4).

**Secretariat**

**June 2015**

Table 1. Biogenic amine (BA) concentrations in samples of cheese (EFSA, 2011)

| Type of cheese | Number of samples | Histamine concentration | | Tyramine concentration | | Putrescine concentration | | Cadaverine concentration | | Sum of BA concentrations | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean (mg/kg) | 95th percentile (mg/kg) | Mean (mg/kg) | 95th percentile (mg/kg) | Mean (mg/kg) | 95th percentile (mg/kg) | Mean (mg/kg) | 95th percentile (mg/kg) | Mean (mg/kg) | 95th percentile (mg/kg) |
| Fresh cheese | 98 | 3.2 – 38 | 20 – 50 | 12.8 – 48 | 89 | 5.5 – 41 | 4 – 50 | 10.7 – 45 | 33.8 – 50 | 32.1 – 172 | 323 – 464 |
| Hard cheese | 1062 | 25 – 65 | 136 | 67.1 – 103 | 475 | 26.6 – 65 | 132 | 47.8 – 83 | 235 | 167 – 318 | 940 – 1030 |
| Washed rind cheese | 676 | 8.5 – 54 | 46 – 50 | 31.6 – 76 | 240 | 32.3 – 72 | 182 | 147 – 186 | 989 | 220 – 388 | 1420 – 1516 |
| Blue cheese | 296 | 21.3 – 63 | 149 | 63.2 – 10 | 453 | 20.9 – 62 | 149 | 83.1 – 12 | 519 | 188 – 351 | 1100 – 1184 |
| Acid curd cheese | 4 | 51.3 - 55 | 102 | 335 | 480 | 449 | 648 | 628 | 980 | 1460 | 2140 |

The statistics are presented using a bounded approach for the handling of non-detected/non-quantified data (therefore they are displayed as ranges). The upper bound of the range estimates the non-detected/non-quantified values using the reported limit of detection (LOD) or limit of quantification (LOQ) respectively. The lower bound of the range instead assumes the non-detected/non-quantified values as zero. When the lower bound and the upper bound of the range are coincident, only one number is presented. When the lower bound is zero, the range is represented by the upper bound prefixed by '<'.

Table 2. Histamine results of Agroscope Liebefeld-Posieux's monitoring programme for biogenic amines in cheese from 1998 to 2008, as presented by E. Jakob at the SAFE/Agroscope Symposium 'Safety issues of traditional Swiss raw milk cheese' held in Brussels on 11-12th December 2008

| | **Number of samples** | **Minimum histamine concentration (mg/kg)** | **Maximum histamine concentration (mg/kg)** | **Median histamine concentration (mg/kg)** | **90$^{th}$ percentile histamine concentration (mg/kg)** |
|---|---|---|---|---|---|
| Appenzeller Käse | 43 | 46 | 571 | 136 | 416 |
| Emmental | 500 | 0 | 1823 | 28 | 244 |
| Gruyère | 358 | 0 | 2265 | 0 | 17 |
| Raclette past. | 22 | 0 | 42 | 8 | 15 |
| Sbrinz | 43 | 0 | 31 | 0 | 30 |
| Tilsit | 35 | 79 | 217 | 98 | 170 |

Table 3. Histamine concentrations in various cheeses as reported in case reports of suspected histamine poisoning.

| Type of cheese | Reported level of histamine (mg/kg) | Reason for measuring | Cause of level if known | Reference |
|---|---|---|---|---|
| Cheddar (Canadian) | N/D | From a lot suspected of producing a toxic response in people but no direct evidence it caused serious problems | Not specified | Chang *et al*. (1985) |
| Cheddar (possibly Canadian) | 400 | Poisoning in a patient being treated for TB with isoniazid | Possibly because the cheese was 'extremely' aged and/or isoniazid treatment | Stratton et al. (1991) citing Kahana and Todd (1981) |
| Cheese | 250 - 1300 | Poisoning in 6 'outbreaks' | Not specified | ten Brink *et al*. (1990) |
| Cheshire | N/D | Poisoning in a patient being treated for TB with isoniazid | Cheese was described as 'very strong' | Uragoda and Lodha (1979) |
| Gouda | 850 | Clinical case/intoxication | Cheese was 2 years old, contamination with 'unusual' type of lactobacilli | Doeglas et al (1967) |
| Gruyère | 300 | Poisoning in 4 people | Not specified | Taylor (1985) |
| Swiss | 1870 | Clinical case/intoxication | 6 cases, control point failure: abnormally long storage period (>18 months) with possible temperature abuse, *Lactobacillus buchneri* present upon sampling | Sumner *et al* (1985) citing Taylor et al (1982) |
| Swiss | >1000 | Poisoning in 38 people | Not specified | Taylor (1985) |

N/D = not detected

Table 4. Histamine concentrations of different cheese as reported in the literature

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Acid curd (Ölmützer quargel) | - | - | 9.1 | 1933.4 | - | Mayer *et al.* (2010) |
| Affineur (with rosé wine) | Hard | - | 85.5 | 223.2 | - | Mayer *et al.* (2010) |
| Almkäse (Tiroler PDO) | Hard | - | 820.6 | 1060.2 | - | Mayer *et al.* (2010) |
| Almkäse (Tiroler PDO) | Hard | - | 1159.7 | 1938.2 | - | Mayer *et al.* (2010) |
| Appenzeller | Semi-hard | - | 51.9 | 480.6 | - | Mayer *et al.* (2010) |
| Asiago d'Allevo | Hard | U | 57.7 | 162.2 | 6 | Spizzirri *et al.* (2013) |
| Asino | - | - | 245.87 | 1550.55 | - | Loizzo *et al.* (2013) citing Innocente *et al.* (2009) |
| Azeitão | - | U | 682 | 1442.2 | - | Loizzo *et al.* (2013) citing Pinho *et al.* (2001) |
| Bergader Edelpilz | - | - | 37.1 | 127.2 | - | Mayer *et al.* (2010) |
| Bergbaron | Semi-hard | - | 34.2 | 687.2 | - | Mayer *et al.* (2010) |
| Bergkäse (Vorarlberger) | Hard | - | 42.6 | 185.6 | 10 - 12 | Mayer *et al.* (2010) |
| Bergkäse (Vorarlberger) | Hard | - | 11.7 | 64.9 | 6 | Mayer *et al.* (2010) |
| Bergkäse (Premium) | Hard | - | 80 | 310 | 10 | Mayer *et al.* (2010) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Bergkäse (Natürlich Organic) | Hard | - | 16.4 | 55.8 | - | Mayer *et al.* (2010) |
| Bergkäse (Vorarlberger) | Hard | - | 397.2 | 448.3 | 12 | Mayer *et al.* (2010) |
| Bergkäse | Hard | - | 65.2 | 412.2 | - | Mayer *et al.* (2010) |
| Blue | - | U | 1041 | 3751.9 | - | Ladero *et al* .(2010) citing Fernández *et al* .(2007) |
| Blue | - | P | 127 | 980.5 | - | Ladero *et al* .(2010) citing Fernández *et al* .(2007) |
| Blue | - | U | 15.7 | 1023 | 0 | Rabie *et al.* (2011) |
| Blue | - | U | 22.8 | 1085 | 1 | Rabie *et al.* (2011) |
| Blue | - | U | 23.2 | 1837.7 | 2 | Rabie *et al.* (2011) |
| Blue | - | U | 35.7 | 2310.2 | 3 | Rabie *et al.* (2011) |
| Caciocavallo Silano | Semi-hard | U | 42 | 147.4 | 4 | Spizzirri *et al.* (2013) |
| Caciocavallo Silano | - | - | 43 | 128 | 1 | Restuccia *et al.* (2011) |
| Caciotta (Brunelli) | Soft | P | 5.5 | 67.7 | 1 | Spizzirri *et al.* (2013) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Caciotta (La Casara) | Soft | P | 5.9 | 67 | 1 | Spizzirri *et al.* (2013) |
| Caciotta | - | High pressure homogenization | 0 - 5.73 | 10.98 - 35.66 | (0 to 27 days) | Lanciotti *et al.* (2007) |
| Caciotta | - | P | 2.73 - 7.3 | 20.1 - 73.37 | (0 to 27 days) | Lanciotti *et al.* (2007) |
| Caciotta | - | U | 0 - 8.37 | 25.55 - 55.55 | (0 to 27 days) | Lanciotti *et al.* (2007) |
| Camembert (President legere, French) | Soft | - | 6.1 | 471.3 | - | Mayer *et al.* (2010) |
| Camembert (Sirius, Austria) | Soft | - | 5 | 121.4 | - | Mayer *et al.* (2010) |
| Cantal | Semi-hard | U | 165.6 | 727.7 | - | Mayer *et al.* (2010) |
| Cantal | Semi-hard | U | 94.7 | 472.3 | - | Mayer *et al.* (2010) |
| Castelmagno | Semi-hard | - | 645.81 | 3464.02 | - | Gosetti *et al.* (2007) |
| Cheddar | - | P | 65.09 | Not specified | 1 | Gardini *et al.* (2012) |
| Cheddar (*S. thermophilus* PRI60 present - a histamine-producing strain) | - | P | 123.5 | Not specified | 1 | Gardini *et al.* (2012) |
| Cheddar | - | P | 68.4 | Not specified | 1.5 | Gardini *et al.* (2012) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Cheddar (*S. thermophilus* PRI60 present - a histamine-producing strain) | - | P | 182.6 | Not specified | 1.5 | Gardini *et al.* (2012) |
| Cheddar (red, Irish) | Hard | - | 25.4 | 83.2 | - | Mayer *et al.* (2010) |
| Cheese (grated, Brazilian) | Not specified | - | 28.8 | 121.3 | - | Vale and Glória (1998) |
| Dutch cheese (Gouda and Maasam) | Not specified | - | 0 - 350 | 2 - 1232 | - | ten Brink *et al.* (1990) |
| Dutch-type | Semi-hard | P | 0.5 - 16.3 | 19.4 - 36.3 | 2 | Komprda *et al.* (2007) |
| Dutch-type | Semi-hard | P | 2.8 - 10.4 | 52.5 - 413.3 | 4.5 | Komprda *et al.* (2007) |
| Dutch-type | Semi-hard | P | 1.8 - 17.1 | 43.5 - 482.2 | 5.5 | Komprda *et al.* (2007) |
| Edam (Austrian) | Semi-hard | - | 3.2 | 31.7 | - | Mayer *et al.* (2010) |
| Emmental | Hard | U | 37.4 | 163.7 | 4 | Spizzirri *et al.* (2013) |
| Emmental (grated) | - | - | 0 - 734.1 (6 samples) | - | - | Ladero *et al.* (2009) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Emmental (grated) | - | - | 0 - 531.9 (8 samples) | - | - | Ladero *et al.* (2009) |
| Emmental (portions) | - | - | 47.9 - 230.3 (3 samples) | - | - | Ladero *et al.* (2009) |
| Emmental (slices) | - | - | 65.7 - 238.5 (3 samples) | - | - | Ladero *et al.* (2009) |
| Emmental (whole) | - | - | 0 - 115.5 (4 samples) | - | - | Ladero *et al.* (2009) |
| Emmental (organic) | Hard | - | 117.5 | 278.4 | - | Mayer *et al.* (2010) |
| Emmental | Hard | - | 23.5 | 301 | - | Mayer *et al.* (2010) |
| Emmental | Hard | - | 19.6 | 109.7 | - | Mayer *et al.* (2010) |
| Feta | Soft | - | 38.2 | 324 | 1 month | Valsamaki *et al.* (2000) |
| Feta | Soft | - | 47 | 330 | 2 months | Valsamaki *et al.* (2000) |
| Feta | Soft | - | 76.4 | 501 | 3 months | Valsamaki *et al.* (2000) |
| Feta | Soft | - | 84.6 | 617 | 4 | Valsamaki *et al.* (2000) |
| Fontina | Semi-hard | U | 10.4 | 126.7 | 3 | Spizzirri *et al.* (2013) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Goats milk | - | U | 43.06 | 677.76 | - | Ladero *et al*. (2010) citing Novella-Rodríguez *et al.* (2004) |
| Goats milk | - | P | 6.34 | 73.43 | - | Ladero *et al*. (2010) citing Novella-Rodríguez *et al.* (2004) |
| Goats milk | - | P | ND - 88.4 | ND - 1228.5 | - | Novella-Rodríguez *et al.* (2003) |
| Gorgonzola (Despar DOP) | - | - | 255.3 | 354 | - | Mayer *et al.* (2010) |
| Gorgonzola | - | - | 23.7 | 63.9 | - | Mayer *et al.* (2010) |
| Gorgonzola (Brazilian) | - | - | 13.5 | 66.1 | - | Vale and Glória (1998) |
| Gouda (with $10^8$ CFU/g of *L. buchneri*) | - | P | 1060 | - | 3 | Joosten and Northolt (1989) |
| Gouda (with $3.0x10^5$ CFU/g of *L. buchneri*) | - | P | 35 | - | 3 | Joosten and Northolt (1989) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) | Histamine | Total biogenic | Ripening | Reference |
|---|---|---|---|---|---|---|

| | | or Unpasteurised (U) milk | concentration (mg/kg) | amine concentration (including histamine) (mg/kg) | (months) | |
|---|---|---|---|---|---|---|
| Gouda (with $6.0x10^6$ CFU/g of *L. buchneri*) | - | P | 410 | - | 3 | Joosten and Northolt (1989) |
| Gouda (Vergeer Kaas, Dutch) | Semi-hard | - | 30.6 | 305.5 | - | Mayer *et al.* (2010) |
| Gouda (medium Vergeer Kaas, Dutch) | Semi-hard | - | 26.1 | 217.6 | - | Mayer *et al.* (2010) |
| Gouda (Austrian) | Semi-hard | - | 4.5 | 33 | - | Mayer *et al.* (2010) |
| Gouda (Brazilian) | - | - | 28.4 | 82.7 | - | Vale and Glória (1998) |
| Grana Padano (Ambrosi) | Extra-hard | U | 23.9 | 329.3 | 22 | Spizzirri *et al.* (2013) |
| Grana Padano (Casearia Cantarelli) | Extra-hard | U | 17.6 | 302.8 | 22 | Spizzirri *et al.* (2013) |
| Grana Padano (CRAI - grated) | Extra-hard | U | 38.1 | 289.5 | 12 | Spizzirri *et al.* (2013) |
| Grana Padano (Levoni) | Extra-hard | U | 21.4 | 325 | 22 | Spizzirri *et al.* (2013) |
| Grana Padano (Sma - grated) | Extra-hard | U | 22.1 | 289.8 | 12 | Spizzirri *et al.* (2013) |
| Grana Padano (Saviola - grated) | Extra-hard | - | 249 | 285.3 | - | Mayer *et al.* (2010) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised | Histamine concentration | Total biogenic amine | Ripening (months) | Reference |
|---|---|---|---|---|---|---|

| | | (U) milk | (mg/kg) | concentration (including histamine) (mg/kg) | | |
|---|---|---|---|---|---|---|
| Grana Padano (Despar - grated) | Extra-hard | - | 87.5 | 113.3 | - | Mayer *et al.* (2010) |
| Grana Padano (Casa Italiana - grated) | Extra-hard | - | 55.2 | 66.5 | - | Mayer *et al.* (2010) |
| Grana Padano (Stabiumi - grated) | Extra-hard | - | 4 | 4.5 | - | Mayer *et al.* (2010) |
| Grana Padano (Zarpellon) | Extra-hard | - | 19.9 | 37.5 | - | Mayer *et al.* (2010) |
| Grana Padano (Despar - DOP) | Extra-hard | - | 21.5 | 42.4 | - | Mayer *et al.* (2010) |
| Grana Padano | Extra-hard | - | 23.7 | 38.2 | 16 | Mayer *et al.* (2010) |
| Greyerzer Swiss | Hard | - | 3.3 | 37.8 | - | Mayer *et al.* (2010) |
| Herby cheese | - | U | 21.9 | - | (1 day) | Sagun *et al.* (2005) |
| Herby cheese | - | U | 46.2 | - | 3 | Sagun *et al.* (2005) |
| Herby cheese | - | - | 0 - 681.5 | 18.0 - 3585.5 | - | Loizzo *et al*. (2013) citing Andic *et al.* (2009) |
| Idiazabal | Semi-hard | - | 103.6 | 522 | - | Loizzo *et al*. (2013) citing Ordoñez *et al.* (1997) |
| Manchego (0.1% starter culture) | - | U | 18.6 | 52.6 | 1 | Fernañdez-Garcia *et al.* (1999) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised | Histamine concentration | Total biogenic amine | Ripening (months) | Reference |
|---|---|---|---|---|---|---|

| | | (U) milk | (mg/kg) | concentration (including histamine) (mg/kg) | | |
|---|---|---|---|---|---|---|
| Manchego (0.1% starter culture) | - | U | 82.1 | 217 | 2 | Fernañdez-Garcia *et al.* (1999) |
| Manchego (0.1% starter culture) | - | U | 188.5 | 435.1 | 3 | Fernañdez-Garcia *et al.* (1999) |
| Manchego (1% starter culture) | - | U | 30.9 | 88.6 | 1 | Fernañdez-Garcia *et al.* (1999) |
| Manchego (1% starter culture) | - | U | 90.2 | 250.5 | 2 | Fernañdez-Garcia *et al.* (1999) |
| Manchego (1% starter culture) | - | U | 226 | 531.1 | 3 | Fernañdez-Garcia *et al.* (1999) |
| Minas (Brazilian) | - | - | 3.3 | 13.2 | - | Vale and Glória (1998) |
| Montasio | Semi-hard | U | 16.8 | 128.2 | 4 | Spizzirri *et al.* (2013) |
| Montasio | Semi-hard | - | 378.1 | 1080.6 | - | Loizzo *et al*. (2013) citing Innocente *et al*. (2002) |
| Moosbacher | Semi-hard | - | 68.4 | 112.9 | - | Mayer *et al.* (2010) |
| Mozzarella (Brazilian) | - | - | 15.7 | 30.4 | - | Vale and Glória (1998) |
| Organic low fat cheese with pepper | Semi-hard | - | 46.2 | 915 | - | Mayer *et al.* (2010) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised | Histamine concentration | Total biogenic amine | Ripening (months) | Reference |
|---|---|---|---|---|---|---|

| | | (U) milk | (mg/kg) | concentration (including histamine) (mg/kg) | | |
|---|---|---|---|---|---|---|
| Organic low fat cheese with pepper | Semi-hard | - | 46.6 | 923.4 | - | Mayer *et al.* (2010) |
| Parmesan (grated) | - | - | 148 | 280.9 | - | Loizzo *et al*. (2013) citing Custódio *et al.* (2007) |
| Parmesan (Brazilian) | - | - | 2.1 | 7.9 | - | Vale and Glória (1998) |
| Parmesan (grated, Brazilian) | - | - | 37.1 | 127.6 | - | Vale and Glória (1998) |
| Parmigiano Reggiano (Ambrosi) | Extra-hard | U | 36.5 | 482.2 | 30 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano (Fiorucci - grated) | Extra-hard | U | 48.2 | 314.2 | 12 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano (Roncoscaglia) | Extra-hard | U | 28.9 | 493.2 | 30 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano (Roncoscaglia) | Extra-hard | U | 34.2 | 333 | 24 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano (San Lorenzo) | Extra-hard | U | 28.9 | 280.3 | 24 | Spizzirri *et al.* (2013) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Parmigiano Reggiano (Sma - grated) | Extra-hard | U | 33.1 | 307.2 | 12 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano (Sma) | Extra-hard | U | 38.4 | 391.3 | 30 | Spizzirri *et al.* (2013) |
| Parmigiano Reggiano | Extra-hard | - | 23.2 | 67 | 18 | Mayer *et al.* (2010) |
| Parmigiano Reggiano | Extra-hard | - | 79.6 | 116.2 | 24 | Mayer *et al.* (2010) |
| Parmigiano Reggiano - DOP Virgilio | Extra-hard | - | 29.3 | 59.3 | - | Mayer *et al.* (2010) |
| Parmigiano Reggiano - DOP S.Paola Caseifico | Extra-hard | - | 58.7 | 84.4 | - | Mayer *et al.* (2010) |
| Parmigiano Reggiano - DOP | Extra-hard | - | 10.9 | 26.9 | 24 | Mayer *et al.* (2010) |
| Pecorino Abruzzese | Semi-hard to hard | P | 76 | 1086 | 2 | Martuscelli *et al.* (2005) |
| Pecorino Abruzzese | Semi-hard to hard | U | 261 | 697 | 2 | Martuscelli *et al.* (2005) |
| Pecorino carmasciano | - | U | 65.5 | 641.9 | - | Loizzo *et al*. (2013) citing Mercogliano *et al.* (2010) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Pecorino Crotonese (Maiorano) | Extra-hard | P | 19.1 | 137.4 | 6 | Spizzirri *et al.* (2013) |
| Pecorino di Farindola | Soft | U | 0 - 21.8 | 209 - 2393 | 3 | Schrione *et al.* (2011) |
| Pecorino | - | High pressure homogenization | 0 - 5.75 | 13.56 - 131.62 | (0 - 21 days) | Lanciotti et al. (2007) |
| Pecorino | - | P | 0 - 23.92 | 96.8 - 872.74 | (0 - 21 days) | Lanciotti et al. (2007) |
| Pecorino | - | U | 0 - 6.32 | 26.46 - 378.42 | (0 - 21 days) | Lanciotti et al. (2007) |
| Prato (Brazilian) | - | - | 16 | 34.4 | - | Vale and Glória (1998) |
| Provolone Valpadana (Auricchio) | Stretched curd | U | 9.7 | 163.1 | 4 | Spizzirri *et al.* (2013) |
| Provolone (Brazilian) | - | - | 10.4 | 101.7 | - | Vale and Glória (1998) |
| Rahmbrie (Austria) | Soft | - | 3.9 | 31.8 | - | Mayer *et al.* (2010) |
| Raschera | Semi-hard | - | 452.36 | 1478.34 | - | Gosetti *et al.* (2007) |
| Ripened | - | U | 510.2 | 1509.3 | - | Ladero *et al*. (2010) citing Fernández *et al*. (2007) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Ripened | - | P | 65.4 | 541.7 | - | Ladero *et al*. (2010) citing Fernández *et al*. (2007) |
| Ripened | Hard | P | ND - 163.6 | ND - 1863.9 | - | Novella-Rodríguez *et al.* (2003) |
| Ripened | Hard | U | ND - 391.4 | 0.9 - 2102.9 | - | Novella-Rodríguez *et al.* (2003) |
| Ripened goat cheese (La Casera) | Hard | U | 42.6 | 200.8 | 6 | Spizzirri *et al.* (2013) |
| Ripened goat cheese (Occelli) | Hard | U | 33.9 | 156 | 6 | Spizzirri *et al.* (2013) |
| Ripened goat cheese (San Lorenzo) | Hard | U | 50.2 | 187.9 | 6 | Spizzirri *et al.* (2013) |
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | ND - 21.6 | ND - 32.4 | (0 days, Sping) | Bonetta *et al.* (2008) |
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | 5.6 - 97.7 | 180.3 - 964 | (20 days, Spring) | Bonetta *et al.* (2008) |
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | ND - 43.5 | ND - 119 | (0 days, Summer) | Bonetta *et al.* (2008) |
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | 135.1 - 1786.1 | 330 - 3908.7 | (20 days, Summer) | Bonetta *et al.* (2008) |
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | ND - 5.3 | ND - 13.4 | (0 days, Winter) | Bonetta *et al.* (2008) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Robiola di Roccaverano | Soft, creamy | U (goats milk) with P (cows milk) | 17.3 - 258.1 | 58.4 - 838 | (20 days, Winter) | Bonetta *et al.* (2008) |
| Roquefort | - | P | ND - 376.6 | 3.0 - 4489.1 | - | Novella-Rodríguez *et al.* (2003) |
| Roquefort | - | - | 9.9 | 100.5 | - | Mayer *et al.* (2010) |
| Roquefort | - | - | 10.6 | 51 | - | Mayer *et al.* (2010) |
| São Jorge | Semi-hard | U (cows milk) | 21 - 933 | 441 - 4322 | 3 | Calhau and Barbosa (2000) |
| São Jorge | Semi-hard | U (cows milk) | 45 - 1384 | 871 - 6388 | 6 | Calhau and Barbosa (2000) |
| Schärdinger Österkron | - | - | 9.2 | 58.6 | - | Mayer *et al.* (2010) |
| Schlierbacher (Klosterkäse Romadur) | - | - | 15.4 | 219.7 | - | Mayer *et al.* (2010) |
| Schlierbacher (Klosterkäse Schloβkäse, classic) | - | - | 8.1 | 39 | - | Mayer *et al.* (2010) |
| Semicotto caprino | - | - | 1.8 | 18.3 | - | Loizzo *et al*. (2013) citing Galgano *et al.* (2001) |
| Semi-ripened | - | - | 2.19 | 36.06 | Not specified | Latorre-Moratalla *et al.* (2009) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Swiss (American) | - | - | 1470 - 5630 | 520 - 6880 | - | Chang *et al*. (1985) |
| Swiss (inoculum level of $10^2$ *L. buchneri*/ml) | - | U | 15 | - | 3 | Sumner *et al.* (1990) |
| Swiss (inoculum level of $10^3$ *L. buchneri*/ml) | - | U | 38 | - | 3 | Sumner *et al.* (1990) |
| Swiss (inoculum level of $10^4$ *L. buchneri*/ml) | - | U | 50 | - | 3 | Sumner *et al.* (1990) |
| Swiss (inoculum level of $10^5$ *L. buchneri*/ml) | - | U | 80 | - | 3 | Sumner *et al.* (1990) |
| Terrincho | - | U | 15.6 | 808.7 | - | Loizzo *et al*. (2013) citing Pinho *et al*. (2004) |
| Terrincho | - | U | 0 - 10.9 | 144.1 - 1137.9 | 1 | Loizzo *et al*. (2013) citing Pintado *et al.* (2008) |
| Tholstrup castello (Danish) | Soft | - | 5.4 | 78.2 | - | Mayer *et al.* (2010) |
| Tilsit (Woerle) | - | - | 168.3 | 548.7 | - | Mayer *et al.* (2010) |

Table 4. Histamine concentrations of different cheese as reported in the literature (continued)

| Type of Cheese | Firmness | Pasteurised (P) or Unpasteurised (U) milk | Histamine concentration (mg/kg) | Total biogenic amine concentration (including histamine) (mg/kg) | Ripening (months) | Reference |
|---|---|---|---|---|---|---|
| Tilsit (Brazilian) | - | - | 16.1 | 65.3 | - | Vale and Glória (1998) |
| Toma | Semi-hard | P | ND - 67 | 195 - 313 | - | Gerrano *et al.* (2003) |
| Toma | Semi-hard | U | 9.0 - 29 | 686 - 1076 | - | Gerrano *et al.* (2003) |
| Toma Piedmontese | Semi-hard | - | 587.63 | 1327.09 | - | Gosetti *et al.* (2007) |
| Unripened | - | U | 110.8 | 479.1 | - | Ladero *et al* .(2010) citing Fernández *et al* .(2007) |
| Unripened | - | P | 60.2 | 82.2 | - | Ladero *et al* .(2010) citing Fernández *et al* .(2007) |
| Unripened | - | P | ND | ND - 5.2 | - | Novella-Rodríguez *et al.* (2003) |

ND = not detected
- = has not been specified in the literature
P = pasteurised
U = unpasteurised
CFU = colony forming units
DOP/PDO = Protected Designation of Origin

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# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## Discussion paper on high histamine levels in cheese

1. Annex B contains information on incidents involving histamine in cheese that the Food Standards Agency has dealt since 2001.

**Note:** The material in the Annexe contains sensitive information and will not be made public when the main paper is released.

**Secretariat**

**June 2015**

# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## Discussion paper on high histamine levels in cheese

**Note:** For copyright reasons the EFSA BIOHAZ Panel's 'Scientific opinion on risk based control of biogenic amine formation in fermented foods' in this Annex is not included in the published version on the COT website. It is available from the EFSA website at http://www.efsa.europa.eu/en/efsajournal/doc/2393.pdf

**Secretariat**

**June 2015**