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

Histamine in cheese: Additional information

Introduction and background

1. Histamine poisoning is a well-established phenomenon that can arise from the consumption of foods, notably scombroid fish, which contain high levels of histamine as a result of bacterial spoilage. Histamine can also be present in foods such as cheese or sausage as a consequence of fermentation.

2. The symptoms of histamine (scombrotoxin) poisoning include flushing, headache, nausea, itching, rash and altered blood pressure, with EFSA (2011) noting fatalities in extreme cases. Data from incidents reported to the Food Standards Agency (FSA) are consistent with this and these reports suggest some individuals have been hospitalised.

3. Incidents of histamine poisoning as a result of high levels of histamine in cheese have increased in recent years. While there is specific legislation regarding histamine levels in fish, there is currently no legislation covering histamine levels in other foods. Therefore the FSA gives advice taking into account data from case reports of histamine poisoning in the literature, and the European Commission's (EC) action level for histamine in fish (200 mg/kg). This level is a useful starting point as the portion sizes for fish and cheese are relatively comparable.

4. The FSA has also begun to include the 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.

COT discussions- June 2015

5. At the June 2015 COT meeting, Members considered a discussion paper (TOX/2015/19) asking for comments and advice on the approach being taken to these incidents. An extract from the paper detailing this approach is attached at Annex A. The minutes of the meeting are attached at Annex B.

6. Members were content with the approach being taken, but raised a number of points on which they would like additional information.

Additional information

7. The trade associations, the Specialist Cheesemakers Association and the Provision Trade Federation (whose members are typically larger companies) surveyed their members and the result of this are attached at Annexes C and D respectively. The Secretariat had hoped to obtain additional information, particularly on the results of routine monitoring from Dairy UK who represent the UK dairy industry, but their members did not feel they had any additional information to add to that which some of their members had already provided to PTF.

Key points from the SCA

8. In general, the majority of SCA members tested the histamine concentration of their cheeses infrequently. Histamine levels were generally lower than 200 mg/kg- 37/40 from cheese made with unpasteurised milk and 46/50 from cheese made with pasteurised milk; only two samples exceeded 400 mg/kg. Of 22 cheesemakers who responded, 20 had not had any reports of allergic reactions from consumers or EHO interest in their cheese. SCA members were not likely to supply artisan cheese to schools or nurseries.

Key points from the PTF

9. The majority of PTF members tested for histamine on a monthly basis. Normal histamine levels would be less than 50 ppm and usually less than 10 ppm. A number of retailers have set specifications for histamine, these are generally 200 ppm or less. It was unclear what would happen to cheese that did not meet specifications.

Summary and discussion.

10. Histamine poisoning can occur as a result of consumption of foods containing high levels of histamine. The number of incidents involving histamine in cheese has increased in recent years. In the absence of specific legislation, the FSA has taken a pragmatic case by case approach, taking into account a number of factors including the EFSA ARfD. COT members were content with this approach but requested additional some information. This is attached at Annexes C and D.

Questions for the Committee

11. Members are asked to consider the information provided by the SCA and PTF and to consider whether :

a) The additional information altered their previous views on the approach taken by the FSA and, if so, how?
b) They have any general comments
c) If they would like any additional information?

Secretariat
June 2016

REFERENCES

EFSA (2011) ‘Scientific Opinion on risk based control of biogenic amine formation in fermented foods’ *EFSA Journal* 9(10) pp.2393

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Extract from TOX/2015/19

Secretariat
June 2016

Current FSA approach to incidents involving histamine

12. 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

13. 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.

14. 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)

15. 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.

16. 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

17. 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

18. 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.

19. 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).

20. 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)).

21. 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 97.5th 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 97.5th 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 97.5th 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)

22. 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.

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Minutes of the June 2015 COT meeting

54. No interests were declared.

55. The Chairman welcomed Mr Terry Jones, the Chair of the Specialist Cheesemakers' Association's (SCA) technical committee, who was in attendance to observe the item and to answer any questions that Members had on a joint submission that had been tabled by the SCA and Provision Trade Federation (PTF).

56. Members had been introduced to the topic of histamine in cheese during the horizon scanning paper (TOX/2015/01) at the meeting in February. At this meeting, Members had been informed that histamine poisoning was a well-established phenomenon that often arose from the consumption of spoiled fish, but that it could also result from the consumption of foods such as cheese where histamine was present as a consequence of fermentation. Members had also been informed that, in the absence of specific legislation, the FSA took a pragmatic approach when responding to incidents involving histamine in cheese. This approach took into account the current regulatory limits for histamine in other foods (e.g. fish), an acute reference dose (ARfD) for histamine taken from the European Food Safety Authority (EFSA) scientific opinion on biogenic amines in fermented foods, which include histamine, tyramine, cadeverine and putrescine (EFSA (2011) *EFSA Journal* 9(10) pp.2393), the results of the available volunteer studies, and multiple exposure scenarios that considered the variability in the consumption of different types of cheese.

57. Following their brief discussion on histamine in cheese at the February meeting, Members had agreed to comment on the approach taken by the FSA to incidents involving histamine in cheese, and on the EFSA scientific opinion on biogenic amines in fermented foods. In order to be able to do so, Members had requested that data on the occurrence of histamine poisoning, information about potentially sensitive individuals, and information on the relationship between histamine concentration and salt content, be provided in a discussion paper. Paper TOX/2015/19 included this information along with information on the metabolism and toxicology of histamine, the key points from the EFSA scientific opinion, and a more detailed description of the current FSA approach.

58. In addition to TOX/2015/19, a brief joint submission was tabled by the SCA and PTF following a meeting held with members of the FSA secretariat on 24th June. COT Members were given a verbal update on this meeting by the secretariat. Overall, the FSA had found the meeting useful as it had provided an opportunity to outline TOX/2015/19, to explain the FSA's approach to incidents involving histamine, and to clarify that the FSA had raised the issue of histamine in cheese with the COT in order to

seek guidance about their approach to incidents, not with a view to establishing regulatory limits.

59. The submission from the SCA/PTF outlined their histamine Working Group's (WG) technical comments on TOX/2015/19, provided a basic description of the results of a questionnaire about histamine testing that had been put to their members following an initial meeting with the FSA in September 2014, and highlighted some of their main concerns as trade associations. An important point that was detailed in the submission, and that had also been discussed at the meeting with the FSA in June, was the WG's concern about the EFSA recommendation to ensure that starter cultures should be encouraged to "*outgrow autochthonous microbiota under conditions of production and storage*". The WG felt that it would not be possible to follow this recommendation as the autochthonous microbiota is largely responsible for the organoleptic characteristics of matured cheeses. The WG also explained that during the maturation of hard cheese, the population of starter lactic acid bacteria (SLAB) declined while the population of non-starter lactic acid bacteria (NSLAB) developed (i.e. the autochthonous microbiota outgrow the starter culture); this appeared to be true of cheeses made from pasteurised milk as well as those made from raw milk.

60. In their submission, the SCA/PTF WG had also explained that the reduction of salt levels in cheese can have a positive or negative effect on the formation of biogenic amines, depending on whether the histidine decarboxylase activity (which converts histidine to histamine) is associated with SLAB, NSLAB, or an unrelated species (whether adventitious or added as part of a ripening culture).

61. Overall, the WG had concluded that the SCA and PTF were keen to protect their customers as well as their members, and would be happy to work with the COT and the FSA to better understand the overall issue, but that, as trade associations, they would have difficulty accepting a criterion (such as a maximum level) for histamine in cheese as the available information was currently limited. The WG also noted that it would be important that attempts to reduce the levels of histamine in cheese did not compromise the microbiological safety of the cheese.

62. During their discussion of TOX/2015/19, COT Members noted that, while histamine does not appear to interact with tyramine, there is a need to recognise the role of putrescine and cadaverine as potentiators of histamine toxicity, although there was currently insufficient information to determine the concentrations at which this potentiation could occur.

63. Members acknowledged that the effects of histamine poisoning can be quite severe and unpleasant but are short-lived. Members considered it notable that the data presented in Annex B, from incidents dealt with by the FSA involving histamine in cheese, showed that most of the individuals in whom symptoms of poisoning were reported were toddlers and young children. Members questioned whether this observation was evidence that young children are more sensitive to the effects of exogenous histamine, or whether the data had been subject to reporting bias (i.e. as multiple children were affected simultaneously, the likelihood of a diagnosis of histamine poisoning was increased). Members also questioned whether the incidents were related to the type of manufacturer involved (i.e. had the cheese been produced by a large or small manufacturer).

64. Based on the incident data provided in Annex B, Members queried whether risk management actions, such as labelling or the provision of catering guidance, might be appropriate to advise against the exposure of young children to mature cheeses where higher histamine levels were more likely, especially in a catering establishment such as a school canteen.

65. In response to the questions on which the views of the Committee were sought, Members commented that the ARfD (50 mg of histamine per meal per healthy adult) that had been established by the EFSA Panel, was sensible and conservative (i.e. adequately protective as it had been based on the responses of healthy and sensitive individuals). Members noted that, although the ARfD did not take into account the possible modulation of histamine sensitivity by other factors such as medication, management of such risks may be better achieved through education of consumers or patients, as is done in the case of tyramine.

66. Members commented that the FSA's approach to assessing the risk from histamine in cheese was sensible and well-founded as it took into account the appropriate measures of exposure, including data from the National Diet and Nutrition Survey (NDNS), and adjusted the EFSA ARfD for toddlers and children by scaling for bodyweight. Members also considered that it was appropriate to build on the risk assessment already established for biogenic amines in fish, but concluded that it was still prudent for the FSA to adopt a case-by-case approach when considering histamine in cheese. Members noted that there was currently too much heterogeneity in the levels of histamine in cheese to establish an 'action' or guidance level that could inform the FSA's approach to risk assessments.

67. Following the Members' discussion, Mr Jones was invited to comment on behalf of the SCA/PTF. Mr Jones commented that the SCA and PTF were committed to working with the FSA and COT on the issue of histamine in cheese. He confirmed that, as with fish, the level of histamine in cheese is variable, and may differ within and between batches

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Information from the Specialist Cheesemakers Association

This information has not been made publicly available as it is commercially confidential

Secretariat, June 2016.

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