TECHNICAL REPORT

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Outcome of a public consultation on the draft risk assessment of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from interested parties on a draft scientific 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 products. This draft scientific opinion was prepared by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel), supported by the Working Group on Glycoalkaloids in feed and food. The draft opinion was endorsed by the CONTAM Panel for public consultation by written procedure on 19 February 2020. The written public consultation was open from 27 February 2020 until 15 April 2020. EFSA received comments from nine different interested parties. EFSA and its CONTAM Panel wish to thank all stakeholders for their contributions. The present report contains the comments received and explains the way they have been considered for finalisation of the opinion. The opinion was adopted at the CONTAM Plenary meeting on 7 July 2020 and published in the EFSA Journal.

Key words: glycoalkaloids (GAs), solanine, chaconine, potato, margin of exposure (MOE), food, feed, public consultation

Requestor: European Commission

Question number: EFSA-Q-2016-00911

Correspondence: biocontam@efsa.europa.eu

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

1.1.1. Background

Many plants in the family Solanaceae contain glycoalkaloids, and they are considered to be natural toxins. The plant glycoalkaloids are toxic steroidal glycosides and the commonest types found in food plants are α-solanine and α-chaconine. Their natural function is probably to serve as stress metabolites or phytoalexins for the protection of the plant when attacked by insects, fungi, etc.

Amongst the most widely cultivated food crops, aubergines, tomatoes and potatoes are in the Solanaceae family, but the levels of glycoalkaloids in tomatoes and aubergines are generally quite low.

The glycoalkaloids of most relevance to food safety are those occurring in the potato. The predominant toxic steroidal glycosides in potato are α-solanine and α-chaconine. They occur in potato tubers, peel, sprouts, berries, leaves and blossoms and their concentration in tubers depends on a number of factors, such as cultivar, maturity and environmental factors. Concentrations of glycoalkaloids are 3 to 10 times greater in the peel than in the flesh. There is considerable variation in glycoalkaloid content among potato cultivars. Storage conditions, especially light and temperature, are mainly responsible for increases in solanine. Although the glycoalkaloid content can increase in the dark, the rate of formation is only about 20% the rate of formation in light. Increases of solanine in the potato peel are closely associated with greening (synthesis of chlorophyll) of the peel. These biochemical processes are independent of each other but are both activated by light.

Bitter or burning sensation in the mouth are sensory impressions which may accompany glycoalkaloid poisoning symptoms from potatoes that include flu-like symptoms such as nausea, vomiting, stomach and abdominal cramps, and diarrhoea. More severe cases of glycoalkaloid poisoning may be accompanied by a variety of neurological effects (i.e. drowsiness, apathy, restlessness, shaking, confusion, weakness, and disturbed vision). There are a few reports of deaths being attributed to glycoalkaloid exposure from the consumption of potatoes, potato leaves, and potato berries.

Potatoes and potato-derived products are listed in the Catalogue of feed materials[1].

1.1.2. Terms of reference

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific 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 products.

1.2. Rationale for the public consultation and brief summary of its outcome

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft opinion together with its annex was released for public consultation from 27 February 2020 to 15 April 2020 by means of an electronical comment submission tool together with explanatory text on the EFSA website (See Appendix A). Comments were received from nine interested parties from five countries. Table 1 provides an overview on the interested parties that have submitted comments through the electronic submission or via email.

[1] Commission Regulation (EU) No 6812013 of 16 January 2013 on the Catalogue of feed materials (OJ L 29, 30.1.2013, p. 1).

Table 1: Overview on stakeholder comments received

Stakeholder	Category [(a)]	Country
Federal Public Service Health, Food Chain Safety and Environment	National authority	Belgium
German Federal Institute for Risk Assessment (BfR)	National authority	Germany
Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	National authority	Norway
Max Rubner-Institut	University/public research institute	Germany
National Institute for Public Health and the Environment (RIVM)	University/public research institute	The Netherlands
European Potato Processors' Association (EUPPA)	Private sector	Belgium
Starch Europe (STARCH EU)	Private sector	Belgium
Antonella Garzelli	Private capacity	United Kingdom
Matthew Walker	Private capacity	United Kingdom

(a): As specified by the commenter.

2. Assessment of comments and use for finalisation of the opinion

The comments received were duly evaluated by the EFSA WG on Glycoalkaloids in feed and food and the CONTAM Panel, and wherever appropriate taken into account for finalisation of the draft opinion. Table 2 provides a detailed list with all comments as received from interested parties together with EFSA responses and explanations how the comments were considered for finalisation of the draft opinion.

Table 2: Stakeholder comments and EFSA responses

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
Belgian Federal Public Service Health, Food Chain Safety and Environment	1	3.5.2. Exposure scenario/exposure model	**Line 3919 -** It would be useful to obtain confirmation whether the occurrence data on unprocessed potatoes were indeed analyzed unpeeled (with the skin). Peeling can be a sample preparation method for a laboratory analyzing GAs in potatoes.	Out of the initial 651 samples only 7 samples were reported explicitly as peeled and were not included in the average. Further, 18 samples reporting 'processed' potatoes under the PRODTREAT variable were also excluded. After the cleaning (see Annex A2), 604 samples were included in the final dataset. Of these, 25 samples were explicitly reported as unpeeled. 440 samples were reported as unprocessed and 8 were reported both as unpeeled and unprocessed. The data providers confirmed they were not able to retrieve additional information on the peeling. Samples reported as unprocessed were considered unpeeled, because peeling implicates a processing step. In the absence of information about peeling or processing it was assumed that the 131 remaining samples were analysed unpeeled.
			Food processing/reduction factors: The use of processing/reduction factors to data on potatoes is indeed a source of uncertainty. 1) It is known that specific varieties are used for the production of specific processed products, hence some varieties are grown for the production of potato crisps, etcetera. 2) experimental reduction factors are not the same as what happens in industry. There is a need to use real occurrence data in commercial samples. In Belgium, a survey for the Federal Public Service Health, Food Chain Safety and Environment is ongoing showing that potato crisps in retail have levels higher than expected from the information in the draft EFSA opinion. Of course, occurrence data on potato crisps should be combined with consumption data for potato crisps.	The CONTAM Panel acknowledged the uncertainty linked to the use of processing factors due to the limited data on processed potato products submitted to EFSA (as described in Section 3.5.2 of the Opinion). EFSA welcomes the submission of occurrence data on GAs in potato and potato products as well as other food groups via the Continuous Call for Data Collection. Such data will be used for future risk assessments.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
German Federal Institute for Risk Assessment (BfR)	2	1.3.2. Analytical methods	**Entire Chapter 1.3.2.2 (Detection methods):** The chapter gives a good overview of past and current methods for glycoalkaloid detection and quantification. However, many of the presented methods are not in use anymore, e.g. gravimetric, colorimetric and GC-FID/NPD methods. It should be clearly stated in this chapter that use of these methods is not recommended due to the analytical drawbacks (in particular lacking specificity) and the availability of better methods (LC-MS).	This section provides a general overview of the methods that have been used in the past and present for the analysis of GAs. Recommendation of analytical methods for the analysis of GAs is outside the remit of EFSA. However, to stress the current state of the art, in the introduction of Section 1.3.2 of the Opinion, a sentence has now been added that states that these unspecific methods are no longer used for quantitative purposes. Furthermore, in the paragraph on GC-FID methods a sentence has now been added that nowadays LC-based methods have replaced GC-based methods. The CONTAM Panel also found it appropriate to add a new sub-section under Section 1.3.2 to acknowledge the availability of GAs and their aglycons as analytical standards, of reference material and of proficiency testing schemes.
	3	1.3.3. Sources	**line 596, p.17:** The species name (here: Solanum) should be written in italic letters as it is done in the rest of the opinion.	Editorial suggestion implemented.
	4	1.3.3.1. Potatoes	**line 603, p.17:** The species name (here: Solanum) should be written in italic letters as it is done in the rest of the opinion.	Editorial suggestion implemented.
	5	3.1.1.2. Humans	**lines 1225/1226, page 34 (3.1.1.2.1):** It is suggested to add "after oral exposure" in the heading of table 5. "Pharmacokinetic parameters (ranges) of α-solanine and α-chaconine in human volunteers after oral exposure (adapted from Mesinga et al., 2005)."	Editorial suggestion implemented.
	6	3.1.2.1. Acute toxicity studies	**lines 1372 and 1377, page 37 (3.1.2.1.2):** Although this information may be found in the tables, it is suggested to add the following information also in the text for an easier reading: Wilson et al. 1961: Which compound was applied and via which route? Baker et al. 1989: Which application route was used?	The information has now been added to the text in the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	7	3.1.2.2. Repeated dose toxicity studies	**lines 1429 to 1431, page 44 (3.1.2.2.1):** It is suggested to move this paragraph to 3.1.2.2 and to mention also table 13 in the text as the content of this section is applicable not only for chapter 3.1.2.2.1 but also for chapter 3.1.2.2.2. Otherwise, it should be separately noted under 3.1.2.2.2 that all these studies investigated effects following oral exposure.	The information has been shifted ahead of Section 3.1.2.2.1 and applies now to Section 3.1.2.2.2 and Table 13 of the Opinion.
			line 1630, page 51; line 1640, page 54; line 1647, page 56 (3.1.2.2): It is highly recommended to add the word "dose" to the header of tables 11, 12 and 13: "Repeated dose oral toxicity studies…".	Editorial suggestion implemented.
	8	3.1.2.3. Developmental and reproductive toxicity studies	**lines 1825 and 1826, page 63 (3.1.2.3.1.4):** Although this information may be found in the tables, it is suggested to add the route of exposure also in the text for an easier reading.	The route of exposure has been added for clarity.
			line 1834, page 64 (3.1.2.3.2): Although this information may be found in the tables, it is suggested to add the route of exposure also in the text for an easier reading.	The route of exposure has been added for clarity.
			line 1903, page 74; line 1906, page 75 (3.1.2.3.2): It is highly recommended to add the word "toxicity" to the header of tables 16 and 17: "Reproductive toxicity studies…".	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	9	3.1.2.4. Immunotoxicity studies	**entire chapter**: It is noted that the studies described within this chapter did investigate the pharmacological potential (anti-inflammatory effects) rather than immunotoxicity. It appears that these studies may be excluded. Since it is already stated in the first sentence that no standard immunotoxicity studies are available and the described studies do not directly address this issue, at least the last sentence of the chapter "*No indication of immunotoxicity was seen in these studies*" should be replaced, e.g. by "The CONTAM Panel notes that the available studies are not appropriate to conclude on the immunotoxic potential of GAs".	The CONTAM Panel acknowledges this comment and the following sentence has been added to Section 3.1.2.4 of the Opinion: "*The CONTAM Panel notes that there is not sufficient information to conclude on the immunotoxic potential of GAs*".
			line 1913, page 76: The word "mg" after 100 mg may be deleted.	Editorial suggestion implemented.
			line 1918, page 76: It appears that the dose of 0 mg/kg bw was added here by mistake. Otherwise the described effect would have been observed also at the control group.	The CONTAM Panel notes this was added by mistake and the 0 mg/kg dose has been deleted.
	10	3.1.2.7. Genotoxicity	**lines 1965 to 1966, page 77 (3.1.2.7.1) and lines 1983 to 1984, page 77 (3.1.2.7.2):** The available studies on the genotoxic potential of GAs are not sufficient to finally conclude on the genotoxic potential of these compounds. Therefore, the conclusion of the panel in chapter 3.1.2.7.1 and 3.1.2.7.2 "…*from the limited number of studies available, there was no evidence for genotoxicity*…" should be supplemented, e.g. by "However, the available data is not appropriate to finally conclude on the genotoxic potential of GAs." Furthermore, such a statement should also be added at the appropriate position in the summary (e.g. line 118), in chapter 3.1.6 (e.g. line 2934 and 2988) and in the conclusion (e.g. line 4021).	The CONTAM Panel acknowledges the comment and the following sentence has been added to the Opinion in the relevant sections: "*However, there is not sufficient information to conclude on the genotoxic potential of these GAs"*.
	11	3.1.2.9. Studies on metabolic effects	**line 2014, page 82 (3.1.2.9.2):** It appears that one "that" has to be deleted.	The duplication has been deleted.
	12	3.1.3.2. GAs from food plants other than S. tuberosum	**line 2321 to 2325, page 91 (3.1.3.2.1):** The first case report presented in this chapter appears of less relevance as the described symptoms most probably arise from the contamination with Datura mental containing scopolamine and atropine. It is suggested to delete this case.	The CONTAM Panel agrees and the study has now been deleted from the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	13	3.1.4. Adverse effects in farm animals, horses and companion animals	**line 2425, page 94:** It is highly recommended to add the word "oral" to the header of table 21: "Acute oral toxicity…".	Editorial suggestion implemented.
			line 2430, page 95; line 2434, page 96; line 2439, page 97: It is highly recommended to add the word "dose" to the header of tables 22, 23 and 24: "Repeated dose toxicity of…".	Editorial suggestion implemented.
	14	3.1.6.1. GAs from edible parts of S. tuberosum	**lines 2877 to 2878, page 108 (3.1.6.1.1):** The last part of the clause "*Based on human data on case reports, outbreaks and studies in volunteers, the CONTAM Panel selected the LOAEL of 1 mg potato TGA/kg bw per day as the reference point for acute exposure to potato TGAs via food*" might be misleading to the reader. It is suggested to replace the sentence, e.g. by "… as the reference point for evaluating the risk following acute oral exposure".	Editorial suggestion implemented.
			line 2936, page 109 (3.1.6.1.1): "*Results from limited developmental toxicity studies…*" It is recommended to specify whether a limited number or quality of studies is meant.	The sentence has now been clarified in the Opinion.
			lines 2951 to 2955, page 109 (3.1.6.1.2): The last part of the clause "*Based on the available information, the CONTAM Panel considered the LOAEL of 1 mg potato TGA/kg bw per day based on the data from case reports, outbreaks and studies in volunteers, as the reference point for acute exposure to potato TGAs via food*" might be misleading to the reader. It is suggested to replace the sentence, e.g. by "… as the reference point for evaluating the risk following acute oral exposure".	Editorial suggestion implemented.
	15	3.2.2.1. Literature on occurrence data on food	**lines 3184 to 3197, page 118 (3.2.2.1.1):** The paragraph is an exact text duplicate from page 116, lines 3164 to 3177. It appears that this paragraph has to be deleted.	The duplication has been deleted.
			line 3309, page 123 (3.2.2.1.1): The term "*consumption potatoes*" in the header of table 32 might be replaced by "table potatoes" or "potatoes for human consumption".	Editorial suggestion implemented.
			line 3313, page 124 (3.2.2.1.1): Missing blank space in the header of table 33: "*Totalglycoalkaloids*" has to be replaced by "Total glycoalkaloids".	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	16	3.3.1. Current dietary acute exposure assessment for humans	**lines 3728 and 3729, page 143:** The term "*dietary acute exposure*" might be replaced by the more common "acute dietary exposure" that is also used in the rest of the opinion.	Editorial suggestion implemented.
			line 3732, page 143: The term "*acute risk assessment*" is misleading as it might be interpreted as a preliminary ad-hoc assessment. The term could be replaced, e.g. by "assessing the risk following acute exposure".	Editorial suggestion implemented.
			table 42, page 143: The word "*durvey*" needs to be replaced by "survey".	The spelling has been corrected.
			lines 3755 to 3756, page 144: The text of the figure header is difficult to interpret: "*Mean daily amounts of main-crop potatoes (grams per day) calculated on consumption days by food source category for Adults and Todders across the different surveys*."	The header of the figure has been revised for clarity.
	17	3.3.2. Previously reported dietary exposure assessments	**line 3788, page 145:** The term "*mean acute estimates*" should be replaced by "mean acute exposure estimates".	Editorial suggestion implemented.
			line 3794, page 145: The phrase "*Median (and upper 97.5% confidence limit) chronic estimates of intake…*" should be replaced by "Median (and upper 97.5% confidence limit) estimates of chronic intake…".	Editorial suggestion implemented.
	18	3.4.1.1. GA from edible parts of S. tuberosum	**line 3843, page 147:** "*Margin of exposure (MOE) values for the range of acute mean and P95 exposure assessment across different studies*". It is suggested to delete the word "assessment" in this header of table 43.	Editorial suggestion implemented.
			lines 3853 to 3854, page 147: The header of table 44 "*Summary statistics of the % of survey days with an intake of potato TGAs below the margin of exposure (MOE) of 10 calculated only for the days of potato consumption…*" might be replaced by "Summary statistics of the % of survey days with an intake of potato TGAs leading to a margin of exposure (MOE) of below 10 calculated only for the days of potato consumption…".	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			lines 3856, page 147: The phrase "(*a) The mean percentage of days below the MOE of 10…*" should be replaced by "(a) The mean percentage of days with intakes leading to MOE values of below 10…".	Editorial suggestion implemented.
	19	3.5.3. Hazard identification and characterisation	**lines 3950 to 3952, page 150:** The clause "*Differences in absorption and excretion were observed for these two GAs in rats and hamsters*, …" should be replaced by "Differences in absorption and excretion between rats and hamsters were observed for these two GAs,…".	Editorial suggestion implemented.
	20	4.1.6. Margin of exposure (MOE) approach	**lines 4049 to 4050, page 153:** The phrase "…, *as the reference point for the acute risk characterisation*" might be replaced by "…, as the reference point for assessing the risk following acute exposure".	Editorial suggestion implemented.
	21	Appendix B	**lines 5144 and 5168/5169, page 185; lines 5191/5192, page 186; lines 5214/5215, page 187 (B.1):** It is confusing why the final number of hits regarding adverse effects of gylcoalkaloids in humans after removal of dublicates is 330 as mentioned in line 5144 whereas the search for the terms "solanine", "chaconine", "glycoalkaloids" in this regard yielded 356, 206 and 541 hit after removal of duplicates, respectively.	The final number of hits 330 refers to the combination of the final identified papers for the three searches (Solanin*, Chaconin* and GAs) from the three databases Pubmed, Scopus and Web of Science without duplicates (single unique entries from the three databases combined, (356 Solanin*, 206 Chanconin* and 541 for the search of general Glycoalkaloids). Those three results (a total number of 1,103) were combined in a single folder and further screened for duplicates. The final number of single entries for the searches resulted in 330 papers.
			line 5225, page 187 (B.1): The listing has to be started with tomato alkaloids here as bullet point a.	Editorial suggestion implemented.
	22	Appendix H	**line 5311 (Table H.1):** The phrase *"(a) The mean percentage of days above the LOAEL…*" might be replaced by "(a) The mean percentage of days with intakes above the LOAEL…".	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	23	Other	With reference to the List of authors (lines 5 and 7, page 1): Dieter Schrenk is mentioned twice as author.	Editorial suggestion implemented.
			With reference to chapter no. 1.1 (lines 365 and 370, page 11): The family name of plants (here: Solanaceae) should be written in normal instead of italic letters as it is consistently done in the rest of the opinion.	Editorial suggestions implemented.
Max-Rubner Insitute	24	1. Introduction	**lines 384-385, page 11 (1.1):** Bitter and burning sensation is in this circumstance described as a symptom associated with GA poisoning and thus appears in this sentence to be a clinical symptom. From another point of view, bitter taste and burning sensation are terms that are used as sensory descriptors. This discrepancy could be solved, if the first part of the sentence would be rewritten; e.g. "Bitter or burning sensation in the mouth are sensory impressions which may accompany glycoalkaloid poisoning symptoms from potatoes that include flu-like symptoms such as nausea, vomiting, …"	Since this comment refers to Section 1.1. Background and Term of Reference as provided by the requestor, the requestor (EC) has been consulted and the text has been modified according to the suggestion.
	25	1.3.1. Chemistry	**lines 428-447, page 12-13:** This section deals with the chemical structure of the relevant alkaloids referring to the Appendix A. It is noticed that no literature is cited in the section mentioned. It is recommended to proof if there really is no need for including a reference.	Some references to relevant reviews have now been added to Section 1.3.1 of the Opinion.
	26	1.3.3.1. Potatoes	**lines 619-621, page 17:** Localization and development in skin and sprouts was visualized impressively by Ha et al. using MALDI-TOF. (Ha, M., Kwak, J. H., Kim, Y., & Zee, O. P. (2012). Direct analysis for the distribution of toxic glycoalkaloids in potato tuber tissue using matrix-assisted laser desorption/ionization mass spectrometric imaging. Food Chemistry, 133(4), 1155-1162.) This reference is suggested to take into account.	The CONTAM Panel acknowledges this information. A sentence describing the work of Ha et al. (2012) has now been added to Section 1.3.3.1 of the Opinion.
			line 670, page 20: The sentence seems to contain a syntax error. It is recommended to delete "as to".	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	27	1.3.3.2. Tomatoes	**lines 681-682, page 20:** There are data from 2018 available. It is recommended to actualize the FAO data on production.	The Opinion has been updated with the FAO data on potato, tomato and aubergine production in 2018.
			lines 704-731, page 21: In this chapter, several references have been cited that show the GA concentration in developing tomato fruit tissue. Additionally, there is a holistic work on this topic available that was performed by Moco et al. using a metabolomic approach. Moco, S., Capanoglu, E., Tikunov, Y., Bino, R. J., Boyacioglu, D., Hall, R. D., ... & De Vos, R. C. (2007). Tissue specialization at the metabolite level is perceived during the development of tomato fruit. Journal of Experimental Botany, 58(15-16), 4131-4146. It is suggested to proof if the work performed by Moco et al. could complement the chapter.	The CONTAM Panel acknowledges this information. The work of Moco et al. (2007) has been incorporated in Section 1.3.3.2 of the Opinion.
	28	1.3.4. Previous risk assessments	**line 843, page 24:** Literal error:…"levels". "level" in the singular form would be correct.	Editorial suggestion implemented.
	29	2.5. Methodology for Exposure assessment	**line 1059, page 29:** Literal error:…"*reductions*". "reduction" in the singular form would be correct.	Editorial suggestion implemented.
	30	3.1.2.1. Acute toxicity studies	**line 1372, page 37 (3.1.2.1.2.):** … "*900–1,000 mg/kg bw*". The value is assumed to be related to tomatine, but it is not mentioned in the text.	The sentence has been revised to clarify to what it refers.
			line 1377, page 37 (3.1.2.1.2.): … "*6,316 mg dw*". The unit seems to be incorrect. It is expected "mg/kg dw"	Units have been corrected.
			lines 1391-1392, page 38 (3.1.2.1.3.): This sentence is redundant with the sentence in lines 1396-1397. The sentence may be deleted in lines 1391-1392.	Editorial suggestion implemented.
			lines 1408, 1409, page 40 (3.1.2.1.3.): Table 7, row 3 (observed effect), in line 11 it is written "lower blood". "lower" should be exchanged by an arrow (↓).	Editorial suggestion implemented.
	31	3.1.2.2. Repeated dose toxicity studies	**lines 1524-1527, page 46 (3.1.2.2.1.):** Which amount of GAs was applied to the experimental animals?	The estimated intakes of GAs in mg/kg bw/day are now given in the text.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	32	3.1.2.3. Developmental and reproductive toxicity studies	**line 1689, page 60 (3.1.2.3.1.1.):** The sentence seems to contain a error as GD8 appears two times. It is recommended to delete "on GD8" at the sentence end.	Editorial suggestions implemented.
			lines 1712-1713, page 61 (3.1.2.3.1.1.): "*Maternal death was observed for 4 and 6 dams respectively, …*" The size of the population should be added here.	The CONTAM Panel could not find any indication for the number of dams treated per group in the study. The best estimation is, that the total group size is represented by the sum of the number of dead dams, resorbed litters and live litters reported, assuming that each dam investigated was pregnant. For consistency, the same information was also added for α-solanine.
			lines 1861-1862 and 1869-1871, page 64 (3.1.2.3.2.): It is suggested to add the information about the length of the application period.	The duration of both experiments was 30 days. This information is now added in the description of the study.
	33	3.1.2.4. Immunotoxicity studies	**line 1931, page 76:** It should be proven if solanidine is to be added in this conclusion.	The study by Emmanuel et al. (2006, abstract only) referred to solasodine and not solanidine, as wrongly indicated in the text. This error has now been corrected and the conclusion does not need to be amended.
	34	3.1.2.7. Genotoxicity	**lines 1986-1984, page 77 (3.1.2.7.2.):** A statement on tomato GAs should be included to stay congruent with the other chapters.	A sentence has now been added in Section 3.1.2.7.2 to clarify that no studies could be identified investigating the genotoxicity of tomato GAs.
	35	3.1.2.9. Studies on metabolic effects	**line 2014, page 82:** Literal error: Two times "that" is written in the sentence.	The duplication has been deleted.
	36	3.1.3. Observations in humans	**lines 2092-2094, page 84**: If the cooked, peeled potatoes contain 240 mg Solanine per kg and the intake of soldiers is estimated to be 300 mg Solanine, this means that the soldiers would have eaten more than 1 kg of potatoes in their meal. This amount seems too high. It is suggested to proof the amount consumed by the soldiers in the original reference.	The amounts and values indicated in the description of the Pfuhl (1899) study are correctly reported.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	37	3.1.3.1. GAs from S. tuberosum	**line 2202, page 86 (3.1.3.1.2.):** The last part of the sentence ("*,…assuming a weight of 150 g per potato*") could be omitted, as the content does not provide the reader with substantial information in this context.	The part of the sentence indicated has now been deleted.
	38	3.1.4.2. Pigs	**lines 2357-2362, page 92:** It seems to be questionable if the potato protein contains enough GA to cause symptoms after consumption by the tested pigs. The study does not contribute to the overall conclusions.	The CONTAM Panel agrees that the study does not contribute to the overall conclusion. The study was mentioned to demonstrate the limitations of the data available.
	39	3.1.5.1. Membrane effects with implications for the gastrointestinal tract	**line 2714, page 104 (3.1.5.1.3.):** "*in processes of neuronal and non-neuronal developmental…*" There seems to be a literal error.	The sentence has now been revised and the missing word was added.
	40	3.1.5.2. Inhibition of cholinesterases (ChEs)	**line 2553, page 100:** "*…body fluids and concentrations used to study…*". It could be added if the inhibitor or the substrate concentration was meant here (or both).	The sentence has been revised to clarify the meaning.
	41	3.1.6.1. GAs from edible parts of S. tuberosum	**line 2812, page 106:** "*Bitter taste, gastric discomfort and nausea may occur within ~30 min after ingestion of ~1 mg potato TGA/kg bw contained in a potato meal*". In contrast to the symptoms mentioned, the bitter taste is not dependent on the GA dosis per kg bw. The taste threshold is dependent on the concentration in the food matrix.	According to the suggestion, reference to bitter taste has been deleted in this Section of the Opinion.
			line 2864, page 107: "*based on the likelihood to develop diarrhoea after ingestion of potato TGA, humans show an approximately 300-fold higher susceptibility (towards this adverse effect of potato TGA) than rats*." The last part of the sentence contains redundant information and could be deleted.	The Panel agrees that a part of the sentence is redundant and deleted this part.
			lines 2919-2921, page 108 - 109: "*To conclude, the data available for repeated dose toxicity are not sufficient to identify a reference point for chronic exposure to potato GAs*." This sentence is redundant with the sentence in lines 2927-2928, and could be deleted.	According to the suggestion, the sentence has now been deleted to avoid the redundancy.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	42	3.2.1. Occurrence data submitted to EFSA	**lines 3003-3008, page 111:** The data collection is explained in this paragraph: "*Data were reported on samples collected between the years 2005 and 2017.*". Looking at Table 28 there is a gap of data submission to the study from 2008 until 2014. Could an explanation be given for this gap?	Data are submitted by data providers on a voluntary basis upon an annual generic call for data by EFSA. The gap seems due to the fact that data on GAs are not regularly/systematically collected nor submitted to EFSA. See also reply to Comment 65.
	43	3.2.2.1. Literature on occurrence data on food	**lines 3313-3314, page 124:** Page 124, Table 33, headings of row 5 (TGA average) and 6 (Range). Are the units fw or dw based?	The concentrations are based on fresh weight. This has now been clarified in the table headings.
	44	3.2.2.1. Literature occurrence data in feed	**line 3366, page 126 (3.2.2.1.3.):** … "*1,402-2,210 mg fw*' The unit seems to be incorrect. It is expected "mg/kg fw".	Editorial suggestion implemented.
			line 3399-3401, page 127: "*No surveys on the levels of GAs in potatoes and potato by-products used as feeds for livestock have 3400 been identified in the open literature.*" Should the companion animals be added here?	Editorial suggestion implemented.
	45	3.2.3. Influence of pre-harvest factors on the content of GAs	**lines 3430 - 3432, page 132:** "*Factors that influence the content of GAs pre-harvest have been briefly described in Section 1.3.3 and 3.2.2.1.1.*" Could the paragraph 3.2.3. be omitted?	The Panel acknowledges that Section 3.2.3 of the version of the draft opinion under public consultation does not add new information, and thus it has been deleted from the final version of the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	46	3.2.4.1.GAs from S. tuberosum	**lines 3469 - 3483, page 132 - 133 (3.2.4.1.1.):** This paragraph deals with packaging and light conditions during storage as well as with application of sprout suppressants. A compatible study was performed by Haase (2010) emphasizing the importance of sprouting on GA formation. **Haase, N. U. (2010). Glycoalkaloid concentration in potato tubers related to storage and consumer offering. Potato Research, 53(4), 297-307.** It is suggested to proof if the work performed by Haase (2010) could complement the chapter.	The CONTAM Panel acknowledges this information and the study has been added to Section 3.2.3.1 of the Opinion for completeness of the information provided.
			lines 3469 - 3483, page 132 - 133 (3.2.4.1.1.): Another publication is to be mentioned in this context: **Olsen, N. L., et al. (2018). "The Impact of Retail Light Source on Greening of Russet Burbank Potato Tubers." American Journal of Potato Research 95(2): 123-129.** This reference is suggested to take into account with regard to the influence of consumer offering which is considered being of high practical relevance.	The CONTAM acknowledges this information and the study has been added to Section 3.2.3.1 of the Opinion for completeness of the information provided.
			lines 3474 - 3475, page 133 (3.2.4.1.1.): "*…although other studies have reported that potatoes stored in polyethylene bags showed higher GA levels that those packaged in mesh or paper (Gosselin and Mondy, 1989).*" "although" indicates a contradiction. However, if the transmission of light that induces GA formation is lower for mesh or paper, there seems to be no contradiction.	The sentence has been revised to delete the word 'although'.
	47	3.2.4.2. GAs from food plants other than S. tuberosum	**lines 3688-3689, page 142:** "*Freeze-drying of the produced tomato homogenate and subsequent storage for 4 weeks at room temperature, resulted in a reduction of the tomatine content of 82–85% (Kyzlink et al., 1981).*" Does the calculated reduction include a correction of moisture loss?	Yes, the calculated reduction takes the moisture loss into account. The sentence has been rephrased to make this clearer.
	48	3.3.1. Current dietary acute exposure assessment for humans	**lines 3739 - 3744, page 143:** Table 42, line 1: "*Range across durveys…*" There seems to be a literal error: surveys.	The spelling has been corrected.
			lines 3755 - 3757, page 144: Figure 8 The colors of some of the food sources are difficult to distinguish. The y and x-axis are small and difficult to read.	The format of Figure 8 has been revised for a better readability.
	49	3.4. Risk characterisation	**line 3840, page 146:** "*Comparison of the acute exposure estimates (see Table 43) to the*". There seems to be a literal error: Table 42.	Editorial suggestion implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	50	References	**line 4223, page 157:** Literal error: "…the effect of variety and drought stress on thea-solanine and a-chaconine contents of potatoes. Journal of the"… Instead of "thea" an "a"	Editorial suggestion implemented.
European Potato Processors' Association (EUPPA) [Three attachments were submitted by this commenter during the public consultation. See **Annex A** of this Technical report.]	51	Summary	**Page 6, recommendations section lines 223-240:** • In addition to the listed recommendations, we recommend also determining the link between greening on potatoes and processed potato products and the association with glycoalkaloid content. Glycoalkaloids can vary widely due to environmental and genetic factors, and can be elevated in certain varieties of stresstolerant potatoes and this increase in glycoalkaloid content is not associated with potato greening or increased toxicity. Glycoalkaloids are used as an indicator of toxicity due to greening in many markets, and the association between greening and glycoalkaloid content should be determined to understand if incidental potato greening is a health risk.	Further information about the evidence available on the link between greening (i.e. chlorophyll formation) and increase in the levels of GAs has now been added in Section 3.2.3.1.1 of the Opinion. A direct relationship between greening of the potato tubers and increase in the GAs levels has not been established, and depends on the potato cultivars and other factors.
			• Determine factors that increase glycoalkaloids and potential mitigation measures. Storage conditions, such as lighting and temperature can impact glycoalkaloid levels in raw potatoes, and chemical treatments such as detergents and sprout inhibitors decrease glycoalkaloid concentrations in raw potatoes. Additionally, processing factors, such as peeling, boiling, frying, and dehydrating potatoes significantly impacts glycoalkaloid concentrations. These different treatments should be factored in when determining acceptable glycoalkaloid levels in the finished product.	Establishing maximum levels of GAs in finished products is a risk management measure and it is out of the remit of EFSA.
			• Animal toxicology and metabolism studies can be difficult to extrapolate to humans due to differences in the route of exposure, metabolism, and other biological factors of the test animal that do not translate to humans. We recommend ascending dose clinical toxicology and toxicokinetic studies using processed potato products with established glycoalkaloid concentrations to determine a lowest observed and no observed effect level for glycoalkaloids; the reference dose should be based on human toxicity and metabolism via the oral route of exposure with the estimated dietary intake of the processed potato product using data on amounts and frequency of product consumption.	The CONTAM Panel followed the strategy, as outlined by EUPPA: toxicokinetic and toxicodynamic studies on human volunteers and human observation studies with oral uptake of specified doses of GAs were used by the Panel to establish a reference dose. For further details please see Section 3.1.6.1 of the Opinion on 'Considerations of critical effects and dose-response analysis for the human risk assessment' and Section 3.4 on 'Risk Characterization'.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	52	3.2.1. Occurrence data submitted to EFSA	**Page 111-112:** It is not clear which potato varieties have been used for the study and whether long term stored potatoes have been assessed in the study	In the exposure assessment made by EFSA all available table potato varieties were used. No sufficient data were available to compare occurrence in different varieties and no information about the length of the storage was available in the occurrence dataset submitted to EFSA nor in the Consumption database.
	53	3.2.2.1. Literature occurrence data in feed	**Page 124, Table 33:** The sample sizes used to determine the average glycoalkaloid levels for processed potato products is very small and should be increased to a statistically significant sample size. This data does not take into account the different varieties of potatoes and associated glycoalkaloid levels, as glycoalkaloid levels can vary significantly across varieties. We recommend gathering data on these products using statistically significant sample sizes as well as accounting for variety-specific glycoalkaloid levels, as well as water content of the product. This would provide a more accurate representation of glycoalkaloid levels in the finished good.	The CONTAM Panel agrees that the available data from the literature on GAs in processed potato products is very limited and for a large part also dated. The Panel had identified the lack of occurrence data on GAs and their aglycones in potato processed products, including foods for infants as an important need and therefore had made a recommendation (see Section 5 of the Opinion). The Panel acknowledges the occurrence data submitted by EUPPA in the context of this public consultation. Due to time constraints, EFSA cannot use additional occurrence data submitted during the public consultation for the dietary exposure assessment in this risk assessment. However, occurrence data submitted in SSD format will be stored and considered for future risk assessments (see also reply to Comment 80).
	54	3.2.4. Influence of storage and processing on the content of GAs	**Page 135, lines 3574-3576** Dehydration of potatoes can increase glycoalkaloid concentrations due to water loss creating a concentrating effect in processed potato products, such as potato flakes and potato flour. A concentration factor for glycoalkaloids in dehydrated potato products is recommended to account for concentration increases that occur as a result of water loss. This same factor adjustment is used for pesticides that concentrate in dehydrated potato products, such as pesticides in potato flakes and chips, allowing a higher residual level in the processed product to account for water loss.	Dehydration of potatoes may result in increased concentrations of GAs in the product. The effect of dehydration is corrected for when the processed food products are converted to their corresponding quantities in the RPC database.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Considering that potato flakes undergo additional processing, the allowable limit of glycoalkaloid concentration should be increased since further processing occurs. Potato flakes are used in mashed potatoes and some potato chips, formed potato products, and as thickeners in soups, gravies and sauces. The final glycoalkaloid threshold should be based on glycoalkaloid concentration in the finished products and potential toxicity.	Processing of potatoes may result in changed concentrations of GAs in the final product. This is corrected for when the processed food products are converted to their corresponding quantities in the RPC database. The establishment of maximum limits for GAs in potato products as well as for the raw commodities is a risk management measure and it is outside the remit of EFSA.
	55	3.3.3. Current dietary exposure assessment for farm animals, horses and companion animals	The peel (skin) of our potatoes, together with other potato by-products as a result of our manufacturing process, have feed as a final destination. As already mentioned, there is a high concentration of glycoalkaloids in the skin of tubers. In case of a MRL will come into force, is there a possibility that a factor will also come for feed? This will be also a challenge for us to be able to comply with.	Establishing maximum levels of GAs in finished products is a risk management measure and it is outside the remit of EFSA.
	56	Other comments	It is important to highlight what the industry does to prevent green potatoes to enter the food chain: Camera detection in several points in the processing line (incoming, after peeling, after cutting).	See reply to Comment 51.
Norwegian Scientific Committee for Food and Environment, Panel on Contaminants	57	Summary	**Line 123-125:** "*Further symptoms, including drowsiness, apathy, confusion, weakness, vision disturbances, rapid and weak pulse, and low blood pressure may be the consequence of dehydration*." What is meant? That other symptoms could not be due to GAs? Or do you mean to say that the signs and symptoms from dehydration are hard to separate from neuro-effects?	The sentence has been modified to clarify that these symptoms maybe the consequence following vomiting and diarrhoea caused by GAs.
	58	3.1.3.1. GAs from S. tuberosum	The heading in 3.1.3.1.4 "*conclusions*" should rather be "summary" since the conclusions of the risk assessment come later.	Editorial suggestions implemented.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	59	3.1.6.1. GAs from edible parts of S. tuberosum	Why were the human data considered insufficient? What does the CONTAM Panel think would be sufficient to establish an ARfD? The reason for saying the data are insufficient is not explained in 3.1.6.1.2. However, the Panel is quite specific in which MOE that is needed to conclude no health concern. ("An MOE higher than 10 indicates that there is no health concern"). It seems thus that an ARfD could have been established based on the available data. Why was it considered necessary with an UF of 3 to extrapolate from LOAEL to NOAEL? It is reasonable that 1 mg/kg bw can be considered a LOAEL based on Harvey et al. (1985) with none of three affected (only bitter taste) and Hellenäs et al. (1992) with 6 out of 7 volunteers affected (nausea, however, could also be placebo effect). The study by Mensinga et al. (2005) indicates however that 1 mg/kg bw is close to a NOAEL. The participants received potato TGA at 0.3, 0.5, 0.7, 0.95, 1.10 and 1.25 mg/kg bw, and one out of two participants at the top dose showed effects. Although the number of participants in each dose group is low, it seems that even an UF 2 would be more than sufficient to extrapolate from LOAEL to NOAEL. We fully agree an UF of 3.2 for toxicodynamic differences is needed.	The human data were considered insufficient to establish an ARfD since from none of the studies in human volunteers with oral administration of GAs in an adequate matrix, such as a potato meal, a NOAEL could be identified. Furthermore, no data indicating a NOAEL in children were available. In Mensinga et al. (2005) the outcome of the study arm in which TGA was administered in solution in doses of 0.3, 0.5 and 0.7 mg/kg bw is considered to be only of limited relevance since it does not reflect realistic conditions of exposure to GA in the presence of a potato matrix. From the subjects receiving 0.95, 1.10 and 1.25 mg TGA/kg bw in mashed potatoes, one of the two subjects in the high dose group developed nausea and started vomiting. In the view of the CONTAM Panel, the results of this study show that a dose as low as 1.25 mg/kg bw may induce adverse effects in certain individuals. However, the study design and in particular the low number of volunteers per group does not allow to draw exact conclusions on dose-adverse effect-relationships. Therefore, an UF of 3 is considered adequate to take the existing uncertainties into account when extrapolating from a LOAEL to a NOAEL.
National Institute for Public Health and the Environment (RIVM)	60	Summary	RIVM would like to congratulate EFSA on the work done and we hope that our comments will be of use in the finalization of the opinion. **Line 179:** EFSA states: '…*reduction factors for the major food processing steps*…'. In other frameworks (e.g. PPR) these are called processing factors. Please consider a harmonized wording across frameworks.	To avoid confusion, in the context of exposure calculations the term 'processing factor' has now been used instead of 'reduction factor'. In the context of the effect of processing on the TGA content the term 'percentage reduction' has been used instead of 'reduction factor'.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Lines 179-183: EFSA states: '*For the exposure assessment, reduction factors for the major food processing steps, comprising peeling and heat processing (boiling, frying, baking), were applied to the occurrence data as follows: reduction factors between 0.25 and 0.75 were attributed to the peeling of potatoes, between 0.2 and 0.9 for frying and deep frying, and between 0.05 and 0.65 for all other cooking methods*.' Lines 177-178 also provide processing factors for microwave cooking and oven baking, but these processing factors were not used in the exposure assessment. Could you please motivate in the relevant section of the opinion why the processing factors for microwave cooking and oven baking were not considered in the exposure assessment.	The selection of processing factors is described in Section 2.5 of the Opinion on 'Methodology for exposure assessment' and is based on the available literature presented in Section 3.2.4. Unfortunately, in the RPC Consumption Database no specific information is available for microwaving and baking events, only for cooking in water (and stewing). For this reason, it is not possible to use specific processing factors for baking and microwaving in combination with the RPC Consumption Database. The available literature furthermore indicates that there are only small differences between processing factors for boiling (0.35–0.95), microwaving (0.55–0.95), baking (0.5–0.8) and drying (0.38-0.71). It is therefore reasonable to assume that the processing factor for boiling covers that of baking and microwaving as well as drying heat treatments.
	61	2.5. Methodology for Exposure assessment	From the description of the text in section 2.5, we gathered that CONTAM Panel estimates the acute exposure by combining the daily consumption patterns of foods by one randomly selected concentration value for the relevant foods, which was combined with a randomly drawn processing factor, resulting in one acute exposure per consumption day. This is done for all consumption days available per age group and survey, resulting in a distribution of acute exposures. The number of acute exposures is defined by the number of days in an age group and survey at which potato(products) are consumed. Consequently, this is repeated a 1000 times, resulting in 1000 distributions. These 1000 distributions are subsequently used to calculate the mean and P95 exposure, and to derive uncertainty intervals around these ' best estimates'. Assuming that the above description indeed describes the procedure taken by CONTAM Panel to assess the acute exposure, we have several observations regarding this procedure: 1. The PPR panel published in 2012 a Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. This guidance contains aspects of probabilistic modelling that	The Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues was not used as such

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			could be relevant for contaminants too. Did the CONTAM panel use this Guidance? If so, could you please refer to this Guidance. If not, could you please make clear why this guidance was considered as not relevant for the current risk assessment of glycoalkaloids.	(considering that it applies to pesticide residues and not to contaminants). An analogous methodology was used (see replies below within this comment).
			2. The text of the draft opinion suggests that the probabilistic approach includes random sampling of concentration data and processing factors and the assumption of peeling potatoes, but not for random of food consumption data. As described in the 2012 Guidance mentioned earlier, also food consumption data should be randomly sampled as part of a probabilistic acute exposure assessment. If this interpretation is correct, could you please explain why consumption data were not randomly sampled? If this interpretation is not correct, could you please revise the text of the section describing the probabilistic approach to clarify this?	The methodology used was based on random sampling of the occurrence data, of the processing steps where the information was not available, and of the processing factors. Random sampling of consumption events was not performed because potatoes are a widely consumed food and GAs are present in all samples. Thus, the CONTAM Panel concluded this would have a limited impact on the results. By only random sampling of occurrence and processing factors, results looked stable already after 500 iterations. Section 2.5 of the Opinion was now been revised to make this clearer.
			3. If consumption data were not randomly sampled, the approach is semi-probabilistic rather than full probabilistic. In this case, we suggest addressing why EFSA denominates the approach as probabilistic rather than semi-probabilistic.	There is not a universal convention for what can be defined as semi-probabilistic or probabilistic. The CONTAM Panel finds that the term 'probabilistic' can be considered appropriate and the variables that have been randomly sampled are described in Section 2.5 of the Opinion.
			4. Was random sampling of input data performed with replacement? If so, please clarify this in section 2.5.	Replacement was used and this has been now clarified in Section 2.5 of the Opinion.
			5. If the above described interpretation of the exposure assessment is correct, the 1000 intake distributions generated per age and survey describe the possible variation in the exposure using different concentration data. Consequently the confidence interval is not an uncertainty interval but describes the variation in the exposure due to variation in the different input variables. To attain a confidence interval, the bootstrap methodology for quantification of uncertainty (proposed in the EFSA Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues published in 2012) should be used. It seems that in the draft opinion, variation has been	The interpretation is correct but the 1,000 iterations and related confidence interval describe the uncertainty, not the variation. The variation is captured by randomly sampling the occurrence and processing factors within each iteration. Thus, the distribution obtained in each iteration captures the variability linked to consumption and occurrence. The 1,000 iterations capture the uncertainty around the results of each iteration.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			assumed as uncertainty. Please consider revising the text if this is correct or clarify the text to avoid confusion.	
			Line 1051 (EFSA 2011b): Please note that the reference EFSA 2011b refers to a report on the development of a food classification and description system for exposure assessment and guidance on its implementation and use (EFSA Journal 2011;9(12):2489. [84 pp.]) and not to a probabilistic approach. We suggest inserting the correct reference here. EFSA might have meant to refer to the 'Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues' (doi: 10.2903/j.efsa.2012.2839).	The reference was indeed incorrect and has been deleted. Clarification has been introduced in the text regarding the exposure assessment methodology applied in this Opinion (see above).
			Lines 1060-1071: It is not clear from the text whether two different processing factors were used for e.g. cooked peeled potatoes (first one for peeling and the second one for cooking). We suggest clarifying this in the text.	The text has been amended to clarify the processing factors used.
			Lines 1066-1069: EFSA states '…*drying, flaking and roasting : 5% each*.' It is unclear to RIVM whether processing factors between 0.05 and 0.65 % were assigned to drying, flaking and roasting. These processes may occur at temperatures different from cooking in water. What was the rationale to assign the processing factor of cooking in water to drying, flaking and roasting? Could you please explain which processing factors were assigned to drying, flaking and roasting and motivate the rationale for assigning these processing factors?	Due to the lack of suitable studies no processing factors for roasting could be established. With respect to drying (dehydration processes, including production of flakes or granules) a number of studies were identified, that have now been added to the Opinion (Section 3.2.3). From the available studies it could be derived that in a (semi)-industrial setting the reduction due to drying is in the range of 29% to 67%. This range is not that much different from what has been found for boiling and steaming. Therefore, also considering that dried products represent only 10% in the Comprehensive Consumption Database, it was decided to use the same processing factors in the exposure calculations.
			Lines 1066-1069: Frequencies of processing: are these frequencies obtained for each country or across countries? In case of across countries: are any (cultural) differences in processing frequencies to be expected between EU countries? Could you please discuss this in the opinion.	An overall processing frequency across countries was obtained. Unfortunately, due to the limited information available it was not possible to characterise differences in processing frequencies among countries.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Lines 1084-1096: The P95, that was also determined by EFSA is not mentioned here. We suggesting adding that the P95 was assessed in section 2.5.	The P95 values are now included in the Opinion.
	62	3.1.1.4. Summary on toxicokinetics	P36 Lines 1314-1315: Here it is stated that both α-solanine and α-chaconine have long serum half-lives, suggesting a possible accumulation. Could EFSA further elaborate if this is covered by the MOE of 10 for acute effects? Some consumers may eat potatoes on a daily basis, for high consumers this may be large amounts. When also the TGA concentration is high, this may lead to high exposure. Due to the long half-life accumulation may occur over the days. According to line 2060 on p83, signs of intoxication may also occur with a latency period up to two days. Taken together, should also exposure on previous days be taken into account in this case? We are aware that strictly speaking this is generally not done in a risk assessment of acute exposure.	After a single intake of 1/0.95 mg GA/kg bw via mashed potato meals, reported half-lives of α-solanine and α-chaconine were in the range of 9.6–13.9 h and 16.9–21.1 h (n = 7; Hellenäs et al., 1992), and 14–18 h and 27–49 h (Mensinga et al., 2005; n = 3), respectively. This indicates considerable variability. Experimental human data on repeated exposure are lacking. The MOE of 10 takes into account the interindividual variability in toxicodynamics (factor of 3.2) and extrapolation from a LOAEL to a NOAEL (factor of 3), considering that the acute local effects in the gastrointestinal tract may be predominant. With respect to chronic exposure, it should be noted that findings related to current consumption habits of potato GAs are suggesting no association with adverse health effects at levels not causing acute effects. Nevertheless, the CONTAM Panel states that the potential for bioaccumulation should be better characterised in additional toxicokinetic studies, as stated in the Recommendations.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	63	3.1.2.3. Developmental and reproductive toxicity studies	**P64 lines 1873-1876**: in these lines it is said that doses of approximately 3.6 mg/kg bw per day of α-solanine resulted in a much lower percentage of successfully weaned pups compared to controls. The observed decrease is most likely due to lactational failure. This dose is much lower than the dose where acute effects takes place in rats (300 mg/kg bw and above). As humans are much more sensitive towards the acute effects than rats, EFSA is requested to discuss in the opinion if it is expected that similar effects on lactation may also occur in humans?	This is one reported study. It was conducted in 1961, and has never been followed up. From the results of the short, 3-page paper it is not possible to discuss whether similar effects may occur in humans. Therefore, a recommendation was made by the CONTAM Panel that more studies are needed. In addition, there are several shortcomings which need to be addressed in future studies. These include the following: (i) Lactational failure was proposed as cause for the death of the pups, because their stomachs contained no milk. Cross fostering failed in a first attempt and was not taken up again. (ii) A mechanistic endocrine link between GAs exposure and lactation is not available. (iii) No food consumption records were kept. (iv) No precise date for the onset of exposure is given, quotation: "*as soon as pregnancy was indicated by increase in weight*". Consultation of a veterinarian doctor revealed that weight gain becomes detectable in pregnant rats only from the 2nd trimester onwards. (v) No duration of exposure is given, quotation: "*some of the rats were on test diets for only a few days before dropping their first litter. They were then kept on the test diet until they had a second litter*." The precise procedure is not specified in material and methods, neither is noted which results have been obtained from which approach.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	64	3.1.6.1. GAs from edible parts of S. tuberosum	3.1.6.1.2. Derivation of a health-based guidance value (HBGV) or margin of exposure (MOE) approach **P109 Lines 2959-2961:** It is stated that an MOE higher than 10 indicates that there is no health concern. This MOE of 10 takes into account the interindividual variability in toxicodynamics and extrapolation from a LOAEL to a NOAEL. There is however, in addition, only a small margin (factor 3-6) between the dose where lethal effects may occur and the LOAEL used for risk assessment. Lethal effects have indeed been occasionally seen in humans. Can EFSA further elaborate on the small margin between the LOAEL and the doses at which occasionally mortality in humans is observed in relation to an acceptable MOE of 10?	About a century ago, fatalities were reported from consumption of green or unripe potatoes. No fatalities have been reported since in Europe. The risk assessment presented here is referring to a LOAEL which is derived from more recent data for which figures are less uncertain. Taking an MOE of 10 is considered to be protective already for mild and moderate adverse effects and by all means for the risk of fatality.
			In addition, if a specific MOE can be indicated, we would prefer to use this as an uncertainty factor for derivation of a HBGV. This is consistent with previous approaches, where weaknesses in the dataset is taken into account in uncertainty factors. In our opinion the MOE is meant as an indicator for prioritization.	See reply to Comment 59.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	65	3.2.1. Occurrence data submitted to EFSA	**Table 28:** Sampling years of 2005, 2007, 2015 to 2017 were included in the exposure assessment. There is a large time gap present in the data and the data of 2005 and 2007 are relatively old. Why were data of 2005 and 2007 included? Did the CONTAM Panel check if there were any significant differences between values obtained from 2005 and 2007 and those from 2015 to 2017 on the other? Please address this in the opinion.	See reply to Comment 42. The data from 2005–2007 were not discarded due to the overall limited number of samples available. In addition, a comparison between the data from 2005–2007 and 2015–2017 revealed no substantial differences between the levels of GAs (mean occurrence (UB): 49.3 and 52.3 mg/kg for the 2005–2007 and 2015–2017 data, respectively).
			Line 3053: EFSA states that '*The minimum and maximum reported concentrations were 1.1 mg/kg and 550.0 mg/kg, respectively*.' Table 29 states a maximum of 550.3 mg/kg. We request to indicate which one is correct.	The CONTAM Panel has revised this value. The Panel noted that this value corresponded to a starch potato variety that is not used for human consumption. This sample has now been excluded for the dataset used to estimate the acute exposure and the estimates have been updated accordingly.
			Lines 3069-3070: Numbers of non-detects are only mentioned in text. It would be useful to also mention the number and percentage of left-censored data in one of the tables. We suggest adding this information in Table 27 or 29 of the opinion. Also, for a good interpretation of the results, an overview of LODs and LOQs would be helpful to the reader. We suggest providing information on the range of LODs and LOQs in Table 27 or 29.	The number of left-censored samples was small: 4 analytical results for α-solanine, 24 results for α-chaconine, and in only 2 samples both GAs were not quantified. The range of LOQs reported for the left-censored results has now been included in the text of the Opinion and also included in Annex A.
			Regarding the EFSA Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues, unit-to-unit variation in residues in acute assessments. Is unit-to-unit variation considered to be applicable for glycoalkaloids?	The CONTAM Panel considers that usually more than one potato is eaten, and no information on the unit-to-unit variation (variation among potatoes within the same composite sample) is available.
	66	3.2.2.1. Literature on occurrence data on food	**The text in lines 3184-3197** is exactly the same as the text in lines 3164-3177. We suggest deleting either of the two texts.	The duplication has been deleted.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	67	3.3.1. Current dietary acute exposure assessment for humans	**In section, 3.3.1, lines 3731 – 3732** state '*A scenario including only days in which there was consumption of main-crop potatoes was considered the most relevant for acute risk assessment*'. Please consider mentioning this information in section 2.5. Could you please also motivate why only consumption days were considered. For certain populations with a low potato consumption, this may reflect only a small number of subjects.	Clarifications has been added to Section 2.5. The rationale behind taking consumption days only, is that it best characterises the acute exposure. Consumption days available for each age group in each survey is available in Table A6 of Annex A.
			Figure 8: lines 1079-1081 state that consumption of main-crop potatoes linked to the consumption of alcoholic beverages (vodka and spirits) was not taken into consideration as the CONTAM Panel considered the transfer of GAs from the potatoes during the distillation and refining process to be negligible. However, alcoholic beverages are shown in figure 8. RIVM would like to ask EFSA why this is the case? In addition, we find this figure hard to read and wonder if the information could just be summarized in the text or in a table. For details, a reference could be made to an annex.	The format of Figure 8 has been revised for a better readability. The reference to the food category 'Alcoholic beverages' in this Figure has now been deleted according to the discussion in Section 2.5.
	68	3.3.2. Previously reported dietary exposure assessments	**Lines 3794-3796:** For chronic exposure it is not mentioned for which country/countries these values were applicable. Please provide this information.	The countries to which the exposure estimates refer to have now been added.

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	69	3.5.2. Exposure scenario / exposure model	**Lines 3916-3920:** For 156 samples with unknown processing/peeling, the CONTAM Panel considered it unlikely that they referred to ~~un~~peeled potatoes. Please motivate why the CONTAM Panel considered this to be unlikely. Did the panel check whether the concentrations of these samples were within the range of concentrations in unpeeled potatoes?	Only 7 samples from one country (Germany) were reported as peeled. The number of samples was considered too small to calculate an average occurrence level from these samples, which could be considered representative of peeled potatoes in the EU. A comparison between peeled and unpeeled potatoes could therefore not be made from the available occurrence data. Most of the samples were reported as unprocessed assuming that this also means unpeeled. For 131 samples (the number of 156 mentioned in the draft opinion was incorrect) no information about the peeling nor the processing was available. These samples were considered unpeeled because, based on expert judgement, this was considered the most common way of sampling and testing main-crop potatoes.
			Lines 3921-3925: EFSA states that '*The ratio between alpha-solanine and alpha-chaconine was found to differ between data submissions, indicating differences between the analytical methodologies.*' It is not clear to RIVM why this indicates differences between analytical methods. Could it (also) be natural variation? Please explain or refer to the section in which this is explained, if such a section is included in the opinion.	Figures 4 and 5 in Section 3.2.1 of the Opinion provide information on the distribution between α-solanine and α-chaconine for the combined results submitted to EFSA. At the level of the individual data submissions, there are differences in the ratio observed between α-solanine and α-chaconine. This can be more readily explained by differences in the analytical methods used (e.g. sample preparation and detection methods) than by differences between varieties. This is now discussed in more detail in Section 3.2.1, see also comment below.
			Lines 3921-3925: '*Use of different analytical methods, different detection techniques and with varying LODs/LOQs. The ratio between alpha-solanine and alpha-chaconine was found to differ between data submissions, indicating differences between the analytical methodologies.*' Could you explain what is meant by different detection techniques and in what way detection techniques differ from analytical methods? We suggest adding a clarification.	The data submitted to EFSA come from only three countries. However, parts of the submitted data have been generated by different laboratories within a country. This can be deduced from the fact that for data from the same country different detection techniques have been reported for parts of the data (HLPC-

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				UV, LC-MS/MS, detection method unspecified or standard detection method). This is also the case for the reported LOQs, which differ between data submissions/parts of data submissions.
			Lines 3924-3925: EFSA states '*This is more likely to result in an underestimation than in an overestimation of the exposure*.' Why does this lead to an underestimation? We suggest referring to the relevant section in which this was addressed or explain.	The differences in analytical methods used may result in an over- or underestimation of the TGA content. There is indeed no reason to expect that this leads to an underestimation. The description of the uncertainty related to the analytical method used has now been changed accordingly. A related analytical issue is that there are indications from the literature that α-chaconine is more susceptible to enzymatic degradation (producing β_2-chaconine and solanidine) than α-solanine (Friedman and McDonald, 1995; Swain et al., 1978). Partial degradation of α-chaconine may occur during sample preparation and analysis unless specific conditions are applied (Friedman et al., 1997; see also Section 1.3.2.1 of the Opinion). For the datasets submitted to EFSA, it could not be determined to what extent the results for individual samples could have been affected by enzymatic hydrolysis. Enzymatic degradation could result in an underestimation of the exposure. This issue is now discussed in more detail in the Opinion in Section 3.2.1 and in Section 5.2 on uncertainty analysis.
			Lines 3929-3932: '*Literature studies, however, report a wide range of reduction factors, introducing uncertainty on the actual reduction during the various processing steps*.' Did the CONTAM Panel use the range of these factors into account by sampling 1000 times from that range and thus the uncertainty around the factors was taken into account and included in the confidence interval? Or did the CONTAM Panel only	The variability of processing factors was taken into account by randomly sampling processing factors within each iteration. The uncertainty was taken into consideration by iterating 1,000 times the random sampling. See also the reply to Comment 61, point 5.

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			take the variability in the factors into account? Also here, uncertainty may have been confused with variability in the exposure assessment. We suggest providing a clarification.	
			Lines 3935-3937: EFSA states that '*It is not known to which extent these food processing steps result in only a partial degradation of GAs (to β- and γ-forms of solanine and chaconine) or degradation to the aglycone (solanidine). This may result in a slight underestimation of the GA content present in food products as consumed'*. EFSA is asked to explain this in view of the toxicity of these substances or to refer to the relevant section addressing the toxicity of β- and γ-forms of solanine and chaconine and solanidine.	There is one study on the effects of a single i.p. application of solanidine in mice and two further studies on repeated oral toxicity of this aglycon in mice (see Sections 3.1.2.1 and 3.1.2.2 of the Opinion). Acute or repeated dose oral toxicity studies on β- and γ-forms of solanine and chaconine could not be identified. Based on this very limited information it is not possible to conclude on the toxicity of solanidine and the β- and γ-forms of solanine and chaconine.
			Lines 3944-3946. A short summary of these uncertainties and limitations (as done for the food consumption data) would be helpful for the reader. We suggest adding such a short summary.	The text in the Opinion has been revised. The main uncertainties are linked to the conversion of the amount consumed for a specific Foodex code into the amount consumed of each raw primary commodity from which the food originated or was assumed to originate.
	70	3.5.4. Summary of uncertainties	**Table 45 Uncertainties**: '*Variability between countries and years'* is mentioned as an uncertainty. A major limitation is that data were obtained from only 3 countries and a large range of years. This is explained in lines 3910-3012, but we suggest also including this in Table 45.	Table 45 has been amended as suggested.
	71	Annex A – Occurrence data in food and feed submitted to EFSA and dietary exposure assessment for humans	**A3:** Excelsheet of annex is called A3, while the table is numbered with an 'X'. This table also contains two typo's: please change 'Referrig' into 'referring' and change 'alpa' into 'alpha'. • Sheet of excel file is called A2 while the table is called A3. Please consider checking this. Also, the title contains a typo: 'continuos' should be 'continuous'.	The typos in Annex A have now been corrected and proper reference to the Annex and its tables has now been made in the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
Starch Europe (STARCH EU) [The contribution submitted by STARCH EU is also available in **Annex B** of this Technical Report.]	72	Summary	Although the EFSA study contains a lot of valuable information on the GA levels in Solanaceae, the study actually uses only a very limited amount of this information. For example, matrix interactions in the diet have not been discussed when determining the LOAEL value based on experiments with human volunteers. We further notice that most of industry information has not been used. This leads to potential underestimation of exposure and further limiting the value and basis of determining any LOAEL.	When considering a LOAEL of 1 mg TGA/kg bw identified from human observations as a reference point for risk assessment, preference was given to the outcome of studies and reports, in which α-solanine and α-chaconine were administered or consumed as part of a potato meal (see Table 20 of the Opinion), taking matrix effects into account and mimicking or representing real exposure conditions at best. As was indicated in Section 3.2.1 of the Opinion the occurrence data submitted by Starch Europe could not be used for the exposure assessment due to uncertainty in the data (e.g. it was not known if the occurrence data referred to dry or wet weight and it was not always known if the samples referred to feed or food for human consumption). Other occurrence data indicated to be available to EFSA was not submitted following the requirements of the EFSA Guidance on Standard Samples Description for Food and Feed, and thus could not be used for the exposure assessment. This was indicated in the Section 'Documentation provided to EFSA'. The additional data submitted by EUPPA during the public consultation (see also response to comment 53) could not be used for the dietary exposure assessment in this risk assessment. However, occurrence data submitted in SSD format will be stored and considered for future risk assessments.
			Starch Europe noticed that the study is completely focused on the toxic effects of GA. The literature searches are based on the presumption that there are only toxic effects. Most probably this is EFSAs mandate, but it makes the study scientifically unbalanced. There is a wealth of information on the beneficial effects of GA, especially the anticarcinogenic effects of GA. For your information we have included a recent review article on this (Att 1). Also, such GA positive publications	The mandate received focuses on the risk assessment related to the presence of GAs in feed and food (See Section Background and TORs) and not on the evaluation of the possible beneficial effects of GAs. Note however, that anti-inflammatory effects of GAs and the beneficial effects on blood lipids are discussed in

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			contain valuable scientific knowledge on GA that should not be excluded from the EFSA exposure assessment.	Sections 3.1.2.4 and 3.1.2.9 of the Opinion.
			Food use of potato and potato products has a long history of safe use, irrespective of how they are grown, stored, sold and used. Today's levels of GA appear to be safe. To the best of our knowledge consuming potatoes and potato products has never led to assignable cause of health issues in the European population. And if so we would expect such information discussed in the study. Only in very exceptional and limited cases or under experimental dietary conditions detrimental effects of consuming GA were reported.	About a century ago, fatalities were reported from consumption of green or unripe potatoes. No fatalities have been reported since in Europe. The risk assessment presented here is referring to a LOAEL of 1 mg/kg bw as a reference point which is derived from more recent data. Taking a MOE 10 is considered to be protective for adverse effects which may be induced by potato-GAs.
			On the basis of this EFSA study we do not see a strong case for lowering the GA level beyond what is today already the standard in many members states. Especially, as mentioned above, it is already reported that there could be important beneficial health effects of GA.	From the risk assessment perspective, the beneficial health effects of GAs are outside the remit of this mandate. Questions related to maximum levels in food are risk management actions and are outside the remit of EFSA.
	73	1.3.1. Chemistry	**Line 448** *GAs are relatively stable to heat and alkaline conditions.* This seems not consistent with applying reduction factor for boiling / frying	As pure substances and in potato matrix, potato GAs have been found stable at temperatures up to 150°C (Nie et al., 2018; Takagi et al., 1990). Frying typically occurs at higher temperatures, while during boiling of potatoes losses of GAs may occur due to extraction by the boiling water (Nie et al., 2018). The heat stability of GAs as pure standards to temperatures up to 150°C has now been added to the text in Section 1.3.1. Note that the stability of GAs (α-solanine and α-chaconine) is also discussed in Section 3.2.4.1.2 of the Opinion under 'Other processing methods'.
			Line 450 and 451. Please quantify poorly soluble and soluble. Also, what is the solubility in fat/oil; what is the Pow; This related to effects of fat in the diet on bioavailability and the potential effect of GA in water solution administered in intake assessment with volunteers	The text has now been revised. The aglycones are not soluble in water, while the intact GAs are slightly soluble. The solubility of α-solanine in water has been added to the text.

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	74	1.3.3.1. Potatoes	**Line 608** *Potato breeding programs have for quite a long time used many primitive forms of cultivated potatoes and their wild relatives as a valuable source of genetic variation*. Add reference e.g. https://www.wur.nl/en/Research-Results/Statutory-research-tasks/Centre-for-Genetic-Resources-the-Netherlands-1/CGN-potato-collection.htm	Some relevant publications in this area have now been added to the text as references (Distl and Wink, 2009; Bradshaw et al., 2006; van Gelder, 1989).
			Line 616 and 617 *However, in general, the tuber concentrations of these other GAs will be low*. Please quantify. Reference? How does this relate to their toxic potential?	In tubers the content of other GAs is less than 5%; references have been added, i.e. Milner et al., 2011; Friedman et al., 1997. The toxicity of (other) GAs was discussed in Section 3.1.2 of the Opinion.
			Line 626 *Potatoes can be classified into four types, namely for 'table use', 'industrial food processing use(s)', 'starch production', and 'other purposes', including colourful potatoes (Mori et al., 2015).* Potato use can be classified… Potato varieties are bred that have characteristics that are more suitable for one or more of use classes.	Editorial suggestion implemented.
			Line 632 Table 1 Kozukue and Mizuno (1989) (reference (6) in the table) write: In the pith, however, a small amount of a-chaconine and only a trace amount of a-solanine were detected. Therefore in the table, "pith; not detected; (6)" is not correct.	This has now been corrected. Kozukue and Mizuno (1989) report concentrations ranging from non-detectable to 0.1 mg/kg in the pith.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	75	1.3.5. Legislation and other standards	**Line 828** Does EFSA has sufficient data on glycoalkaloid content in potatoes in EU member states or other countries where there is no TGA potato standard or guideline or recommendations for (new) potato varieties set??	The occurrence data used for the estimation of the exposure was submitted by three countries, i.e. Germany, the Netherlands and Sweden. The CONTAM Panel notes that there are no sufficient data available to draw any conclusion whether in countries with no national legislation or recommendation on the maximum limits of GAs in potato and potato products, the GA levels are higher than in countries with such standards in place, and vice versa.
			Line 856 (FDA) poisonous plant database, link after March 31, 2020: https://www.cfsanappsexternal.fda.gov/scripts/Plantox/Detail.CFM?ID=6537	The link to the US-Food and Drug Administration Poisonous Plant Database has been updated.
			Line 871 Methodology; Studies that report beneficial non-toxic effects are systematically ignored by this search method, while these studies can provide valuable information on absorption, dose response etc	See reply to Comment 72.
	76	2.5. Methodology for Exposure assessment	**Line 1042** Use of RPC Consumption database to convert FoodEx codes to amount of RPC **Line 1065-1071** Reduction factors. Also **Line 4077-4080** Reduction factors ……and these were applied to the occurrence data. **Line 4073** occurrence data in the RPC was used. It is not clear from the text how the reduction factors are applied. Based on Table 38 (line 3612) it is concluded that reduction factors for frying are determined based on dry weight to dry weight. While in the exposure assessment are converted to amounts RPC as fresh weight. And line 4077-4080 indicate that the reduction factors are applied on the RPC. This would be fine if dry matter of both food and RPC are similar and correct reverse yield factor is applied. However in case of potato crisps there is a large difference between dry matter in crisps and in RPC and the reversed yield factor (slicing and frying) is unclear. Please, provide an example for Crisps showing how the conversion to reduction factor is applied by EFSA.	The RPC model uses conversion factors (reverse yield factors) and ingredient percentages of composite food products that can be found in Annex A of EFSA (2019). The reverse yield factor takes into account the change in moisture content due to the effect of the processing step (i.e. frying and slicing). The reduction in the TGA content due to the processing steps (e.g. processing factors for peeling and for deep frying) are estimated from the available literature as described in section 3.2.3.1.2 of the Opinion. These processing factors are not affected by differences in moisture content. The conversion that is applied to potato crisps is as follows: crisps are considered to consist of 65% potatoes (the rest is fat and salt, see Annex A.4). The reverse yield factor for deep frying combined with slicing is 1.92 (see Annex

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				A.5 of EFSA, 2019). Example: 50 g of crisps consumed correspond to 62.4 g of main-crop potatoes (50 g x 65/100) x 1.92 = 62.4 g). For a raw potato that has a TGA concentration of 100 mg/kg and assuming the potatoes to be peeled before drying, the TGA exposure due to the consumed crisps is calculated as follows: 62.4 g of main-crop potatoes × (100 mg/kg TGA × processing factor for frying extracted from a normal distribution within range of 0.1 and 0.8) × processing factor for peeling extracted from a normal distribution within range of 0.35 and 0.95).
	77	3.1.2.9. Studies on metabolic effects	**Line 2036** *To conclude, there is experimental evidence for the formation of undigestible complexes between alpha-tomatine and cholesterol in the gastrointestinal tract of rodents, which may enhance fecal elimination of sterols.* How might formation of complexes affect bioavailability or absorption of GAs. Also in light of the studies with human volunteers that received experimental "diets' with no fat present (Mensinga et al 2005, Hellenäs 1992;). Is perhaps the way of experimental dosing over estimating the absorption of GAs by humans from normal fat containing diets.	In experimental models the formation of undigestible complexes with cholesterol has been studied and described for a-tomatine and not for potato GAs. For potato GAs there are no experimental or volunteer studies showing interference of cholesterol with the absorption of potato GAs in the gastrointestinal tract.
	78	3.1.3.1. GAs from S. tuberosum	**Line 2058 and 2059** *At doses > 1 mg/kg bw, potato GAs are considered to be toxic to humans*. Literature reference?	Reference to JECFA (1993) has now been included to support this statement in the Opinion. Further specific relevant references are given in Table 20 of the Opinion.
	79	3.1.6.1. GAs from edible parts of S. tuberosum	**Line 2953** *Based on the available information, the CONTAM Panel considered the LOAEL of 1 mg potato TGA/kg bw per day based on human data from case reports, outbreaks and studies in volunteers, as the reference point for acute exposure to potato TGAs via food*. The establishment of the 1 mg/kg bw/d as LOAEL is a very important step and deserves or even requires a more comprehensive explanation on how it was established. This ' *based on human data from case reports, outbreaks and studies in volunteers'* is far to generic and lacks reasoning	Cross-reference has been made to Section 3.1.3.1 and Table 20, providing a detailed description of the studies to support the identification of the LOAEL if 1 mg/kg bw per day.

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	80	3.2.1. Occurrence data submitted to EFSA	**Line 3004** *The major contributor of data on GA in terms of number of results was Germany (73% of the results) while the Netherlands and Sweden contributed with 21% and 6%, respectively*. 94% of the data comes from countries having a limit of GA 100 mg/kg in potatoes. What is the chance that this underestimates the true GA content of potatoes consumed all over EU.	The CONTAM Panel acknowledges that the dataset submitted to EFSA is limited as only data from three Member States are available. Nevertheless, the available data may present a good impression of the TGA content present in potatoes for human consumption in the EU considering the following: (i) The three Member States indicated are responsible for about 30% of the potato production in the EU (FAOSTAT data 2018). (ii) Part of the data submitted by the Member States comes from retail potatoes that were produced in other Member States. The TGA content in these samples was not statically different from that in the home-grown potatoes. It should also be noted that the probabilistic approach in the current risk assessment takes a wide range of variables into account (differences in consumption, in TGA content and in processing factors). The uncertainty related to the actual TGA content is therefore considered to be covered by the confidence intervals calculated in the exposure assessment.
			Line 3085-3087 *The European Starch Industry Association submitted data to EFSA concerning 1,728 samples including samples on dietary fibre and potato proteins, pulp, juice and starch and on potatoes used for starch production (Table 29). Due to uncertainty on the occurrence data reported (e.g. it was not known if the occurrence data referred to dry or wet weight and it was not always known if the samples referred to feed or food for human consumption) and the difficulties expressed by the data provider in retrieving this information, these data were not included in the exposure assessment*. We note that data submitted by European Starch Industry Association, but also data submitted by European Snacks Association (Line 4137) and European Potato Processors' Association (Line 4143) are not used in the exposure assessment. Could this lead to potential underestimation of GA presence in potato products?	As it was indicated in Section 2.2.1 of the Opinion and under 'Documentation provided to EFSA', the occurrence data indicated to be available by the European Snacks Association (ESA) and by the European Potato Processor's Association (EUPPA), was not submitted in a timely manner or following the requirements of the EFSA Guidance on Standard Samples Description for Food and Feed, and thus could not be used for the exposure assessment (see response to Comment 53). The limited occurrence data submitted to EFSA to perform the exposure assessment (from three countries only) introduces uncertainty on the representativeness of the overall statistics. Possible differences in GA levels in potatoes, due

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				to the use of different cultivars, location, different growing conditions, and year to year variability, across European countries may result in over- or underestimation of exposure for certain food consumption surveys (see Section 3.5.1 of the Opinion). The occurrence data submitted by EUPPA during the Public Consultation could not be analysed and validated by EFSA. From a preliminary comparison, the levels in potato samples seem to be in the same range compared to the data included in the current assessment. However, a detailed analysis would be required for a robust comparison.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	81	3.2.2.1. Literature occurrence data in feed	**Line 3052 and 3052** The mean UB occurrence in the RPC main-crop potatoes was 52.0 mg/kg with a P95 of 117.0 mg/kg. The minimum and maximum reported concentrations were 1.1 mg/kg and 550.0 mg/kg, respectively. **Line 3309 Table 32**. Summary results of surveys… This table indicate higher average TGA levels in consumption potatoes. How is this taken into account in the assessment, what considerations have been made based on the data in table 32 regarding the GA value used for RPC in the exposure assessment.	The CONTAM Panel acknowledges that occurrence data presented in the literature may differ from the data submitted to EFSA. The main purpose of the data presented in this table (as well as other tables in this Opinion describing survey data) is to provide background information on the GA levels in raw and processed products reported in other studies. The data as such is not used in the exposure assessment by EFSA. Only data submitted to EFSA in the prescribed format can be used for the assessment (after necessary validation steps have been conducted, as described in Sections 2.2.2 and 3.2.1 of the Opinion).
			Line 3313 Table 33 total glycoalkloids in laboratory processed commercial potato products. Have the GA levels that follow from the conversion from FoodEX foods into RPC and vise versa been compared to the values found in the lab research? Where is verified that the GA levels e.g. assigned to French fries, crips, flakes etc have been assessed well?	The approach taken did not characterise the occurrence in the individual original foods. The range of occurrence values assigned to eating events concerning French fries, crisps, etc, is likely very wide as the occurrence values were randomly chosen from the full occurrence dataset related to main-crop potatoes. The same applies to the processing factors that were randomly chosen from a wide range (for frying and deep frying between 0.1 and 0.8, and for peeling between 0.25 and 0.75).
	82	3.2.4.1. GAs from *S. tuberosum*	**Line 3631 table 40.** Please be aware that Takagi et al. (2009) write in the title of the original article that in fried potatoes the amount of GA is expressed on Raw weight. This would mean that the GA values are erroneous expressed as 'mg/ kg fried potato as is' as indicated in the heading of table 40.	A footnote has now been added to clarify that the results are expressed as raw weight, corrected for water loss during frying, as was indicated by the authors.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	83	4.2.1. Food	**Line 4077-4080** Reduction factors ……and these were applied to the occurrence data. **Line 4073** occurrence data in the RPC was used. It is not clear from the text how the reduction factors are applied. Based on Table 38 (line 3612) it is concluded that reduction factors for frying are determined based on dry weight to dry weight. While in the exposure assessment are converted to amounts RPC as fresh weight. And line 4077-4080 indicate that the reduction factors are applied on the RPC. This would be fine if dry matter of both food and RPC are similar and correct reverse yield factor is applied. However in case of potato crisps there is a large difference between dry matter in crisps and in RPC and the reversed yield factor (slicing and frying) is unclear. Please, provide an example for Crisps showing how the conversion to reduction factor is applied by EFSA	See reply to Comment 77.
	84	Other comments	In general; where is the information that GA intake does lead to assignable cause of health problems in the potato consuming population. Cases that have been reported are rare and exceptional. In general; The report summarizes lots of scientific studies and includes data collection etc but these are not considered in important steps in the study, nor discussed in relation to the chosen basis assumptions (LOAEL, GA in RPC, reduction factors) for the exposure assessment.	The CONTAM Panel has described the evidence available in Section 3.1.3 and also in Section 3.3.2 on exposure assessments reported in the literature. The data used to inform the risk assessment is described in Section 2. The considerations and how these data has been used to conclude on the risk for human and animal health are described in Section 3 and sub-sections therein.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
Antonella Garzelli (private capacity) [The attachment submitted by this commenter during the public consultation is listed and available in **Annex C** of this Technical report.]	85		NUTRIONAL RESEARCH "NONLYONE" writer Doct Antonella Garzelli italian researcher POSITION MANAGEMENT AT FAIR TRADE LONDON FIELD HEALTH AND FOOD INDEX 1 Instruction how to read this document 2 Question number 3 Risk 4 Label 5 General food supplements 6 Abbreviations 7 Biography 8 Contacts 9 Tables Figures 1 HOW TO READ THIS DOCUMENT With the aim to be an active member of the authority food that refer to be productive and symplify with knowledge and research and practise on the market guarantee the safety and legal conditions From the number 3 the evidence of the risk that requires label the product one is extract from the risk assessment one is extract from partner company of authority food trusted sources in order to support the edible line of the field SIMPLIFY this is my value the word means make something simpler or easier to do or understand refer to mathematical concept that you should to consider in the procedural organization like this READ THE DOCUMENT ATTACHMENT refer to Question number: EFSA-Q-2016-00811	EFSA has disregarded the comment due to the fact that the comment sent was not in the scope of the consultation, since considerations on labelling of food products are outside the remit of the risk assessment of contaminants. The affiliation of Ms Garzelli mentioned in the EUSurvey as "EFSA Staff" is not correct. She is not and has not been EFSA staff.
Matthew Walker (private capacity)	86	-	1. The report is asked for by the European Commission aiming to add a scientific opinion to review the overall evidence of epidemics (medical) such that the consequences for human health can be firmly identified. The greatest concerns (for national authorities and the WHO) are all the cancers, diabetes, obesity and the most frequent six non	The methodology for the identification of studies to inform the risk assessment is detailed in Section 2.1 and Appendix B. Besides the literature search outsourced, complementary searches were performed to ensure that the

[The contribution and attachments submitted by this commenter during the public consultation are listed and available in **Annex D** of this Technical report.]	communicable diseases. The European Union is notably the most afflicted. For example, the file for the ANSES of France (Agence National de Sécurité et Santé) is Nutrivigilance 2016-006 (concerning the potato and it's biocontamination). The Draft Assessment of the Mandate explains that it contains not one phrase about non communicable diseases because the methodologies for examining the epidemics (including in Oncology) omit the specific toxin (glycoalkaloid) or lack a useful technique. The good sense of your report is noticed. 2. The reading list (delivered by Prague). Most of the list reveals that the necessary work has not yet been done, therefore one can not yet draw a conclusion. That deduction and the contents of the Draft are almost identical to those of Kuiper-Goodman and Nawrot of Health Canada (Bureau of Chemical Safety) of 1990. The principle difference is that Goodman and Nawrot put up front the imperative for a Mandate to do that work instead of reading. The "very great effort" specified remains to be done (thirty years later). It is encouraging to see the sense of the EFSA Draft. Readers may perceive that the 200 pages about rare intoxications are interesting (in biochemistry), however what's to notice (and take very seriously) – are the 500 pages missing. What's to be resolved is that which the Draft omits. Rather than testing the perception of The Commission (will they notice), one deduces that the Mandate is not yet able to be satisfied. That is an ordinary objective observation which signals that a Mandate is required to do some work. ITT observes (and contributes) that more than half of the notes "No evidence found" are because "No reading material presented". Of those reasons, two thirds are deficiencies in the Reading List, while one third are because the necessary work remains to be done. Taking into account that Professor More succeeded in installing a program of education in epidemiology (and human health) within the EFSA and that certain members of the CONTAM panel understand very well the significance of mixtures (in exposure terms), keeping this Mandate open (and not yet finished) were logical and acceptable. The subject of non communicable diseases is else than negligible and saturated with medical observations that nutrition is the most probable cause (due to the largest number of indicators).	studies available on GAs in several areas (e.g. toxicokinetics, toxicity in experimental animals, etc) relevant to the remit of the mandate were retrieved. The CONTAM Panel finds this methodology appropriate for the identification of studies to inform on the risk for animal and human health related to the presence on glycoalkaloids in feed and food, in particular potatoes and potato-derived products. Besides the literature search outsourced, complementary searches were performed to ensure that the studies available on GAs in the areas relevant to the remit of the mandate were retrieved. The CONTAM Panel identified several knowledge gaps and there is a need to improve the risk assessment for humans and to reduce the uncertainties. The Panel has formulated a list of recommendations to address these needs as described in Section 5 of the Opinion.

	3. Administrative points. It's unstated why the list from Prague omitted the research and conclusions of the Harvard Medical School (Gestational Type 1 Diabetes) which established a unique cause (potato). That figured even in newspapers in France (for example Le Figaro, written by Anne Prigent). This is already known to the public. While the Chan Medical School of Public Health considered only the carbohydrate (at first), much is to be learnt from the fact that potatoes are biocontaminated carbohydrate.	The CONTAM Panel discussed the available epidemiological studies relevant for a possible association between repeated intake of GAs, e.g. by the consumption of potatoes, and health risks, e.g. congenital abnormalities or cancer (see Section 3.1.3.1.3 of the Opinion). However, due to missing information on the GA levels in the potatoes or GA intake, the Panel concludes that the designs and outcomes of these studies do not allow concluding on any causal relationship between the repeated intake of potato GAs and human health risks and that they therefore are not considered informative for the risk assessment of GAs in food.
	It's unstated why the list missed the Inflammatory Bowel Disease investigation identifying Potato glycoalkaloids (2002, Patel B, Schutte R, Sporns P et Al).	The study by Patel et al. (2002) was not missed and it was cited in the Opinion in Section 3.1.5.1 to inform on membrane effects of GAs and implications for the gastrointestinal tract.
	4. Fish. The chapter on effects on fish shows that the reading list from Prague lacked the conclusion of the vast expertise of Norway. Taking into account the needs for protein (carnivore fish), Norway hoped to pass the protein of potato on a very large scale. Only 5% of added potato protein caused a serious incident, limited by a fast reaction by the Security organisation. The scientific team heading the enquiry conclude that the biocontamination of glycoalkaloids is responsable. A potential environmental catastrophe (for the fjords, within the cages and due to effluent) was avoided. One recalls that a single batch can take up to four years to evolve. VKM Vitenskapskomiteen for Mattrygghet (Norwegian Scientific Committee for Food Safety) Norway already publish: "No estimate can be suggested for the maximum level of alkaloids in fish diets due to lack of relevant scientific information. It can however, be stated that the potato alkaloids are very toxic and should not be present in feed." The effects at the incidence (paralysis) were modified to "severe appetite loss" and the total loss of reproduction modified to "rainbox trout embryos exhibit a toxic response to chaconine, solasidine, repin and solanine" (Crawford, Kocan 1993). Toxic response means the	Reference to the Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety (2009) and references therein has now been made in Sections 3.3.3 and 3.1.4.5 of the Opinion.

	glycolakaloids kill them. Therefore the biocontamination levels are specified as 0% and 0% (2009). ISBN 978-82-8082-299-4 (05.02.2009). Also available as "Criteria for Safe Use of Plant Ingredients in Diets for Aquacultured Fish". Numerous nations follow the EFSA activity. Tanzania has the intention to increase fish farming in the vast lake (for a greater food supply to the nation) and finds itself surrounded by potato suppliers (more usually for exportation) and close promotion by Finland and Belgium. They are less likely to provoke a colossal accident with their project, being (it seems) better informed. The Draft reveals that the list of Prague is incomplete and that the EFSA read without initiating communication with authorities already competent in fish farming.	
	5. The readers may draw their own conclusions. It is considered best to note the request (placed by the Direction of EFSA Parma) to Brussels for a change of priorities, that which this subject of biocontam merits (noted as "sensitive"). The punctual, expert and justified request (from Parma in 2017) was refused. Brussels can no longer pretend that it wasn't warned to pay attention. The quality of this Draft Opinion for this Mandate shows faults due to the consequences.	EFSA and the CONTAM Panel received from the European Commission the request for a scientific opinion on the risks for animal and human health related to the presence of glycoalkaloids in feed and food. In the course of time, EFSA made two requests for extension of deadlines which were accepted by the EC. All correspondence is publicly available at the EFSA website under Register of questions.
	6. Cancer. While the Draft Opinion suggests that existing techniques are inadequate for assessing potato consumption and resulting cancer, it were usual in a report of this type to explain why, show why and demonstrate it with the reference approach implied by the Panel as better and available. That's a normal requirement. Example 1: Lene A Asli, Olsen, Braaten, Lund and Skele report in 2017 (in the Journal of Nutrition and Cancer Volume 69). "Results showed that high potato consumption was associated with a higher risk of CRC (hazard ratio [HR]: 1.32, 95% confidence interval [CI]: 1.10, 1.60 for ≥3 potatoes per day versus 0–7 potatoes per week). The same association was found for rectal cancer (HR: 1.68, 95% CI: 1.19, 2.36), and same tendencies were found for colon cancer (HR: 1.20, 95% CI: 0.96, 1.50). When stratified by body mass index (BMI) (<25 and ≥25 kg/m2),	See reply to point 3 above. The relationship between the intake of potatoes and risks of cancer in the gastrointestinal tract has been investigated as mentioned in Section 3.1.3.1.3 of the Opinion. A causal relationship between diets with the consumption of large quantities of potatoes and increased risks of cancers of the brain, breast, endometrium, lung and thyroid was not found (Hopkins, 1995; Tice, 1998). Moreover, the CONTAM Panel noted that the design and outcome of existing studies did not allow concluding on the causal relationship between intake of potato GAs and cancer risks.

	significant associations were found with BMI <25 kg/m2 for CRC (HR: 1.48, 95% CI: 1.15, 1.89) and rectal cancer (HR: 1.95, 95% CI: 1.25, 3.06)." Example 2: Potato consumption is associated with total and cause-specific mortality: a population based cohort study and pooling of prospective studies with 98,569 participants. 2020 Feb 11;16(2):260-272. doi: 10.5114/aoms.2020.92890. eCollection 2020. "3433 deaths occurred during the mean follow-up of 6.4 years. In multivariate adjusted models, total (42%), CVD (65%), cerebrovascular (26%) and cancer (52%) mortality risk was greater in individuals with higher potato consumption than those with the lowest intake ($p < 0.001$ for all comparisons). These findings should be taken into consideration for public health strategies, establishing the position for potatoes in the food pyramid". These examples are clearer than most and the second puts forward the facts to the Food Safety Authorities who debate whether a nutrition will receive a waiver (derogation) or product recall.	
	7. Nonetheless one hopes that the Draft can put forward (more evident, with more emphasis) the topic of it's limitations rather than remaining silent to see if the readers will notice it for themselves. This is normal in all objective disciplines and every profession. Our Institute wishes you a fruitful continuation (with this Mandate still open, in favour of the populations, based on your best principles).	The limitations and uncertainties in the risk assessment are discussed in Section 3.5 and the Panel made a number of recommendations in order to reduce those uncertainties and improve the risk assessment.

	87	Abstract	**Line 18** "no evidence of health problems. . . . .has been identified" is rather "the reading list used (concentrating on glycoalkaloid research) omitted most literature concerning health problems for humans (epidemiology compared to potato consumption), specifically Non Communicable Diseases, therefore little or no evidence was presented".	See replies to Comment 86.
			Line 79 "metabolic profiles in experimental animals could not be characterised". **Line 84** "No further information available on metabolism and excretion of potato GAs in humans". **Line 86** "no toxicokinetic data in animals and humans". **Line 89** "Reliable data on other potato GAs or tomato and aubergine GAs and their aglycones are missing". **Line 104** "Developmental studies have been performed mainly in hamsters treated with GAs and their aglycones for only one day or for a short, very restricted time period during gestation". **Line 109** "No NOAEL or LOAEL could be identified". **Line 116** "From the limited number of studies available, there was no evidence for genotoxicity". That is very unusual use of english. "no evidence" meant "no literature presented because no work done".	The CONTAM Panel based the risk assessment on the available published scientific literature in the open domain and reported the available information to inform the risk assessment.
	88	Summary	**Line 119** "No long-term chronic toxicity/carcinogencity study for . . . . .GAs or for the respective aglycones could be identified". Unfortunately untrue. Prague visited many such studies (registered by the Berlin based researchgate tracker). The Panel may, perhaps, find it acceptable to state that "Of the long-term chronic toxicity/carcinogencity studies found by literature search, Prague forwarded none to the EFSA working group". Of course it's up to the Contam Panel to explain why not. The major reason for the Mandate is, of course, the Food Safety alarm notice Nutrivigilance 2016-006 of the ANSES of France due to a carcinogencity study (2015) and the second study (2016) forwarded to all nations, the WHO, the FAO and the EFSA was published (also as a food safety alarm) on precisely the 22 november 2016. ITT asked for that date (the night before the EFSA mandate was received 23 november) to illustrate to the Panel members that ITT is thoroughly integrated within the European Commission and internationally. An engineer is asked to present it, to guarantee impartiality (no prior responsibility for the existing toxicity thresholds nor recent choices in Europe to modify them).	The CONTAM Panel did not identify any long-term chronic toxicity study either by the outsourced literature search or additional searches and updates of the scientific literature performed before adoption of the Opinion.
			Line 127 "Results from limited volunteer studies suggest possible difference in the human population with respect to the individual susceptibility towards adverse effects". ITT (Walker) offers that nearly	Endogenous fatty acids and fatty acids in food may exert effects on many physiological and

	all GA modes of action depend on binding EPA/DHA and Branched Chain Fatty Acids. Free EPA/DHA is liberated during illness or present in other nutrition. ITT (Walker) presents only the facts (no models) of all world population results (double-blind) as the victims demonstrating three major points. The Fatty Acids amplify the toxicity because the Solanaceae plant plans it's minimalist GA toxin to economise it's own effort and resources. Other plants do this too. No study has done a human biocontam mixtox (GA/fatty acid) controlled experiment anywhere and all animal experiments require perfect health. That's why a world epidemiology analysis was offered, to find the circumstances in what 5 billion participants had already done (in 2012) without researcher intervention and with very variable background health states (triple blind measure). As usual for clinical trials also (of pharmaceutics), the human experience and measures surpass and supercede initial speculative animal experiments. It's quite alright for the EFSA to mention this fact as Medically trained who read, know it already.	pathological processes. However, this aspect was not the focus of the current Opinion.
	Secondly it's presented (ITT, 2016, using only incidence rates results) that the GA toxin has an action when it is the lesser of the two ingredients, the intended toxin victim providing the greater fatty acid partner. The harm, the epidemics and the evidence illustrate the complex effect of ratios where (mostly) the mode of action by GA is worst when it is the lesser in the chemical reaction (the EPA/DHA very high). The point of the conclusions is that toxicity thresholds are useless when the reaction and mode of action is so sophisticated with the GA mode acting like a gas leak (to explode in toxicokinetic rate rather than trickle the aglycone. Researchers have to know the toxic ration to be able to give their models something to look for). Aflatoxin (in comparison) synthesises it's own Fatty Acid to prepare a complete toxin before the epoxide phase. While this is difficult news for the Commission and the WHO, it's more directly of help if the EFSA mentions that it does have copies and did read them. The Contam Panel is requested to refrain from expressions typical for first time readers about breakthroughs renaming them as "assertions" or "theory" (the actual word used in the very recent examination of Cancer/Potato done in Iran). The group in Iran do state that their use of the model was only "quantitative" which means neither mixtox, nor taking into account the chemical fact (new to them) nor any effort at toxicokinetic examination. The "old" method produced no correlations at all and that is to be expected. The EFSA Contam Panel view that those methods are	Endogenous fatty acids and fatty acids in food may exert effects on many physiological and pathological processes. However, this aspect was not the focus of the current Opinion.

	insufficient for this subject is noted and true. Many may not like the facts presented and what that implies, because their prior education was without knowledge of basic chemistry that often it takes two molecules to cause histological damage. It's unexpected yet has to be learnt.	
	Thirdly. Unlike the Aflatoxin method, the GA intoxication creates the Cell Cancer Initiation metabolite C17H34N3O7S (molar mass 424.211) later, within the victim. Humans can and do usually convert the metabolites of the biocontaminated meal into useful sugar molecules without difficulty, which is very impressive. However, when that defence is compromised (due to ill health such as HPV virus) the initiation occurs and there's another cancer victim. Some Quantum Chemistry was applied to double-check the ITT presentations and the Contam Panel may need help from Physical Chemistry expertise. It's unlikely that Cox's models (1972) will ever produce consistent identification of GA effects without guidance about the need to offer the model the key ratios of Fatty Acid/GA with their amplifications. Haphazard and conflicting reports are to be expected until that guidance is given.	From the literature, no evidence for genotoxic potential and thus tumour initiating potential of potato GAs could be identified (see Section 3.1.2.7 of the Opinion). A putative GA metabolite with a molecular mass of 424.211 and a molecular formula of C17H34N3O7S could not be retrieved from the scientific literature and available open databases.
	Line 130 "adverse effects of GA may be due to the ability to complex with membrane 3beta hydroxy sterols". ITT offers that (from a toxicologists point of view) the complete mode can best be measured along the hexane toxicity pathway. However, not only is a deliberate mixtox GA/EPA/DHA experiment dangerous but now unethical (because evidence of harm and it's mode has already been presented by ITT, including 5 billion measures of incidences and survivals, for a whole year). Researching any single cancer type incidence rates of 20 in 10000 during one year in humans is categorically unfeasible using human volunteers in a three day toxicokinetics scenario (Netherlands) or an animal laboratory setting using ten animals for two days. It's regrettable; however the EFSA fortunately suggests that in 2021 it will have acquired some qualifications in epidemiology and may already be prepared to do a mixtox analysis. A biocontam mixtox review may be the first (of many) yet a very good idea.	The CONTAM Panel is not aware of the 'hexane toxicity pathway' in the context of GAs. Endogenous fatty acids and fatty acids in food may exert effects on many physiological and pathological processes. However, this aspect was not the focus of the current Opinion.
	Line 155. "The experimental data available for repeated dose toxicity are not sufficient to identify a reference point for chronic exposure to	The CONTAM Panel considered all reliable studies to assess the risks for human health

	potato GAs". The unusual feature of the report is comparing to line 149 which commences "Assuming the main symptoms . . . .". It's unexpected to see the term "assume" (which appears twice) anywhere in a report of this significance to medical science. "The Panel considered that the possible interindividual variability in toxicodynamics is more relevant that the interindividual variability in toxicokinetics". That's a hypothesis and insufficient to justify an MOE, LOAEL or NOAEL about any toxin. The amplification of toxicity (by rates) depending on what else the victim eats and his or her actual health at the moment of ingestion can be scientifically investigated. Work needs to be done to ascertain the true character of the GA capability and dispersion into tissues. Were the EFSA Panel to be firm about that normal technical observation (on something as important as this subject), the Commission were better placed to organise the Working Groups who will do work.	following dietary exposure to GAs. Scientific data on the impact of dietary habits and health status on the effects of GAs is missing.
	Line 156. "no evidence of health problems associated with repeated or long-term intake of GA via potatoes has been identified" is very out of date. Reports from 2015, 2016, 2017 and 2019 are uploaded. The report AOMS is specific about the health problem. Death. "These findings should be taken into consideration for public health strategies, establishing the position for potatoes in the food pyramid". That does, of course, mean that the researchers decline to recommend a waiver or derogation themselves, yet recognise that it's up to the EFSA and others to choose (probably best a recall). China is the furthest advanced in this matter (2019), already researching centrifuge processing (yet failing so far to remove all GA to zero%) and consulting with industry (Tereos) to learn if using potato for ethanol production will be viable instead (2000 installations already in China). China FSA is neither nor more less inclined to discretion about it's Working Group meetings; the difference is that China does new work rather than only read.	The mandate from the EC to EFSA asked for a scientific opinion on the risks for animal and human health related to the presence of GAs in feed and food, in particular in potato and potato-derived products. Risks and benefits of potato consumption not directly related to GAs are outside the remit of this mandate.
	New item relating to **Line 156**. ITT has asked for a brochure for the public to give them the original method for knowing about the risk of potato toxic tubers - now. The method dates from circa 1200 AD, needs no apparatus, is without danger, can be done by any level of education and works. To distribute it in 2020, ITT (Walker) will use printed material, so members of the Panel or the Public need only to read (in that particular case) and participate for a four minute exercise. A	

	printed preview is available for the CONTAM Panel only on request, in French or English or both. The short brochure in french has a further and longer demonstration of ITT skill (small book only in French) which covers ITT activity in depth, across four or five disciplines. The public will be able to learn about ITT competence directly, without distortions of opinions by biased or anxious administrators. A completely fresh look, without reproach. Nothing adversarial. ITT is aware of confrontations with interested parties, those with conflicts of interest and criticisms of the EFSA. ITT offers, instead something kind, useful, pertinent and precise, to the CONTAM Panel members too.	
	Lines 160 to 206 and section 2.5 (Lines 1046+) methodology. The summary implies that the CONTAM Panel infer an overview instruction to search for and find LOAEL, NOAEL and MOE or to explain where the existing values originated. This is the usual EFSA business. Yet the Mandate (on this occasion) asks for much more, is completely open – to something new. The Prague team (Biochemistry) also misunderstood the Mandate as seeking a ratification of an existing norm, therefore provided information (or lack of) about that with very little attention to human exposure analyses and none at all to the Food Safety Alarm (of France, provided by ITT 2016), therefore missing entirely it's content and the implications. While the Commission may note the procedure followed by the Mandate Working Group explains how simplistic (quantitative only) deductions are made, the Commission is aware of the presentation of other results and reports implying something new has to be learnt. It's quite alright if the summary remains as it is so that the Commission learns if the EFSA can do it (only by reading). The Mandate omitted to guide that the breakthrough concerns the alarm that GA is relatively inert until bound with EPA/DHA/Branched Chain Fatty Acids.	GAs may interact with sterols in the cell membranes. There are no peer-reviewed data in the scientific literature indicating that interactions of GAs with fatty acids may increase the toxicity of GAs.
	Integrated Laboratory Systems (Zeiger, Tice) remark already in 1998 " The relationship between the consumption of potatoes and cancer risk has been investigated but remains undetermined. Casecontrol studies reporting increased risks of digestive tract tumors (e.g., colon, esophagus, rectal, and stomach cancer) associated with high levels of potato consumption are matched by an equal number of studies reporting a decreased risk for these same cancers." ITT has investigated and presented why (twice).	See reply to Comment 87, part 3.

	The RPC Consumption Database may be sufficient to submit to a mixtox analysis now. ITT notes (2015), with caution, that disease epidemiology for Multiple Sclerosis indicates the mixtox saturates and only nations outside the European consumption habits/diets can provide the contrast that all models need to function. In that particular example, even with Epidemiological expertise, the RPC Consumption Database is known to be insufficient. Linear and non-linear basic algorithms applied in the 2019 Tehran (Iran) cancer investigation were unable to detect the multiple ratio effect either. The subject requires technique and work to do it.	The exposure assessments performed by EFSA focus on the European population. Since available occurrence data did not cover all the food categories containing potatoes in the Consumption Database, the CONTAM Panel decided that the best approach for the exposure assessment would be to use the occurrence values in the RPC (main-crop potatoes and new potatoes) and the RPC Consumption Database. This is mentioned in Section 2.5 of the Opinion. The mandate of EFSA includes the exposure assessment to GAs by the European population.
	Line 142 might benefit from Line 829+. Citing other authorities (and BfR's choice to halve the GA content in 2018) is else than a suitable justification technique. The Mandate implies that putting those improvisations (quantitative only) into question is necessary and something new is required from the CONTAM Panel to explain why. For example Line 823. "Since case reports in humans indicate a lethal dose of 3–6 mg/kg bw, whereas the LD 50 for mice and rats is at least 300-fold higher, BfR pointed to the considerable higher sensitivity of humans compared to rodents." This observation were usually found at that top of the report, near or in Line 142. Then readers may continue while considering the questions why and when are humans vulnerable and which illnesses may result, else than death, before death. That's why the Mandate is completely open, not requiring nor requesting a NOEL. Notably, BfR gave regulations about quantities of potatoes per day, given to Industry providers, without any publicity for medical personnel nor the public.	The line number indicated refers to Section 1.3.5 on Legislation and other standards. This section provides a summary of existing legislation, standards or recommendations on the maximum limits of GAs in food in European countries or beyond. EFSA has performed its own risk assessment as reported in Section 3 according to the mandate received from the EC.
	ITT is aware how Prague chose search criteria, why certain literature is claimed as excluded (yet gathered and read with caution) and that the EFSA or other authorities may choose to enquire or not as they deem fit. The ITT reports were Food Safety Alarms, required and requested as a Public Duty (by law also). These are most often prepared and filed by Food suppliers recently aware of an accident within 24 hours. Unsuitable for an annual scientific research journal. The ITT reports were distributed very quickly due to the deductions (from epidemiology already done, the gold standard for decisions) showing a pandemic situation (across very many non communicable diseases). China, Norway, Iran, Denmark, Poland, Greece, Great Britain understood and	Information on the literature search and selection for relevance made to inform the risk assessment can be found in Section 2.1 of the Opinion. The CONTAM Panel has applied an MOE approach to assess the health risks and has also made a number of recommendations to improve the assessment and reduce the uncertainties. The establishment of maximum levels of GAs in food or related measures are outside the remit of EFSA.

		passed to action on most of the topics. One former EFSA employee (now toxicology advisor to the HSA of the United Kingdom) unfortunately replied that "People just need to remember to cut off the green bits". It is hoped that the CONTAM Panel take into account that ITT is well aware of the administrative obligations, interpretations, statements, derogations (for substances or supplies considered "important"), all the laws and regulations and how they were established, without need of authoritative instructions nor orders about it. Many nations understand this – of immediate concern due to new evidence and demonstrated. The EFSA is invited to name the analyses "novel methodology" if that helps give the topic a category acceptable to research scientists who do work.	
89	2.3.2. Feed consumption data	**Line 1023.** Fish. Limited success is inaccurate. All embryons are killed outright. Norway VKM has already concluded the issue (what happened). Therefore the biocontamination levels are specified as 0% and 0% ISBN 978-82-8082-299-4 (05.02.2009). The reason to mention this (including the partial paralysis of the fish) is because fish tissue is with a very high EPA density. ITT knows why VKM chose to reduce the warning to "fish may lose appetite" when the facts are far more significant. VKM realised this and mention only that there's "insufficient information" to explore why, without placing a work order. Evidently, others may then continue to suggest that there's "no evidence" when it's because there's "no work done".	Reference to the Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety published in 2009 has now been made in Section 3.3.3 and Section 3.1.4.5 of the Opinion and references included therein in the Section on adverse effects in fish.
90	1.3.5. Legislation and other standards	**Line 862**. Evidence from 1924 and 1996 is suggested as authoritative, because the OECD cite it. Not what the Mandate asks for.	Section 1.3.5 on Legislation and other standards provides a summary of existing legislation, standards or recommendations on the maximum limits of GAs in food in European countries or beyond. EFSA has performed its own risk assessment as reported in Section 3 according to the mandate received from the European Commission.

91	2.1. Methodology for data collection, selection of evidence and study appraisal	**Line 873.** Extensive literature search. The project was then limited (by Prague) from "extensive" to "narrowed", correctly declaring the search methods used. The additional complementary searches are stated as only "Web of Science, PubMed and Scopus". However, the ITT Food Safety Alarm reports (2015, 2016, Walker) were found, downloaded and read. It's understood that the Panel may feel that original, new mixtox analysis already done by someone else is very surprising and very difficult news. It is hoped that the Panel may specify (to the Commission) what was read, why simple presentation is striking and useful and what work orders and education are necessary to evaluate (in the scientific context).	Information on the literature search and selection for relevance made to inform the risk assessment can be found in Section 2.1 of the Opinion.
92	3.1.2.2.1. GAs and aglycones from edible parts of S. tuberosum	**Line 1462**. "Potatoes were admixed as powder at high concentrations to the diet (of mice) presumably causing dietary imbalances of macro- and micronutrients". "Increased absolute and relative weights of pancreas were observed at the highest TGA dose of 23.2 mg/kg bw per day. The CONTAM Panel agrees with the assumption of the authors that the effects on the pancreas may be due to presence of trypsin inhibitor activity in the potato powder and not caused by GAs. Consequently, no NOAEL was derived for this study". ITT is unsurprised to see the word "assumption". The Mandate suggests the CONTAM Panel assume nothing, to find out also whether they will report absolutely objectively. ITT hopes to alert the Contam Panel to reflect again on the Friedman report in question which (on careful reading) contains a very significant observation.	The animal experiments published, including the studies by Friedman et al. applied doses being lethal for humans. Therefore, these studies were considered inappropriate to draw conclusions for the health risks of humans exposed to considerably lower doses of GAs via food.
		Furthermore, ITT is aware that the Panel had a useful disagreement, discussing this point, which might serve as a more accurate and interesting statement for the Commission.	Following scientific discussions on possible approaches for the risk assessment, the CONTAM Panel was unanimous in the approach taken and endorsed the draft Opinion for public consultation and adopted the Opinion without disagreements among its members.
		Animal experiments are else than trusted by Pathologists and Pharmaceutical science due to the vast numbers of differences, the fact that the animals are in perfect health at start, denied alternative selfselected liquids or nutritions and effects on humans are always examined to replace (completely) animal testing. What animal experiments can do is reveal histological damage to vital organs.	See reply to Comment 51, part 3.

	That is often their only value. It occurred in these experiments therefore to be emphasised rather than dismissed. If anything is to be learnt from animal testing – this is it. The useful fact is that the researchers (1992) did no further work (yet) to determine which substance caused the damage.	
	In addition, readers of the report with experience in Oncology may need some overview help. Trypsin inhibitor is found to be associated with adverse prognosis for cancer victims and regularly used to prepare life expectancy information for the patient and their family (possible recovery or imminent death). Whether in tissue and/or in serum, the usual indication is poor survival, particularly associated with liver metastasis. ITT will present another report (in 2020) with the full database (as for 2016 yet much larger). To preview, the most recent analysis learns that the liver is the major detoxification organ for potato aglycones yet the pancreas suffers a dysfunction causing the Diabetes epidemics for nations (the worst are else than European). The liver can be relieved of the load, yet only be dumping toxins into the bloodstream for later expulsion by the lungs and treatment in the kidneys (European diets/fluids do that). That full circulation, however brief, enables the cycloalkane metabolite to initiate cancer in nearly every organ with the worst possible results for the largest organ (the skin), known as Melanoma. In this way, medical science notices the switch (disease exchange) from Diabetes to Cancer without yet being able to explain it. As developing nations adopt western customs and diet behaviour (only rarely or even only once), the expulsion from the liver is always more probable and cancer epidemics soar. The World Health Organisation appeals (desperately) for Western Science to react and investigate absolutely any and every possible avenue of evidence without relent. The ITT report of 2020 will enable the EFSA to participate in the reality of the imminent catastrophies rather than read about what was or was not done. ITT can warn the Panel, to help prepare, respectfully, that one of it's options is to keep the Mandate open, as not yet resolved due to work not done.	The CONTAM Panel is not aware of a 'cycloalkane metabolite' in the context of GAs toxicity. From the literature, no evidence for genotoxic potential and thus tumour initiating potential of potato GAs could be identified (see Section 3.1.2.7 of the Opinion).
	Line 1489. ITT contributes that variable proportions of potato powder and spiked GA will cross several ratios of the EPA/GA mixtox. Therefore greater doses (for example 33mg/kg bw) will very often cancel the	See replies to Comment 89.

	toxicity. This is, of course, basic chemistry. Citing more quantitative studies risks assuming there's nothing to be done and may cause avoidance of the very simple evaluation possible.	
	Line 1522. "The Tusino study authors speculated that alterations were rather due to trypsin inhibitor activity than the GA content in the diet (2013). Consequently, no NOAEL or LOAEL could be derived". This illustrates again the focus on NOAEL. The Mandate is larger in scope (deliberately so). The useful fact is that, due to speculation, it remains unkown if the GA or the trypsin inhibitor was responsible (or both). ITT request that the CONTAM Panel pulls out and forward the facts only (which design the work requirements).	The Panel agrees that the effects of GAs and trypsin inhibitors need to be kept apart, which was followed in the present Opinion.

(a): Comments are shown as received from the commenters.

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Abbreviations

ARfD	Acute reference dose
bw	Body weight
CONTAM Panel	Panel on Contaminants in the Food Chain
dw	Dry weight
EU	European Union
EUPPA	European Potato Processors' Association
FAO	Food and Agricultural Organization
FDA	Food and Drug Administration
FID	Flame ionization detector
fw	Fresh weight
GAs	Glycoalkaloids
GC	Gas chromatography
HPLC	High pressure liquid chromatography
LC	Liquid chromatography
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
LOD	Limit of detection
LOQ	Limit of quantification
MALDI	Matrix assisted laser desorption/ionization
MOE	Margin of exposure
MS	Mass spectrometry
NOEL	No-observed-effect level
NOAEL	No-observed-adverse-effect level
NPD	Nitrogen phosphorous detector
RPC	Raw primary commodities
TGA	Total glycoalkaloids
TOF	Time of flight
UB	Upper bound
UF	Uncertainty factor
UV	Ultraviolet
WHO	World Health Organization
ww	Wet weight

Appendix A – Explanatory note to Public Consultation

EFSA's Panel on Contaminants in the Food Chain (CONTAM) has launched an open consultation on the draft scientific 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 products. This document presents an estimation of the acute human dietary exposure to glycoalkaloids, and an assessment of the human health risks related to this dietary exposure. No risk assessment was possible for any of the farm animal species.

Interested parties are invited to submit written comments by **15 April 2020**.

Please use the electronic template provided: https://ec.europa.eu/eusurvey/runner/Public_Consultation_GAs to submit comments and refer to the line and page numbers. To submit additional data to support your comments or files, there is an upload function available in the tool (for a maximum size of 1Mb file). Otherwise you can also contact specific unit's functional mailbox: biocontam@efsa.europa.eu

Please note that comments will not be considered if they:

- are submitted after the closing date of the consultation
- are presented in any form other than what is provided for in the instructions and template
- are not related to the contents of the document
- contain complaints against institutions, personal accusations, irrelevant or offensive statements or material
- are related to policy or risk management aspects, which are out of the scope of EFSA's activity.

EFSA will assess all comments which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant. Due to time constraints, EFSA cannot use additional occurrence data submitted during the public consultation for the dietary exposure assessment in this risk assessment. However, occurrence data submitted in SSD format will be stored and used for future risk assessments.

Copyright-cleared contributions

Persons or organizations participating in a Public Consultation of EFSA are responsible for ensuring that they hold all the rights necessary for their submissions and consequent publication by EFSA. Comments should inter alia be copyright cleared by taking into account EFSA's transparency policy and practice to publish all submissions. In case the submission reproduces third-party content in the form of charts, graphs or images, the required prior permissions of the right holder(s) should have been obtained by the PC respondent

Publication of contributions

Contributions will be published (as part of an EFSA report published together with the final opinion) and may be re-used by EFSA in a different context. It should be noted that contributions submitted by individuals in a personal capacity will be published as such, indicating the author's first and family name, unless a substantial justification for protection is provided by the respondent. Contributions submitted on behalf of an organization are also made publicly available and attributed to the organization in question.

Submit comments (deadline: **15 April 2020**)

Published: 27 February 2020

Annex A – Contribution submitted by EUPPA

The following xls files were submitted by EUPPA together with his contribution to the public consultation:

- **GA consultation _ occurrence reporting UK and FR**
- **GAs SSD2 simplified – BELGAPOM**
- **GAs SSD2 simplified – BPOGK (003)**

Due to time constraints, EFSA cannot use additional occurrence data submitted during the public consultation for the dietary exposure assessment in this risk assessment. However, occurrence data submitted in SSD format will be stored and considered for future risk assessments.

Annex B – Contribution submitted by STARCH EU

The following file was submitted by STARCH EU together with his contribution to the public consultation:

- **2020.04.15__Starch_Europecomment_-_draft_EFSa_opniion_on_GA**

This file is available on the EFSA Knowledge Junction community on Zenodo at: http://doi.org/10.5281/zenodo.3952756

- **Friedman, 2015, glycoalkaloids, eggplants, potatoes, tomatoes, anticarcinogenic mechamisms**

This file corresponds to the following citation: Friedman M, 2015. Chemistry and Anticarcinogenic Mechanisms of Glycoalkaloids Produced by Eggplants, Potatoes, and Tomatoes. Journal of Agricultural and Food Chemistry, 63, 3323-3337. https://doi.org/10.1021/acs.jafc.5b00818

Annex C – Contribution submitted by Antonella Garzelli

The following file was submitted by Antonella Garzelli together with his contribution to the public consultation:

- **DOCANTONELLA_GARZELLI_GA_Question_numberEFSAQ201600811**

This file is available on the EFSA Knowledge Junction Community on Zenodo at: http://doi.org/10.5281/zenodo.3952763

Annex D – Contribution submitted by Matthew Walker

The following files were submitted via email by Matthew Walker to the public consultation:

- **ITT to EFSA – Public Consultation GA in food and feed**

This file is available on the EFSA Knowledge Junction Community on Zenodo at: http://doi.org/10.5281/zenodo.3952772

- **ITT CancerCauseDeclarationforFAOWHO.**

This file is available on the EFSA Knowledge Junction Community on Zenodo at: http://doi.org/10.5281/zenodo.3952772

- **ITT CancerInitiationmetaboliteofpotato20042016.**

This file is available on the EFSA Knowledge Junction Community on Zenodo at: http://doi.org/10.5281/zenodo.3952772

- **ITT Food Safety Alert – Nutrivigilance ANSES 2016-006.**

This file is available on the EFSA Knowledge Junction Community on Zenodo at: http://doi.org/10.5281/zenodo.3952772

- **AOMS Mortality (2019) London, Lodz, Thessalonika_Art_39831-10.**

  This file corresponds to the following citation: Mazidi M, Katsiki N, Mikhailidis DP, Pella D, Banach M, on behalf of the Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group, 2020. Potato consumption is associated with total and cause-specific mortality: a population-based cohort study and pooling of prospective studies with 98,569 participants. Archives of Medical Science, 16, 260–272. https://doi.org/10.5114/aoms.2020.92890

- **GA Antidote 10886_2005_Article_BF01012098.**

  This file corresponds to the following citation: Johns T, 1986. Detoxification function of geophagy and domestication of the potato. Journal of Chemical Ecology, 12, 635-646.

- **Harvard MS Gestational Diabetes bjm.h6898.full.**

  This file corresponds to the following citation: Bao W, Tobias DK, Hu FB, Chavarro JE and Zhang C, 2016. Pre-pregnancy potato consumption and risk of gestational diabetes mellitus: prospective cohort study. BMJ 2016;352:h6898. DOI: 10.1136/bmj.h6898

- **Norway potatoconsumptionandriskofcolorectalcancer**

  This file corresponds to the following citation: Asli A, Olsen A, Braaten T, Lund E and Skeie G, 2017. Potato Consumption and Risk of Colorectal Cancer in the Norwegian Women and Cancer Cohort. Nutrition and Cancer, 69, 564-572. DOI: 10.1080/01635581.2017.1295086.

- **Renwick 1974 Spina Bifida. Storage and half life toxins.**

  This file corresponds to the following citation: Renwick J, Possamai AM and Munday MR, 1974. Potatoes and spina bifida. In: Persaud TVN (eds) Problems of Birth Defects. Springer, Dordrecht. DOI: https://doi.org/10.1007/978-94-011-6621-8_42

- **VKM 07 604.**

  This file corresponds to the following citation: Norwegian Scientific Committee for Food Safety, 2009. Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety. Criteria for safe use of plant ingredients in diets for aquacultured fish. Available at: https://vkm.no/download/18.2994e95b15cc5450716356b2/1498419374011/1232b28f3b.pdf