

ADOPTED: 18 December 2017

doi:10.2903/j.efsa.2018.5160

Human acute exposure assessment to tropane alkaloids

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Abstract

Tropane alkaloids (TA) are secondary metabolites occurring in several plant families, including Solanaceae. The most studied TAs are (-)-hyoscyamine and (-)-scopolamine, which in contrast to the (+)-enantiomers are formed naturally. The racemic mixture of (-)-hyoscyamine and (+)-hyoscyamine is called atropine. In 2013, the EFSA CONTAM Panel carried out an acute dietary exposure assessment for the sum of (-)-hyoscyamine and (-)-scopolamine (group Acute Reference Dose (ARfD) 16 ng/kg body weight (bw)), and identified a potential concern for toddlers. This scientific report provides a more extensive acute dietary human exposure assessment of TA presenting 44,184 analytical results of 7,391 samples on 31 TA sampled between 2009 and 2019 in 17 European countries and one association (Tea & Herbal Infusions Europe). Most of the analytical results (95%) were left censored (i.e. below the limit of detection or below the limit of quantification). High concentrations were reported for atropine and scopolamine in tea and herbal infusions, cereal bars and spices. The mean and 95th percentiles (P95) acute dietary exposures to the sum of atropine and scopolamine were highest in infants, toddlers and other children. For the sum of atropine and scopolamine, the group ARfD (16 ng/kg bw per day) was exceeded, under the UB assumption, at the mean level in infants, toddlers and other children, and at the P95 in all age classes. Under the 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 for atropine, in adolescents as well. Very large differences were observed between the LB and UB estimated exposure levels across all age classes. Overall, the main contributors to the co-exposure of atropine and scopolamine were, both at the LB and UB, bread and other grain milling products for all age classes.

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Keywords: tropane alkaloids, atropine, scopolamine, occurrence, exposure

Requestor: European Commission

Question number: EFSA-Q-2016-00565

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Amendments: The report was updated in 2019 after a request for correction regarding certain data records and receipt of new consumption and occurrence data submitted to EFSA since 2016. The results of the new exposure estimates (data from 2009 to 2019) are in the same order of magnitude as the ones in the previously published version. The previous version of the report is available on request.

Acknowledgements: EFSA specially thanks Lutz Edler and Annette Petersen for providing valuable comments and for reviewing the final version. EFSA wishes to acknowledge all European competent institutions, academia, Member State bodies and other organisations that provided occurrence data on tropane alkaloids, as well as all European competent institutions that supported the data collection for the Comprehensive European Food Consumption Database. This Scientific report was endorsed by the EFSA Panel on Contaminants in the Food Chain by written procedure on 18 December 2017.

Suggested citation: EFSA (European Food Safety Authority), Arcella D, Altieri A, Horváth Zs, 2018. Scientific report on human acute exposure assessment to tropane alkaloids. *EFSA Journal* 2018;16(2):5160, 29 pp. doi:10.2903/j.efsa.2018.5160

ISSN: 1831-4732

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Summary

Tropane alkaloids (TA) are secondary metabolites occurring in several plant families, such as Brassicaceae, Solanaceae and Erythroxylaceae. Although more than 200 different TA have been identified in various plants, respective data on toxicity and occurrence in food are limited. The most studied TA are (-)-hyoscyamine and (-)-scopolamine, which in contrast to the (+)-enantiomers are formed naturally. The racemic mixture of (-)-hyoscyamine and (+)-hyoscyamine is called atropine. The risk for public health related to the presence of TA as contaminants in food and feed was assessed in an EFSA scientific opinion delivered in 2013 (EFSA CONTAM Panel, 2013). The CONTAM Panel established a group Acute Reference Dose (ARfD) of 16 ng/kg bw for the sum of (-)-hyoscyamine and (-)-scopolamine, assuming equivalent potency. In view of the toxicological profile of TA, the CONTAM Panel concluded that the ARfD would also protect against effects of long-term exposure. Based on the limited available information, the CONTAM Panel concluded that the dietary exposure of toddlers could be up to seven times the group ARfD and could exceed the group ARfD on approximately 11 to 18% of consumption days.

In 2015, the European Commission (EC) issued a Recommendation¹ to Member States with the involvement of food business operators, on the monitoring of the presence of TA in food and to provide results to EFSA by October 2016. In 2016, EFSA published the results of an ad hoc data collection study on the occurrence of TA in food in nine European countries (Mulder et al, 2016).

Following a request by the EC in September 2016, present report was originally describing estimated human acute dietary exposure to TA taking into account occurrence data available from 2009 to 2016. The report was updated in 2019 after a request for correction regarding certain data records. New consumption and occurrence data submitted to EFSA since 2016 were included in the estimates. It was noted that the results of these new exposure estimates (considering data from 2009 to 2019) are in the same order of magnitude as the ones in the previously published version.

The data used for the assessment were checked for potential errors or inconsistencies and cleaned. A final dataset of 44,184 analytical results on food (i.e. 6,943 for atropine, 6,897 for scopolamine, 14,851 on other Datura-type TA, and 15,493 on other TA) was used for the analysis of occurrence and the estimation of acute human dietary exposure to TA. The data were sampled between 2009 and 2019 in 17 European countries and one association (Tea & Herbal Infusions Europe).

The data were organised according to the FoodEx1 food classification and description system (EFSA, 2011a). Since TA do not exhibit chronic toxicity, human dietary exposure was estimated as acute exposure scenario for atropine, scopolamine, the sum of atropine and scopolamine, and the sum of all Datura-type TA for which quantified results were reported. The exposure scenario was estimated using consumption data at individual level from the EFSA Comprehensive food consumption database. The calculation was done per individual and food group, based on Lower Bound (LB) and Upper Bound (UB) occurrence levels, on the daily individual consumption and using individual body weights. Exposure estimates were summarised by age class as minimum and maximum across dietary surveys of the mean and P95 of exposure.

Most of the analytical results (95%) were left censored, namely reported as less than the limit of detection (LOD) or than the limit of quantification (LOQ). The analytical techniques used to analyse the toxins were based on LC-MS/MS (97%) and high performance liquid chromatography (HPLC) (about 2%), whereas for 1% of the results (included in the assessment) no information was provided about the analytical methods used.

High occurrence values were found for atropine in 'Hempseed' (77.2 µg/kg), 'Spices' (i.e. coriander seed, mean MB, 35.0 µg/kg, fennel seed, mean MB, 6.1 µg/kg) 'Tea and herbs for infusions' (mean MB on unspecified tea 6.71 µg/kg, green tea 10.01 µg/kg), 'Cereal bars' (mean MB, 6.3 µg/kg); for scopolamine in 'Hempseed' (64.9 µg/kg), 'Tea and herbs for infusions' (mean MB in Chamomile flowers 11 µg/kg, green tea 10 µg/kg), and 'Spices' (i.e. coriander seed, mean MB, 22 µg/kg); and for calystegines in 'potatoes and potato products' (mean MB, 107 mg/kg for calystegine A3).

¹ Commission Recommendation (EU) 2015/976 on 19th June 2015 on the monitoring of the presence of tropane alkaloids in food (OJ L 157,23.6.2015, p.97).

The mean acute dietary exposure to the sum of atropine and scopolamine were highest in infants (range from 1 to 19 ng/kg bw per day (minimum LB to maximum UB)), toddlers (range 2 to 19 ng/kg bw per day (minimum LB to maximum UB)), and other children (range 1 to 18 ng/kg bw per day (minimum LB to maximum UB)). The P95 of acute dietary exposure to the sum of atropine and scopolamine were highest in infants (range 0.05 to 53 ng/kg bw per day (minimum LB to maximum UB)), toddlers (range 3 to 54 ng/kg bw per day (minimum LB to maximum UB)), and other children (range 1 to 42 ng/kg bw per day (minimum LB to maximum UB)).

Under the UB assumption, the group ARfD was exceeded for atropine and scopolamine at the P95 in infants, toddlers, other children and for atropine in adolescents as well. For the sum of atropine and scopolamine at the mean level the group ArfD was exceeded in infants, toddlers and other children, and at the P95 in all age classes. The p95 dietary exposure of infants could be up to three times the group ARfD and could exceed the group ARfD on approximately 3 to 21% of consumption days. Under the LB assumption, the group ARfD was exceeded for the sum of atropine and scopolamine at the P95 in toddlers and other children.

Overall, the main contributors to the co-exposure of atropine and scopolamine were, both at the LB and UB, bread and other grain milling products for all age classes. Compared to the 2013 EFSA CONTAM Panel opinion (based on 124 analytical results), the present report, based on a much larger occurrence dataset (44,184 analytical results) allowed us to estimate dietary exposure in all age classes and in a much wider number of food categories. The major factor possibly influencing the uncertainty in the exposure assessment was the large number of left censored data, leading to large differences between the LB and UB estimated exposure levels across all age classes. Other sources of uncertainty include the representativeness of food consumption and occurrence data, different dietary survey methodologies.

Table of contents

Abstract.....	1
Summary.....	3
1.1. Background and Terms of Reference as provided by the requestor	9
1.1.1. Background	9
1.1.2. Terms of reference.....	9
2. Data and Methodologies	9
2.1. Data.....	9
2.1.1. Occurrence data (food)	9
2.1.2. Human consumption data.....	11
2.1.3. Food classification	11
2.2. Methodologies	13
2.2.1. Human dietary exposure assessment	13
2.2.2. Statistical analysis	13
3.1. Occurrence of tropane alkaloids in food	14
3.1.1. Occurrence of atropine and scopolamine	17
3.1.2. Occurrence of other tropane alkaloids	18
3.1.3. Occurrence of calystegines	20
3.2. Acute dietary exposure assessment of tropane alkaloids in humans.....	21
3.2.1. Acute dietary exposure to atropine and scopolamine	21
3.3. Uncertainty analysis	25
3.3.1. Exposure model/exposure scenario	25
3.3.2. Summary of uncertainties	25
References.....	27
Glossary	28
Appendix: Supporting tables	29

1. Introduction

Tropane alkaloids (TA) are secondary metabolites occurring in several plant families, such as Brassicaceae, Solanaceae and Erythroxylaceae (including coca). The group of TA comprises more than 200 compounds occurring especially in the Solanaceae family arising from the esterification of tropine with a variety of acids (e.g. acetic acid, propanoic acid, isobutyric acid, isovaleric acid and atropic acid). Plant extracts containing TA (e.g. (-)-hyoscyamine and (-)-scopolamine) have been used in human medicine for centuries for treatment and diagnosis of a wide range of disorders, including wounds, gout and sleeplessness, pre-anaesthesia, asthma, and to facilitate ophthalmological examination.

The most studied TA are (-)-hyoscyamine and (-)-scopolamine, which in contrast to the (+)-enantiomers are formed naturally. The racemic mixture of (-)-hyoscyamine and (+)-hyoscyamine is called atropine. Figure 1 shows the most important structural features of TA. The common structural element is the tropane skeleton, a two-ringed structure characterised by a pyrrolidine and a piperidine ring sharing a single nitrogen atom and two carbon atoms. TA are esters of hydroxytropanes (α -tropanol, α -tropane-diol or α -tropane-triol) with short-chain acids such as acetic acid, propanoic acid, isobutyric acid, isovaleric acid, 2-methylbutyric acid, tiglic acid, (+)- α -hydroxy- β -phenylpropionic acid, tropic acid and atropic acid. The asymmetric α -carbon of tropic acid esters allows the formation of two stereoisomers. Hyoscyamine is the ester of tropane-3 α -ol (3 α -hydroxytropane) and S-(-)-tropic acid. Detailed information on the structures and chemical information on relevant TA have been provided in the EFSA opinion of 2013 (EFSA CONTAM Panel, 2013) and in the EFSA external scientific report (Mulder et al., 2016).

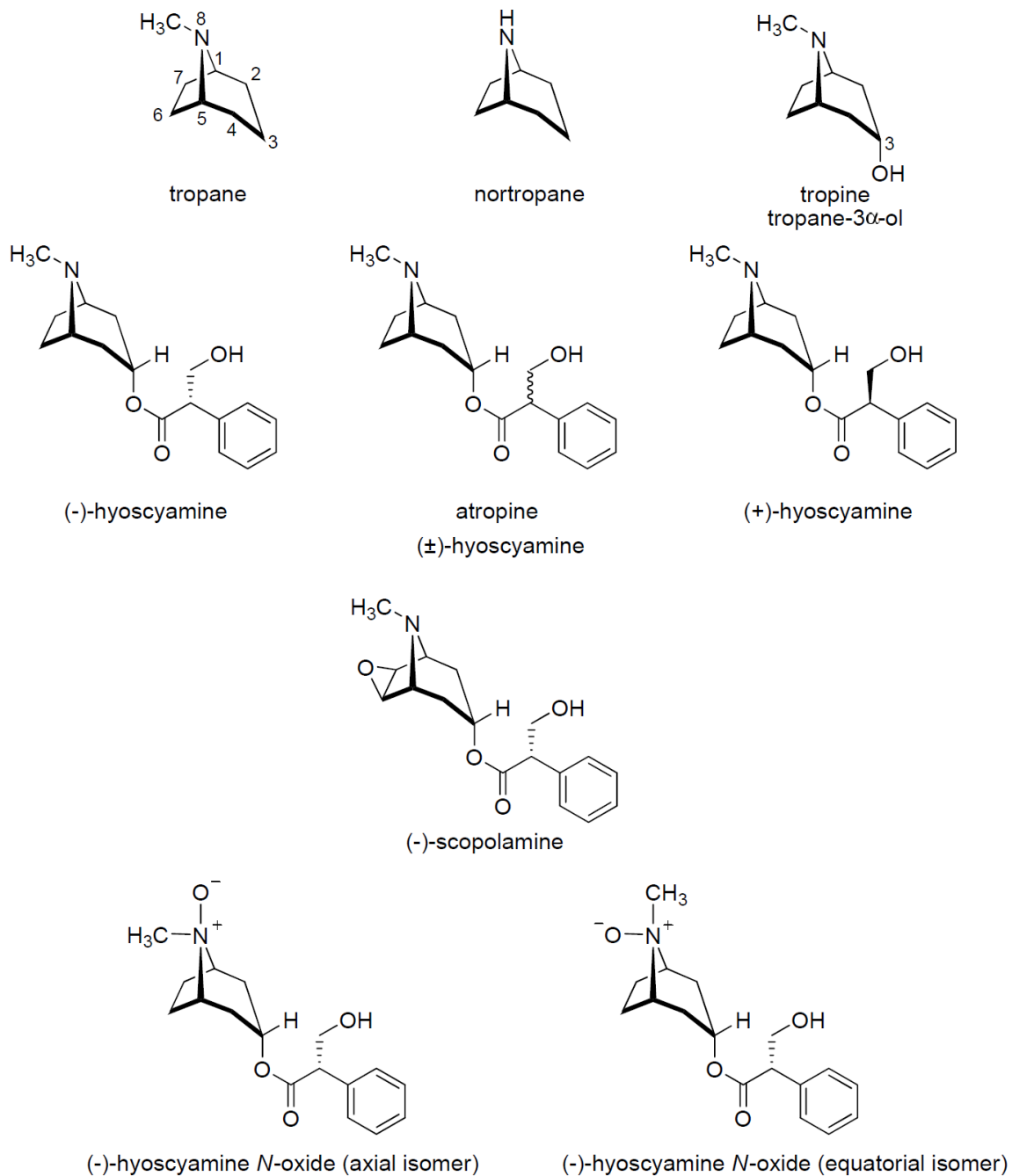


Figure 1. Structures exemplifying most common TA: Tropane [(1R, 5S)-8-methyl-8-azabicyclo[3.2.1]octane], nortropine and tropine, (+)/(-)-hyoscyamine, atropine and (-)-scopolamine

In 2013, the risks to public health related to the presence of TA in food were evaluated by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) in a Scientific Opinion (EFSA CONTAM Panel, 2013). Although more than 200 different TA have been identified in various plants, respective data on toxicity and occurrence in food were limited. Therefore, the CONTAM Panel performed a risk assessment of (-)-hyoscyamine and (-)-scopolamine, the two TA for which occurrence and toxicity data were available. The pharmacological effects of (-)-hyoscyamine and (-)-scopolamine occur within a short time after administration, and therefore the CONTAM Panel concluded that it was appropriate to establish an Acute Reference Dose (ARfD) for these substances. Due to the common mode of action through receptor interaction, the CONTAM Panel considered it appropriate to establish a group ARfD for (-)-hyoscyamine and (-)-scopolamine. Based on the results for decreased heart rate in a human volunteer study, the CONTAM Panel established a group ARfD of 16 ng/kg bw expressed as the sum of (-)-hyoscyamine and

(-)-scopolamine, assuming equivalent potency. In view of the toxicological profile of TAs, the CONTAM Panel concluded that ARfD would also protect against effects of long-term exposure.

In the EFSA Scientific Opinion of 2013, the results on TA were based on 124 food samples from two Member States. Most of the food samples were left-censored (below limit of detection/limit of quantification) and a reliable exposure estimate was only possible for one food category (i.e. 'Simple cereals which have to be reconstituted with milk or other appropriate nutrition liquids') and one age class (i.e. toddlers). Based on the limited information, the CONTAM Panel estimated that the dietary exposure of toddlers could be up to 7 times the group ARfD and could exceed the group ARfD on approximately 11 to 18% of consumption days.

In order to generate more occurrence data on the presence of TA in food, the Commission adopted Recommendation 2015/976/EU² on the monitoring of the presence of TA in food, in particular processed cereal based foods for infants and young children, including buckwheat, sorghum, millet, maize and their flour, cereal-based food for infants and young children, breakfast cereals, grain milling products, grains for human consumption, gluten free products, food supplements, teas and herbal infusions, and legume vegetables (without pods), pulses and oilseeds and derived products.

In 2014, EFSA published a call for proposals to collect occurrence data of TA in cereal-based products from retail stores across different regions in Europe. In 2016, EFSA published the results of the outsourced project on the occurrence of TA in food (Mulder et al., 2016). The report included occurrence data on 1,709 samples of plant-derived food products, mainly produced in Europe, analysed for TA. Samples were collected from 9 EU countries and analysed for 24 TA. Samples analysed comprised 268 single component flours (i.e. buckwheat, millet, corn), 260 cereal-based foods for young children age 6-36 months (i.e. breakfast cereals, biscuits and other cereal-based foods), 219 breakfast cereals, 164 biscuits and pastry, 114 bread, 81 pasta, 121 dry (herbal) teas, 78 legumes and stir-fry mixes. Some 308 potato samples, 90 aubergine samples and six bell peppers samples were analysed for six calystegines. All samples were analysed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). One or more TA were detected (above the LOD) in 21% of single component flours, 20% of cereal-based foods for young children age 6-36 months, 7% of breakfast cereals, 15% of biscuits and pastry, 16% of bread, 70% of dry (herbal) tea, 26% of legumes and stir-fry mixes, 100% of potatoes and 93% of aubergines. The highest TA concentrations were detected in cereal-based foods for young children and dry herbal tea samples.

Following a request received from the European Commission in September 2016, EFSA performed an update of the acute human exposure assessment to TA of the EU population, based on occurrence (from 2009 to 2016) and consumption data from the EFSA Database. The report was updated in 2019 after a request for correction regarding certain data records. New consumption and occurrence data submitted to EFSA since 2016 were included in the updated version. Consequently, the present report provides occurrence results for the most common TA compounds and an acute dietary exposure assessment for atropine, scopolamine, the sum of atropine and scopolamine, and the sum of all Datura-type TA, a subgroup of TA, for which quantified data were provided from 2009 to 2019. It was noted that the results of the new exposure estimates are in the same order of magnitude as the previously published ones.

² Commission Recommendation (EU) 2015/976 of 19 June 2015 on the monitoring of the presence of tropane alkaloids in food (OJ L 157,23.6.2015, p97).

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

1.1.1. Background

Following the outcome of EFSA's scientific opinion on TA in food and feed (EFSA CONTAM Panel, 2013), the Commission adopted on the 19th of June 2015 the Commission Recommendation (EU) 2015/976 on the monitoring of the presence of TA in food to collect more occurrence data on the presence of TA in food.³ In the Recommendation it was requested to provide the analytical results on a regular basis and at the latest by the end of October 2016 to EFSA.

In addition, given the potential health concern identified for toddlers, the Commission has adopted strict maximum levels of TA in processed cereal-based foods and baby foods for infants and young children, containing millet, sorghum, buckwheat or their derived products.⁴

An Article 36⁵ grant project was carried out, following a call for proposals (GP/EFSA/BIOCONTAM/2014/01), for a study on the occurrence of TA in food for human consumption, from different regions in Europe to serve as supporting information to the CONTAM Panel for future exposure assessments for TA. Besides the analysis of (-)-hyoscyamine and (-)-scopolamine, the call covered also the analysis of other TA in food to characterise TA that are occurring in food as contaminants. The data obtained had to be submitted to EFSA in September 2016.

In addition, analytical data on TA submitted until June 2019 to EFSA's continuous collection of chemical contaminant occurrence data in food were considered.

1.1.2. Terms of reference

In accordance with Art. 31 (1) of Regulation (EC) No 178/2002, the Commission asked EFSA for an updated human exposure assessment to TA taking into account the occurrence data available in the EFSA database.

2. Data and Methodologies

2.1. Data

2.1.1. Occurrence data (food)

The data used for the present scientific report derived from 2 different sources: 1) analytical data submitted by Member States (i.e. Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Luxembourg, Netherlands, Poland, Slovenia, Spain and United Kingdom) and one association via a continuous annual call for data and 2) analytical data obtained through an Article 36 grant (GP/EFSA/BIOCONTAM/2014/01) (Mulder et al., 2016). All data were submitted to EFSA according to the data model 'Standard sample description version 1' (SSD1) (EFSA, 2010a) by different data provider organisations and stored in the EFSA scientific data warehouse (SDWH). The SSD data model contains different data elements (database fields) and several coded standard terminologies for non-free-text data elements. The field names and terms mentioned in the present report refer to the SSD1 model.

Based on the mandate received from the EC (M-2016-0180), data listed in Table 1 and with a sampling date from 2009 to 2019 were extracted from the SDWH on the 3rd of June 2019. The analytical results on TA cover a total of 31 compounds of the following classes of compounds: low molecular weight TA (i.e. nortropinone, tropinone, 6-Hydroxytropinone, scopoline, scopine, pseudotropine), Convolvulaceae-

³ Commission Recommendation (EU) 2015/976 of 19 June 2015 on the monitoring of the presence of tropane alkaloids in food (OJ L 157,23.6.2015, p97).

⁴ Commission Regulation (EU) 2016/239 of 19th of February 2016 amending Regulation (EC) No 1881/2006 as regards maximum levels of tropane alkaloids in certain cereal-based food for infants and young children (OJ L 45, 20.2.2016, p.3).

⁵ Article 36 of the Regulation (EC) No 178/2002 from the European Parliament and Council laying down the principles and requirements of food law, establishing the EFSA and laying down procedures in matters of food safety foresees the possibility to financially support a networking of organisations operating in the fields within the EFSA's mission.

type TA (i.e. benzoylecgonine, cocaine, convolamine, convolidine, convolvine, fillalbin), Datura-type TA (i.e. atropine, scopolamine, scopolamine acetate, α -hydroxymethyl atropine, anisodamine, anisodine, apoatropine, apohyoscyne, homatropine, littorine, noratropine, norscopolamine, 3 α -phenylacetoxytropane), and calystegines (i.e. calystegine A3, calystegine A5, calystegine B1, calystegine B2, calystegine B3, calystegine B4). As the biosynthesis of TA in food leads to (-)-hyoscyamine and (-)-scopolamine, any analytical results where no stereoselective separation is achieved were, thus, regarded and reported as 100% (-)-hyoscyamine or (-)-scopolamine.

Table 1 lists the available data, after the data cleaning described in section 3.1. The initial dataset included 45,035 analytical results from 7,751 analytical samples on food for human consumption. The dataset was subsequently analysed in order to exclude non-pertinent data, identify possible issues and prepare the data for occurrence and exposure analysis.

Table 1: List of TA available in the EFSA occurrence database after data cleaning

ParamCode	Name	N of analytical results	%
Low molecular weight tropane alkaloids			
19303	Nortropinone	1305	2.95
19309	Tropinone	1305	2.95
19281	6-Hydroxytropinone	1305	2.95
19308	Scopoline	1305	2.95
19306	Scopine	1305	2.95
19305	Pseudotropine	1305	2.95
Convolvulaceae-type tropane alkaloids			
12458	Benzoylecgonine	1	0.002
12460	Cocaine	18	0.04
19295	Convolamine	1305	2.95
19296	Convolidine	1305	2.95
19297	Convolvine	1305	2.95
19298	Fillalbin	1305	2.95
Datura-type tropane alkaloids			
11927	Atropine	6943	15.71
11929	Scopolamine	6897	15.61
19282	Scopolamine acetate	1305	2.95
19283	α -Hydroxymethyl Atropine	1305	2.95
19284	Anisodamine (6-hydroxyhyoscyamine)	1429	3.23
19285	Anisodine	1429	3.23
19286	Apoatropine	1305	2.95
19287	Apohyoscyne (Aposcopolamine)	1429	3.23
19299	Homatropine	1429	3.23
19300	Littorine	1305	2.95
19301	Noratropine	1305	2.95
19302	Norscopolamine	1305	2.95
19304	3 α -Phenylacetoxytropane	1305	2.95
Calystegines			
19289	Calystegin A3	404	0.91
19290	Calystegine A5	404	0.91
19291	Calystegine B1	404	0.91
19292	Calystegine B2	404	0.91
19293	Calystegine B3	404	0.91
19294	Calystegine B4	404	0.91

2.1.1.1. Data analysis

The initial data set was carefully evaluated by applying several data cleaning and validation steps, including a comprehensive check of the units of measurement and how the results were expressed (e.g. fresh weight/dry weight). Special attention was paid to the codification of food samples under the FoodEx classification (EFSA, 2011a). The outcome of the data analysis is shown in section 3.

The left-censored data were treated by the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO, 2009). The same method is indicated in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010b) as an option in the treatment of left-censored data. The guidance suggests that the lower-bound (LB) and upper-bound (UB) approach should be used for chemicals likely to be present in food (e.g. naturally occurring contaminants, nutrients and mycotoxins). At the LB, results below the LOQ and LOD were replaced by zero; at the UB, the results below the LOD were replaced by the LOD and those below the LOQ were replaced by the value reported as LOQ. The middle-bound (MB) was calculated by assigning a value of LOD/2 or LOQ/2 to the left-censored data.

2.1.2. Human consumption data

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at individual level. It was first built in 2010 (EFSA, 2011b; Huybrechts et al., 2011; Merten et al., 2011). Details on how the Comprehensive Database is used were published in the Guidance of EFSA (EFSA, 2011b). The latest version of the Comprehensive Database updated in 2018 contains results from a total of 60 different dietary surveys carried out in 25 different Member States covering 119,458 individuals. The most recent survey within each country and age classes (i.e. 43 dietary surveys from 25 Member States) were used in this assessment. A detailed description of the surveys included in this assessment by country, survey period, number of subjects and age class is provided in Table A1 of the Appendix.

The dietary studies allow to classify subjects in different age classes as described in Table 2. Four additional surveys provided information on specific population groups: 'Pregnant women' (≥ 15 years to ≤ 45 years old, Latvia; 17 years old to 46 years old, Portugal) and 'Lactating women' (≥ 28 years to ≤ 39 years old, Greece; 18 years old to 45 years old, Estonia). Consumption data were collected using single or repeated 24- or 48-hour dietary recalls or dietary records covering from 3 to 7 days per subject. Because of the differences in the methods used for data collection, direct country-to-country comparisons can be misleading.

Table 2: Age classes considered in the EFSA Comprehensive European Food Consumption Database

Age class	Age range
Infants	< 12 months old
Toddlers	≥ 12 months to < 36 months old
Other children	≥ 36 months to < 10 years old
Adolescents	≥ 10 years to < 18 years old
Adults	≥ 18 years to < 65 years old
Elderly	≥ 65 years to < 75 years old
Very elderly	≥ 75 years old

2.1.3. Food classification

The analytical results were classified according to the FoodEx1 food classification system (EFSA, 2011a). FoodEx is a food classification system developed by EFSA in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. The system consists of a large number of individual food items aggregated into food groups

and broader food categories in a hierarchical parent-child relationship. It contains 20 main food groups at the first level, which are further divided into subgroups having 140 items at the second level, 1,261 items at the third level and reaching about 1,800 end-points (food names or generic food names) at the fourth level.

2.2. Methodologies

2.2.1. Human dietary exposure assessment

In the present report, acute dietary exposure to TA was estimated by using a probabilistic approach (EFSA, 2011c). Acute dietary exposure to TA was calculated on a per day basis for comparison with the ARfD. In Table A1 of the Appendix the number of available subjects for each age class used in the acute exposure assessment is provided.

Acute exposure was assessed for each reporting day by multiplying the total daily consumption amount for each food by one occurrence level randomly drawn among the individual results available for that type of food. Respective exposures from the different foods consumed that day (by the considered subject) were then summed and finally divided by the individual's body weight. This process was iterated 100 times for each reporting day for each survey. The 95% confidence interval was defined as the interval between the 2.5th and 97.5th percentiles obtained from the 100 iterations. For the calculations of exposure, the LB-UB approach for the occurrence data was used. It was decided to present the LB as well as the UB because, due to the large proportion of left censored data, the LB and the UB could differ substantially as an indication of a high level of uncertainty.

2.2.2. Statistical analysis

All analyses were run using the SAS® Statistical Software. Frequency tables per sampling year, sampling country and food group were produced to describe the TA data collection. Descriptive summary statistics of concentration levels per food group were calculated. The Guidance on the use of the Comprehensive Food Consumption Database indicates that P95 estimates obtained with less than 60 observations may not be statistically robust and therefore they were not reported. (EFSA, 2011b).

3. Assessment

3.1. Occurrence of tropane alkaloids in food

After the extraction from the SDWH, the data were analysed in order to assess quality and consistency. The following sections describe the outcome of the data cleaning process.

The initial dataset on food comprised 7,751 samples representing 45,035 analytical results on TA. Potential duplicates were identified comparing several variables of the database (i.e. sampling country, sampling area, origin area, FoodEx1 code, text describing the product, product treatment, sampling year, sampling month, year of analysis, evaluation of results, limit of detection (LOD), limit of quantification (LOQ), concentration value (RESVAL), sample code and data transmission ID). Thirty duplicate records were identified and excluded from the present assessment. In addition, forty-six analytical results were not included in the assessment because they were reported generically as TA, with no indication on the specific compound.

'Grain as crops' (Foodex level 2) refers to samples of unprocessed grains of unknown end-use. These grains are usually not considered when estimating human dietary exposure, especially when other data on grains for human consumption are available, thus they were not included in the dataset (n=50 analytical results).

With respect to the sampling strategy⁶, 37,016 analytical results originated from objective or selective sampling, 82 from suspect sampling, 874 from convenient sampling, 7,063 were not specified. The 82 results derived from suspect sampling were excluded from the present analysis.

Eighteen analytical results on atropine and scopolamine reported by one MS were excluded from the dataset after the Member State providing the data clarified that the results referred to unprocessed feed samples that were misclassified as food.

In this exposure assessment, only analytical data not exceeding the maximum limits and LOQ set in the respective EU legislation were considered.^{7,8} Thus, 669 analytical results which were not compliant with COMMISSION RECOMMENDATION (EU) 2015/976 and Commission Regulation (EU) 2016/239 were not considered in the present assessment. Namely, analytical results with LOQs for atropine and scopolamine higher than 10 µg/kg for agricultural commodities, ingredients, food supplements and herbal teas, results with LOQs higher than 2 µg/kg for finished foods (e.g. breakfast cereals), and 1 µg/kg for cereal-based foods for infants and young children.

Some of the samples were analysed and reported more than once for the same compound. In these cases, the mean of the analytical results related to each sample was calculated and used in the assessment in order to avoid bias.

The final dataset included 7,391 samples representing 44,184 analytical results on TA occurrence in food for human consumption. The most frequently reported TA were atropine (6,943, 15.7 %) and scopolamine (6,897, 15.6%), followed by anisodamine (1429, 3.2%), anisodine (1429, 3.2%), apohyoscine (aposcopolamine) (1429, 3.2%), homatropine (1429, 3.2%), apoatropine (1305, 2.95%), 6-hydroxytropinone (1305, 2.95%), scopolamine acetate (1305, 3.3%), alpha-Hydroxymethyl atropine (1305, 3.3%), convolamine (1305, 2.95%), convolidine (1305, 2.95%), convolvine (1305, 2.95%), fillalbin (1305, 2.95%), littorine (1305, 2.95%), noratropine (1305, 2.95%), norscopolamine (1305, 2.95%), nortropinone (1305, 2.95%), 3-alpha-Phenylacetoxytropine (1305, 2.95%), pseudotropine (1305, 2.95%), scopine (1305, 2.95%), scopoline (1305, 2.95%), tropinone (1305,

⁶ Objective sampling is based on the selection of a random sample from a population on which the data are reported; Selective sampling is based on the selection of a random sample from a subpopulation (or more frequently from subpopulations) of a population on which the data are reported. The subpopulations are often determined on a risk basis; Convenient sampling is based on the selection of a sample for which units are selected only on the basis of feasibility or ease of data collection; Suspect sampling is based on samples taken repeatedly from the same site as a consequence of evidence or suspicion of (illegal) contamination. Suspect samples are usually taken as a follow-up of demonstrated non-compliance with legislation (EFSA, 2010a).

⁷ COMMISSION REGULATION (EU) 2016/239 of 19 February 2016 amending Regulation (EC) No 1881/2006 as regards maximum levels of tropane alkaloids in certain cereal-based foods for infants and young children (OJ L 45, 20.2.2016,p.3).

⁸ COMMISSION REGULATION (EU) 2015/976 of 19 June 2015 on the monitoring of the presence of tropane alkaloids in food (OJ L 157,23.6.2015, p97).

2.95%), calystegine A3 (404, 0.9%), A5 (404, 0.9%), B1 (404, 0.9%), B2 (404, 0.9%), B3 (404, 0.9%), and B4 (404, 0.9%).

Out of the 7,391 samples and 44,184 analytical results of the final dataset, 1,709 samples (23% of the final dataset) representing 32,319 analytical results (73% of the final dataset) derived from the ad hoc data collection through the Article 36 study (Mulder et al., 2016). It is notable that 82% of the analytical results originated from 1,709 samples (32% of the final dataset), as the samples used in the Article 36 study were tested for different TA. These samples included plant derived products (e.g. flours, cereal based foods, biscuit and pastry, bread, pasta, dry (herbal) teas, legumes and stir-fry mixes), produced mainly in Europe, collected from retail stores between 2015 and 2016 in 9 EU countries (Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, the United Kingdom), and samples analysed for 24 TA. Thirty-two percent of the samples were analysed for 24 different TA.

Considering the entire dataset, analytical results were submitted by 17 European countries mainly from Spain (16%), and the UK (15%) and the European Tea and Herbal Association (15%). The European Tea and Herbal Association submitted samples taken in Germany, United Kingdom, India, Poland and Turkey. Samples from India and Turkey were considered to be distributed to the European market and therefore they were not excluded from the assessment. Figure 1 gives the distribution of the food analytical results included in the final data set by sampling country. The detailed distribution of the results included in this assessment by country and year is provided in Tables A5-A6 of the Appendix. About 87% of the data were sampled between 2015 and 2016. The methodology of data sampling for the data collected via the Article 36 study is described in detail in the EFSA external scientific report (Mulder et al., 2016).

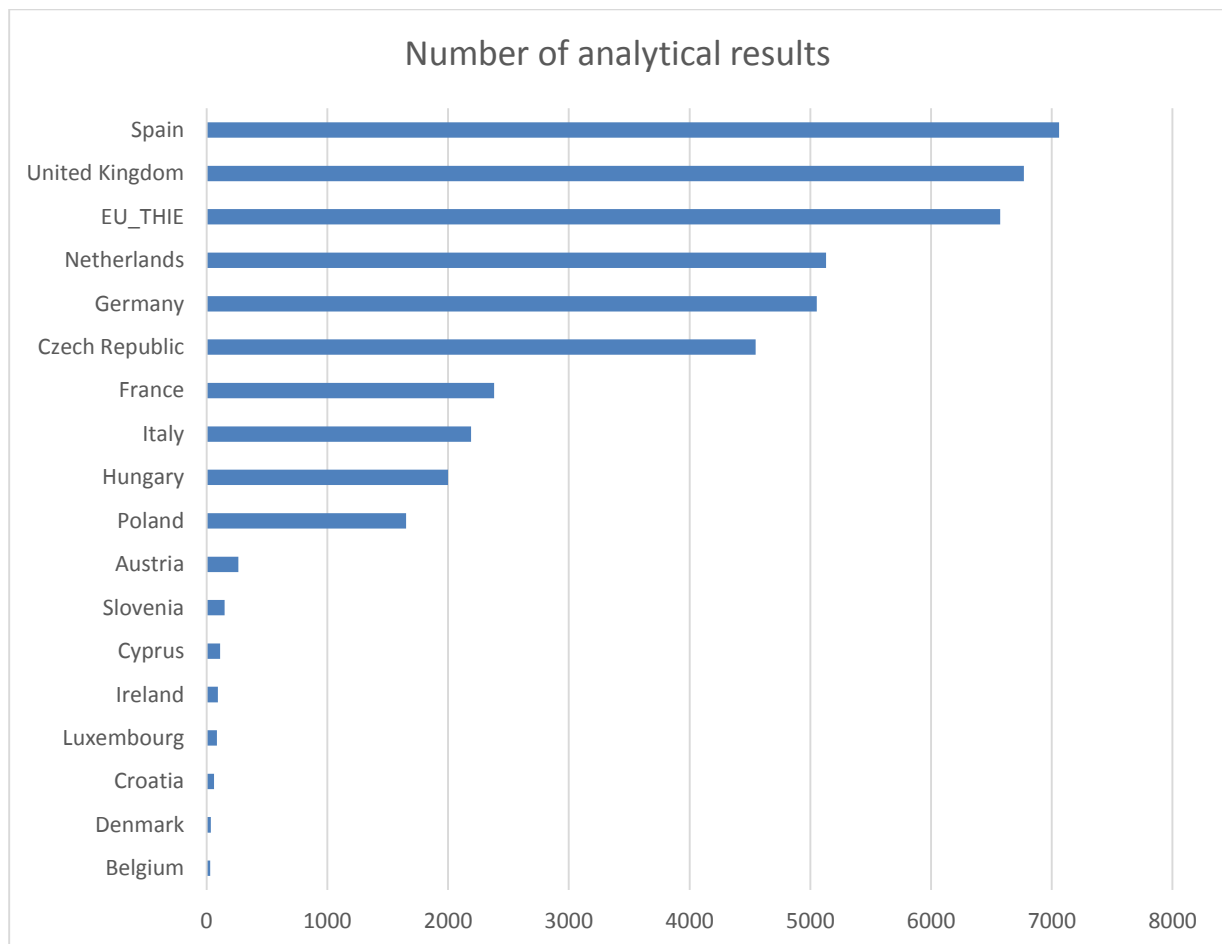


Figure 2. Frequency distribution of the food analytical results included in the final data set by sampling country

The unit of measurements were checked for consistency by comparing the order of magnitude of the values provided for RESVAL (i.e. concentration value), LOD and LOQ across the database. All results were expressed as whole weight, in $\mu\text{g}/\text{kg}$.

Ninety-three percent of the results were reported as corrected for recovery or as the best possible estimate, while the remaining 7% were reported as not corrected for recovery or the information on the recovery status was not reported.

The analytical techniques were based on LC-MS/MS (96%) and high performance liquid chromatography (HPLC) with CF detector (about 2%). In 1% of the analytical results used in this assessment the analytical technique applied was not specified. A detailed distribution of the analytical methods is provided in Table A7 of the Appendix.

The Appendix (Tables A2-A4) provides detailed information on the occurrence of TA in the different food groups (Foodex level 1 - 3). The concentration values of occurrence are presented according to the substitution approach for left-censored data described as Mean, Median, P75 and P95, by the LB, MB and UB.

Left-censored results

The left-censored limits in the TA dataset were within the typical range reported in the scientific literature (i.e. approximately 0.1-20 $\mu\text{g}/\text{kg}$ for TA, except calystegines with 0.25-2.5 mg/kg) (Mulder et al., 2016). The LODs and LOQs were reported for the majority of the results (N=36,776 and N=43,699, respectively on a total of 44,184 analytical results) and ranged from 0.0033 to 10 $\mu\text{g}/\text{kg}$ for the LOD, and from 0.01 to 10 $\mu\text{g}/\text{kg}$ for the LOQ, for all data excluding calystegines. For calystegines, the LOD and LOQ were reported for the entire dataset and the values ranged from 250 to 1000 $\mu\text{g}/\text{kg}$ for the LOD and from 1000 to 2500 $\mu\text{g}/\text{kg}$ for the LOQ.

The Appendix (Table A8) shows the distribution of the analytical results by reported LOQ for different TA and food commodities relevant for the dietary exposure to TA. Table 3 gives the frequency distribution of TA by quantification status of the analytical results. Overall, only 5% of the results were quantified. Among the remaining 95% left-censored analytical results, 76% were reported as below the LOD, and 19% as below the LOQ.

For homatropine, α -hydroxymethyl atropine, scopolamine acetate, 3 α -phenylacetytropane, 6-hydroxytropinone, scopoline, anisodine and littorine 100% left censored data were reported.

Table 3: Number of analytical results of TA reported as quantified/not quantified in the final data set of food samples

Tropane alkaloid	N of analytical results		
	Not quantified (n)	Quantified (n, %)	
Low molecular weight tropane alkaloids			
Nortropinone	1303	2	0.2
Tropinone	1295	10	0.8
6-Hydroxytropinone	1305	0	0
Scopoline	1305	0	0
Scopine	1304	1	0.1
Pseudotropine	1256	49	3.8
Convolvulaceae-type tropane alkaloids			
Benzoyllecgonine	0	1	100
Cocaine	17	1	5.6
Convolamine	1300	5	0.4
Convolidine	1286	19	1.5

Convolvine	1291	14	1.1
Fillalbin	1285	20	1.5
Datura-type tropane alkaloids			
3 α -Phenylacetoxytropane	1305	0	0
Atropine	6225	718	10.3
Apoatropine	1301	4	0.3
Anisodamine (6-hydroxyhyoscyamine)	1414	15	1.1
Anisodine	1429	0	0
Scopolamine	6510	387	5.6
Scopolamine acetate	1305	0	0
α -Hydroxymethyl Atropine	1305	0	0
Homatropine	1429	0	0
Littorine	1305	0	0
Noratropine	1304	1	0.1
Norscopolamine	1295	10	0.8
Apoxyoscine (Aposcopolamine)	1428	1	0.1
Calystegines			
Calystegine A3	59	345	85.4
Calystegine A5	387	17	4.2
Calystegine B1	351	53	13.1
Calystegine B2	21	383	94.8
Calystegine B3	400	4	1
Calystegine B4	232	172	42.6

3.1.1. Occurrence of atropine and scopolamine

The following paragraphs describe the frequency MB distribution of the occurrence of TA in food samples. Detailed information on the levels of TA with all food samples in the final data set is given in the Appendix (Table A2-A4).

Atropine

Quantified analytical results were found at FoodEx level 1 in 'Grains and grain-based products' (mean MB = 1.32 $\mu\text{g}/\text{kg}$), 'Vegetables and vegetable products' (mean MB = 4.84 $\mu\text{g}/\text{kg}$), 'Legumes, nuts and oilseed' (mean MB = 4.51 $\mu\text{g}/\text{kg}$), 'Non-alcoholic beverages' (mean MB = 3.96 $\mu\text{g}/\text{kg}$) 'Herbs spices and condiments' (mean MB = 2.64 $\mu\text{g}/\text{kg}$), 'Food for infants and young children' (mean MB = 0.22 $\mu\text{g}/\text{kg}$), and 'Snacks, desserts, and other foods' (mean MB = 0.99 $\mu\text{g}/\text{kg}$).

For 'Grains and grain based products', the highest mean MB values were found at Foodex level 3 in 'Cereal bars' (mean MB = 6.27 $\mu\text{g}/\text{kg}$), 'Other milling products' (mean MB = 6.05 $\mu\text{g}/\text{kg}$), and 'Corn grain' (mean MB = 3.3 $\mu\text{g}/\text{kg}$).

For 'Vegetables and vegetable products', the highest mean values were found at Foodex level 3 in 'Tea and herbs for infusions (Solid)' unspecified (mean MB = 6.71 $\mu\text{g}/\text{kg}$), 'Peppermint (*Mentha piperita*)' (mean MB = 4.73 $\mu\text{g}/\text{kg}$), and 'Camomile flowers (*Matricaria recutita*)' (mean MB = 2.75 $\mu\text{g}/\text{kg}$).

For 'Legumes, nuts and oilseeds', the highest mean values were found at Foodex level 3 in 'Hempseed' (mean MB 77.22 $\mu\text{g}/\text{kg}$) and 'Sunflower seed (*Helianthus annuus*)' (mean MB = 3.19 $\mu\text{g}/\text{kg}$).

For 'Non-alcoholic beverages' the highest mean values were found at Foodex level 3 in 'Green tee, infusion' (mean MB = 10.01 µg/kg), 'Tea (Infusion)' unspecified (mean MB = 5.61 µg/kg), and 'Herbal tea, infusion' (mean MB = 1.87 µg/kg).

For 'Herbs spices and condiments', the highest mean value was found at Foodex level 3 in 'Coriander seed' (mean MB = 34.98 µg/kg), and 'Fennel seed' (mean MB = 6.05 µg/kg).

For 'Food for infants and young children', the highest mean value was found at Foodex level 3 in 'Tee for infants and young children' (mean MB = 0.66 µg/kg) while in 'Ready-to-eat meal for children, cereal-based', 'Cereals with an added high protein food which are or have to be reconstituted...' and 'Cereal-based food for infants and young children' the mean MB values were 0.22 µg/kg).

For 'Snacks, desserts, and other foods' the mean MB value for 'Popcorn' at FoodEx level 3 was 1.54 µg/kg.

Scopolamine

Quantified analytical results were found at Foodex level 1 in 'Grains and grain-based products' (mean MB = 0.99 µg/kg), 'Vegetables and vegetable products' (mean MB = 3.52 µg/kg), 'Legume, nuts, and oilseeds' (mean MB = 3.74 µg/kg), 'Non-alcoholic beverages' (mean MB = 4.18 µg/kg), 'Herbs, spices and condiments' (mean MB = 2.2 µg/kg), 'Food for infants and young children' (mean MB = 0.22 µg/kg), and 'Snacks, desserts, and other foods' (mean MB = 0.44 µg/kg).

For 'Grains and grain-based products', the highest mean values were found at Foodex level 3 in 'Buckwheat milling products' (mean MB = 2.64 µg/kg), 'Other milling products' (mean MB = 2.2 µg/kg), 'Pasta, raw' (mean MB = 1.98 µg/kg) .

For 'Vegetables and vegetable products', the highest mean values were found at Foodex level 3 in 'Camomile flowers (*Matricaria recutita*)' (mean MB = 11.11 µg/kg) and 'Peppermint (*Mentha piperita*)' (mean MB = 3.96 µg/kg).

For 'Legume, nuts, and oilseeds', the highest mean values were at Foodex level 3 in 'Hempseed' (mean MB 64.9 µg/kg) and 'Sunflower seed (*Helianthus annuus*)' (mean MB = 1.98 µg/kg).

For 'Non-alcoholic beverages' the highest mean values were found at Foodex level 3 in 'Green tee, infusion' (mean MB = 10.01 µg/kg), 'Tea (Infusion)' unspecified (mean MB = 5.61 µg/kg), and 'Herbal tea, infusion' (mean MB = 2.31 µg/kg).

For 'Food for infants and young children', the highest mean value was found at Foodex level 3 in 'Cereals with an added high protein food which are or have to be reconstituted...' and 'Cereal-based food for infants and young children' (mean MB = 0.22 µg/kg for both).

For 'Snacks, desserts, and other foods' the mean MB value for 'Popcorn' at FoodEx level 3 was 0.55 µg/kg.

3.1.2. Occurrence of other tropane alkaloids

3.1.2.1. Occurrence of other *Datura*-type tropane alkaloids

For **anisodamine**, quantified results were found at Foodex level 1 in 'Grains and grain-based products' (mean MB = 0.11 µg/kg) and in 'Vegetables and vegetable products' (mean MB = 0.44 µg/kg).

In 'Grains and grain-based products', anisodamine was found at Foodex level 3 in 'Millet grain' (mean MB = 0.2 µg/kg), 'Buckwheat milling products' (mean MB = 0.1 µg/kg), and 'Cereal bars' (mean MB = 0.2 µg/kg). In 'Vegetables and vegetable products', anisodamine was found at Foodex level 3 in 'Peppermint (*Mentha piperita*)' (mean MB = 1.32 µg/kg) and 'Tea and herbs for infusions (Solid)' (mean MB 0.44 µg/kg).

For **apoptropine**, quantified results were found at Foodex level 1 in 'Grains and grain-based products', and at Foodex level 3 in 'Millet grain', 'Buckwheat milling products', 'Other milling products' and 'Cereal bars' (mean MB = 0.1 µg/kg each).

For **noratropine**, the highest quantified mean value was found at Foodex level 3 in 'Tea and herbs for infusions (Solid)' (mean MB = 0.22 µg/kg).

For **apohyoscine**, the highest quantified mean value was found at Foodex level 3 in 'Millet grain' (mean MB = 0.11 µg/kg).

For **norscopolamine**, the highest quantified mean values were found at Foodex level 1 in 'Grains and grain-based products' (mean MB = 0.11 µg/kg) and in 'Vegetables and vegetable products' (mean MB = 0.33 µg/kg). For 'Grains and grain-based products' it was found at Foodex level 3 in 'Millet grain' (mean MB = 0.33 µg/kg), and 'Buckwheat milling products' (mean MB = 0.11 µg/kg). In 'Vegetables and vegetable products', it was found at Foodex level 3 in Peppermint (*Mentha piperita*) (mean MB = 0.66 µg/kg) and 'Tea and herbs for infusions (Solid)' (mean MB 0.33 µg/kg).

3.1.2.2. Occurrence of Convolvulaceae-type tropane alkaloids

For **convolamine**, quantified results were found at Foodex level 1 in 'Vegetables and vegetable products' (mean MB = 0.22 µg/kg) and in 'Foods for infants and young children' (mean MB = 0.11 µg/kg). For 'Vegetables and vegetable products' at Foodex level 3 in 'Tea and herbs for infusions (Solid)' (mean MB = 0.22 µg/kg), and for 'Foods for infants and young children' in 'Ready-to-eat meal for children, cereal-based' (mean MB = 0.44 µg/kg).

For **convolidine**, quantified results were found at Foodex level 1 in 'Vegetables and vegetable products' (mean MB = 0.99 µg/kg) and in 'Food for infants and young children' (mean MB = 0.33 µg/kg). For 'Vegetables and vegetable products', at Foodex level 3 the highest mean values were in unspecified 'Vegetables and vegetable products' (mean MB = 4.4 µg/kg), in 'Peppers, paprika (*Capsicum annuum*, var. *grossum* and var. *longum*)' (mean MB = 4.95 µg/kg) and in Camomile flowers (*Matricaria recutita*) (mean MB = 1.1 µg/kg), while for 'Foods for infants and young children' at Foodex level 3 in 'Ready-to-eat meal for children, cereal-based' (mean MB = 3.85 µg/kg), and in 'Biscuits, rusks and cookies for children' (mean MB = 0.22 µg/kg).

For **convolvine**, highest mean values among the quantified results were found in 'Vegetables and vegetable products' at Foodex level 3 in 'Tea and herbs for infusions (solid)' (mean MB = 10.1 µg/kg) and 'Peppers, paprika (*Capsicum annuum*, var. *grossum* and var. *longum*)' (mean MB = 1.21 µg/kg).

For **fillalbin**, quantified results were found at Foodex level 1 in 'Vegetables and vegetable products' (mean MB = 0.88 µg/kg) and in 'Foods for infants and young children' (mean MB = 0.44 µg/kg). For 'Vegetables and vegetable products' at Foodex level 3 in unspecified 'Vegetables and vegetable products' (mean MB 4.29 µg/kg) 'Tea and herbs for infusions (Solid)' (0.22 µg/kg), in 'Peppers, paprika (*Capsicum annuum*, var. *grossum* and var. *longum*)' (mean MB = 5.61 µg/kg), and for 'Foods for infants and young children' at Foodex level 3 in 'Biscuits, rusks and cookies for children' (mean MB = 0.22 µg/kg) and in 'Ready-to-eat meal for infants and young children' (mean MB = 8.91 µg/kg).

3.1.2.3. Occurrence of low molecular weight tropane alkaloids

For **nortropinone**, quantified results were found at Foodex level 1 in 'Vegetables and vegetable products' (mean MB = 0.99 µg/kg).

For **pseudotropine**, quantified results were found at Foodex level 1 in 'Grains and grain-based products' (mean MB = 0.33 µg/kg) and in 'Vegetables and vegetable products' (mean MB = 7.37 µg/kg), and 'Food for infants and young children' (mean MB = 1.1 µg/kg). For 'Grains and grain-based products' it was found at Foodex level 2 in 'Grains for human consumption' (mean MB = 0.33 µg/kg), 'Grain milling products' (mean MB = 0.33 µg/kg), 'Bread and rolls' (mean MB = 0.33 µg/kg), 'Breakfast cereals' (mean MB = 0.22 µg/kg), 'Fine bakery wares' (mean MB = 0.33 µg/kg). For 'Vegetables and vegetable products' it was found at Foodex level 2 in 'Fruiting vegetables' (mean MB = 14.1 µg/kg), 'Tea and herbs for infusion' (mean MB = 2.09 µg/kg) and unspecified 'Vegetables and vegetable products' (mean MB =

51.15 µg/kg). For 'Food for infants and young children' quantified results were found at Foodex level 2 in 'Ready-to eat meal for infants and young children' (mean MB = 14.32 µg/kg) and 'Cereal-based food for infants and young children' (mean MB = 0.33 µg/kg).

For **scopine**, the highest quantified mean values were found at Foodex level 1 in 'Grains and grain-based products', at Foodex level 2 in 'Grains for human consumption' (mean MB = 0.22 µg/kg).

For **tropinone**, quantified results were found at Foodex level 1 in 'Vegetables and vegetable products' (mean MB = 0.77 µg/kg) and at Foodex level 2 in 'Tea and herbs for infusion (Solid)' (mean MB = 0.55 µg/kg), and 'Vegetables and vegetable products, unspecified' (mean MB = 1.98 µg/kg).

3.1.3. Occurrence of calystegines

Calystegines A3 were quantified at Foodex level 1 in 'Starchy and roots and tubers' (mean MB = 106,357 µg/kg) and in 'Vegetable and vegetable products' (mean MB = 2,920 µg/kg). For 'Starchy roots and tubers' it was found at Foodex level 3 in 'New potatoes' (mean MB = 93,915 µg/kg), in 'Main-crop potatoes' (mean MB = 110,842 µg/kg), 'Mashed potatoes powder' (mean MB = 116,750 µg/kg), 'Potato boiled' (mean MB = 56,111 µg/kg), Sweet potatoes (mean MB = 1,275 µg/kg). For 'Vegetable and vegetable products', at Foodex level 3 in Legume vegetables' unspecified (mean MB = 11,700 µg/kg) and 'Aubergines (egg plants) (*Solanum melongena*)' (mean MB = 2,596 µg/kg).

Calystegines A5 was quantified at Foodex level 1 in 'Vegetable and vegetable products' (mean MB = 474 µg/kg) and in 'Starchy and roots and tubers' (mean MB = 786 µg/kg). For 'Vegetables and vegetable products' it was found at Foodex level 3 in 'Aubergines (egg plants)(*Solanum melongena*)' (mean MB = 470 µg/kg), 'New potatoes' (mean MB = 764 µg/kg), 'Main-crop potatoes' (mean MB = 784 µg/kg), and at Foodex level 3 in 'Sweet potatoes' (mean MB = 2,950 µg/kg).

Calystegines B1 was quantified at Foodex level 1 in 'Vegetable and vegetable products' (mean MB = 3,549 µg/kg), and in 'Starchy and roots and tubers' (mean MB = 449 µg/kg). For 'Vegetable and vegetable products' it was found at Foodex level 3 in 'Aubergines (egg plants) (*Solanum melongena*)' (mean MB = 3883 µg/kg), 'Legume vegetables' unspecified (mean MB = 1,760 µg/kg) and in 'Sweet potatoes' (mean MB = 37,850 µg/kg).

Calystegines B2 was quantified at Foodex level 1 in 'Vegetable and vegetable products' (mean MB = 13,724 µg/kg), and in 'Starchy and roots and tubers' (mean MB = 51,143 µg/kg). For 'Vegetables and vegetable products', it was found at Foodex level 3 in 'Aubergines (egg plants)(*Solanum melongena*)' (mean MB = 14,635 µg/kg) and in 'Legume vegetables' unspecified (mean MB = 14,380 µg/kg). For Starchy and roots and tubers' at Foodex level 3 in 'New potatoes' (mean MB = 43,398 µg/kg), 'Main-crop potatoes' (mean MB = 53,583 µg/kg), 'Mashed potato powder' (mean MB = 47,400 µg/kg), in 'Potato boiled' (mean MB = 19,722 µg/kg), and in 'Sweet potatoes' (mean MB = 41,400 µg/kg).

Calystegines B3 was quantified at Foodex level 1 in 'Starchy and roots and tubers' (mean MB = 246 µg/kg), which includes in Foodex level 3 'Main-crop potatoes' (mean MB = 251 µg/kg), and Mashed potato powder' (mean MB = 1,600 µg/kg).

Calystegines B4 was quantified at Foodex level 1 in 'Starchy and roots and tubers' (mean MB = 3,633 µg/kg) and in 'Vegetables and vegetable products' (mean MB = 273 µg/kg). For 'Vegetables and vegetable products', it was found at Foodex level 3 in 'Legume vegetables' unspecified (mean MB = 1,040 µg/kg). For 'Starchy and roots and tubers' it was found at Foodex level 3 in 'New potatoes' (mean MB = 3,505 µg/kg), 'Main-crop potatoes' (mean MB = 3,683 µg/kg), 'Mashed potato powder' (mean MB = 8,100 µg/kg), 'Potato boiled' (mean MB = 2,178 µg/kg), and in 'Sweet potatoes' (mean MB = 2,000 µg/kg).

3.2. Acute dietary exposure assessment of tropane alkaloids in humans

3.2.1. Acute dietary exposure to atropine and scopolamine

The acute dietary exposure to TA was estimated on a per day basis for comparison with the ARfD (i.e. 16 ng/kg bw for the sum of atropine and scopolamine). Food categories with 100% left censored results were excluded to avoid biasing the exposure estimation by including food categories where TA are not expected, or the reported results consistently indicate the absence of TA.

Tables A9-A11 in the Appendix show in detail the estimated mean and P95 of exposure (expressed in ng/kg bw per day, under the UB assumption) across all dietary surveys and age classes, whereas the main results are reported in the following paragraphs and in Tables 6 and 7. Each exposure statistic is given as minimum to maximum calculated under the LB and the UB assumptions. The dietary surveys for which the number of subjects was less than 60 for a particular age class were excluded from the evaluation of the P95 of exposure.

Atropine

Acute dietary exposure to atropine among the different age classes is given in Table 6, calculated under the LB and UB assumptions. The mean acute dietary exposure ranged from 0.27 to 12.09 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest mean acute dietary exposures to atropine were found for infants (range from 0.27 to 12.09 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 1.11 to 10.15 ng/kg bw per day, minimum LB to maximum UB) and other children (range from 0.65 to 10.05 ng/kg bw per day, minimum LB to maximum UB).

The P95 of acute dietary exposure to atropine ranged from 0.01 to 30.15 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest P95 exposures were found for infants (range from 0.01 to 28.38 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 1.7 to 30.15 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 0.47 to 24.41 ng/kg bw per day, minimum LB to maximum UB).

Scopolamine

Acute dietary exposure to scopolamine among the different age classes is shown in Table 6, calculated under the LB and UB assumptions. The mean dietary exposure ranged from 0.16 to 8.94 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest mean exposures were found for infants (range from 0.16 to 8.94 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 0.77 to 8.4 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 0.51 to 8.41 ng/kg bw per day, minimum LB to maximum UB). The P95 of acute dietary exposure to scopolamine ranged from 0.0 to 25.84 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest P95 exposures were found for infants (range from 0.0 to 23.6 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 0.18 to 25.84 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 0.01 to 22.97 ng/kg bw per day, minimum LB to maximum UB).

Co-exposure to atropine and scopolamine

Co-exposure to atropine and scopolamine was calculated as the sum of atropine and scopolamine in the same food samples for the different age classes. For the sum of atropine and scopolamine where either one of the two analytical results was not reported, an imputation method using the mean occurrence of the food group of concern was used to estimate the missing values.

Acute dietary co-exposure to atropine and scopolamine among the different age classes is shown in Table 6, calculated under the LB and UB assumptions. The mean dietary exposure ranged from 0.64 to

18.91 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest mean acute exposures were found for infants (range from 0.97 to 18.91 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 1.82 to 18.65 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 1.13 to 18.13 ng/kg bw per day, minimum LB to maximum UB). The P95 of acute dietary exposure ranged from 0.05 to 54.14 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest P95 acute exposures were found for infants (range from 0.05 to 53.32 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 3.14 to 54.14 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 1.35 to 47.91 ng/kg bw per day, minimum LB to maximum UB).

Large differences were observed between the LB and UB estimated exposure levels across all age classes.

Under the UB assumption, the group ARfD was exceeded both for atropine and scopolamine at the P95 in infants, toddlers, other children and for atropine for adolescents as well.

For the sum of atropine and scopolamine at the mean level the group ARfD was exceeded in infants, toddlers and other children, and at the P95 in all age classes. The p95 dietary exposure of infants could be up to three times the group ARfD, and could exceed the group ARfD on approximately 3 to 21% of consumption days.

Under the LB assumption, the group ARfD was exceeded for the sum of atropine and scopolamine at the P95 in toddlers and other children.

Overall, the main contributors to the co-exposure of atropine and scopolamine were, both at the LB and UB, bread and other grain milling products for all age classes.

Table 6: 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

		Atropine									
Age group	N	Mean dietary exposure (ng/kg bw per day)				N	P95 dietary exposure (ng/kg bw per day)				
		LB Min	LB Max	UB Min	UB Max		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	N	Mean dietary exposure (ng/kg bw per day)				N	P95 dietary exposure (ng/kg bw per day)				
		LB Min	LB Max	UB Min	UB Max		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	N	Mean dietary exposure (ng/kg bw per day)				N	P95 dietary exposure (ng/kg bw per day)				
		LB Min	LB Max	UB Min	UB Max		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.

Co-exposure to the sum of Datura-type tropane alkaloids

Co-exposure to the sum of Datura-type TA was calculated as the sum of Datura-type TA for which quantified results were available, namely: atropine, apoatropine, anisodamine (6-hydroxyhyoscyamine), scopolamine, noratropine, norscopolamine, apohyoscyne (aposcopolamine). For 3 α -phenylacetoxytropane, anisodine, scopolamine acetate, α -hydroxymethyl atropine, homatropine and littorine only left-censored data were available. For the sum of atropine, scopolamine and other Datura-type TA where any one of the individual TA values was not reported, an imputation method using the mean occurrence of TA in the food group of concern was used to estimate the missing results.

Acute dietary exposure to the sum of Datura-type TA among the different age classes is shown in Table 7, calculated under the LB and the UB assumptions. The mean dietary exposure ranged from 0.29 to 25.75 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest mean exposures were found for infants (range from 0.29 to 21.78 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 1.61 to 25.75 ng/kg bw per day, minimum LB to maximum UB), and other children (range from 0.9 to 24.7 ng/kg bw per day, minimum LB to maximum UB). The P95 of acute dietary exposure ranged from 0.1 to 61.98 ng/kg bw per day (minimum LB to maximum UB) across different age classes. The highest P95 exposures were found for infants (range from 0.1 to 58.84 ng/kg bw per day, minimum LB to maximum UB), toddlers (range from 1.19 to 61.98 ng/kg bw per day minimum LB to maximum UB), and other children (range from 0.71 to 59.19 ng/kg bw per day minimum LB to maximum UB).

Table 7: Summary statistics of probabilistic acute dietary exposure assessment to the sum of Datura-type tropane alkaloids across European dietary surveys (ng/kg bw per day) by age group. The corresponding 95% confidence intervals are presented in the brackets

Datura-type tropane alkaloids					
Age group	N	Mean dietary exposure (ng/kg bw per day)			
		LB Min	LB Max	UB Min	UB Max
Infants	11	0.29 (0.05-2.16)	11.72 (1.41-48.11)	4.46 (3.99-6.21)	21.78 (12.61-38.37)
Toddlers	15	1.61 (0.33-5.35)	6.83 (1.92-17.8)	12.43 (11.09-14.11)	25.75 (23.2-30.9)
Other children	21	0.9 (0.39-1.66)	10.85 (7.03-15.25)	11.15 (10.56-12.39)	24.7 (22.03-29.53)
Adolescents	21	1.01 (0.49-2.19)	5.62 (3.31-8.76)	7.23 (6.09-10.7)	20.51 (18.38-23.37)
Adults	23	0.85 (0.54-1.57)	3.43 (2.28-4.95)	4.96 (4.38-5.81)	11.62 (10.87-12.94)
Elderly	20	0.66 (0.37-1.28)	3.25 (1.3-5.68)	4.18 (3.79-5.07)	9.73 (8.35-11.83)
Very elderly	16	0.65 (0.36-1.18)	3.27 (1-9.18)	5.28 (4.97-5.8)	10.59 (8.08-16.78)
P95 dietary exposure (ng/kg bw per day)					
Age group	N	LB Min	LB Max	UB Min	UB Max
Infants	10	0.1 (0-0.31)	6.71 (6.06-7.67)	15.79 (13.86-18.27)	58.84 (48.06-74.84)
Toddlers	12	1.19 (0.68-1.98)	21.89 (6.55-74.49)	32.63 (29.8-35.92)	61.98 (45.85-92.46)
Other children	21	0.71 (0.27-1.18)	16.69 (13.26-21.2)	32.37 (30.85-34.48)	59.19 (53.89-67.11)
Adolescents	21	1.31 (0.72-2.31)	10.68 (6.92-17.13)	19.01 (16.89-21.3)	45.2 (41.52-49.46)
Adults	23	0.94 (0.5-1.46)	7.32 (6.01-9.2)	12.29 (11.2-13.69)	27.83 (25.8-29.91)
Elderly	20	0.84 (0.39-1.67)	6.65 (4.02-11.03)	11.2 (10-13.2)	22.31 (18.56-26.73)
Very elderly	15	1.07 (0.71-1.47)	7.5 (3.01-14.36)	13.79 (12.1-16.48)	23.54 (17.62-32.04)

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.

3.3. Uncertainty analysis

3.3.1. Exposure model/exposure scenario

The final dataset used to estimate exposure, including 44,184 analytical results on 31 TA from 17 EU countries and one association (Tea & Herbal Infusions Europe), is considerably larger than the one used in the EFSA scientific opinion of 2013. This larger dataset allowed us to obtain more robust and comprehensive results on occurrence and exposure across different food groups and age classes. The majority of the samples belonged to the food groups 'Grains and grain-based products', 'Food for infants and young children', and 'Vegetables and vegetable products'. For atropine and scopolamine, 'Sugar and confectionary', 'Products for special nutritional use' and 'Composite food' were excluded from the dietary exposure assessment because all available analytical results were below the LOQ and LOD.

The high number of left-censored data is a major source of uncertainty which leads to the large difference of the results between the LB and the UB exposures in all age classes. The uncertainty in the exposure assessment depends also on the representativeness of the geographical regions, seasons, contamination sources and agricultural practices, as well as on the methodology used for the food consumption surveys.

The distribution of the data among reporting countries was relatively geographically balanced since 17 countries provided data and about 50% of the data were from 3 different countries. Data from THIE association also covered more countries.

Conversely, the occurrence dataset is considered to be representative for food for human consumption on the EU market considering that the data used for the assessment are from a wide selection of food products (e.g. flours, cereal-based foods for young children, bread, dry herbal teas, legumes).

3.3.2. Summary of uncertainties

In Table 8, a summary of potential sources of uncertainty is presented for TA. The Table also reports an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the exposure.

Table 8: Summary of qualitative evaluation of the impact of uncertainties on dietary exposure to TA

Sources of uncertainty	Direction ^(a)
Different methodologies / representativeness / underreporting / misreporting / no portion size standard in the consumption data	+/-
Large proportion of left censored data in the final dataset	+/-
Using the substitution method at the lower bound (LB)	-
Using the substitution method at the upper bound (UB)	+
Imputation of missing results for the calculation of the sum of TA	+/-
Considering only occurrence data in food for which the LOQs were reported to be below the LOQ cut-off values defined in the corresponding legislation	+/-

(a): + = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure.

The major factor possibly influencing the uncertainty in the exposure assessment was the large number of left censored data. Other sources of uncertainty include the representativeness of food consumption data, i.e. use of different dietary survey methodologies, standard portion sizes, representativeness of samples included in surveys. In this exposure assessment, only analytical data not exceeding the maximum limits and LOQ set in the respective EU legislation were considered. However, exposure calculations were repeated without any restriction and the results did not differ substantially from the results presented in this report.

Conclusions

The EC requested EFSA to perform an updated human exposure assessment to TA taking into account the occurrence data available in the EFSA database, including data collected via the Article 36 study (Mulder et al., 2016). In conclusion,

- 44,184 analytical results corresponding to the requested criteria were extracted from the EFSA database and analysed to determine the occurrence levels in different food groups and to estimate the human acute dietary exposure to TA
- The distribution of the occurrence data among reporting countries was relatively geographically balanced since 17 countries provided data and about 50% of the data were from 3 different countries
- Most of the analytical results (95%) were left-censored. The data were processed using the substitution method to compute LB, MB and UB occurrence values
- High occurrence values of atropine and scopolamine were found in certain tea, herbs for infusions, spices, hempseed, cereals, and for calystegines in potato products
- The young age classes (i.e. infants, toddlers, and other children) showed higher acute exposure levels compared to the other age classes. The highest mean and P95 acute exposure estimations in the young age classes were observed for the sum of atropine and scopolamine and ranged from 1 to 54.14 ng/kg bw per day, minimum LB to maximum UB. Under the UB assumption, the group ARfD was exceeded (separately) both for atropine and scopolamine at the P95 in infants, toddlers, other children and for atropine for adolescents as well. For the sum of atropine and scopolamine at the mean level the group ArfD was exceeded in infants, toddlers and other children, and at the P95 in all age classes. Under the LB assumption, the group ARfD was exceeded for the sum of atropine and scopolamine at the P95 in toddlers and other children.
- The p95 dietary exposure of infants could be up to three times (under the UB assumption) the group ARfD and could exceed the group ARfD on approximately 3 to 21% of consumption days
- Overall, among processed foods the main contributors to the co-exposure of atropine and scopolamine were, at the UB, bread and cereal-based foods, and, at the LB, tea and herbal infusions for all age classes
- Sources of uncertainty include mainly the large number of left censored data.

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Glossary

EC	European Commission
EFSA	European Food Safety Authority
EFSA CONTAM opinion	Opinion of the EFSA CONTAM Panel on the risks to public health related to the presence of TA in food, in particular fruit and vegetables, issued in 2014
EU	European Union
FoodEx	EFSA food classification and description system
LB	Lower bound
LC	Left-censored values. i.e. analytical values reported as <LOD or <LOQ
LOD	Limit of Detection
LOQ	Limit of Quantification
Paramcode	Internal identifier of the chemical substance
MB	Middle bound
P95	95 th percentile
RESVAL	Field of the EFSA standard sample description used to record the measured concentration value for a particular analysis
SDWH	EFSA Scientific Data Warehouse
SSD	Standard Sample Description (SSD1 = version 1)
THIE	European Tea and Herbal Association
UB	Upper bound

Appendix: Supporting tables

Supporting tables can be found in the online version of this output, under the section 'Supporting information', at: <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5160/full>

Table A1: Dietary surveys considered for the acute human dietary exposure assessment

Table A2: Distribution of analytical results by occurrence level Foodex level 1 ($\mu\text{g}/\text{kg}$)

Table A3: Distribution of analytical results by occurrence level Foodex level 2 ($\mu\text{g}/\text{kg}$)

Table A4: Distribution of analytical results by occurrence level Foodex level 3 ($\mu\text{g}/\text{kg}$)

Table A5: Distribution of analytical results by country

Table A6: Distribution of analytical results by occurrence level by country and sampling year

Table A7: Distribution of analytical results by analytical method

Table A8: Distribution of analytical results by LOQ ($\mu\text{g}/\text{kg}$)

Table A9: Acute Exposure to atropine (UB) (ng/kg)

Table A10: Acute Exposure to scopolamine (UB) (ng/kg)

Table A11: Acute exposure to the sum of atropine and scopolamine (UB) (ng/kg)