TOX/2020/19

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

Discussion paper on the draft EFSA opinion on "Risks for animals and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products."

Introduction

1. Glycoalkaloids are a group of nitrogen-containing compounds which are naturally produced by Solanaceae plant family. This family includes popular vegetables such as potatoes, tomatoes and aubergines. The main role of glycoalkaloids are to protect plants against pest attacks and pathogens.

2. The potato contains the glycoalkaloids α-chaconine and α-solanine, The tomato contains the glycoalkaloids α-tomatine and α-dehydrotomatine, the aubergine contains the glycoalkaloids α-solamargine and α-solasonine. The potato contains the highest levels of glycoalkaloids in comparison to the tomato and aubergine.

3. The EFSA CONTAM panel have published a draft opinion on "the risks for animal and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato derived product" for public consultation. Following a review of available animal and epidemiological data it was decided by the CONTAM panel, that the human risk assessment would be based on epidemiological data.

4. The CONTAM Panel identified a lowest-observed-adverse-effect level of 1 mg total potato glycoalkaloids/kg bw per day as a reference point for the risk characterisation based on acute exposure.

5. This paper summaries the steps that were used by the CONTAM Panel to establish the Margin of Exposures (MOEs), in order for the Members to discuss and submit their comments.

Background

Previous Evaluations

6. Bömer and Mattis (1924) conducted a study on batches of German potatoes from the 1922 harvest, where it was noted that exceptional levels of solanine content were observed. It was reported that potatoes that contained

a total glycoalkaloid content of 257 to 583 mg/kg potatoes caused intoxication or other health problems. These effects were not reported for potatoes that contained levels which were less than 200 mg/kg. Unpeeled, uncooked potatoes that contained 200 mg TGA/kg were considered to be safe for consumption.

7. The Joint Food and Agricultural Organisation/World Health Organisation (FAO/WHO) Expert Committee on Food Additives (JECFA) assessed the toxicity of α-chaconine and α-solanine (JECFA, 1992, 1993). In their evaluation in 1992-1993, the kinetic effects (absorption, distribution, biotransformation and excretion), toxicity and teratogenicity, in rodents and humans were examined. It was concluded that a safe level of intake could not be determined based on the available experimental and epidemiological data. The Committee also stated that mechanical damage, blighting, sprouting, processing and the storage conditions of a potato can lead to increased levels of α-chaconine and α-solanine. JECFA concluded that the daily consumption of potatoes containing 20 – 100 mg of α-chaconine and α-solanine was of no concern, provided that the potatoes were handled and grown under adequate conditions.

8. In 1990, the Swedish National Food Administration carried out a risk assessment on the health risks related to glycoalkaloids (solanine) in potatoes based on a Nordic view. It was recommended that the average total glycoalkaloid concentration in new potato varieties should not exceed 100 mg/kg (Nordic Working Group on Food Toxicology and Risk Assessment, 1990).

8. In 2015, members of a family in Baden-Württemberg (Germany) experienced symptoms of a stomach-ache and vomiting after consuming jacket potatoes and boiled potatoes (with skin). As a result of this, the German Federal Institute for Risk Assessment (BfR) published a preliminary assessment on the acute toxicity of glycoalkaloid occurrence in potatoes (BfR, 2018). The tested potatoes contained 236 mg total glycoalkaloids/kg (141 mg α-solanine and 95 mg α-chaconine per kg). Based on the available epidemiological data the BfR derived a no-observed-adverse-effect-level of 0.5 mg/kg/bw/d. To ensure that sensitive populations were included in the assessment the BfR advised that the total glycoalkaloid (TGA) content of potatoes should not be higher than 100 mg/kg fresh weight.

9. Since glycoalkaloid, notably solanine, levels are thought to be higher in green, damaged or sprouting areas of the potato, current FSA advice is to remove these areas before consuming.

Summary of 2019 EFSA evaluation

Toxicokinetics

10. In experimental animals, the potato glycoalkaloids α-chaconine and α-

solanine, showed low oral bioavailability. Higher absorption and slower excretion rates were seen in hamsters in comparison to rats. The metabolic profiles of potato glycoalkaloids in experimental animals could not be characterised.

11. In humans, α-chaconine and α-solanine are systematically absorbed following ingestion. For both substances, relatively long serum half-lives were reported suggesting accumulation potential. The blood clearance of the respective aglycone solandine appeared slow. Levels of solanidine were regularly detected in the blood of human volunteers in numerous studies, suggesting hydrolysis of glycoalkaloids.

12. There are no toxicokinetic data on tomato and aubergine glycoalkaloids and their aglycones in experimental animals or humans.

Toxicity

13. An extensive literature search was conducted to identify relevant studies in relation to the toxicity of glycoalkaloids in *in vitro* models, experimental animals and in humans. Details of the searching strategies which were used to identify the relevant studies are detailed in Appendix B of the EFSA opinion.

Observations in animals

14. In acute toxicity studies, no adverse effects of α-solanine were observed at a dose of 250 mg/kg body weight per day and in mice no adverse effects were observed at a dose of 1000 mg/kg body weight per day. Reliable data on other potato glycoalkaloids, tomato and aubergine glycoalkaloids and their aglycones are missing.

15. In repeated oral dose studies, mice showed non-specific effects, such as reduced body weight and relative liver weight with indication of similar potencies of α-chaconine and α-solanine after one week of daily treatments with 416.6 mg of α-solanine or 409 mg of α-chaconine/kg bw. The aglycone solanidine increased the absolute and relative liver weight at 190.9 mg/kg bw per day in mice, suggesting a different effect of the aglycone compared to the glycoalkaloids. Hamsters showed non-specific effects, such as reduced body weight and relative liver weight with indication of similar potencies of α-chaconine and α-solanine after a 5-day treatment with 100 mg/kg of α-chaconine and α-solanine.

16. The tomato glycoalkaloids, α-tomatine, and its aglycone, tomatidine, exerted no effects in rats, when administered at 20 mg/kg bw per day for a period of 200 days. At higher doses, tomatidine reduced the cholesterol uptake and increased faecal sterol and coprostanol excretion in hamsters and rats. In mice, 1–2 weeks' treatment with the aubergine glycoalkaloid, α-solasonine, increased the body weight gain at 424.4 mg/kg bw per day, while

its aglycone, solasodine, decreased body weight gain and caused gastric gland degeneration and liver toxicity at 160 mg/kg bw per day.

17. Developmental studies were performed mainly in hamsters treated with potato glycoalkaloids and their aglycones for a day or at a very restricted time period during gestation. The results indicated that effects in the central nervous system occurred at doses of 165 mg/kg bw per day and above for glycoalkaloids, and 115 mg/kg bw per day and above for aglycones.

18. There was no evidence of genotoxicity of the potato glycoalkaloids α chaconine and α-solanine, and the aglycone, solanidine, as well as for the aubergine glycoalkaloid, α-solamargine.

19. No long-term chronic toxicity/carcinogenicity studies were identified for potato, tomato or aubergine glycoalkaloids or for their respective aglycones.

Observations in humans

20. The CONTAM Panel selected kinetic studies and reports on intoxications in humans where acute toxic effects such as gastrointestinal systems of vomiting, diarrhoea and abdominal pain were observed following ingestion of potato glycoalkaloids. These effects were observed at a total potato glycoalkaloids of 1 mg/kg bw or more. The respective studies are reported in table 20 of the EFSA report.

21. No relevant data has been identified to suggest that there is an association between glycoalkaloid related health problems in humans based on a repeated or long-term intake of potatoes.

Critical effects and derivation of a health-based guidance value

22. The mode of action of glycoalkaloids were investigated. It was stated that the adverse effects of glycoalkaloids may be due to their ability to complex with membrane 3β-hydroxyl sterols, thereby causing disruption and loss of integrity of cell membranes. It was concluded that following oral exposure, these effects may affect the mucosa of the gastrointestinal tract and cause symptoms such as nausea, vomiting and diarrhoea as observed in intoxicated humans.

23. It was also reported that glycoalkaloids inhibit acetylcholinesterase (AChE) and serum butyrylcholinesterase (BuChE) by a reversible competitive mode of action. The relative potency of inhibition of α-chaconine and α-solanine are similar. The aglycones exert either weak or no inhibitory effects. It was suggested that excess levels of acetylcholine at the neuronal and neuromuscular junctions after enzyme inhibition may also contribute to the symptoms of nausea, vomiting and diarrhoea as observed in intoxicated humans.

24. At high doses, it was reported that α-tomatine may lead to the

formation of a non-absorbable complex with cholesterol and other sterols in the enteral lumen which may impair the absorption of cholesterol. A reduced uptake of cholesterol by the liver was reported in a rat study (Cayen et al, 1971).

25. The panel assumed that the main symptoms of glycoalkaloid toxicity was due to the local irritation of the gastrointestinal mucosa rather than inhibition of AChE activity. The possible interindividual variability in toxicodynamics was considered more relevant that the interindividual variability in toxicokinetics.

26. The CONTAM panel considered the use of rodent data on acute toxicity was not appropriate to establish a reference point for acute exposure to potato glycoalkaloids in humans. Instead, the panel selected the LOAEL of 1 mg potato total glycoalkaloids bw per day as reference point for acute risk characterisation, based on human data from case reports, outbreaks and studies in volunteers.

Exposure assessment

27. Occurrence data in the raw primary commodities (RPC) (main crop potatoes and new potatoes) and the RPC Consumption Database were used for the exposure assessment.

28. The panel decided to combine the occurrence of new potatoes and main crop potatoes and the mean upper bound (UB) occurrence (sum of α-chaconine and α-solanine). The mean UB was 52 mg/kg and the 95th percentile occurrence was 117 mg/kg. The minimum and maximum reported concentrations were 1.1 mg/kg and 550.3 mg/kg, respectively.

29. A probabilistic approach was used by EFSA to estimate the acute dietary exposure to total potato glycoalkaloids, including only days in which there was consumption of main-crop potatoes. An exposure assessment was not conducted for glycoalkaloids in the tomato and aubergine as no occurrence data were available. Reduction factors for the major food processing steps, comprising peeling and heat processing (boiling, frying, baking) were applied to the occurrence data. Reduction factors between 0.25 and 0.75 were attributed to the peeling of potatoes, between 0.2 and 0.9 for frying, and between 0.05 and 0.65 for all other cooking methods.

30. In Table 1, the mean UB exposure to potato total glycoalkaloids across surveys ranged from 26.0 µg/kg bw per day in adults to 193.4 µg/kg bw per day in toddlers. The 95th percentile exposure ranged from 88.2 µg/kg bw per day in adults to 617.9 µg/kg bw per day in toddlers (up to 1,057.9 µg/kg bw per day in the upper limit of the 95% confidence interval).

Table 1: Summary statistics of the probabilistic acute dietary exposure assessment to potato total glycoalkaloids across European dietary surveys (µg/kg bw per day) by age group including only days with consumption. The corresponding 95% confidence intervals are presented in the brackets.

	Range across surveys of acute dietary exposure (µg/kg bw per day)			
	Mean	Mean	P95[a]	P95[a]
Age group	Minimum (LB)	Maximum (UB)	Minimum (LB)	Maximum (UB)
Infants	35.4 (19.3 – 68.8)	133.0 (124.1 – 143.8)	349.1 (319.5 – 382.6)	422.0 (376.0 – 468.4)
Toddlers	66.6	193.4	254.8	617.9
	(63.1 – 70.6)	(140.7 – 248.1)	(237.3 – 272.9)	(369.4 –
				1,057.0)
Children	54.7	167.1	178.7	518.6
	(49.0 – 62.1)	(143.9 – 194.0)	(150.8 – 210.4)	(364.0 – 747.2)
Adolescents	35.5	122.8	116.3	377.4
	(32.5 – 39.2)	(109.4 – 138.0)	(102.4 – 133.0)	(314.9 – 447.1)
Adults	26.0	91.7	88.2	277.2
	(22.7 – 30.1)	(86.6 – 97.6)	(73.7 – 106.7)	(255.6 – 302.4)
Elderly	29.1	80.0	96.7	240.4
	(21.0 – 40.8)	(68.1 – 95.8)	(89.1 – 104.7)	(189.3 – 309.6)
Very elderly	32.3	79.6	96.5	250.0
	(29.2 – 36.1)	(62.0 – 108.0)	(84.1 – 110.6)	(170.3 – 385.9)

bw= body weight; P95: 95th percentile
([a])=One dietary survey had less than 60 days in the Infants and Toddlers age groups, therefore, these were not included in calculation of the 95th percentile exposure

31. UK occurrence and consumption data taken from DNSIYC And NDNS were reported in the EFSA opinion. In table 2, the mean exposure to potato total glycoalkaloids ranged from 44.5 µg/kg bw per day in adults to 115.6 µg/kg bw per day in toddlers. The 95th percentile exposure ranged from 139.3 µg/kg bw per day in adults to 389.3 µg/kg bw per day in toddlers. The UK specific exposure values for toddlers and adults falls in between the mean LB and UB exposure values reported by EFSA. The UK specific 95th percentile exposure value for adults is between the LB and UB exposure values reported by EFSA. The UK specific 95th percentile exposure value for toddlers falls in between the LB and UB exposure values reported by EFSA.

Table 2: UK specific data extrapolated from probabilistic acute dietary exposure assessment to potato total glycoalkaloids across European dietary surveys (µg/kg bw per day)

Age group	Country	Survey	Number of subjects	Mean exposure (µg/kg bw per day)	P95 exposure (µg/kg bw per day)
Infants	United Kingdom	DNSI YC 2011	2683	101.4	347.5
Toddlers	United Kingdom	NDNS years 1-3	3073	103.5	332.5
Toddlers	United Kingdom	DNSI YC 2011	2683	115.6	389.3
Other Children	United Kingdom	NDNS years 1-3	3073	92.6	296.3
Adolescents	United Kingdom	NDNS years 1-3	3073	61.5	195.6
Adults	United Kingdom	NDNS years 1-3	3073	44.5	139.3
Elderly	United Kingdom	NDNS years 1-3	3073	42.5	129.2
Very elderly	United Kingdom	NDNS years 1-3	3073	42.7	131.3

Risk Characterisation

32. The CONTAM panel decided that the available data on acute toxicity was inadequate to establish a health-based guidance value. The health-based guidance MOE value of 10 was established by EFSA to assess the possible health concern from acute exposure to potato glycoalkaloids via consumption. A MOE below 10 indicates a potential health concern, whereas a MOE higher than 10 indicates that there is no health concern. The MOE of 10 takes the extrapolation from a LOAEL to a NOAEL (a factor of 3) and the interindividual variability in toxicokinetics into account.

33. The LOAEL of 1 mg potato total glycoalkaloid/kg bw in humans was selected and used as a reference point to characterise the acute exposure risk from potato glycoalkaloids.

34. The acute dietary exposure was calculated using a probabilistic approach with applied reduction factors to take the processing of potatoes into consideration.

35. The calculated acute exposure estimates (Table 1) were compared to the reference point of 1 mg potato total glycoalkaloid/kg bw resulting in the MOE values presented in Table 3. The MOEs calculated for the younger age groups indicate a potential health concern based on the food consumption surveys, particularly in the maximum mean exposure, as well as the P95

exposures in all surveys. The MOEs calculated for the adult age groups

indicate a potential health concern based on the food consumption surveys with the maximum P95 exposures.

Table 3: Margin of exposure (MOE) values for the range of acute mean and P95 exposure assessment across different surveys.

	Mean exposure	Mean exposure	P95 exposure	P95 exposure
	Minimum	Maximum	Minimum	Maximum
Infants	28	8	3	2
Toddlers	15	5	4	2
Children	18	6	6	2
Adolescents	28	8	9	3
Adults	39	11	11	4
Elderly	34	13	10	4
Very elderly	31	13	10	4

30. Due to the lack of occurrence data in food and the limited information on the adverse effects in experimental animals and humans, the risk to human health could not be characterised for tomatoes and aubergines.

31. The CONTAM considered that the uncertainties on the risk assessment of acute exposure to potato glycoalkaloids in food is moderate, and that the identified uncertainties are either an over or underestimation of the risk.

32. Members are invited to read the Opinion and comment on the approach used by EFSA.

Questions for the Committee

33. Does the Committee:

i) agree with the selection of the critical study for the derivation of the HBGV?

ii) agree with the MOE established for potato glycoalkaloids?

iii) have any comments on the implications of the proposed MOE for the UK diet.

iv) Have any other comments on this draft opinion?

Secretariat
March 2020

References

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Annex 1 to TOX/2020/19/

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This Annex contains the EFSA opinion on the "Risks for animals and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products."

This opinion can also be accessed at:
http://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-glycoalkaloids-food