



TECHNICAL REPORT

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Outcome of a public consultation on the draft scientific opinion on the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from the interested parties on a draft scientific opinion on the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels prepared by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel), supported by the Working Group on hydrocyanic acid in food. The draft opinion was endorsed by the CONTAM Panel for public consultation at its plenary meeting on 14 November 2018. The written public consultation was open from 27 November 2018 to 25 January 2019. EFSA received comments from seven 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 19 March 2019 and published in the EFSA Journal.

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Key words: cyanide, cyanogenic glycosides, health based guidance values, risk assessment, public consultation

Requestor: EFSA

Question number: EFSA-Q-2018-00688

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1. Introduction

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

1.1.1. Background

On 1 March 2016, the Panel on Contaminants in the Food Chain (CONTAM) adopted the scientific opinion on acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels¹.

The CONTAM Panel established an ARfD for cyanide of 0.02 mg/kg bw (20 µg/kg bw) for use in assessing the risks associated with the presence of cyanogenic glycosides in apricot kernels

Cyanogenic glycosides are also present in other food such as linseed and cassava.

Furthermore, maximum levels for hydrocyanic acid are established in nougat, marzipan or its substitutes or similar products (50 mg/kg) canned stone fruits (5 mg/kg) and alcoholic beverages (35 mg/kg) by Regulation (EC) No 1334/2008² and 7 grams of hydrocyanic acid per hectolitre of 100 % vol. alcohol in stone fruit spirits and fruit marc spirit, established by Regulation (EC) No 110/2008.³

In the scientific literature there is evidence that this acute reference dose is applicable to unprocessed foods with cyanogenic glycosides also containing intact plant β-glucosidase. It is mentioned that for some foods the approach may be overly conservative due to the delayed and/or incomplete release of cyanide from the cyanogenic glycosides depending on many factors, as was demonstrated for linseed. In case of missing or inactivated β-glucosidase, the hazard potential would be much lower⁴.

Furthermore, in the scientific opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on hydrocyanic acid in flavourings and other food ingredients with flavouring properties⁵, adopted on 7 October 2004 the following is concluded: 'Cassava flour is used as a staple food mainly outside Europe; a consumption of 200 g/person would lead to an estimated intake level of 30 µg HCN/kg bw for a 60 kg adult. In accordance with the JECFA view such an intake would not be associated with acute toxicity. The highest level of HCN found in retail marzipan paste is 20 mg HCN/kg. Assuming on one sitting a person of 60 kg consumes 100 g marzipan containing such a level, that intake would be equivalent to 2 mg HCN or to 0.03 mg/kg bw.'

It is appropriate to consider the need to take regulatory measures as regards the presence of cyanogenic glycosides in foods which are not yet regulated at EU level and to assess the appropriateness of existing maximum levels for hydrocyanic acid in food to provide a high level of human health protection.

Therefore, it is appropriate that EFSA assesses the applicability of the Acute Reference Dose (ARfD) for cyanogenic glycosides in raw apricot kernels to other food in which cyanogenic glycosides are present. In case it is concluded that the ARfD for cyanogenic glycosides in raw apricot kernels is not applicable to other foods in which cyanogenic glycosides are present, EFSA is requested to assess the human health risks of the presence of cyanogenic glycosides in foods other than raw apricot kernels.

¹ EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2016. Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. EFSA Journal 2016;14(4):4424, 47 pp doi:10.2903/j.efsa.2016.4424 http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4424.pdf

² Regulation (EC) No 1334/2008 of the European Parliament and of Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, pp. 34.

³ Regulation (EC) No 110/2008 of the European Parliament and of the Council of 15 January 2008 on the definition, description, presentation, labelling and the protection of geographical indications of spirit drinks and repealing Council Regulation (EEC) No 1576/89. OJ L 39, 13.2.2008, pp. 16.

⁴ Abraham K, Buhrke T and Lampen A, 2016. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. Archives of Toxicology, 90, 559-574.

⁵ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2004.105/epdf>

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 human health risks related to the presence of hydrocyanic acid in foods other than raw apricot kernels and products derived from apricot kernels (ground, milled, cracked, chopped).

In particular, the scientific opinion should inter alia comprise:

1. Evaluation of the applicability of the ARfD established for cyanogenic glycosides in raw apricot kernels for other foods in which cyanogenic glycosides are present
2. Evaluation of the relevance of chronic effects related to the human dietary exposure to cyanogenic glycosides
3. Estimation of acute and (if relevant) chronic dietary exposure of the EU population, including consumption patterns of specific (vulnerable) groups of the population

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 annexes was released for public consultation from 17 December 2018 to 25 January 2019 by means of an electronic comment submission tool together with explanatory text on the EFSA website (See Appendix 1). Comments were received from seven interested parties from four countries. Table 1 provides an overview on the interested parties that have submitted comments.

Table 1: Overview on stakeholder comments received

Stakeholder	Category ^(a)	Country
Bundesverband der Deutschen Süßwaren-industrie (BDSI)^(b)	Private sector	Germany (DE)
Chocolate, Biscuits & Confectionery of Europe (CAOBISCO)^(b)	Private sector	Belgium (BE)
Carmen Pfannkuchen	Private sector (no employer given)	Germany (DE)
Food and Drink Europe	Private sector	Belgium (BE)
Institute of Food Science and Technology (IFST)	NGO	The United Kingdom (UK)
Food Standards Agency	National authority	The United Kingdom (UK)
RIVM (National Institute for Public Health and the Environment)	University/Public research	The Netherlands (NL)

(a): as declared by the stakeholder.

(b): BDSI and CAOBISSCO have submitted identical comments but separately.

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

The comments received were duly evaluated by the EFSA WG on Hydrocyanic acid in Food and wherever appropriate considered for the finalisation of the draft opinion. Table 2 provides a detailed list with all comments 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	EFSA response
Bundesverband der Deutschen Süßwaren-industrie (BDSI) & Chocolate, Biscuits & Confectionery of Europe (CAOBISCO)^(a)	1	General comments	On its website, the EFSA summarises: "In the new draft opinion, our experts have concluded that it is unlikely that consumption of such foods (including almonds and almond based products such as marzipan) would pose a health concern." To date there are no findings to indicate that the consumption of marzipan or similar processed products might have posed a health risk to corresponding consumers. Hence the long-standing statutory maximum levels for hydrocyanic acid also have a tried and tested record in the view of the manufacturers of marzipan raw pastes, marzipan, persipan, and similar products. The maximum level for hydrocyanic acids in nougat, marzipan, and similar products is set at 50 mg/kg and laid down in Regulation (EC) 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in and on food. In addition, the levels set by the German Food Code Commission's (DLMBK) Guidelines on Oilseeds and Pastes and Confectionery produced therefrom are compliant with the statutory regulations and limit the use of bitter almonds. The level of bitter almonds in a marzipan raw paste may not exceed 12% of the overall almond content. For manufacturers it is a matter of extreme economic significance that their traditional framework for freedom of choice in their formulations will be retained. Given the many uses of marzipan raw masses and marzipan, manufacturers require sufficient space in maintaining a diverse range of formulations. Among the various products, marzipan goods are certainly the first worth mentioning. A considerable share of the raw marzipan pastes produced and marzipan pastes processed in Germany is additionally required for further processing into various compound foods (block chocolate, chocolates, sweet bakery products, Stollen, cakes, pastries, etc.). Buyers of marzipan and raw marzipan pastes include companies in the confectionery industry, the chocolate industry, and the fine bakery wares industry, not forgetting artisan bakers and confectionery shops. Persipan is also primarily used as an ingredient in compound foods (e.g. in Dominosteine or similar fine bakery wares).	Noted.
	2	Assessment (overall chapter)	The BDSI/CAOBISCO welcomes the fact that the current EFSA scientific opinion takes into consideration the human clinical trial "Bioavailability of cyanide after consumption of a single meal of foods containing high	Noted.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			levels of cyanogenic glycosides: a crossover study in humans” from 2016. In calculating the threshold of the acute reference dose (ARfD) for marzipan/ persipan, a correction factor of 12 was used, drawing on scientifically substantiated findings that it is not the hydrocyanic acid content level in the food alone that is decisive in assessing the toxicity, but also its bioavailability in the human organism. (Source: Abraham K, Buhrke T and Lampen A, 2016. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. Archives of Toxicology, 90, 559–574). The study published by Abraham in 2016 showed, by way of human clinical trial, that the bioavailability of free cyanide in the blood is dependent on the type of ingested food. Criticism of the EFSA’s New ARfD: In the view of the BDSI/CAOBISCO, setting the acute reference dose (ARfD) for consumption of a single meal to 20 µg /kg of body weight for cyanogenic glycosides is a too conservative value, as is also described in the current EFSA scientific opinion. We draw attention to the fact that Germany’s Federal Institute for Risk Assessment (BfR) considers an ARfD of 75 µg/kg as appropriate. In this respect, we refer to the BfR’s scientific opinion of 24 March 2016. • In this context, the BfR criticises the safety factor of 3.16 used by EFSA in its study of 2016 to account for the fluctuations in toxicity which, in the view of the BfR, need not necessarily be taken into consideration. • The BfR bases its opinion on the fact that the threshold blood cyanide level of 20 µm used in the toxicological assessment already includes various safety factors (Rumack 1983). • What is more, the equivalent cyanide dose established by EFSA in the various test persons was five times above the ARfD of 20 µg/kg of body weight proposed by EFSA without, however, leading to clinical symptoms (EFSA, EFET, BfR [2016] Acute health risks related to consumption of raw apricot kernels and products thereof).	The ARfD is not new, it was established in the 2016 opinion (EFSA CONTAM Panel, 2016). As already noted in the EFET-BfR-EFSA joint document of 2016 (EFSA- EFET-BfR, 2016), the study of Abraham et al. (2016) was conducted with a small number of healthy adult volunteers and the absence of information of cyanide specific data on individual sensitivity (i.e. covering specifically susceptible individuals in the population). Therefore, EFSA retains its position with regard to application of the default uncertainty factor for toxicodynamics and consequently the ARfD of 20 µg cyanide/kg bw.
	3	Conclusions (overall chapter)	Consequences of the EFSA Evaluation Basically it is all a question of achieving the greatest possible consumer safety level without restricting the consumer’s choice of traditional products. For reasons of consumer health protection, the BDSI/CAOBISCO welcomes the setting of maximum levels for hydrocyanic acid in bitter apricot kernels intended for distribution to the end consumer for direct consumption. However,	Noted.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			the hydrocyanic acid levels in raw bitter apricots kernels also fluctuate between 1,000 und 4,400 mg/kg. Moreover, their direct consumption leads to a speedy enzymatic release which causes an immediate spike in blood cyanide levels. In the case of marzipan and similar processed goods, the maximum level is set at 50 mg/kg. What is more, only a 12th of the hydrocyanic acid measured is released and has an impact on the body's blood cyanide levels. Added to this are the additional safety factors involved in setting the EFSA's ARfD, as mentioned by the Federal Institute for Risk Assessment (BfR).	
	4	Recommendations	According to scientific opinion, a reduction in the maximum values for marzipan and similar products in the EU Flavourings Regulation as a possible conclusion of a regulatory consequence would not achieve any greater degree of consumer protection. Hence a change in the maximum limits should not be derived from this. This should be correspondingly stated by the EFSA in its recommendations.	Setting maximum limits is not within the remit of EFSA and therefore no recommendations with that regard can be given in the opinion.
Carmen Pfannkuchen	5	3.3.9. Estimation of the amount of certain foods that can contain CNGs that could be consumed without exceeding the ARfD	In Table 23, I guess there are faulty data. In column with the age, you mention two times adolescents, I guess you mean one time young adulescents and one time adulescents. The ARfD of 20 µg/kg bw in line 1816 is given also In the table 23. But there you mention 0.2 mg/kg bw. It seems to be an conversion mistake. I guess it should be 0.02 mg/kg bw. When you calculate with the ARfD of 0,02 mg/kg, the acceptable portions are lower. I did the calculation also for the mean value of cyanid in linseed. When you compare the acceptable values and the 97,5th portions of flaxseed (highest values for linseed, consumption Database), we can see that the intake of cyanid would be to high. Because of that the risk chrarakterisation does not fit also. It might be nessecairy to have a deeper look, before linseed with the mean cyanid value isn't marktable anymore. If there are any questions don't hesitate to ask. It might also be possible I didn't understand right. <i>EFSA Note: See Appendix 2 for alternative calculations CN for exposure to linseed.</i>	Tables 23 and 24 have been corrected accordingly. Indeed the back calculations confirm the importance of linseed as a source of exposure, however, from the calculations presented in Section 3.4. (Exposure assessment) it becomes obvious that linseed is not a major contributor to cyanide exposure via food in the EU.
Food and Drink Europe	6	General comments	FoodDrinkEurope would like to thank EFSA for the opportunity to comment on this draft Scientific Opinion. We welcome EFSA's statement that "In the new draft opinion, our experts have concluded that it is unlikely that consumption of such foods (including almonds and almond based products such as marzipan) would pose a health concern." To	Noted.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			date there are no findings to indicate that the consumption of marzipan or similar processed products might have posed a health risk to corresponding consumers.	
	7	3.3.4. Derivation of health-based guidance values	[p 44, lines 1307-1310] In our view, setting the acute reference dose (ARfD) for consumption of a single meal to 20 µg/kg of body weight for cyanogenic glycosides is a too conservative value, as is also described in the current EFSA scientific opinion. We draw attention to the fact that Germany's Federal Institute for Risk Assessment (BfR) considers an ARfD of 75 µg/kg as appropriate. In this respect, we refer to the 2016 BfR's scientific opinion, which is based on the fact that the threshold blood cyanide level of 20 µM used in the toxicological assessment already includes various safety factors (Rumack 1983) and therefore the safety factor of 3.16 considered by EFSA in its study of 2016 to account for the fluctuations in toxicity would not be necessary. In addition, the equivalent cyanide dose established by EFSA in the various test persons was five times above the ARfD of 20 µg/kg of body weight proposed by EFSA without, however, leading to clinical symptoms (EFSA-EFET-BfR, 2016). References: Rumack BH, 1983. Cyanide poisoning. In: Newball HH (ed.). Respiratory Care of Chemical Casualties, 2480 Proceedings of the Symposium on Respiratory Care of Chemical Casualties (McLean, Virginia, 28-2481 30 November 1983). US Army Medical Research and Development Command, Ft Detrick, Fredrick, 2482 MD.186 pp. Joint EFSA- EFET-BfR document, 2016. Acute health risks related to consumption of raw apricot kernels and products.	See response to comment number 2.
	8	3.3.7 Exposure assessment	[p 54, lines 1559-1573] We welcome the fact that the current EFSA scientific opinion takes into consideration the human clinical trial "Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans" (Abraham et al., 2016). In calculating the threshold of the acute reference dose (ARfD) for marzipan/persipan, a correction factor of 12 was used, drawing on scientifically substantiated findings that it is not the hydrocyanic acid content level in the food alone that is decisive in assessing the toxicity, but also its bioavailability in the human organism. This study also showed, by way of human clinical trial, that the bioavailability of free cyanide in the blood is dependent on the type of ingested food. References: Abraham K, Buhrke T and Lampen A, 2016. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study	Noted.

Stakeholder	Comment number	Chapter	Comment	EFSA response
			in humans. Archives of Toxicology, 90, 559–574.	
Institute of Food Science and Technology (IFST)	9	General comments	Thank you for the opportunity to comment on this consultation. IFST's Scientific Committee has provided the following general comments on this consultation: • IFST welcomes the EFSA risk assessment; particularly that EFSA rightly stresses that exposure is dependent both on the glycoside concentration in the food and on the presence of enzymes that break it down to cyanide. It is a complex and detailed picture. • IFST questions the technical robustness of trying to calculate a "European" exposure level. Cyanogenic glycosides are an example of a contaminant that is so specific to local diets that the EU-wide picture loses all resolution. • For example: ○ Most of EFSA's data comes from Germany, where marzipan consumption would skew the dietary intake compared to the UK. ○ Cassava flour is only consumed by certain ethnic groups. ○ EFSA don't appear to have considered bamboo shoots, which are also consumed by some ethnic groups. • IFST recommends the calculation of more localised exposures, limited to geographic areas or diets where the risk is higher. This would then help in targeting any future risk management that might be needed.	Indeed, most of the occurrence data came from Germany and are thus not representative for all European countries. This is mentioned in the Uncertainty section. For cassava and cassava-derived products very few occurrence and consumption data are available which is pointed out in the Uncertainty section. Therefore it was not possible to quantify the amount of cassava consumed by certain ethnic groups and in consequence this is not addressed in the opinion. EFSA has considered bamboo shoots in section on Occurrence data on food reported in previous assessments. However, based on the lack of appropriate occurrence and consumption data these could not be considered in the assessment. Your suggestion for considering localised exposures limited to geographic areas and the lack of information on certain food commodities has been considered and is now reflected in the Recommendations section of the opinion.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
Food Standards Agency	10	General comments	The comments submitted below were provided by Members of the UK Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). In general the COT agrees with the assessment.	Noted.
	11	1.3.3. Previous risk assessments	It would be helpful to explain why the UF in the previous EFSA evaluation was 1.5 as it should not be necessary to look it up to understand the present evaluation.	The section has been updated accordingly.
	12	3.1.1. Toxicokinetics	Line 865: The need to define kinetics of parent glycosides using improved methodology is agreed as the available data is with less sensitive assays. This is important to define any chronic effects and for a valid chronic risk assessment following long term ingestion.	Noted.
	13	3.3. Toxicity	Line 998: It is probable that there is a general over estimate of CN exposure based on maximum conversion to CN . This has delivered conservative acute risk assessment. Understanding the distribution of hydrolytic enzymes in the foods and Inter-individual differences in detoxification pathways important. Total release by hydrolysis and overestimate of exposure in food- very conservative Line 1109. How likely is it that CNGs are genotoxic in the absence of any evidence of genotoxicity of cyanide? At present, the issue is left somewhat open. No data, but no conclusion. It is important to highlight that the toxic effects of cyanide are generally based on exposure to inorganic CN rather than endogenously produced CN.	As a conservative approach, maximum conversion had to be assumed in the absence of data. Where data was available, factors (see Section 3.4. Exposure assessment of the opinion) have been used. There are no genotoxicity data available on isolated CNGs and in consequence no firm conclusions can be made in the opinion. A sentence on QSAR analysis has been added (see Section 3.1.3 of the opinion). As reported in the human observations of both this opinion, and the 2016 opinion (EFSA CONTAM Panel, 2016), there are cases of mortality associated with consumption of CNG-containing foods. Indeed cyanide is produced also endogenously and it has been proposed that it plays a role as a neuromodulator in the central nervous system. However, it is present physiologically only in very minor concentrations. A sentence has been added in the Toxicokinetics section accordingly.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
	14	3.3.1. Animals	Line 971 : The rationale for dismissing the effects on the cauda epididymis is unclear. The fact that the subdivisions obtained by dissection were relatively crude was more likely to have obscured a change in a more specific sub-compartment (dilution effect of other sub-compartments) than otherwise. Effects were also seen in liver, kidney and thyroid in more than one study (and species). There is some consistency here with effects observed in humans.	The CONTAM Panel thinks that the rationale for dismissing the effects on cauda epididymis has been explained clearly in the section on Animal toxicity. To explain in more detail additional text has been added to the opinion. In addition to methodological uncertainties associated with this endpoint the absence of other dose-dependent effects in typical target organs in the NTP study indicates a lack of biological plausibility. Effects on liver, kidney and thyroid were observed in some studies and species but as noted there is a lack of consistency between studies and limitations in the studies, which together do not allow identification of a critical effect or reference point to be used in derivation of a chronic health based guidance value. The observations in humans consuming poorly processed cassava are impacted by malnutrition and the role of cyanide cannot be determined.
	15	3.3.2. Observations in humans	Line 1125 : The toxic and lethal threshold values for humans are based on a communication by Rumack (1983) published in the proceedings of a symposium. It would be useful if more detail could be provided.	The CONTAM Panel agrees that the rationale behind the toxic and lethal threshold values is scant. Already for the opinion of 2016 (EFSA CONTAM Panel, 2016), where the rationale was first presented the author was contacted by EFSA but could not add further detail on the rationale. This has been pointed out as an uncertainty both in the 2016 opinion (EFSA CONTAM Panel, 2016) and again in the present opinion (see section on Uncertainties).

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			Line 1323: Given that CONTAM has used epidemiological studies in which a causal relationship has not been clearly established as the basis of health-based guidance values for a number of contaminants in the recent past, it is not entirely clear why at least some guidance on minimally toxic levels in humans on long term exposure cannot be considered here (perhaps based on MOEs for effects on the thyroid). I agree that it would be difficult to establish a HBGV for chronic toxicity	In previous situations where the CONTAM Panel has used epidemiological data, the populations concerned have been more relevant to the European population. In this instance the impact of malnutrition and limited diet means that it is not possible to identify a reference point to be used in a MOE approach. This has been clarified in Section 3.1.6. on Derivation of a HBGV of the opinion.
	16	3.3.7 Exposure assessment	The traditional UK diet is generally low in cyanogenic glycosides while other countries have a higher intake because of different diet. There is potential for unexpectedly high intakes in different ethnic groups in UK. It is important to quantify the potential intake by different members of current EU population .	We agree that it can be assumed that diets and uptake of CNGs via food varies between EU countries and also (probably even to a greater extent) between different ethnic groups. However, based on the lack of consumption data on certain food commodities and the fact that most of the occurrence data are only from one country (i.e. Germany) the exposure assessment is not representative for European countries. This has been pointed out in the Uncertainty section. Likewise could the differential uptake and exposure in different ethnic groups could not be assessed. Text along these lines has been added in the Uncertainties section. In addition, a recommendation on this was added in the respective section.
RIVM (National Institute for Public Health and the Environment)	17	General comments	RIVM would like to compliment EFSA on the work done and we would like to indicate our agreement with the general approach of the opinion. We feel that using adjustment factors in the exposure assessment is a pragmatic method to correct for differences in bioavailability and release of cyanide from different foods, even though these factors were derived from one study only. However, apart from some clarifications in different parts of the draft opinion, we do question the rejection of the 13-week NTP studies to derive a chronic HBGV. We feel that the current argumentation does not fully justify this and therefore	Thank you. The effect of CN on male reproductive system and its use to derive a chronic HBGV has been carefully re-examined by the working group and the CONTAM Panel. (See response to comment number 14.)

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			we would like to suggest further examination of this part of the risk assessment. We thank EFSA for the opportunity to comment on the draft opinion and we include some specific remarks and questions that may be of use in finalising it.	
	18	Abstract	L15-18: There is no reference in the abstract to the correction factors for release/bioavailability that have been applied in the case of linseed/persipan/marzipan. We suggest including this information in the abstract, because it is a key issue in this opinion on other foods than raw apricot kernels.	Agreed.
	19	Summary	L105, "For foods other than raw apricot kernels..., this ARfD is likely to be over-conservative...": As ARfDs are normally not derived for foods but for compounds (as also stated in this paragraph), we would like to suggest to amend the sentence to "For exposure to cyanide from foods other than raw apricot kernels, bitter almonds and cassava roots, this ARfD is likely to be over-conservative because of the lower bioavailability /slower release of cyanide from those foods."	Agreed. The sentence has been amended accordingly.
	20	1.3.1. Chemistry	Table 1: Several substances seem to contain an R- or S- group, which are reflections of their 3D configuration. We suggest to include a clarification on the isomers in the text of the table and/or body text (eg. include them in the reported name of CNG, or explain at the bottom of the table the meaning of the R and the S, or to give also a chemical name that includes the R- or the S- [e.g. prunasin = (R)-(beta-DGlucopyranosyloxy)phenylacetonitrile]).	Clarification has been added in form of a footnote to Table 1. Additionally, a sentence on the chirality of CNGs has been inserted in the text appertaining to Table 1.
	21	1.3.2. Analytical methods	L397: For completeness, we suggest to indicate that EC Directive 71/250/EEC is no longer in force.	Reference to the Directive has been omitted.
	22	3.0. Assessment (overall chapter)	It seems that the hierarchy level of numbering of the different sections is not correct, especially under chapter 3.	The hierarchy of numbering has been corrected.
	23	3.3.1. Animals	L967-980: In two 13 week studies with NaCN, one in mice and one in rats, dose dependent reductions in cauda epididymis weights were observed in both species. In addition, statistically significant decreases in epididymal sperm motility (at cyanide doses of 1.4 mg/kg bw per day and higher) and spermatid count (at the highest dose of 12.5 mg/kg bw per day) were observed in the study in rats, but not in the study in mice (NTP 1993; USEPA, 2010). JECFA (2012) based the PMTDI of 20 µg/kg bw per day on the lowest BMDL1SD (the BMDL for a BMR of one standard deviation of the control mean) for reduction in absolute cauda epididymis weight. EFSA considers that the effects on the cauda epididymis weight observed in the 13 weeks studies in rats and mice could not be used to derive a chronic HBGV.	See responses to comments 14 and 17.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			EFSA provides three reasons for not using the epididymis data. However, the arguments underpinning EFSA's conclusion may need further clarification: • Firstly, EFSA argues that the effects were not consistently found. It is however not clear from the provided information if effects on the (cauda) epididymis weight were assessed in other studies. Could this be clarified? • Secondly, EFSA states that it could not verify the biological plausibility of the effect. Could EFSA elaborate on that? As indicated above, we note that the observed effect was treatment-(dose)-related, and accompanied by associated effects. Usually in such a case, biological plausibility is assumed, unless strong arguments are available that the observation is biologically not plausible. In our opinion, such arguments are missing from the opinion. • EFSA argues that a precise separation of each part of the epididymis, including cauda, by gross anatomical dissection is associated with a high level of uncertainty. This implies that EFSA considers that the effects may be artifacts. However, the data on the cauda epididymis weights as presented in the NTP study do show clear dose-dependent decreases by NaCN treatment in both mice and rats, and the measurements also show small standard errors. In view of this, how is the assumption of EFSA justified? L1018-1020: Referring to the repeated dose studies as "All three studies were single dose studies" could be interpreted in different ways. For clarity, we suggest to replace this part of the sentence with 'In all three studies only one dose level was used' or 'In all three studies animals were only dosed with one dose level'. L 1109-1111. It is stated here that no data are available on genotoxicity of CNGs. We suggest to include some reasoning to explain whether the absence of genotoxicity data for CNGs raises a concern or not and /or if a recommendation for genotoxicity studies should be included. We note that the CNGs in table 1 do not seem to bear structural alerts, and that the different hydrolysis products (i.e. the sugar moieties, the CN- and the non-cyanide containing residues (i.e. acetone, benzaldehyde, p-hydroxybenzaldehyde, 2-butanone) could be discussed.	Agreed. Text has been amended accordingly. See response to comment 13.
	24	3.3.4. Derivation of health-based	L1307-1310: We suggest to include a clarification on how the differences in bioavailability and release are taken into account.	Agreed. Text has been amended accordingly.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
		guidance values		
	25	3.3.7 Exposure assessment	L1565-1566 "For these foods, the ARfD of 20 µg/kg bw is likely to be overconservative": We refer to our comments on Line 105. L1559-1573: No information is provided about how the correction factors for release/bioavailability were included in the exposure assessment. This information is provided in section 3.3.10 (uncertainties) and section 4.8 (conclusions). We suggest including it here. L1575, Table 18: The correction factor of 3 is for ground linseed. We suggest amending the entry 'linseed' accordingly. L1582: No reference to Annex B1 and B2 is provided here. We suggest including this information here.	Agreed. Text has been amended accordingly. This information is provided in this section. See subsection on "Availability of cyanide from the intake of CNGs from particular foods" where it reads first paragraph where the application of the correction factors is described in detail. The correction factor is applicable for all linseed. It is based on ground linseed as a worst case assumption. Therefore no amendment has been made. Further clarification has been inserted in Table 18. Agreed. Reference to Annexes B. 1 and B.2 has been added.
	26	3.3.8 Risk characterisation	L1716-1718, the sentence: "... lower and the ARfD is likely to be over-conservative": we refer to our comments on Line 105.	Agreed. Text has been amended accordingly.
	27	3.3.9 Estimation of the amount of certain foods that can contain CNGs that could be consumed without exceeding the ARfD	L1782: Regulation on spirits should be No 110/2008 (such as in L635).	Corrected.
	28	3.3.10. Uncertainties	L1839-1840: The new guidance on uncertainties has not been fully implemented in this opinion. Could you specify which parts of the new guidance were included and which impact this may have had on the current uncertainty assessment? L1886: Table 25 should read Table 26 Table 26: The uncertainty regarding the methodology used to assess the chronic exposure is missing from the table. This source results in a potential overestimation of the chronic exposure to CN.	The new guidance has not been applied. Text has been amended accordingly. The uncertainties regarding exposure assessment apply both for the acute and the chronic exposure assessment.

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Stakeholder	Comment number	Chapter	Comment	EFSA response
			• As stated earlier, please consider adding the uncertainty related to the limited data for most of the food subcategories to the table. This is a very important source of uncertainty in the assessment. • In the acute and chronic exposure assessment, consumed linseed was assumed to be ground linseed. Could this not be a potential source of underestimation?	This uncertainty is already listed in the table. No. This is rather a source of an overestimation because of the higher bioavailability of cyanide in ground linseed.
		4.6. Health-based guidance values	L1987-1989 "For foods... the ARfD is likely to be over-conservative": we refer to our comments on Line 105.	Agreed. Text has been amended accordingly.
	29	5. Recommendations	L2075-2076: "Additional occurrence data for cyanide are needed for raw and processed food commodities CNGs or cyanide": This recommendation is not clear, we suggest to revise this sentence.	Agreed. Recommendation has been amended accordingly.

(a): BDSI and CAOBISCO have submitted comments separately but they contained identical information.

References

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Appendix 1: 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 health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels. This document presents an evaluation of the applicability of the ARfD established for cyanide in raw apricot kernels for other foods containing cyanogenic glycosides, an evaluation of the relevance of chronic effects related to human dietary exposure to cyanogenic glycosides, estimations of acute and chronic dietary exposure to cyanogenic glycosides and an assessment of human health risks related to acute dietary exposure to cyanogenic glycosides.

Interested parties are invited to submit written comments by 25 January 2019.

Please use the electronic template provided: https://ec.europa.eu/eusurvey/runner/PC_CNG_IN_FOOD 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

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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 organisation are also made publicly available and attributed to the organization in question.

Submit comments (deadline: 25 January 2019)

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Appendix 2: Alternative calculations CN exposure through linseed

ARfD EFSA multiplication with correction factor (0,02 mg/kg * 3)	person	bw	tolerable intaking cyanid per person	content of cyanid in flaxseed*	amount of linseed until the ARfD will be exhaust	max. portions for linseed 97,5 th (Source EFSA Consumption Database)	exhaustion of the ARfD, by eating the 97,5th portion
(mg/kg KG)		(kg)	(mg/kg)	mg/kg	(g)	(g)	(%)
0,06	toddler	8,7	0,52	407	1	7	520
	toddler	11,9	0,71	407	2	7	380
	toddler	15,9	0,95	407	2	7	285
	other children	14	0,84	407	2	11	516
	other children	23,1	1,39	407	3	11	313
	other children	37	2,22	407	5	11	195
	young adolescent	29,4	1,76	407	4	22	498
	young adolescent	43,4	2,6	407	6	22	338
	young adolescent	62	3,72	407	9	22	236
	adolescent	45	2,7	407	7	22	326
	adolescent	61,3	3,68	407	9	22	239
	adolescent	83	4,98	407	12	22	177
	adult	52	3,12	407	8	101	1,314
	adult	73,9	4,43	407	11	101	925
	adult	100	6	407	15	101	683

* the highest reported concentration by EFSA.

ARfD EFSA multiplication with correction factor (0,02 mg/kg * 3)	person	bw	tolerable intaking cyanid per person	content of cyanid in flaxseed**	amount of linseed until the ARfD will be exhaust	max. portions for linseed 97,5th (Source EFSA Consumption Database)	exhaustion of the ARfD by eating the 97,5th portion
(mg/kg KG)		(kg)	(mg/kg)	mg/kg	(g)	(g)	(%)
0,06	toddler	8,7	0,52	192,1	3	7	245
	toddler	11,9	0,71	192,1	4	7	179
	toddler	15,9	0,95	192,1	5	7	134
	other children	14	0,84	192,1	4	11	244
	other children	23,1	1,39	192,1	7	11	148
	other children	37	2,22	192,1	12	11	92
	young adolescent	29,4	1,76	192,1	9	22	235
	young adolescent	43,4	2,6	192,1	14	22	159
	young adolescent	62	3,72	192,1	19	22	112
	adolescent	45	2,7	192,1	14	22	154
	adolescent	61,3	3,68	192,1	19	22	113
	adolescent	83	4,98	192,1	26	22	83
	adult	52	3,12	192,1	16	101	620
	adult	73,9	4,43	192,1	23	101	436
	adult	100	6	192,1	31	101	323

** the reported mean in the draft.