CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON CONTAMINANTS IN FOODS

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DISCUSSION PAPER ON TROPANE ALKALOIDS IN FOODS

(Prepared by Electronic Working Group chaired by China, co-chaired by Saudi Arabia)

BACKGROUND

1. Tropane alkaloids (TAs) are natural plant toxins occurring in several plant families, such as Brassicaceae (*B. oleracea*), Solanaceae (*Atropa belladonna L., Datura stramonium L., and Hyoscyamus niger L.*) and Erythroxylaceae (including coca). The tropane alkaloids are responsible for the toxic effects of some of these plants and are found in all parts of the plants. The group of tropane alkaloids comprises more than 200 compounds and the wide range of compounds occurring especially in the Solanaceae family arises from the esterification of tropine with a variety of acids.

2. Plant extracts containing TAs have been used for centuries in human medicine. In the Chinese history, Hua Tuo, a Chinese physician who lived during the late Eastern Han dynasty, had used the *Datura* combing with liquor as a general anaesthetic called mafeisan (literally "cannabis boil powder"). In western history, atropine (the racemic mixture of (-)-hyoscyamine and (+)-hyoscyamine) and scopolamine have been used throughout history in medicine, generally administered at low doses as drugs in the form of salts, such as atropine sulfate, or as semi-synthetic derivatives such as homatropine bromide or N-butylscopolamine bromide (Aehle, E, et al, 2010).

3. Considering the scientific advice of FAO/WHO Expert Meeting (2020) on tropane alkaloids and Members' divergent views, the 15th session of the Codex Committee on Contaminants in Foods (CCCF) had noticed the need to establish an EWG to prepare a discussion paper on tropane alkaloids to look into the need and feasibility of possible follow-up actions for consideration by CCCF16. However, no member country took the mission.

4. CCCF16 (2023) reconsidered this item and agreed to establish an EWG, chaired by China and co-chaired by Saudi Arabia, to prepare the discussion paper on tropane alkaloids to look into the need and feasibility of possible follow-up actions for consideration by CCCF17[1]. The list of participants of the electronic working group is attached as Appendix III.

5. The purpose of this discussion paper is to introduce background information on the toxicology, analysis, data, health risk and management related to the presence of tropane alkaloids in food. The discussion document mainly revolves around comments related to the Joint FAO/WHO Expert Meeting (FAO/WHO, 2020) and EFSA (EFSA CONTAM Panel, 2013, 2016, 2018 and 2022) (Appendix II). A new work proposal is presented in Appendix I based on the summary and conclusions of the discussion paper.

WORK PROCESS

6. The draft documents were circulated twice, and comments were received from Belgium, Brazil, China, Saudi Arabia, the United States of America, the United Kingdom, Japan, WFP (World Food Programme), ISDI (International Special Dietary Foods Industries) and FoodDrinkEurope. The list of participants in the EWG is presented in Appendix III.

1 REP 23/CF16, paras. 106-113.

SUMMARY OF KEY POINTS OF DISCUSSION

Feasible actions

7. Almost all of EWG members support to initiate work first on a *Code of Practices* (CoP) prior to consideration of MLs. A CoP including all steps of agricultural practices and transformation would be more useful for decreasing TAs in food than MLs. Proper implementation of control measures will help to prevent contamination, and furthermore, will facilitate the detection of the point/s of entry of TAs into supply chains.

8. Developing the globally agreed MLs for TAs is hampered by a lack of available occurrence data with official methods and associated sampling strategies. Until now, there are no validated official methods for tropane alkaloids available, and there are no international laboratory proficiency tests for analytical methods for tropane alkaloids yet. Before setting MLs, it is crucial to establish a standard and validated analytical method for tropane alkaloids.

9. Sampling plays a crucial part in the precision of the determination of the levels of plant toxins in a certain lot since plant toxins within a lot may be heterogeneously distributed. The risk of setting of ML without suitable sampling procedures is that acute toxic levels may be missed. If CCCF in parallel also consider whether or not starting work for establishing MLs, it would be necessary to establish sampling methods for the monitoring/control of the levels of plant toxins in food. One member suggested that the Regulation (EU) 2023/2782[2] and 2023/2783[3] could be used as reference.

10. An additional comment was made that maybe CCCF could consider extending the *Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed* (CXC 74-2014)) to include also tropane alkaloids, as the weed control measures should be the same.

11. One member questioned whether CCCF should take risk management action on tropane alkaloids at this time. Before making decision, maybe CCCF should request more information from JECFA or Members. JECFA assessment did not address global exposures, it focused on exposures from the specific food products formulated for the WFP and the general diet in countries where WFP is active.

More data and full-scale risk assessment

12. Some members pointed that data on TAs appeared to be almost exclusively from Europe. If we want to discuss MLs, a data call for TAs may be necessary. Besides, if Members could offer more TAs data related to the harvested crops in the post harvest and pre processing stages, it would be helpful for a better understanding of mitigation and application of GAP.

13. Some members recommended expanding the scope of the risk assessment to include not only the most studied commodities in relation to TA occurrence such as buckwheat, millet, maize and sorghum, but also wheat and other cereals.

Food commodity

14. We also discussed what commodities we should focus on for the TAs risk management.

15. Priority ones should be globally traded commodities, and the potential contamination with weed seeds containing tropane alkaloids raises concerns about food safety.

16. The first one is cereals (millet, sorghum, buckwheat, corn, wheat, rye, oat, barley and rice), especially WFP foods. And herbs and spices, legumes (such as soybeans), oilseeds (such as canola), processed cereal-based food for infants and young children are also mentioned.

CONCLUSION AND RECOMMENDATIONS

17. Atropine and scopolamine were the most frequently detected TAs. The data on toxicity and other information on occurrence in feed and food was only available for atropine and (-)-scopolamine. Therefore, we advise the risk management should focus on these compounds.

18. Although the JECFA and EFSA evaluations appeared to reach different conclusions, considering the contamination incidents caused by TAs, it is paramount that the proper control strategies are established to reduce the exposure of TAs to consumers.

2 Commission Implementing Regulation (EU) 2023/2782 of 14 December 2023 laying down the methods of sampling and analysis for the control of the levels of mycotoxins in food and repealing Regulation (EC) No 401/2006.

3 Commission Implementing Regulation (EU) 2023/2783 of 14 December 2023 laying down the methods of sampling and analysis for the control of the levels of plant toxins in food and repealing Regulation (EU) 2015/705.

19. Since the limited data, CCCF could initiate work first on a Code of Practices (CoP) , drafting a new CoP or extending the CXC 74-2014 to include also tropane alkaloids. The CoP should cover mitigation strategies preventing/handling growth of plants that produce tropane alkaloids, with a special attention for *Datura* weeds, as well as post-harvest measures such as sorting, and extra precautions for processed cereal-based food for infants and young children. The CoP can also cover monitoring issues.

20. In order to discuss whether or not starting work for establishing MLs in the next step, the CCCF may consider to issue a call for data on the presence of TAs (atropine and/or scopolamine) in all kinds of food, especially TAs data related to the harvested crops in the post harvest and pre processing stages, as well as milling products and consumer products, including foods for infants and young children. Members should be encouraged to submit complete data sets that include individual sample results rather than only aggregate data. In the call for data, there should be attention for appropriate methods of sampling and analysis. The method of sampling should take into account the heterogeneity and data should be representative for the lot.

21. Since there is JECFA assessment did not address global exposures, it focused on exposures from specific food products formulated for the WFP and the general diet in countries where WFP is active. If JECFA could do the full-scale risk assessment for TAs in foods, it would be helpful to support the discussion of developing the MLs in the future.

22. CCCF is invited to consider if there is sufficient information available in the discussion paper (Appendix II) to support new work on a code of practice or revision of the Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed (CXC 74-2014).

23. Based on the above assessment, to review the project document accordingly (Appendix I) and to establish an EWG to prepare a CoP for the prevention and reduction of tropane alkaloids or to revise the Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed (CXC 74-2014).

24. If the discussion paper needs further development, CCCF is invited to identify gaps or information that should be further developed in order to guide the work of the EWG.

25. CCCF is further invited to request the JECFA Secretariat to issue a call for data and request JECFA to carry out full-scale risk assessment for further discussing the necessity for elaborating MLs for TAs in food.

APPENDIX I

Proposal for new work

1) Purpose and scope of the project

The purpose of the proposed new work is to develop a code of practice (CoP) or extend the *Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed* (CXC 74-2014) to include also tropane alkaloids (TAs). The scope of the work is to complete a CoP to prevent or avoid TAs contamination.

2) Relevance and timeliness

The Joint FAO/WHO Expert Meeting (FAO/WHO, 2020) provided some expert scientific advice.. There is already a Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed (CXC 74-2014) which could be adapted to include TAs.

3) Main aspects to be covered

This work will address measures for prevention of TAs including mitigation strategies preventing /handling growth of plants that produce tropane alkaloids, with a special attention for *Datura* weeds, as well as post-harvest measures such as sorting, and extra precautions for processed cereal-based food for infants and young children.

4) Assessment against the criteria for establishment of work priorities

(a) **Consumer protection from the point of view of health and fraudulent practices**. To protect consumer health, exposure to TAs should be prevented or reduced. A CoP providing recommendations to governments, farmer and food business operators will help prevent contaminated food from entering the market.

(b) Diversification of national legislations and apparent resultant or potential impediments to international trade. Currently, best practices and legislations. Development of a COP or update of the existing CoP is needed to ensure that information on recommended practices for preventing and reducing TAs exposure is available to all member countries. It also will provide the means to enable exporters to ensure reduced risk of TAs and to assist in compliance with any MLs that may be established in the future.

(c) Scope of work and establishment of priorities between the various sections of the work.

The CoP will address all relevant measures for prevention or reduction of TAs at the different steps in the food chain.

(d) **Work already undertaken by other international organizations in this field.** Work on TAs has been undertaken by several organizations such as JECFA, EFSA, WFP, and can be consulted in development of a CoP. These organizations have made recommendations but have not offered a COP.

5) Relevance to Codex Strategic Goals

(a) **Goal 1 Address current, emerging and critical issues in a timely manner.** Establishing a CoP for prevention or reduction of TAs in food or updating the CXC 74-2014 will address the current need for guidance to ensure the health of consumers.

(b) Goal 2 Develop standards based on science and Codex risk-analysis principles. This work will apply risk analysis principles in the development of a CoP by using scientific data and recommendations from FAO/WHO and other recognized expert bodies to support a reduction in exposure of consumers to TAs.

(c) Goal 3 Increase impact through the recognition and use of Codex standards. The proposed CoP ensures that information on recommended practices to avoid and prevent TAs consist of current best practices and are available to all member countries, especially those with fewer resources to devote to this topic.

(d) Goal 4 Facilitate the participation of all Codex Members throughout the standard setting process. Developing a COP through the Codex Step process will make information on recommended practices to prevent and reduce TAs available to all Codex members.

(e) **Goal 5 Enhance work management systems and practices that support the efficient and effective achievement of all strategic plan goals.** A CoP will help ensure development and implementation of effective and efficient work management systems and practices by providing basic guidance for countries and producers to keep highly TAs-contaminated food out of the marketplace.

6) Information on the relationship between the proposal and other existing Codex documents

This proposal may concern an update of the existing *Code of Practice for Weed Control to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Food and Feed* (CXC 74-2014).

7) Identification of any requirement for any availability of expert scientific advice

The Joint FAO/WHO Expert Meeting (FAO/WHO, 2020) and EFSA (EFSA CONTAM Panel, 2013, 2016, 2018 and 2022) has already provided some expert scientific advice.

8) Identification of any need for technical input to the standard from external bodies

Currently, there is no identified need for additional technical input from external bodies.

9) The proposed timeline for completion of the new work, including the starting date, proposed date for adoption at Step 5 and the proposed date for adoption by the Commission.

Work will commence following recommendation by CCCF17 and approval by CAC in 2024. Completion of work is expected by 2028 or earlier

APPENDIX II

DISCUSSION PAPER ON TROPANE ALKALOIDS IN FOODS

INTRODUCTION

1. Information available from the EFSA Scientific opinion on tropane alkaloids in food and feed shows the structures of the Datura tropane alkaloids (EFSA, 2013). The group of Datura tropane alkaloids can be divided into three subgroups: the 'regular' Datura-type tropane alkaloids (containing a tropane ring esterified to a phenylacetic acid derivative, Figure 1), such as (-)-hyoscyamine and (-)-scopolamine; Convolvulaceae-type tropane alkaloids (structures not shown); and low molecular weight tropane alkaloids (structures not shown).

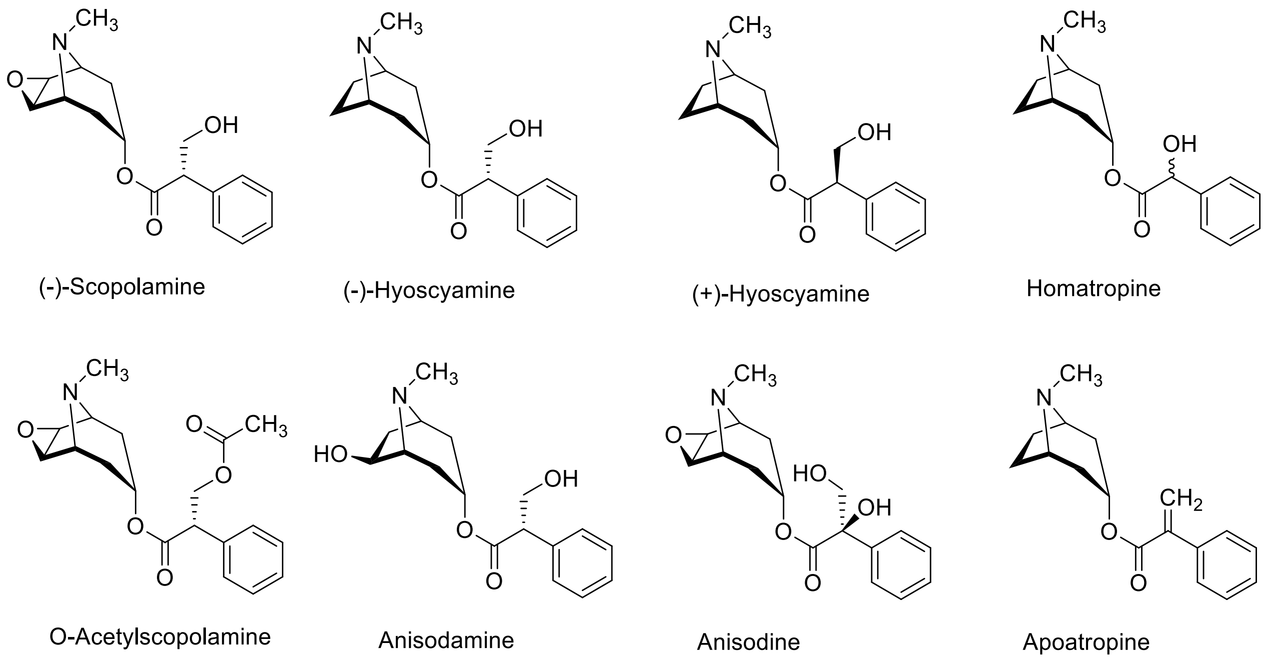

Figure 1 Chemical structures of representative Datura-type tropane alkaloids

2. Although more than 200 different tropane alkaloids have been so far identified in various plants, respective data on their occurrence in food and feed and on toxicity are limited. The most studied tropane alkaloids are (-)-hyoscyamine and (-)-scopolamine, which in contrast to the (+)-enantiomers are formed naturally. (-)-Hyoscyamine and (-)-scopolamine are the alkaloids found in the highest concentrations and most frequently in tropane alkaloid producing plants. Twenty-four different tropane alkaloids were monitored, but atropine and scopolamine comprised 83% of the reported tropane alkaloid content (Mulder et al., 2016). In addition to data on toxicity, information on occurrence in feed and food was only available for (-)-hyoscyamine and (-)-scopolamine. The risk assessment for tropane alkaloids in food and feed by EFSA (EFSA CONTAM Panel, 2013) and the Joint Expert Meeting of FAO/World Health Organization (FAO/WHO, 2020) also focused on atropine (the racemic mixture of (-)- and (+)-hyoscyamine) and scopolamine. Therefore, this paper could only perform a discussion on these compounds.

3. Seeds from Brugmansia, Datura, and Hyoscyamus species are the likeliest materials to contaminate grains (and subsequently grain-based foods) because their density, size, and shape are similar to grains. Low-density vigorous plants can produce up to 30000 seeds per plant (Jimsonweed, CALS). Seeds of D. stramonium have been reported in linseed/flaxseed, soybean, millet, sunflower and buckwheat. In the seeds, atropine and scopolamine accounted for 66% and 20% (percentage estimated using total ion current) of the total tropane alkaloid content, respectively (El Bazaoui, 2011). Based on the guidance document on physical Datura stramonium seed contamination, the estimated concentration of atropine in seeds ranges from 4000 to 13000 mg/kg (FAO and WHO, 2020).

4. In the study reported by Mulder et al. (2016), 1709 samples of plant-derived food products, mainly produced in Europe and collected in nine European countries, were analyzed for tropane alkaloids. One or more tropane alkaloids were detected in 21.3% of single component flours, 20% of cereal-based food for young children aged 6-36 months, 15.8% of bread, 26.2% of legumes and stir-fry mixes, and 14.6% of biscuits. Due to the large number of samples and broad scope of sampled food matrices, this is the most significant study currently available on tropane alkaloid levels in food, even though samples were obtained only from markets in European countries.

5. A total of 58 notifications and alerts were reported by RASFF for atropine and scopolamine in the period 1994 to 31 December 2022 (Nijs et al., 2023). The reports covered seven food product categories as well as the category feed. A total of thirty-nine reports were from the product category ‘cereals and cereal-based products’, seven reports from ‘cocoa and cocoa preparations, coffee and tea’, five reports from ‘dietetic foods, food supplements, fortified foods’, four reports from ‘herbs and spices’ and one report each from the categories ‘food additives and flavorings’, ‘fruits and vegetables’ and ‘nuts, nut products and seeds’. For 28 of the 39 reports in the product category ‘cereals and cereal-based products’, tropane alkaloid concentrations were reported for the sum of atropine and scopolamine, which ranged from 4.0 to 1014 µg/kg. A maximum of 20,835 µg/kg of the sum of atropine and scopolamine was reported in 2018 for whole cumin seeds (RASFF 2018.0774). Most reports within the product category ‘cereals and cereal-based foods’ were on ‘corn-based food, popcorn’ (13 reports), on ‘millet and millet-based food’ (11 reports) and on ‘buckwheat’ (9 reports). From some incidents, multiple RASFF reports were filed by various EU countries. The results indicate that tropane alkaloids-containing weeds occur in many fields on which cereals are grown. After harvest, the weeds (seeds) are not fully removed and are ground in the flour for food production.

6. In China, literature has reported multiple food poisoning incidents caused by accidental ingestion of *Datura stramonium* L. or poisoning caused by seeds of *Datura stramonium* L. mistakenly mixed with cereals (Guo et al., 2022; Liu et al., 2022).

TOXICOLOGY AND HEALTH EFFECTS FROM EPIDEMIOLOGY

7. Tropane alkaloids exert their pharmacological and toxicological effects mainly by acting as competitive antagonists of the muscarinic acetylcholine receptors, both at the level of the central and peripheral nervous systems. Several studies showed that (-)-hyoscyamine is mainly responsible for the antimuscarinic activity of atropine, with the (+)-enantiomer having a 30- to 300-time lower affinity for the muscarinic receptors. The main antimuscarinic effects of tropane alkaloids in the peripheral system are the decreased production of secretions from the salivary, bronchial and sweat glands, dilation of the pupils and paralysis of accommodation, increased heart rate, inhibition of micturition, reduction in gastrointestinal tone and inhibition of gastric acid secretion. At toxic doses, (-)-hyoscyamine and (-)-scopolamine cause stimulation of the central nervous systems with restlessness, disorientation, hallucinations and delirium. As the dose increases, stimulation is followed by central depression, leading to death from respiratory paralysis. Below the antimuscarinic dose ranges, atropine and (-)-scopolamine show cholinomimetic activity, resulting in paradoxical effects such as increased gastric contraction frequency and amplitude, and decreased heart rate. The exact mechanism by which the cholinomimetic activity occurs is not known.

8. In 2013, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) published a scientific opinion on the risks to human and animal health related to the presence of tropane alkaloids in food and feed (EFSA CONTAM Panel, 2013). The CONTAM Panel selected the decrease in heart rate as the critical effect and they found it occurred at lower doses than the other peripheral antimuscarinic effects. For this effect, the CONTAM Panel established a group acute reference dose (ARfD) of 0.016 µg/kg body weight (bw) for the sum of (-)-hyoscyamine and (-)-scopolamine, assuming equivalent potency.

9. In 2020, a Joint FAO/WHO Expert Meeting assessed the risks related to the presence of tropane alkaloids in food in response to two cases of contamination outbreaks that occurred in the supply chain of food aids in 2019 (FAO/WHO, 2020). In April 2019, the consumption of a batch of fortified cereals contaminated by high levels of (-)-scopolamine and (±)-hyoscyamine led to the hospitalisation of about 300 people and five deaths in the Republic of Uganda. A second incident involved unprocessed sorghum distributed as food aid to the Republic of South Sudan. FAO/WHO measured that in healthy male adults, a dose of 1.54 µg/kg bw was considered to be a ‘clinically significant minimal acute effect dose’, based on the reduction of salivary secretion.

10. The FAO/WHO performed benchmark dose (BMD) analyses for several study endpoints, including salivary secretion at 1.5 and 3.5 h, sweat secretion at 1.5 and 3.5 h and pupil size at 4 h, in all cases using a benchmark response (BMR) of 5%. For the decrease in salivary secretion $BMDL_{05}$ of 0.3 and 0.2 µg/kg bw per day were calculated at 1.5 and 3.5 h, respectively. For the other endpoints, the FAO/WHO considered the $BMDL_{05}$ estimates of low confidence in view of the wide BMDL/BMDU intervals. In parallel, the no observed effect levels (NOEL) and lowest observed effect levels (LOEL) were identified for all the endpoints and derived as summarised in Table 1. The decreased heart rate and salivary secretion were considered the most sensitive biological effects. In relation to the decreased heart rate, the FAO/WHO concluded that although it represented a sensitive indicator of biological effects, the magnitude observed was not likely to cause adverse effects in healthy individuals. The FAO/WHO acknowledged that the applied BMR of 5% did not represent a level of adversity in relation to the effect on salivary secretion, but it was rather used as a sensitive biomarker of antimuscarinic effects. The lowest dose at which a non-statistically significant decrease in salivary secretion was observed in the

Perharič et al. (2013) study (i.e. the LOEL of 1.54 µg/kg bw) was eventually considered by FAO/WHO as 'a clinically significant minimal acute effect dose' for the antimuscarinic effects of (-)-hyoscyamine and (-)-scopolamine in healthy male adults.

11. The JOINT FAO/WHO expert meeting was unable to estimate the degradation factors for use in dietary exposure assessments due to several limitations. These limitations include the small number of relevant cooking studies, the uncertainty surrounding the results of these studies, the absence of information on degradation products in these studies, and the lack of information on how specific food matrix and food processing techniques will affect the degree of atropine and scopolamine loss. Since Perharič et al., (2013) reported a loss of atropine (37%) and scopolamine (58%) during cooking, the corresponding doses have been adjusted accordingly, with the NOEL and $BMDL_{05}$ adjusted to 0.15 and 0.20 µg/kg bw, respectively. Clearly, more information is needed on the effects of processing on tropane alkaloids.

Table 1 Summary of critical effect levels (µg/kg bw) identified by FAO/WHO for the sum of (-)-hyoscyamine and (-)-scopolamine.

Effect	NOEL	LOEL	$BMDL_{05}$
Decreased heart rate	0.15	0.46	-
Decreased salivary secretion	0.46	1.54	0.2-0.3
Decreased sweat secretion	1.54	4.62	-
Increased pupil size	4.62	15.41	-

12. The comparison of the hazard characterisations of the toxicological and pharmacological effects of (-)-hyoscyamine and (-)-scopolamine performed by the CONTAM Panel and the FAO/WHO demonstrated main differences in the interpretation of the results of the human clinical study performed by Perharič et al. (2013).

13. EFSA (EFSA, 2022) stated that it was not straightforward to quantitatively compare the differences from the assessments of the CONTAM Panel and the FAO/WHO, in view of the different applied approaches and the different scopes of the assessments. Given the existing uncertainties, the ARfD established by the CONTAM Panel should be retained without modifications as protective towards the general population including susceptible subgroups. In conclusion, based on the comparison with the FAO/WHO assessment, an update of the CONTAM Panel assessment on the risks to human health related to the presence of tropane alkaloids in food is not considered necessary.

ANALYTICAL METHODS

14. Various analytical methods can be used to determine tropane alkaloids in various samples, including food, medicine, plants, and biological fluids (Gonzalez Gomez et al., 2022). Gas chromatography-mass spectrometry (GC-MS), liquid chromatography with different detectors (UV, mass spectrometry (MS), tandem mass spectrometry), capillary electrophoresis, enzyme-linked immunosorbent assay (ELISA), and thin-layer chromatography (TLC) have been widely used. However, due to the complexity of the matrix and the typically low concentration of analytes, only a few methods are sufficient to determine and monitor the residues of tropane alkaloids in food. In general, multiple residual methods are currently used for dietary exposure assessment. Currently, only MS methods can accurately measure trace amounts of tropane alkaloids in food and feed. Two MS based methods have been used, in combination with either gas chromatography (GC) or liquid chromatography (LC) as standards of analysis.

15. GC coupled to MS is an effective method for quickly and reliably identifying a broad spectra of potential compounds in cases of intoxication. However, it is not the preferred technique for analyzing and quantifying tropane alkaloids in food. Although the determination of tropane alkaloids can be carried out without derivatization, derivatization reactions are commonly employed in GC analysis since atropine and scopolamine may dehydrate at high temperatures and form apoatropine and aposcopolamine.

16. LC-MS is the most used technique for the determination of atropine and scopolamine in food and biological matrices. Reversed-phase chromatography on C18 stationary phases and mobile phases containing methanol or acetonitrile and ammonium salts (formate, acetate) or formic acid have been used for the separation of tropane alkaloids, mainly without enantiomeric separation of (+)- and (-)-hyoscyamine. For the separation of the enantiomers of atropine, chiral columns are required, and there are limited methods available for the determination of these enantiomers in food. Sample matrix effects may cause difficulties meeting tolerances for identity confirmation using MS. Therefore, clean-up steps in the sample preparation procedures need to be included, and quantitation is usually carried out using a matrix-matched calibration curve or isotopically labelled standards. When separation of the enantiomers of atropine is not possible, it is appropriate to analyze and report the concentration of atropine instead.

17. Diverse sample preparation procedures for the extraction of tropane alkaloids from food and plant matrices and clean-up procedures are described in the literature. Tropane alkaloids contain a tertiary amine in their structure, which is protonated in acidic media. The protonated species of tropane alkaloids are more water-soluble in comparison to their free bases and this property allows a selective extraction of the analytes from the matrix with the exclusion of lipophilic compounds. Therefore, solid-liquid extraction with mixtures of water and polar organic solvents has enabled selective extraction of the alkaloids in the presence of lipophilic compounds. The addition of formic acid to the solvent enhances the extraction efficiency, whereas in alkaline media, hydrolysis of the ester alkaloids occurs (Dräger, 2002). Jandric et al. (2011) extracted tropane alkaloids from ground wheat using an adapted QuEChERS procedure (stands for Quick, Easy, Cheap, Effective, Rugged and Safe). A non-aqueous solid-phase extraction method using silica based strong cation exchange has been successfully employed for the enrichment of tropane alkaloids and for the determination of atropine and scopolamine in extracts from *Scopolia tangutica* by LC-diode array detector (DAD) and LC-MS (Long et al., 2012). A microwave-assisted extraction followed by QuEChERS dispersive solid-phase extraction was used for the determination of atropine and scopolamine in *Datura* genera (leaves and seeds) by GC-MS (Ciechomska et al., 2016).

18. In the study reported by Mulder et al. (2016), tropane alkaloids were analyzed in a large number of samples (n=1709) by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). This method was developed and validated in-house and was considered fit for purpose. This method comprised 24 Datura tropane alkaloids, and the limits of quantification (LOQ) for the various food groups were, depending on the type of tropane alkaloids, 0.5-5 µg/kg in single flours and cereal-based foods, dry (herbal) teas and legumes and stir-fry mixes and 0.0067-0.0333 µg/L in tea infusion. The limits of detection (LOD) ranged from 0.05-2.5 µg/kg in single flours, cereal-based foods, dry (herbal) teas and legumes and stir-fry mixes and from 0.0017-0.0133 µg/L in tea infusion. In this method, quantification is performed by the isotopic dilution approach, using two internal standards (atropine-d_3 and scopolamine-d_3).

19. Overall, solid-phase extraction and QuEChERS are the most commonly used sample preparation methods. Additionally, it cannot be ignored that the sampling method and the mixing uniformity of the sample pretreatment are crucial before sample preparation, and need to be fully considered in subsequent analytical method study.

20. LC-high resolution (HRMS) is a state-of-art technique for correctly screening tropane alkaloids in food and feed. Rollo et al. (2023) released a research article on a QuEChERS method combined to LC-HRMS for the accurate and sensitive simultaneous determination of pyrrolizidine and tropane alkaloids in cereals and spices. The main attribution of this technique is its compound identification capability. In this work, the authors followed an identification criterion adopted from Health and Food Safety, EU (SANTE). They were (i) a precursor ion detected with a mass accuracy below 5 ppm; (ii) retention time of the analyte in the extract should correspond to that of the calibration standard with a tolerance of ±0.1 min; (iii) minimum number of ions for HRMS are two ions with mass accuracy below 5 ppm, including at least one fragment ion. Compounds were considered “identified” when all criteria were met, “detected” when only one criterion (i) was fulfilled, and “not found” when no one of these criteria was met. As well this LC-HRMS provide high sensitivity, for TAs, the obtained limit of detection (LOD) is 0.1 µg/kg and the LOQ is 0.4 µg/kg. Romera-Torres et al. (2020) performed a comprehensive tropane alkaloids analysis and retrospective screening of contaminants in honey samples using LC-HRMS. One of 19 honey sample were positive and contained 27 µg/kg of scopolamine. They use LC-HRMS for both targeted TAs and post-targeted contaminant analyses.

LEVEL OF TROPANE ALKALOIDS IN FOOD COMMODITIES

21. The GEMS/Food database contains data on the levels of scopolamine in 4,289 food products from 2006 to 2022. Most of the analytical results (90.3%) are left censored, namely reported as 0. According to the GEMS/food database, there are several food categories with high maximum values of scopolamine. These include cereals or cereal-based products (460.0 µg/kg), legumes, nuts and oilseed (389.6 µg/kg), stimulant beverages, dried and diluted excluding cocoa products (133.7 µg/kg), starchy roots and tubers NES (34.1µg/kg), herbs, spices and condiments (22.0 µg/kg) and food for infants and small children (21.9 µg/kg). The average level of scopolamine in various food categories, in descending order, is 5.9 µg/kg for starchy roots and tubers NES, followed by 2.4 µg/kg for legumes, nuts and oilseed, 1.6 µg/kg for stimulant beverages, dried and diluted excluding cocoa products, 1.2 µg/kg for cereals or cereal-based products, 0.8 µg/kg for herbs, spices and condiments. The average level of scopolamine is low in other food categories or not detected. Tables 2 summarizes the average and maximum concentrations of scopolamine in various foods.

22. FAO/WHO and EFSA assessed the levels and patterns of tropane alkaloids contamination of food commodities on the basis of occurrence data from the literature and from data submitted by Italy, South Korea, Spain, France, Netherlands and so on. Tables 2 and 3 summarize the average and maximum concentrations of scopolamine and

atropine in various foods, respectively.

23. According to FAO/WHO 2020 reports, the maximum level of scopolamine is detected in grains and grain-based products (1863 µg/kg), followed by 50 µg/kg for non-alcoholic beverage, 15.2 µg/kg for food for infants,12.9 µg/kg for legumes nuts and oilseed. The maximum level of atropine is detected in grains and grain-based products (15528 µg/kg), followed by 65.6 µg/kg for food for infants.

24. EFSA collected data on the content of tropane alkaloids in food, with emphasis on 24 TAs including atropine and scopolamine in 2016 (EFSA, 2016). EFSA focus on the analysis of atropine and scopolamine in 2018, covering the most complete variety of foods and the latest data (EFSA, 2018). Most of the analytical results (95%) were left censored, namely reported as less than the LOD or than the LOQ. According to EFSA 2018 reports, the highest mean of scopolamine in various food categories, in descending order, is 64.9 µg/kg for legumes nuts and oilseed, followed by 11.11 µg/kg for non-alcoholic beverages, 3.52 µg/kg for vegetables and vegetable products, 2.64 µg/kg for grains and grain-based products, 2.2 µg/kg for herbs spices and condiments, 0.55 µg/kg for snacks and desserts. The highest mean of atropine in various food categories, in descending order, is 77.22 µg/kg for legumes, nuts and oilseed, 34.98 µg/kg for herbs spices and condiments, 6.27 µg/kg for grains and grain-based products, 4.84 µg/kg for vegetables and vegetable products, 0.22 µg/kg for infant foods.

25. According to the published literatures in Europe from 2014 to 2022, the maximum level of scopolamine is detected in legumes nuts and oilseed (94 µg/kg), followed by 1.5-75 µg/kg for non-alcoholic beverage, 27 µg/kg for snacks and desserts, 2.8-21 µg/kg for grains and grain-based products; the maximum level of atropine is detected in grains and grain-based products(83.9 µg/kg). These data from the published literatures are also listed in tables 2 and 3, respectively.

Table 2 Summary statistics for Scopolamine concentrations (μg/kg) in the different food samples from GEMS/Food database 2006-2022, FAO/WHO 2020, EFSA 2018 and the literatures.

FOOD CATEGORIES	COMMODITY	N	YEAR	COUNTRY	POSITIVE SAMPLES	MAXIMUM (μg/kg)	AVERAGE	REFERENCE
Infant foods	Food for infants and small children	1026	2014-2017	WHO	38	21.9	0.10	GEMS/Food，2006-2022
	Cereal-based products for infants and young children	226	2010–2014	Netherlands	18	15.2	-	FAO/WHO,2020
	Infant foods	46	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	14	0.51	-	FAO/WHO,2020
	Cereal based food for infants	35	2017–2019	Singapore	3	2.46		FAO/WHO,2020
	Baby food (pap biscuits crackers snack and grissines)	18	-	Spain France and Italy	1	2.80	-	FAO/WHO,2020
	Food for infants and young children	-	2018	Europe	-	-	0.22	EFSA,2018
	Cereals with an added high protein food which are or have to be reconstituted Cereal-based food for infants and young children	-	2018	Europe	-	-	0.22	EFSA,2018
	Cereal-based products for infants and young children	21	2011、2012、2014	Europe	7	38.9	1.5	Mulder Patrick P J，2015

Grains and grain-based products	Cereals and cereal-based products	2524	2013-2018	WHO	124	460.00	1.2	GEMS/Food ，2006-2022
	Grains and grain-based products	-	2018	Europe	-	-	0.99	EFSA,2018
	Breakfast cereal products	30	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)		0.38	-	FAO/WHO,2020
	Maize containing cereal products	13	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	2	0.16	-	FAO/WHO,2020
	Super cereal and Super cereal Plus	510	60 in 2019; rest unknown	WFP different locations	380	1863	-	FAO/WHO,2020
	Bread and pasta	33	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	5	0.16	-	FAO/WHO,2020
	Biscuits and baked goods	32	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	5	0.7	-	FAO/WHO,2020
	Millet sorghum and other flours	25	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	3	12.9	-	FAO/WHO,2020
	Other milling products	-	2018	Europe	-	-	2.2	EFSA,2018

	Buckwheat milling products	-	2018	Europe	-	-	2.64	EFSA,2018
	Pasta raw	-	2018	Europe	-	-	1.98	EFSA,2018
	Breakfast cereal products	113	2022	Europe	18	15.2	-	Gonzalez-Gemez_Foods_2022
	Buckwheat milling products	26	2018	Europe	-	10.4	-	Martina Cirlini,2018
	Millet sorghum and other flours	7	2022	Europe	4	2.8	-	Vuković Gorica , 2022
		31	2015	Europe	8	10.2	--	Shimshoni Jakob Avi,2015
Non-alcoholic beverages	Non-alcoholic beverages	-	2018	Europe	-	-	4.18	EFSA,2018
	Herbal teas	20	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	20	34.1	-	FAO/WHO,2020
	Herbal tea and infusions extracts and tablets	60	-	Italy	5	50	-	FAO/WHO,2020
	Herbal tea infusion	-	2018	Europe	-	-	2.31	EFSA,2018
	Herbal teas	26	2017	Germany	7	14.0	-	FAO/WHO,2020
	Black and green teas	9	2015–2016	United Kingdom of Great Britain and Northern Ireland	1	0.15	-	FAO/WHO,2020
	Green tea	-	2018	Europe	-	-	10.01	EFSA,2018
	Tea	-	2018	Europe	-	-	2.31	EFSA,2018
	Camomile flowers	-	2018	Europe	-	-	11.11	EFSA,2018
	Peppermint (Mentha piperita)	-	2018	Europe	-	-	3.96	EFSA,2018

	Herbal teas	33	2022	Europe	5	1.5	-	Martinello Marianna，2022
		44	2019	Europe	1	75	-	KIM DAI JIN，2019
Vegetables and vegetable products	Vegetables and vegetable products (including fungi)	42	2015-2017	WHO	0	0	0	GEMS/Food，2006-2022
	Vegetables and vegetable products	-	2018	Europe	-	-	3.52	EFSA,2018
Legumes nuts and oilseed	Legumes nuts and oilseed	172		WHO	6	389.6	2.40	GEMS/Food，2006-2022
	Oilseeds	12	2015–2016	United Kingdom of Great Britain and Northern Ireland new data	1	12.9	-	FAO/WHO,2020
	Hempseed	-	2018	Europe	-	-	64.9	EFSA,2018
	Legumes nuts and oilseed	-	2018	Europe	-	-	3.74	EFSA,2018
	Sunflower seed	-	2018	Europe	-	-	1.98	EFSA,2018
Snacks and desserts	Honey,Corn chips and other foods	56	2016-2017	WHO	5	1.8	0.10	GEMS/Food，2006-2022
	Popcorn	-	2018	Europe	-	-	0.55	EFSA,2018
	Snacks, desserts and other foods	-	2018	Europe	-	-	0.44	EFSA,2018
	Honey,Corn chips and other foods	19	2020	Europe	1	27		omera-Torres Ana，2020
Herbs spices and condiments	Herbs, spices and condiments	33	2014-2017	WHO	5	22.0	0.8	GEMS/Food，2006-2022
	Herbs spices and condiments	-	2018	Europe	-	-	2.2	EFSA,2018
Products for special nutritioanal use	Products for special nutritional use	7	2014-2017	WHO	-	0	0	GEMS/Food,2006-2022

Starchy roots and tubers NES	Starchy roots and tubers NES	32	2014-2017	WHO	12	34.1	5.9	GEMS/Food,2006-2022
Stimulant beverages, dried and diluted excluding cocoa products	Stimulant beverages, dried and diluted excluding cocoa products	397	2014-2017 , 2022	WHO	69	133.7	1.6	GEMS/Food,2006-2022

-：The original report does not have this data

Table 3 Summary statistics for Atropine (or Hyoscyamine) concentrations (µg/kg) in the different food samples from EFSA 2018 and FAO/WHO 2020

FOOD CATEGORIES	COMMODITY	N	YEAR	COUNTRY	POSITIVE SAMPLES	MAXIMUM (µg/kg)	AVERAGE	REFERENCE
Infant foods	Cereal-based products for infants and young children	226	2010–2014	Netherlands	21	65.6	-	FAO/WHO,2020
	Infant foods	46	2015–2016	United Kingdom of Great Britain and Northern Ireland	14	3.73	-	FAO/WHO,2020
	Cereal based food for infants	35	2017–2019	Singapore	3	4.81	-	FAO/WHO,2020
	Baby food (pap biscuits crackers snack and grissines)	18	-	Spain France and Italy	1	11.5	-	FAO/WHO,2020
	Cereal based infant foods containing millet	20	2015–2016	United Kingdom of Great Britain and Northern Ireland		3.73		EFSA,2018
	Food for infants and young children	-	2018	Europe	-	-	0.22	EFSA,2018
	Cereal-based products for infants and young children	18	2011、2012、2014	Europe	6	8.8	0.44	Mulder Patrick P J，2014
Grains and grain-based products	Breakfast cereal products	30	2015–2016	United Kingdom of Great Britain and Northern Ireland	2	0.67	-	FAO/WHO,2020
	Maize containing cereal products	13	2015–2016	United Kingdom of Great Britain and Northern Ireland	2	0.63	-	FAO/WHO,2020
	Super cereal and Super cereal Plus	510	60 in 2019; rest unknown	WFP different locations	380	15528	-	FAO/WHO,2020
	Bread and pasta	33	2015–2016	United Kingdom of Great Britain and Northern Ireland	5	0.63	-	FAO/WHO,2020
	Biscuits and baked goods	32	2015–2016	United Kingdom of Great Britain and	5	1.23	-	FAO/WHO,2020

				Northern Ireland (for EFSA survey)				
	Millet sorghum and other flours	25	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	3	9.8	-	FAO/WHO,2020
	Cereal bars	30	2015	Switzerland	1	5.0	-	FAO/WHO,2020
	Cereal bars	-	2018	Europe	-	-	6.27	EFSA,2018
	Grains and grain-based products	-	2018	Europe	-	-	1.32	EFSA,2018
	Other milling products	-	2018	Europe	-	-	6.05	EFSA,2018
	Corn grain	-	2018	Europe	-	-	3.30	EFSA,2018
	Maize containing cereal products	39	2022	Europe	7	3.98	-	Vuković Gorica , 2022
	Bread and pasta	26	2018	Europe	-	83.9	-	Martina Cirlini , 2018
	Millet sorghum and other flours	31	2022	Europe	12	58.8	-	Vuković Gorica , 2022
		31	2015	Europe	12	58.8	-	Shimshoni Jakob Avi,2015
Non-alcoholic beverages	Non-alcoholic beverages	-	2018	Europe	-	-	3.96	EFSA,2018
	Herbal teas	20	2015–2016	United Kingdom of Great Britain and Northern Ireland (for EFSA survey)	20	-	129	FAO/WHO,2020
	Herbal tea and infusions extracts and tablets	60	-	Italy	5	69	-	FAO/WHO,2020
	Herbal tea infusion	-	2018	Europe	-	-	-	EFSA,2018
	Herbal teas	26	2017	Germany	7	72.0	-	FAO/WHO,2020
	Camomile flowers	-	2018	Europe	-	-	2.75	EFSA,2018
	Peppermint (Mentha piperita)	-	2018	Europe	-	-	4.73	EFSA,2018
	Herbal teas	33	-	Europe	5	0.88	-	Martinello Marianna , 2022

Vegetables and vegetable products	Vegetables and vegetable products	-	2018	Europe	-	-	4.84	EFSA,2018
Legumes nuts and oilseed	Oilseeds	12	2015–2016	United Kingdom of Great Britain and Northern Ireland new data	1	9.8	-	FAO/WHO,2020
	Hempseed	-	2018	Europe	-	-	77.22	EFSA,2018
	Legumes nuts and oilseed’	-	2018	Europe	-	-	4.51	EFSA,2018
	Sunflower seed	-	2018	Europe	-	-	3.19	EFSA,2018
Snacks and desserts	Popcorn	-	2018	Europe	-	-	1.54	EFSA,2018
	Snacks desserts and other foods	-	2018	Europe	-	-	0.99	EFSA,2018
	Honey,Corn chips and other foods	40	2020	Europe	9	3.8	-	Marianna Martinello，2020
Herbs spices and condiments	Herbs spices and condiments	-	2018	Europe	-	-	2.64	EFSA,2018
	Coriander	-	2018	Europe	-	-	34.98	EFSA,2018
	Seed	-	2018	Europe	-	-	6.05	EFSA,2018

-：The original report does not have this data

DIETARY EXPOSURE

26. The dominant foods contributing to acute dietary tropane alkaloids exposure in each country were all dietary staples; rice (People's Republic of Bangladesh, the Lao People's Democratic Republic, the Republic of the Philippines), corn (the Plurinational State of Bolivia, the Republic of Uganda, the Republic of Zambia) and sorghum (the Republic of Zambia). (FAO/WHO, 2020).

Before the 2019 incident in Uganda, mean acute dietary tropane alkaloids exposures for young children (Super Cereal plus for young children, 6- 59 months), children (Super Cereal) and women (Super Cereal) were 130, 45 and 26 ng/kg bw, respectively, with 95th percentile estimates of 550, 220 and 120 ng/kg bw, respectively. After the incident and implementation of additional risk management measures (monitoring, raw material source selection and improved grain cleaning), the mean acute dietary tropane alkaloids exposures for the three sub-populations were 17, 11 and 6 ng/kg bw, respectively, with 95th percentile estimates of 54, 32 and 18 ng/kg bw, respectively. (FAO/WHO, 2020)

27. FAO/WHO reports use the MOE approach. Three specific risk groups were identified: pregnant and lactating women (15-44 years), children (5-15 years) and young children (6-59 months). For the general diet, compared to a clinically significant minimal acute effect dose of 1.54 µg/kg bw, MOEs for the general population (children and women of reproductive age) ranged from 3080 to 3850 (mean) and 440-616 (95th percentile) for combined exposures to hyoscyamine and scopolamine. These MOEs were not considered to be of concern by the expert meeting. For doses required to produce potentially adverse effects (e.g. increased heart rate, decreased saliva, dry mouth and sweat secretions and pupil dilation at 4.62 µg/kg bw), the MOEs would be three times greater.

28. In 2018, EFSA published a scientific report on human acute exposure assessment to tropane alkaloids (EFSA, 2018). Since tropane alkaloids do not exhibit chronic toxicity, human dietary exposure was estimated as acute exposure scenario for atropine, scopolamine, and the sum of atropine and scopolamine. Table 4 summarized statistics of probabilistic acute dietary exposure assessment to atropine and scopolamine (at the LB-UB) across European dietary surveys (ng/kg bw per day) by age group.

(i) **Atropine**: The highest mean acute dietary exposures to atropine were found for infants (range from 0.27 to 12.09 ng/kg bw per day), toddlers (range from 1.11 to 10.15 ng/kg bw per day) and other children (range from 0.65 to 10.05 ng/kg bw per day).The highest P95 exposures were found for infants (range from 0.01 to 28.38 ng/kg bw per day), toddlers (range from 1.7 to 30.15 ng/kg bw per day), and other children (range from 0.47 to 24.41 ng/kg bw per day).

(ii) **Scopolamine**: The highest mean exposures were found for infants (range from 0.16 to 8.94 ng/kg bw per day), toddlers (range from 0.77 to 8.4 ng/kg bw per day), and other children (range from 0.51 to 8.41 ng/kg bw per day). The highest P95 exposures were found for infants (range from 0.0 to 23.6 ng/kg bw per day), toddlers (range from 0.18 to 25.84 ng/kg bw per day), and other children (range from 0.01 to 22.97 ng/kg bw per day).

(iii) **Co-exposure to atropine and scopolamine**: The highest mean acute exposures were found for infants (range from 0.97 to 18.91 ng/kg bw per day), toddlers (range from 1.82 to 18.65 ng/kg bw per day), and other children (range from 1.13 to 18.13 ng/kg bw per day). The highest P95 acute exposures were found for infants (range from 0.05 to 53.32 ng/kg bw per day), toddlers (range from 3.14 to 54.14 ng/kg bw per day), and other children (range from 1.35 to 47.91 ng/kg bw per day).

29. Large differences were observed between the LB and UB estimated exposure levels across all age classes. For the sum of atropine and scopolamine, the group ARfD was exceeded, under the UB assumption, at the mean intake level of infants, toddler and other children, and at the P95 in all age classes. Under LB assumption, the group ARfD was exceeded for the sum of atropine and scopolamine at the P95 in toddlers and other children. UB P95 exposure exceeded the ARfD for both atropine and scopolamine (separately) in infants, toddlers and other children, and in adolescents as well. Overall, among dietary and non-dietary supplements, bread and other grain milling products are the main factors contributing to the simultaneous intake of atropine and scopolamine in people of all ages.

Table 4 Summary statistics of probabilistic acute dietary exposure assessment to atropine and scopolamine (at the LB-UB) across European dietary surveys (ng/kg bw per day) by age group. The corresponding 95% confidence intervals are presented in the brackets. (EFSA, 2018)

Atropine										
Age group	Mean dietary exposure (ng/kg bw per day)					P95 dietary exposure (ng/ bw per day)				
	N	LB Min	LB Max	UB Min	UB Max	N	LB Min	LB Max	UB Min	UB Max
Infants	11	0.27(0.06-2.55)	8.25(2.61-22.86)	1.29(0.76-3.65)	12.09(6.61-24.15)	10	0.01(0-0.22)	12.43(9.28-17.14)	5.77(3.58-8.53)	28.38(21.99-37.13)
Toddlers	15	1.11(0.54-1.99)	4.99(1.99-12.66)	4.71(3.75-6.4)	10.15(6.45-23.77)	12	1.7(0-9.53)	14.19(3.2-36.9)	14.92(11.76-18.22)	30.15(18.14-66.57)
Other children	21	0.65(0.37-1.25)	6.36(4.64-8.45)	3.78(3.46-4.36)	10.05(7.87-12.43)	21	0.47(0.26-0.89)	11.31(8.36-15.86)	13.96(13.18-15.08)	24.41(21.64-27.58)
Adolescents	21	0.66(0.38-1.24)	3.4(2.02-5.83)	2.83(2.58-3.11)	7.76(6.19-9.75)	21	1.01(0.54-1.78)	7.05(5.09-10.29)	8.27(7.4-9.22)	18.94(17.13-21.07)
Adults	23	0.54(0.36-0.87)	2.14(1.47-2.94)	1.77(1.47-2.42)	4.31(3.85-5.04)	23	0.64(0.38-1.14)	4.95(4.15-6.25)	5.11(4.58-5.6)	11.8(10.85-12.79)
Elderly	20	0.37(0.13-0.92)	1.97(0.86-4.55)	1.49(1.15-2.56)	3.83(2.67-5.79)	20	0.47(0.24-0.96)	5.05(2.63-9.2)	4.51(3.89-5.52)	9.97(8.1-12.29)
Very elderly	16	0.36(0.2-0.62)	2.33(0.55-5.06)	1.73(1.55-2.25)	4.13(2.86-6.4)	15	0.56(0.31-0.94)	6(3.09-14.74)	5.81(4.64-6.93)	10.56(8.01-14.83)
Scopolamine										
Age group	Mean dietary exposure (ng/kg bw per day)					P95 dietary exposure (ng/ bw per day)				
	N	LB Min	LB Max	UB Min	UB Max	N	LB Min	LB Max	UB Min	UB Max
Infants	11	0.16(0.01-0.92)	3.67(0.47-12.65)	1.2(0.69-3.78)	8.94(5.08-23.19)	10	0(0-0)	2.48(2.11-2.95)	5.28(3.35-7.8)	23.6(19.62-31.68)
Toddlers	15	0.77(0.1-3.75)	3.18(0.02-19.19)	4.28(3.58-5.89)	8.4(5.65-18.83)	12	0.18(0-0.53)	6.75(1.66-21.82)	14.36(11.93-16.38)	25.84(17.73-40.39)
Other children	21	0.51(0.25-1.27)	4.76(3.29-6.83)	3.52(3.18-4.35)	8.41(6.56-10.69)	21	0.01(0-0.12)	8.75(7.25-10.32)	13.46(12.21-15.29)	22.97(20.13-26.04)
Adolescents	21	0.43(0.28-0.68)	2.76(1.48-4.44)	2.42(1.99-3.85)	6.51(5.35-8.52)	21	0.28(0.05-0.67)	6.06(4.8-7.6)	7.99(7.09-9.29)	17.09(15.96-18.77)
Adults	23	0.37(0.27-0.45)	1.38(0.92-2.22)	1.6(1.35-2.49)	3.51(3.16-3.94)	23	0.23(0.12-0.38)	2.57(1.91-3.47)	4.91(4.42-5.39)	10.88(10.3-11.52)
Elderly	20	0.28(0.1-0.76)	1.19(0.57-2.67)	1.29(1.07-1.6)	3.2(2.37-4.54)	20	0.17(0.07-0.3)	2.49(1.23-4.26)	4.49(3.86-5.28)	8.5(6.68-11.05)
Very elderly	16	0.22(0.08-0.73)	1.43(0.31-5.49)	1.56(1.4-1.83)	3.67(2.47-7.55)	15	0.15(0.03-0.29)	3.08(1.11-8.89)	5.14(4.19-6.6)	9.16(7.04-12.39)
Sum of atropine and scopolamine										
Age group	Mean dietary exposure (ng/kg bw per day)					P95 dietary exposure (ng/ bw per day)				
	N	LB Min	LB Max	UB Min	UB Max	N	LB Min	LB Max	UB Min	UB Max
Infants	11	0.97(0.73-1.61)	12.44(3.09-56.16)	2.17(1.46-3.53)	18.91(11.29-41.72)	10	0.05(0-0.61)	14.15(9.94-18.98)	10.85(7.44-16.26)	53.32(42.08-65.2)
Toddlers	15	1.82(0.13-5.77)	8.16(2.7-22.22)	8.88(7.35-12.49)	18.65(12.12-34.83)	12	3.14(1.09-7.99)	20.53(5.68-61.83)	28.77(24.38-34.04)	54.14(34.52-92.31)
Other children	21	1.13(0.62-2.3)	10.69(7.08-14.77)	7.3(6.66-8.16)	18.13(14.66-22.73)	21	1.35(0.75-1.91)	18.59(14.33-24.62)	27.1(23.63-30.49)	47.91(41.82-53.96)
Adolescents	21	1.08(0.53-1.93)	6.23(3.42-10)	5.19(4.12-9.01)	14.03(12.08-17.01)	21	1.97(0.97-3.31)	12.26(9.77-15.95)	16(14.22-17.81)	35.4(32.23-38.99)
Adults	23	0.87(0.41-1.53)	3.49(2.43-4.73)	3.3(2.8-4.3)	7.81(6.99-8.93)	23	1.31(0.85-2.06)	7.65(6.4-9.29)	9.94(8.96-11.08)	22.35(21.06-23.8)
Elderly	20	0.64(0.24-1.81)	3.11(1.4-5.92)	2.75(2.24-3.53)	7.05(5.14-11.11)	20	1.05(0.34-2.13)	7.27(4.38-12.22)	8.98(7.5-10.76)	18.11(15.26-22.64)
Very elderly	16	0.65(0.31-1.3)	3.81(1.2-10.04)	3.26(2.91-3.83)	7.6(5.16-12.88)	15	1.11(0.72-1.53)	8.64(4.98-19.63)	10.61(8.16-13.37)	19.14(15.24-27.91)

bw: body weight; N=number of surveys. Min: minimum; Max: maximum. P95, 95th percentile, LB lower bound, UB upper bound. One-one dietary survey had less than 60 participants in the infants and the very elderly age group, three surveys had less than 60 participants in the toddlers age group; therefore, these were not included in calculation of the 95th percentile exposure.

RISK MANAGEMENT CONSIDERATION

30. Currently there are no international regulations in place for tropane alkaloids, with neither Codex maximum levels nor a Code of Practice available for these contaminants. There are some regulations that define limits for the presence of noxious seeds in grains.

31. Codex standards[4] for various cereals and pulses include a provision“The products covered by the provisions of this standard shall be free from the following toxic or noxious seeds in amounts which may represent a hazard to human health. – Crotolaria (Crotalaria spp.), Corn cockle (Agrostemma githago L.), Castor bean (Ricinus communis L.), Jimson weed (Datura spp.), and other seeds that are commonly recognized as harmful to health”. As part of a Good Agricultural Practices screening program for cereal grains and legumes, size exclusion and visual inspection of screenings could be implemented at an early stage post-harvest to ensure the final product meets the generic Codex standard of being free from noxious weeds in amounts that would represent a hazard to human health.

32. China Grain Standard (GB 2715-2016) requires the number of Jimson weed (Datura spp.), Crotolaria (Crotalaria spp.), Corn cockle (Agrostemma githago L.), Castor bean (Ricinus communis L.) and other seeds that are commonly recognized as harmful to health in grain (including maize, sorghum, wheat, oats, naked oat, barley and hull-less barley) should not exceed 1 seed per kg of grain.

33. The United States has similar standards for grains under 7 CFR Part 810 Subparts B, D-M. Grains and seeds will be considered to be Sample Grade or distinctly low quality if they contain 3 or more crotalaria seeds or 2 or more castor beans as follows: corn, mixed grain, wheat (per 1 kg); barley, flaxseed, oats, rye, triticale (per 1 1/8 to 1 ¼ quarts); and sunflower seeds (per 600 g). For sorghum and soybeans, the standard is 2 crotolaria seeds and 1 castor bean (per 1 kg).[5]

34. The Republic of South Africa Foodstuffs, Cosmetics and Disinfectants Act has been updated to specify no more than 1 *Datura* seed per kg of various agricultural products, including maize, soya beans and wheat (Republic of South Africa, 2002).

35. Until now, only the European Union (EU) has set MLs for tropane alkaloids in foods. Commission Regulation (EU) 2023/915[6] sets maximum levels for atropine and scopolamine in grains, processed cereal based foods and baby foods for infants and young children, and herbal infusions (Table 5).

Table 5 Maximum levels for atropine and scopolamine in food

Tropane alkaloids	**Maximum level (µg/kg)**		**Remarks**
	Atropine	**Scopolamine**	
Baby food and processed cereal-based food for infants and young children, containing millet, sorghum, buckwheat, maize or their derived products	1.0	1.0	Derived products relate to products containing at least 80 % these cereal products. The sampling for the control of compliance with the maximum level shall be performed in accordance with the provisions provided for in point J of Annex I to Regulation (EC) No 401/2006. The maximum level applies to the product as placed on the market.
	Sum of atropine and scopolamine		For the sum of atropine and scopolamine, maximum levels refer to lower bound concentrations, which are calculated on the assumption that all the values below the limit of quantification are zero.
Unprocessed millet grains and sorghum grains	5.0		The maximum level applies to unprocessed cereal grains placed on the market before first-stage processing.

4 Standard for Certain Pulses (CXS 171-1989); Standard for Sorghum Grains (CXS 172-1989); Standard for Maize (Corn) (CXS 153-1985); Standard for Wheat and Durum Wheat (CXS 199-1995); Standard for Oats (CXS 201-1995).

5 eCFR : 7 CFR Part 810 -- Official United States Standards for Grain. Additional reference for sample sizes is the USDA grain handbook found here: AMS-GD-2020-11 - FGIS Handbooks | Agricultural Marketing Service (usda.gov) . Listed as Book II - Grading Procedures (pdf)

6 Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006 (Text with EEA relevance)

Unprocessed maize grains	15	Except unprocessed maize grains for which it is evident e.g. through labelling, destination, that it is intended for use in a wet milling process only (starch production) and except unprocessed maize grains for popping. The maximum level applies to unprocessed maize grains placed on the market before first-stage processing.
Unprocessed buckwheat grains	10	The maximum level applies to unprocessed buckwheat grains placed on the market before first-stage processing.
Maize for popping Millet, sorghum and maize placed on the market for the final consumer Milling products of millet, sorghum and maize	5.0	-
Buckwheat placed on the market for the final consumer Milling products of buckwheat	10	-
Herbal infusions (dried product) and ingredients used for herbal infusions (dried products) except products listed in I.	25	'Herbal infusions (dried product)' refers to: — herbal infusions (dried product) from flowers, leaves, stalks, roots, and any other parts of the plant (in sachets or in bulk) used for the preparation of herbal infusion (liquid product); and —instant herbal infusions. In the case of powdered
Herbal infusions (dried product) and ingredients used for herbal infusions (dried products) of exclusively anise seeds	50	Herbal infusions (dried product)' refers to: — herbal infusions (dried product) from flowers, leaves, stalks, roots, and any other parts of the plant (in sachets or in bulk) used for the preparation of herbal infusion (liquid product); and —instant herbal infusions. In the case of powdered extracts, a concentration factor of 4 has to be applied.
Herbal infusions (liquid product)	0.20	-

36. Other international guidance or intervention levels include those recommended by the 2020 FAO/WHO expert meeting for hyoscyamine and scopolamine in WFP products, namely SUPER CEREAL, SUPER CEREAL PLUS and Lipid-Based Nutrient Supplements, which were based on recommended intake quantities and population body weights. Based on the recommended intake of various WFP products of 100 g/day, a combined hyoscyamine/scopolamine concentration in dry food of less than approximately 30 µg/kg (in Super Cereal) or 10 µg/kg (in Super Cereal Plus and Lipid-based Nutrient Supplements) should be health protective for adults and children respectively. These concentrations are proposed as operational limits that may be extended to other cereal and grain products when consumed in comparable quantities. If higher quantities are consumed, appropriate adjustment of the values would be necessary.For emergency situations where food security needs to be taken into consideration it would be expected that guidance levels of 90 µg/kg (Super Cereal) and 30 µg/kg (Super Cereal Plus and Lipid-based Nutrient Supplements) should still be protective against severe toxicity for adults and children respectively. These emergency guidance levels were derived from a clinically significant minimal acute effect dose (i.e. based on increasing heart rate, decreased salivation and decreased sweat secretions).

SOME PRACTICES THAT MAY PREVENT TAs CONTAMINATION OF FOODS

37. TAs may enter the food network at a number of points, including during cereal cultivation (e.g., from root water uptake and contaminated compost), harvesting (following combined harvest of problem weeds with the cereal grains accidentally, as well as coharvested due to its structural similarity with cereal grains) and indeed processing as was the case in the Uganda incident.

38. Adequate application of good practices (such as GAP, GMP) and food safety and quality management systems (such as HACCP and ISO 22000) , from the start of cereal cultivation through to the final stages of manufacturing of food products can aid in the reduction of seeing toxic plants including *D. stramonium* in cereal fields.

39. Although several plant families contain TAs, the most virulent invasive species are from *Datura stramonium*. *Datura stramonium* commonly grows in cereal fields and produce TAs (e.g., hyoscyamine and scopolamine) which may accidentally contaminate cereals (and cereal-based foods) at occasionally high levels. So how to prevent *Datura stramonium* contaminate food would be the key point of control strategies for reducing TAs contamination of agricultural commodities

40. Abia et al.(2020) also summaries the agricultural conditions that may favour TAs contamination in agricultural commodities and food products (Annex I). They also highlight some potential associations between changing climate and agricultural practices that may influence TAs contamination of foods. Lastly, they reveal some potential agricultural and industrial practices that may prevent foodstuffs from being contaminated by TAs.

41. One member suggested that the Code of Practice for the Prevention and Reduction of Tropane Alkaloids in Food could make use of information including pictures/videos already distributed, for example by Arvalis on YouTube, a leaflet ‘Managing toxic weeds in vegetable crops and beyond’ on the website of PROFEL, the leaflet on ‘*Datura sp*. as a potential risk for agricultural production in Belgium’, and the ‘Guidance document on physical *Datura stramonium* seed contamination’ of FAO/WHO.

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ANNEX I TO APPENDIX II

Table 1 Proposed intervention areas and efforts needed toward preventing crops/foods contamination by tropane alkaloids (TAs) and associated health implications and management

Control focus	Condition favoring TAs contamination of foodstuffs and/or challenges in managing TAs incidences	Control strategy
1. Prevent TAs plant growth in cereal fields	TAs plants (e.g., *Datura* spp.) commonly grow in cereal Fields	· Educate/train farmers on how to identify TAs plants in their farms (as safety measure, good agricultural practices [GAP]) · Train and encourage farmers to routinely inspect their cereal farms for presence of TAs plants (guidelines may be needed)
	TAs-contaminated compost.	Encourage farmers to visually screen materials prior to compost making and utilization.
	Poor handling and disposal of TAs plants in cereal fields and which later reoccurrences.	· Train farmers on proper disposal of TAs plants (digging out, cutting off, hand hoe) and collected in a suitable marked bag and disposed of properly. · In case of reoccurrences, adjust crop rotation patterns
	Roots water uptake from TAs deposits present is soil.	
2. Prevent TAs food contamination	*Datura spp.* may cross-contaminate some cereal-based foods growing in the same area, and as such, TAs may be found in cereal flours.	· Educate and provide farmers with easy to follow information and communications on pesticides choice and regulations around pesticides use against weeds, as well as residual levels in foods. · *NB: Viewing strict pesticide legislation (right types, amounts, vis-à-vis species and maximum limits in foods), pesticide application alone is not sufficient*.
	Datura spp. germinate and develops late on the field and in some cases, may still be green (i.e., growth phase with strong sap flow) while the cereal is ready for harvest. During harvest of edible cereal crops, the pressure from combined harvest (i.e., green *Datura* plant and edible cereal plant) will force the sap to leak and wet the edible cereal (i.e., sap leakage wetting or contaminating the crop).	Proper disposal of TAs plants is needed (see point 1above).
	Accidental harvest of *Datura* seeds, leaves, etc. along with the cereal crop or other edible plant parts due to close resemblance with crop.	Train farmers on proper identification of the problem weeds leaves, seeds, etc. in the field and during harvest (as a part of GAP) followed by proper disposal (see point 1 above).
	Challenges involved in seeds and or plant parts sorting (and cleaning prior to processing) because of the similarities between TAs plants seeds, leaves and other plant parts with edible crops.	· In case of visible contamination, proper sorting of cereal seeds and or any other TAs plant mimicking plant part is required during harvest as well as prior to food processing. · *NB:Where the seeds are not markedly different, separation is very difficult, thus, common practices for cleaning cereals are not always sufficient to remove the TAs producing weed plant parts and seeds*.
	Strict pesticide residue limits, for example, in foods for infants and young children may constraint farmers' application of pesticides, and perhaps, difficult to stop growth of, and cross-contamination by problem weed in cereal fields.	· Farmers should contact the appropriate regulatory body in their areas and inquire which pesticide (and what dose) is authorized for what plants/crops · Farmers report presence of problem weeds if identified in their fields.
3. Mitigate effects of the complexity surrounding the combined strict pesticide regulations and changing climate.	Effects of climate change on plant growth, water, and drought resistance.	Employ a combination of mitigation strategies to prevent poison weed growth, for example, pesticides application and immediate removal, collection, and disposal of the weeds.

	The invasive nature of *Datura stramonium* may lead to the unpredicted presence of TAs in foods, for example, it has spread from eastern and southern to northern European countries as a result of climate change.	Proper identification of problem weeds (see point 1 above).
	Organic foods production is partly associated with increased exposure to plant toxins (e.g., TAs) considering its concept of "no pesticide application"— *pesticides could have prevented growth of problem weeds to an extent*	Train farmers (organic and conventional) and other major stakeholders on GAP/GMP to ensure their crops/foodstuffs meet safety quality and standards
	Presence of TAs in foods may partly reflect inadequate implementation of good practices (GAP and GMP) and food safety management systems (such as hazard analysis critical control point, HACCP and ISO 22000).	· Train farmers on GAP/GMP in terms of understanding the issues of food contaminants, for example, TAs · Encourage routine inspections for potential contaminants, for example, TAs across the entire food networks–*Note that inspection and proper disposal of problem weeds at farm level will help address problems* · Consistent application of GAP/GMP may reduce levels of TAs in cereals and cereal products to levels lower than regulatory maximum levels of eradicate it. · Hold food company operators and all across the food chain to applying HACCP and or ISO 22000 or any other food safety control systems
4. Consumers' demand for organic foods	Producers may in part be more process-minded and so need to be accountable for any contamination levels exceeding regulatory maximum limits.	· Set up an Indicative Values (e.g., 250 ppb for TAs in the sorghum, millet and buckwheat) used to manufacture cereal-based foods for infants and young children. · Raise awareness on and enforce legislation to drive cereal suppliers to implement better preventive measures at the field level and work on improved mechanical sorting (GAP/GMP).
5. Policy and action measures towards mitigating food intoxication situations such as TAs	Inadequate or poor or lack of prompt intervention/ preventive measures to protect the public in cases of TAs food intoxication.	·Issue clear warning (through the appropriate channels) to the public asking them not to consume the suspected foods/products. ·Immediate withdrawal of the contaminated batches from the market to help prevent further exposures/outbreaks.
	Inadequate or poor surveillance of suspected adverse reactions and quality control of the ingredients, for example, an originally nontoxic food product may potentially become toxic if TAs is present as contaminant.	·Carry out lab testing on representative samples ·Carry out thorough investigations (surveillance of suspected adverse reactions—quality control in the sourcing and processing of foods ingredients/plant materials) along the food supply chain/system ·Sampling for toxicological analysis including samples from exposure victims and healthy controls. ·Establish the extent of the problem and reasons for the TAs contamination (report).
	·Inadequate or poor communication with the public on safety issues as well as poor reporting mechanisms in cases of any suspected incidence.	·Promote and improve quality and safety communication with the public ·Encourage the public to report any adverse reactions ·Encourage proper medical diagnosis and treatment for victims of exposure
	·Inadequate compliance with regulations (safety quality and standards)	·Encourage and promote enforcement and compliance with regulations/regulatory measures pertaining TAs
	·Late and inadequate awareness raising among health personnel as well as victims about the profile of food intoxications	·Encourage and promote early awareness among health personnel as well as victims

APPENDIX III

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