Andrea LUGASI [1]

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Tropane alkaloids in food – real and perceived risks

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1. Summary

Tropane alkaloids occur in many plant families and their toxic effects can cause mild symptoms or even death, depending on the dose. They are most commonly introduced into the human body through contamination, misuse or deliberate abuse due to their intoxicating effects. They are present in food for general consumption, sometimes causing documented poisoning, due to inadequate cleaning of cereals, pulses or other grain crops, but especially organic products produced without chemicals. The EU legislation published in 2021 set tolerances for tropane alkaloids for a relatively wide range of plant materials, and therefore consistent compliance with the regulation will reduce the food safety risk from tropane alkaloid contamination, although food poisoning incidents in recent years have highlighted the need to broaden the range of food substances covered.

[1] Budapest Business School, Faculty of Commerce, Hospitality and Tourism, Department of Hospitality

Andrea LUGASI Lugasi.Andrea@uni-bge.hu https://orcid.org/0000-0001-9895-2365

2. Introduction

Tropane alkaloids are secondary metabolites commonly found in plants. Their food safety risk has come to the fore in the last few years, mainly in relation to accidental contamination of food. In particular, crops grown using chemical-free technologies may pose a food safety risk, as the ban on the use of herbicides may lead to the proliferation of weeds containing tropane alkaloids. Various parts of weeds but mainly seeds can be introduced into products for human consumption, resulting in contamination that cause acute poisoning.

In recent years, contaminated food has been found in the Hungarian market and food poisoning cases attributed to tropane alkaloids have occurred in the commercial catering sector. Thus, the risk may affect the final consumer through both prepackaged food and catering. In the light of poisoning incidents over the last decade and so, the need to regulate tropane alkaloids at Community level has been brought to the fore there is reason for optimism that the recent EU legislation, if applied consistently, can provide sufficient protection for the consumer.

3. Chemical structure, occurrence

The tropane alkaloids are characterised by an azabicyclo[3.2.1]octane ring structure (bicyclic amine, in which a pyrrolidine and a piperidine ring, one N and two C atoms, are shared) ***(Figure 1)***. The amino group is, as is typical for alkaloids, mostly methylated **[1]**.

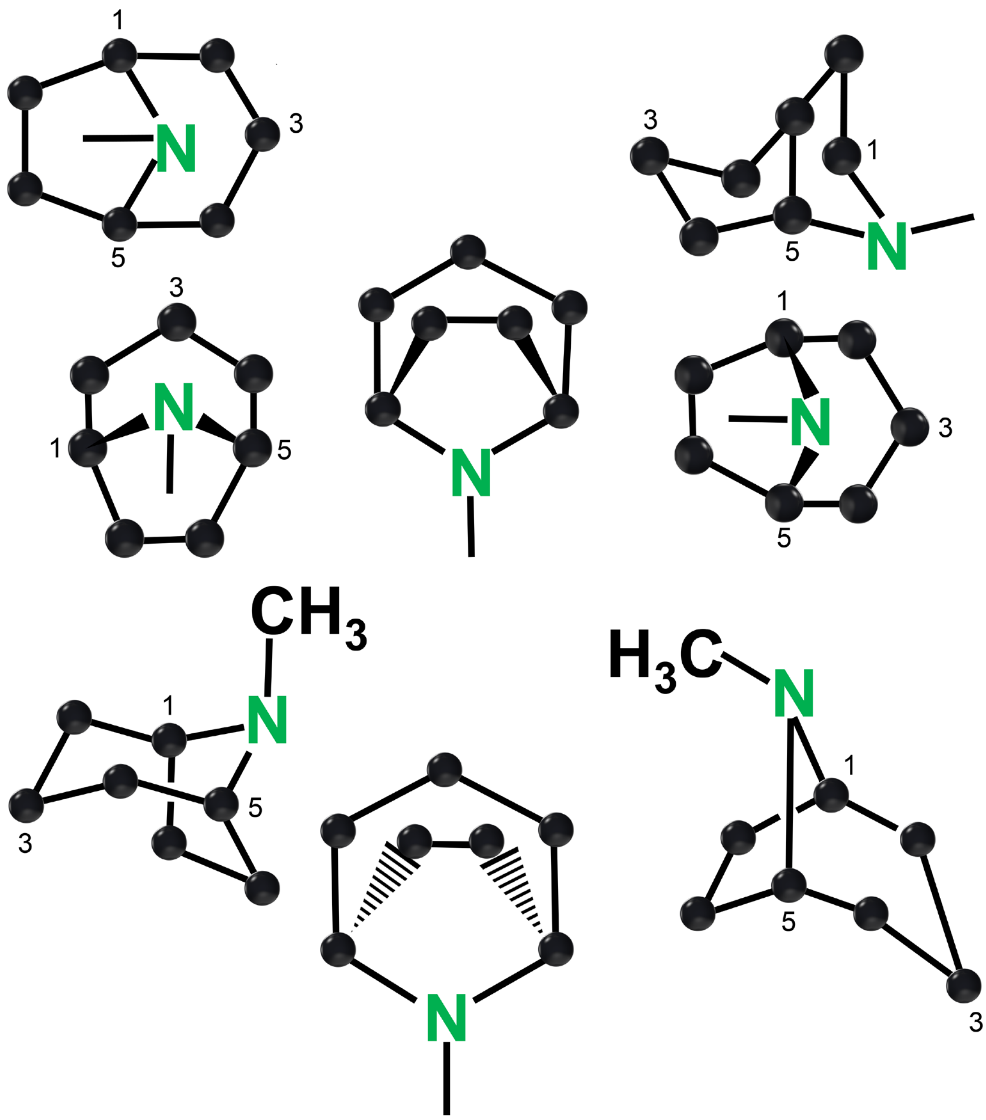

Figure 1 Structure of tropane alkaloids (1R, 5S)-8-methyl-8-azabicyclo [3.2.1] octane ***[1]***

The tropane alkaloids include about 200 different molecules, including mono-, di- and tri-esters, as well as carboxylated and benzoylated compounds **[2, 3]**. The most important and most commonly occurring tropane alkaloids are atropine and Scopolamine. Atropine is in fact a racemic mixture of D-hyoscyamine and L-hyoscyamine (Figure 2) **[4]**, the latter being predominantly responsible for the physiological effects (anticholinergic effect) which will be discussed later **[5]**.

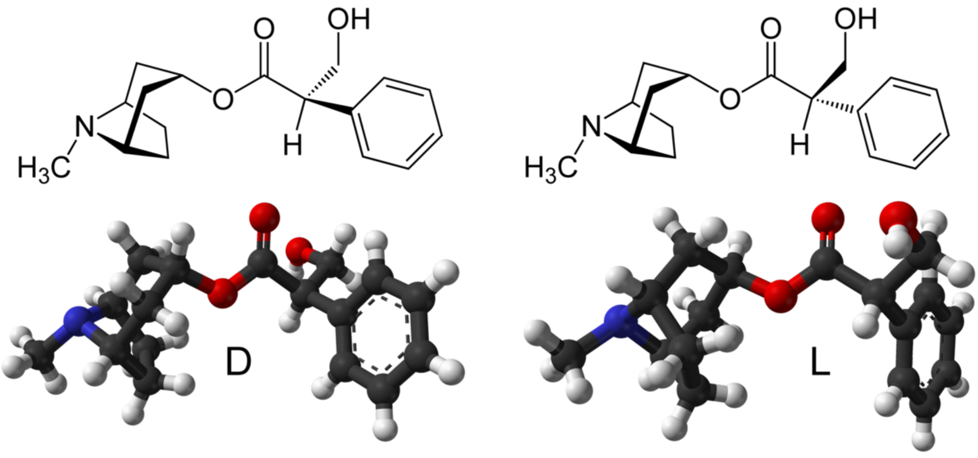

Figure 2 Structure of D- and L-hyoscyamine ***[4]***

Atropine - depending on the dose - is a potentially lethal poison, named after Atropos (The Inflexible One) in Greek mythology, one of the Moirai (Goddesses of Fate), who cuts the thread of life with her scissors and thus decides who will die (Figure 3) **[6, 7]**. Atropine is listed in the 8th edition of Hungarian Pharmacopoeia as Atropineum.

Figure 3 The Three Fates Clotho, Lachesis, and Atropos by Giorgio Ghisi ***[7]***

Tropane alkaloids are found in various plant families, such as *Brassicaceae* (*Cruciferae*) (“mustard” family), *Convolvulaceae* (“bindweeds” family), *Erythroxylaceae* (“coca” family), *Euphorbiaceae* (“spurge” family), *Olacaceae*, *Proteaceae*, and *Rhizophoraceae* (“mangrove” family), but most commonly in the *Solanaceae* (“nightshade” or “potato”) family [2]. The latter family includes about 100 genera and 3000 species. In particular, the genera *Datura*, *Brugmansia*, *Hyoscyamus*, *Atropa*, *Scopolia*, *Anisodus*, *Przewalskia*, *Atropanthe*, *Physochlaina*, *Mandragora*, *Anthotroche*, *Cyphantera*, and *Duboisia* are rich in tropane alkaloids **[2]**. The well-known members of the *Solanaceae* family are mandragora, henbane, nightshade and jimson weed as well as their edible relatives, potato, tomato and eggplant. The tropane alkaloids are most abundant in the genera *Datura* and *Brugmansia*. The best known plants containing tropane alkaloids and their constituents are summarised in Table 1.

Table 1. Plants and plant parts containing tropane alkaloids based on Adamse et al. ***[8]***

Plant			Tropane alkaloids (TA)	Plant parts contain tropane alkaloids
Botanical name	**Hungarian name**	**English name**		
Atropa belladonna	Nadragulya	Deadly night-shade	Scopolamine, hyoscyamine, atropine, kalistegin	Berry, leaf, root
Datura stramonium	Csattanó maszlag	Jimsonweed, thornapple	Scopolamine, hyoscyamine, atropine	Leaf, root, seed, flower
Datura suaveolens (*Brugmansia suaveolens*)	Angyaltrombita	Angel's tears, snowy angel's trumpet	Scopolamine, hyoscyamine	Leaf, flower, seed
Datura tatula	Métel	Jimsonweed, thornapple	Atropine	Leaf, flower, seed
Duboisia myopoides	Parafa	Corkwood	Scopolamine, atropine	Leaf
Hyoscyamus niger	Bolondító beléndek	Henbane, black henbane, stinking nightshade	Scopolamine, hyoscyamine, atropine, kalistegin	Leaf, flower, seed
Lycium barbarum	Közönséges ördögcérna	Wolfberry, goji berry	Atropine	Berry
Mandragora officinarum	Mandragóra	Mandrake	Scopolamine, hyoscyamine, atropine	Root, berry
Calystegia sepium	Sövényszulák	Hedge false bindweed	Kalistegin	Leaf, root
Convolvulus arvensis	Apró szulák, mezei szulák	Field bindweed	Kalistegin	Leaf, root
Physalis alkekengi	Lampionvirág, páponya	Bladder cherry, Chinese lantern, etc.	Kalistegin	Leaf
Physalis peruviana	Perui földicseresznye, poha, zsidócseresznye	Cape gooseberry, goldenberry	Tigloidin, seco tropane alkaloids	Root
Erythroxylum coca	Kokacserje	Coca	Several alkaloids, including cocaine	Leaf

Some of the plant species containing tropane alkaloids described above may be consumed as food, for example members of the *Brassicaceae* (*Cruciferae*) and *Solanaceae* families, but human exposure is not expected as plant parts consumed by humans, such as potato tubers or tomato fruits, do not contain tropane alkaloids. However, almost all of the plants containing high levels of tropane alkaloids in various plant organs can be found as weeds in the environment of cultivated or free-growing but edible plants, and therefore exposure of tropane alkaloids from them is most often due to accidental consumption **[8]**. Table 2 shows the alkaloid content of the most common weeds containing tropane alkaloids in various plant parts, including *Datura stramonium* and *Atropa belladonna*.

Table 2. Tropane alkaloid content of different plant species and plant parts (mg/kg dry matter)

Species (place of origin)	Plant part	(-)-Hyoscyamine	(-)-Scopolamine	Total tropane alkaloids	Reference
D. stramonium (USA)	Seed	1690-2710	360-690	2050-3400	**[9]**
D. stramonium (Italy)	Root Shoot Leaf Flower Seed	Nd121 1-915 134-831 270-299 170-387	Nd-14 Nd-129 16-73 66-106 12-89	Nd-135 1-1044 172-378 336-405 182-476	**[10]**
D. stramonium (different variants)	Leaf Seed	425-1655 710-1380	230-715 520-1275	1000-1855 1235-2655	**[11]**
D. stramonium (Italy)	Seed	1280	680	1960	**[12]**
D. stramonium (D. *var. tutala*) (Hungary)	Shoot Leaf Flower	360-5910 430-4710 1690-3970	20-3320 130-1790 1360-2740	380-8830 560-6430 3050-6710	**[13]**
D. ferox (Argentina)	Root, Shoot Fruit Leaf Seed	x	36-900 29-200 40-3200 130-210 1500	x	**[14]**
D. ferox (Argentina)	Seed	Nd	610-820	610-820	**[15]**
A. belladonna (Germany)	Root Leaf	5290 2500-9200	51 20-280	x	**[16]**
A. belladonna (Europe)	Root Leaf Seed	500-3700 500-4900 1200-6900	nd-900 nd-500 nd-500	500-4000 700-5100 1300-7300	**[17]**
A. belladonna (Germany)	Root, shoot Leaf Seed	3700 1800-3900 960-1400 2800-9200	100 70-130 90-130	x	**[18]**
A. belladonna (Iran)	Root Shoot Leaf	570-880 740-770 190-1200	17-31 28-180 23-470	x	**[19]**
A. acuminata (Iran)	Leaf	900-1200	140-470	x	**[19]**
A. baetica (Spain)	Root	1000-10000	600	x	**[20]**
H. niger (Bulgary)	Seed	140	430	570	**[21]**

nd: not detectable
x: no information available

4. Physiological effects

The tropane alkaloids are antimuscarinic compounds, blocking the muscarinic receptors of smooth muscles in the bronchi, of glands and of nerve endings, inhibiting muscle contraction and secretion, as well as increasing the release of neurotransmitters. The tropane alkaloids are parasympathetic neuromuscular paralysers, which affect cardiac and respiratory frequency, they are smooth muscle antispasmodics and they also reduce saliva, gastric juice and protein secretion. At doses of 3.0 to 8.0 mg they excite the central nervous system, but above 10 mg they paralyse its function. The compounds are characterised by their rapid and complete absorption through the mucous membrane **[22]**.

The human physiological effects of atropine vary widely depending on the dose. Ingestion of 0.5 mg of the compound causes a slight slowing of the heart rate and mild dry mouth, and it inhibits the secretion of sweat. A dose of 1.0 mg produces more severe dry mouth, a feeling of thirst, rapid heart rate and dilated pupils. At 2.0 mg, rapid heart rate, palpitation, dilated pupils and blurred vision occur. At intakes above 5.0 mg, the above symptoms are accompanied by slurred speech, restlessness, headache and dry and hot skin. At intakes above 10.0 mg, the above symptoms are accompanied by a rapid and weak pulse, blurred vision, skin erythema, ataxia, hallucination, delirium and finally coma **[23]**.

The primary symptoms of atropine poisoning are dilated pupils, inhibited saliva production, hyperthermia and decreased respiratory rate and heart rate. The central nervous system is also affected, and drowsiness and depression may occur. The final outcome of the poisoning process is circulatory failure and coma. Individual sensitivity is highly variable, with lethal doses ranging from 100 to 1000 mg, 10 mg in children. Scopolamine intoxication also results in dilated pupils, inhibition of saliva production, a decrease in heart rate at low doses, but an increase at higher doses. Its effect on the central nervous system is the opposite of atropine, i.e. it stimulates it. The lethal dose of scopolamine is 100 mg, which causes respiratory paralysis and eventual death **[24]**.

Poisoning can occur on a single exposure, with an incubation period of up to 6 hours, and the route of exposure is most often oral, but inhalation also occurs. Tropane alkaloids are absorbed via the gastrointestinal tract **[25]**. Toxic effects often occur within 60 minutes of ingestion and sub-lethal clinical signs may persist for up to 24-48 hours **[26]**. Without treatment, consumption of 2-5 berries (seeds) of deadly nightshade can be fatal for children and 10-20 berries for adults. Jimson weed poisoning can be detected 60 minutes after ingestion. Clinical signs persist for 24-48 hours. A jimson weed seed weighs about 8 mg, therefore about 100 seeds are equivalent to 10 mg of atropine **[27]**.

Acute therapy is immediate decontamination (gastric and/or bowel lavage, enema), but it can be applied to 12 hours after poisoning. The antidote for poisoning is physostigmine (0.02 mg/kg body weight), which should be used with caution because of its significant cardiac side effects **[28]**. Symptomatic supportive treatment may include physical cooling, sedation, fluid replacement, beta-blocker administration and catheterisation. When providing first aid, the priority is to prevent the absorption of poison by vomiting, gastric emptying or giving activated charcoal, reducing thirst with fluid intake and reducing body temperature with an ice compress **[29]**.

5. Interesting facts about tropane alkaloids

There are more than 520 tropane base compounds that have a CAS number. The CAS registration number of tropane is 529-17-9 **[30]**. In the CAS database, cocaine [50-36-2] was the first tropane derivative registered, while tesofensine [402856- 42-2] was the last **[31, 32]**. Most naturally occurring tropane derivatives are natural deliriants. The term “Bella donna” (*Atropa belladonna*) means “beautiful lady” and was given its name in the Renaissance era because ladies often dripped into their eyes a juice from the atropine-containing fruit of *A. belladonna*, which dilated their pupils and made them look beautiful **[33]**.

Between the 1910s and the 1960s, a mixture of scopolamine and morphine was used as a sleeping pill to produce twilight sleep during childbirth. The administration of the mixture induced a semi-conscious state during labour and the birth process was lost from the mother’s memory **[34]**.

Jimson weed was named after Jamestown, USA, where British soldiers were poisoned in 1676 by eating a vegetable salad, with symptoms of delirium and hallucinations for 11 days **[35]**.

Homatropine was a synthetic drug, a semi-synthetic ester synthesised by Ladenburg and marketed by the E. Merck Company in 1883 as a pupil dilator **[36]**. The best known tropane derivative is cocaine, which has been used as a drug and narcotic since 3000 BCE. Examples of cocaine-containing products included toothache pastilles **[37]** and French Tonic Wine **[38]** **[39]** ***(Figure 4-5)***. Coca Cola is another popular drink containing cocaine-free extracts of coca bush. Initially, Coca Cola did contain cocaine, and the cocaine-free version appeared after the enactment of the Pure Food and Drug Act of 1906 **[40]**. Figure 6 shows an advertisement for Coca Cola from 1902 **[41]**.

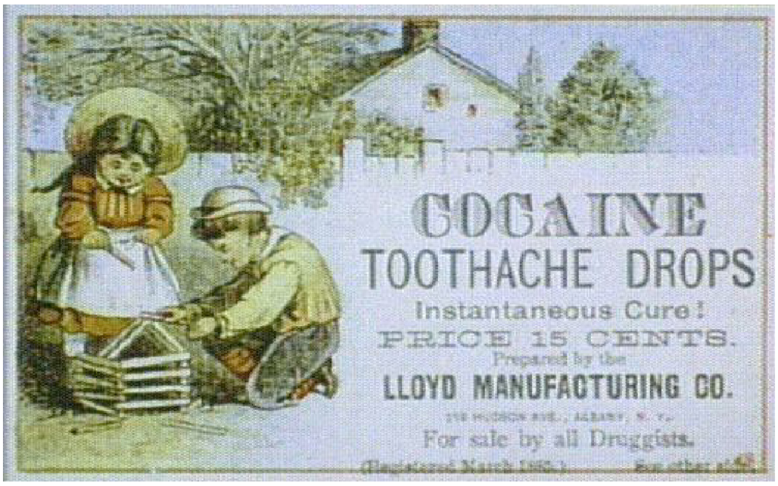

Figure 4 An advertisement for a cocaine toothache pastille from 1885 [37]

Figure 5 Jules Chéret, Vin Mariani. Popular French tonic wine..., 1894. Lithographic poster, published by Imprimerie Chaix; 123 × 86.3 cm. ***[38, 39]***

Figure 6 Coca Cola advertisement from 1902 ***[41]***

The structure of tropane alkaloids and cocaine was described by Richard Martin Willstätter (1872-1942). In 1903 he discovered the method of synthesising tropane, a discovery considered a fundamental milestone in organic chemistry. Willstätter also won the Nobel Prize in Chemistry in 1915, mainly for his discovery of the structure of chlorophyll and other plant pigments **[42]**.

Tropane derivatives are among the most economically important pharmacons **[43]**. The pharmaceutical industry produces more than twenty tropane-based active pharmaceuticals with a wide range of uses: pupil dilators, antiemetics, anticonvulsants, analgesics and bronchodilators **[5]**. L-hyoscyamine is used for peptic ulcer, irritable bowel syndrome and Parkinson's disease, cocaine is a local analgesic, tiotropium bromide is used for COPD, and ipratropium bromide is used for asthma **[8]**.

6. Use, administration and intentional and unintentional consumption of tropane alkaloids

The tropane alkaloids, mainly atropine, are officially listed as medicinal products in the European Pharmacopoeia VII (VII Ph. Eur.) and have a wide range of therapeutic uses, treatment of dilated pupils, nausea, motion sickness, intestinal spasms, bradycardia and other cardiac and respiratory diseases **[44]**. Atropine is recommended in traditional Chinese medicine for the treatment of arthritis **[45]**.

In folk medicine, atropine is used to relieve nerve spasms, rheumatism and spasms, and in asthma cigarettes (inhalation) to reduce bronchospasms and salivation **[46]**, but its use as a home remedy can be dangerous due to the potential r to overdose. It is also used as a drug because of its hallucinogenic effects **[46]**.

In case of unintentional use or contamination, poisoning may occur due to misguided use or aftereffects, intentional ingestion, or abuse (overdose) of the plant material. Contamination occurs mainly during the cultivation and harvesting of edible plants, when weeds containing tropane alkaloids, mainly *Datura stramonis*, *Atropa belladonna* and *Hyosciamus niger* species, appear in large quantities among edible plants.

Commercial seeds sold in bulk, soya and other legumes, cereals and pseudocereals (wheat, maize, sorghum, millet, buckwheat), sunflower and linseed may be contaminated with seeds of jimson weed, angel trumpet or henbane. These weeds mature with the grain forage and are mixed into the forage at harvest. Weed seeds are similar in size, shape and colour to the seeds of edible crops, so they are difficult to remove by sorting or cleaning. This type of contamination can also lead to serious poisoning. For example, in Uganda in 2019, a humanitarian food aid product (known as Super Cereal, a product made from maize and soya) was contaminated with tropane alkaloids from jimson weed, resulting in 300 people being hospitalised and five deaths **[47]**.

Of particular relevance to human nutrition are contaminated cereals, pseudocereals and pulses, as these foods are part of the diet of almost all age groups. One of the most studied pseudocereals in relation to the occurrence of tropane alkaloids was buckwheat (*Fagopyron esculentum* L.), which is rich in polyphenols, vitamins and proteins, and is also gluten-free. Other gluten-free crops, such as amaranth, chickpeas, green peas, maize, rice, millet, quinoa and their products, breads, pastries, pasta, confectionery and snacks are becoming increasingly popular not only among gluten-sensitive consumers but also among those who are more health-conscious. This makes it increasingly important to carefully monitor the presence of tropane alkaloids in these products. There are many publications in the literature that show the tropane alkaloid contamination of such raw materials, some of which are presented in Table 3.

Table 3. Tropane alkaloid contamination of foods according to Gonzales-Gómez et al. [48]

Sample (number of samples)	Atropine-containing samples (concentration)	Scopolamine-containing samples (concentration)	Reference
Breakfast cereal, breakfast cereal with milk, biscuits, cake (113 samples)	21 breakfast cereals (0,09–65,6 μg/kg)	18 breakfast cereals (0,28–15,2 μg/kg)	**[49]**
Flours (buckwheat, millet, corn), cereal-based foods for children, breakfast cereals, biscuits, pastries, breads, legumes cooking oil mixes, oilseeds (1305 samples)	46 flours (0,5–149 μg/kg), 42 cereal-based foods for children (0,5–3,73 μg/kg), 15 breakfast cereals (0,5–90,83 μg/kg), 24 biscuits, pastries (0,5–1,85 μg/kg), 18 bread (0,5–3,80 μg/kg), 20 legumes, cooking oil mixes, oilseeds (0,5–0,11 μg/kg)	46 flours (0,5–199 μg/kg), 42 cereal-based foods for children (0,5–1,86 μg/kg), 15 breakfast cereals (0,5–17,64 μg/kg), 24 biscuits, pastries (0,5–0,65 μg/kg), 18 bread (0,5–0,36 μg/kg), 20 legumes cooking oil mixes, oilseeds (0,5–0,09 μg/kg)	**[50]**
Buckwheat, buckwheat flour and pasta; soy and soy flour; hulled millet and millet flour; flaxseed and flaxseed meal (15 samples)	1 buckwheat (<1 μg/kg) 1 millet flour (13 μg/kg)	1 buckwheat (<2 μg/kg) 1 millet flour (23 μg/kg)	**[51]**
Organic buckwheat flour, pasta and pastries (26 samples)	1 flour (83,9 μg/kg) 1 pasta (21,3 μg/kg) 1 pastry (13,9 μg/kg)	1 flour (10,4 μg/kg) 1 pasta (5,7 μg/kg)	**[52]**
cereal-based foods for children (biscuits, snacks, grissini) (18 samples)	1 snack (11,5 μg/kg)	1 snack (2,8 μg/kg)	**[53]**
Wheat, corn, rice, oat and millet flour, mixed cereal flours, cereal products for babies, cereal-based products (95 samples)	1 tomato rice flakes (9,6 μg/kg)	1 tomato rice flakes (2,6 μg/kg)	**[54]**

Sample (number of samples)	Atropine-containing samples (concentration)	Scopolamine-containing samples (concentration)	Reference
Buckwheat and buckwheat flour, quinoa, amaranth, teff flour, refined corn flour, corn flour, blue corn flour, sorghum flour, hulled millet, green and red lentil flour, chickpea flour, pea flour (15 samples)	3 Buckwheat and buckwheat flour (6,7–21 µg/kg), 1 quinoa (7,1 µg/kg), 1 teff flour (78 µg/kg), 1 refined corn flour (7 µg/kg), 1 sorghum flour (15 µg/kg), 1 hulled millet (6,9 µg/kg)	1 of teff flour (28 µg/kg)	**[55]**
Green tea, black tea, chamomile, fennel, lemongrass, peppermint, rooibos (70 samples)	1 fennel (83 µg/kg) 8 peppermint (20–208 µg/kg)	1 fennel (11 µg/kg) 8 peppermint (20–208 µg/kg) 1 chamomile (2.1 µg/kg) 1 of rooibos (2 µg/kg)	**[56]**
Dried herbs (for infusion) (121 samples)	85 dried herbs (0,0067–295 µg/kg)	85 dried herbs (0,0067–134 µg/kg)	**[55]**
Thyme, basil, coriander (16 samples)	5 thyme (<5–5,7 µg/kg) 5 basil (9–11,7 µg/kg) 4 coriander (9,9–42 µg/kg)	2 thyme (<5 µg/kg) 1 coriander (34 µg/kg)	**[57]**

Common poisoning, especially in the cases of children, comes from consuming a misidentified plant, for example mistaking the fruit of nightshade for blueberry. There are records of misidentification of *Atropa belladonna* for mallow leaves (Malva silvestris); of the leaves of Datura stramonium when used as herbal infusion for nettle, mallow leaf and *Symphytum officinale;* of the root of jimson weed for *Arcticum lappa* when using traditionally as blood-cleansing, diuretic and skin-cleansing herbal infusion; and *Datura* flower for *Paulownia* (foxglove tree) as a green salad **[8, 58]**. For excellent summaries of poisoning cases related to contamination, mistaken identification or intentional overdose, see, among others, the publications by Adamse et al. 2010 and 2014 **[8, 58]**.

The presence of tropane alkaloids in food of animal origin (milk, eggs, meat) from animal feed contamination can be the result of carry-over intake. In the case of raw feed, the relevance and possibility of this is very limited, as animals refuse to eat feed contaminated with tropane alkaloids because of the characteristic and unpleasant taste and smell of the weed. In the case of a dried feed mixture, the presence of weed seeds is no longer detected by the animals, so the resulting exposure is possible. Tropane alkaloids are not sensitive to heating and drying. 72 to 100% of the toxin can be detected in the product after baking bread made from flour contaminated with *Datura* seeds **[9]**, so it is understandable that its presence in dried feed can be significant. However, in dried feed mixtures, the presence of dry *Datura* seeds can cause severe toxicity and mass mortality in farm animals, especially pigs, which are sensitive to the toxin **[59]**. According to EU Directive 2002/32/EU, a 'worst case exposure' estimate of 3000 mg/kg *Datura ferox* seed intake in feed may cause severe adverse reactions in piglets **[60]**. However, the absorption, degradation and elimination of tropane alkaloids is a rather rapid process and they are not stored in organs and tissues, and therefore human poisoning is not expected when consuming farm animal meat **[59]**.

Other cases of poisoning are from intentional use or overdose, partly when used as a drug because of hallucinogenic effects, or for therapeutic purposes (arthritis treatment, anaesthesia). Pathological cases of intentional intoxication are homicide and suicide. In some cases, atropine is also used as an antidote for organophosphate poisoning **[61]**.

Unfortunately, Hungarian data on tropane alkaloid contamination of food and resulting poisonings are not available, although data regarding accidental or intentional poisoning are available from the Hungarian Toxicological Information Service **[62]**. According to these data, *Brugmansia* and *Datura* species were the most common poisoning species in Hungary. According to a survey conducted between 2005 and 2017, *Brugmansia* species accounted for 1-7%, *Datura* species for 1-16%, *Convallaria majalis* for 6-20% and *Taxus baccata* for 8-19% of the plant taxa that regularly caused poisonings.

7. Impact of food processing on tropane alkaloids

Tropane alkaloids are relatively heat stable. Studies by List and Spencer have shown that processing soybeans also reduces the amount of hyoscyamine and scopolamine present as impurities, with 90% of the former and 84% of the latter remaining in the defatted soybean meal. In unrefined soybean oil, about 0.1%

of the original alkaloid content was present, and more than 90% of this was lost due to alkaline refining and washing of the oil **[63]**. During baking of wheat bread contaminated with cracked jimson weed seeds, heat treatment reduced the concentration of tropane alkaloids by 0-28% **[9]**. Cooking of žganci (porridge-like dish) made from buckwheat flour contaminated with tropane alkaloids reduced the concentrations of atropine and scopolamine by 60 and 40%, respectively **[64]**.

Marín-Sáez et al. studied buckwheat and millet flours contaminated with *Datura stramonium* and *Brugmansia arborea*, subjected to rising (37 °C) and baking (190 °C) processes **[65]**. During the rising process, the concentration of tropane alkaloids decreased (13-95% degradation), whereas under baking conditions they almost disappeared (94-100% degradation). Also, Marín-Sáez's research group investigated the degradation of tropane alkaloids from pasta and green tea **[66]**. Pasta was boiled at 100 °C for 10 minutes, tea was prepared with water at 100 °C and allowed to cool for 5 minutes. The pasta and green tea were contaminated with seeds of *Datura stramonium* and *Brugmansia arborea*, while the coca leaf tea was analysed directly. Degradation studies showed that the concentration of tropane alkaloids decreased and this was dependent on the compound, with the greatest degradation being observed for the compounds tropinone, tropane, cuscohygrine and tropine, but it was also observed that the compounds migrated to the aqueous phase during cooking **[66]**.

The latest study reports on the tropane alkaloid content of gluten-free bread sticks made from corn flour contaminated with jimson weed. Thermal degradation studies showed a decrease in the amount of tropane alkaloids during baking (180 °C, 20 minutes), ranging from 7-65% for atropine and 35-49% for scopolamine and anisodamine, depending on the conditions used **[67]**.

8. Food safety legislation in feed and food

The presence of tropane alkaloids as potentially toxic compounds in foods for general consumption, food supplements, foods for particular nutritional uses and food served in catering is undesirable. The marketing of safe food is a fundamental requirement and is therefore governed by EC Directive 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety **[68]**.

The European Union has had to wait a long time for effective regulation. Surprisingly, the regulation for farm animals was introduced before the regulation for humans. Regulation 2002/32/EC on undesirable substances in animal feed stipulates that weed seeds and unground or uncrushed fruits, including the seeds of the jimson weed seeds containing alkaloids, glucosides or other toxic substances, either singly or in combination, may be present up to a maximum of 3000 mg/kg, and *Datura stramonium* L. seeds at a maximum of 1000 mg/kg in animal feed with a moisture content of 12% **[60]**.

In its statement, the European Food Safety Authority (EFSA) concluded in 2008 that tropane alkaloids do not enter the food chain via food of animal origin and therefore do not pose a risk to consumers. However, the scientific panel that drafted the position paper drew attention to the importance of validating methods for the measurement of tropane alkaloids **[59]**.

5 years later, in 2013, EFSA issued a new expert opinion on tropane alkaloids in food and feed **[69]**. Based on the available data, EFSA established an Acute Reference Dose (ARfD) of 0.016 µg/kg body weight expressed as the sum of (-)-hyoscyamine and (-)-scopolamine, assuming equivalent potency. In addition, it concluded that, although information is rather limited, it indicates that the dietary exposure of young children to tropane alkaloids may significantly exceed the group acute reference dose.

Based on the EFSA's opinion, Commission Regulation (EC) No 2016/239/EC **[70]** amending Regulation (EC) No 1881/2006 **[71]** was published setting maximum levels for certain contaminants in foodstuffs as regards maximum levels for atropine and scopolamine in processed cereal-based foods and baby foods for infants and young children containing millet, sorghum, buckwheat or products thereof. Accordingly, the maximum levels for atropine and scopolamine in those foods are set at 1.0 µg/kg each.

In its 2013 position paper **[69]**, the EFSA highlighted the need for more detailed characterisation of tropane alkaloids naturally occurring or present as contaminants in food and feed, and for the collection of analytical data on their occurrence in cereals and oilseeds. Collection of these analytical data was carried out on the basis of the Recommendation of the European Commission to food business operators in the Member States to monitor tropane alkaloids **[72]**. The Recommendation called on the food safety authorities of the Member States to monitor the presence of tropane alkaloids with the active involvement of food business operators in foodstuffs, in particular in cereals and cereal products (buckwheat, sorghum, millet, maize and flours thereof), cereal-based foods for infants and young children, breakfast cereals, mill products, seeds for human consumption, gluten-free products, food supplements, teas and herbal teas, leguminous vegetables (without pods), pulses and oilseeds and products derived from them **[72]**.

In 2016, a summary study presenting the results of an ad hoc data collection study on the prevalence of tropane alkaloids in food in nine Member States was published **[50]**. Following the assessment of the results, in 2018 EFSA issued a scientific report on acute dietary exposure of the EU population to tropane alkaloids **[73]**. The report was updated in 2019. This report describes the estimated human acute dietary exposure to tropane alkaloids based on data from 17 European countries and one association, Tea & Herbal Infusions Europe, using nearly 45 000 analytical data from about 7,900 food samples (6 943 atropine and 6 897 scopolamine measurements, 14 851 other *Datura*-type tropane alkaloids and 15 493 other tropane alkaloids) from 2009-2016 to 2019. The most abundant tropane alkaloids were atropine (in 15.7% of the samples); and scopolamine (in 15.6% of the samples) **[73]**.

High levels of atropine contamination were present in hemp seeds (77.2 μg/kg), in various spices (e.g. coriander seeds 35.0 μg/kg, fennel seeds, 6.1 μg/kg), teas and brews (green tea 10.01 μg/kg), in cereal bars (average 6.3 μg/kg). Scopolamine was present in relatively high concentrations in hemp seed (64.9 μg/kg), in teas and infusions (chamomile flower 11 μg/kg, green tea 10 μg/kg) and spices (coriander seed 22 μg/kg), while calystegine A3 contamination was detected in potatoes and potato products (107 μg/kg) **[73]**.

The combined average acute dietary exposure to atropine and Scopolamine was highest in infants: 1-19 ng/kg bw/day, but the exposure in older children was similarly high: 2-19 ng/kg bw/day in young children and 1-18 ng/kg bw/day in children under 18 years of age. Acute exposure to tropane alkaloids was estimated to exceed the acute reference intake (16 ng/kg bw/day) in many population groups (but especially in the young, vulnerable age group) and it was also found that bread and cereal products were the largest contributors to the combined exposure to atropine and scopolamine for all age groups. The survey data indicate that tropane alkaloids, in particular atropine and scopolamine, are present in the food chain in quantities to cause concern.

On this basis, Regulation (EC) No 1881/2006 was amended again in 2021 to set maximum levels for cereals, cereal products and certain herbal sources **[74]** (Table 4).

Foodstuffs listed in the Annex to Regulation 2021/1408 that were lawfully placed on the market before 1 September 2022 may remain on the market until their date of minimum durability or use-by date. The regulation continues to give priority to foods intended for infants and young children and maintains the previous values of 1-1 μg/kg for atropine and scopolamine. In addition, a wide range of foods of plant origin, cereals (maize, millet, sorghum), pseudo-cereals (buckwheat) and herbs are also affected. In view of the case of caraway seed contamination poisoning in Hungary (see below), the range of foods covered appears to be incomplete and it would have been appropriate to include herb seeds in the maximum level for tropane alkaloids.

Table 4. Maximum permitted levels of tropane alkaloids (atropine, scopolamine) in foodstuffs under Regulation (EC) No 1881/2006, consolidated version ***[70, 74]***

Foodstuffs	**Maximum level (μg/kg)**	
	Atropine	**Scopolamine**
Processed cereal-based foods and baby foods for infants and young children, containing millet, sorghum, buckwheat, maize or their derived products	1,0	1,0
	Sum of atropine and scopolamine	
Unprocessed millet and sorghum	5,0 as from 1 September 2022	
Unprocessed maize with the exception of unprocessed maize intended to be processed by wet milling and unprocessed maize for popping	15 as from 1 September 2022	
Unprocessed buckwheat	10 as from 1 September 2022	
Maize for popping Millet, sorghum and maize placed on the market for the final consumer Milling products of millet, sorghum and maize	5,0 as from 1 September 2022	
Buckwheat placed on the market for the final consumer Milling products of buckwheat	10 as from 1 September 2022	
Herbal infusions (dried product) with the exception of the herbal infusions referred to in below cell	25 as from 1 September 2022	
Herbal infusions (dried product) of anise seeds	50 as from 1 September 2022	
Herbal infusions (liquid)	0,20 as from 1 September 2022	

The EU Directive 46/2002/EC and the Hungarian legislation [(37/2004). IV. 26. decree of the Minister of Health (ESZCSM)] on food supplements do not provide specific guidance on substances harmful to health, their use in food supplements, the permitted amounts, limits, etc. **[75, 76]**. However, the Expert Panel convened after the accession to the European Union by the National Institute of Pharmacy and Nutrition (formerly the National Institute for Food and Nutrition Science, OÉTI) in 2006 has compiled a list of plants not recommended for use in food, including food supplements **[77]**.These include a number of plants or parts of plants containing tropane alkaloids, such as *Atropa belladonna*, *Hyosciamus niger*, *Mandragora officinarum*, *Scopolia* sp., *Datura stramonis*, *Solanum nigrum*, *S. dulcimara*, *Brugmansia* sp. It is worth noting that the fruit (fruit, goji berry) of *Lycium barbarum* was previously included in this negative list, given that a publication in 1989 **[78]** reported that the fruit contained (as determined by thin layer chromatography - TLC) 0.95% atropine and 0.29% (-)-hyoscyamine. The author also indicates that these tropane alkaloids are present in similar amounts in the root and in the fresh shoot. However, Drost-Karbowska, in her 1984 publication, does not report tropane alkaloids in *Lycium barbarum* fruit **[79]**. Adams, in 2006, detected 19 μg alkaloids/kg fruit using HPLC-MS techniques, while Potterat (2010) could not confirm the presence of tropane alkaloids in fruit **[80, 81]**. With reference to the latter data, the negative list mentioned above does not currently include *Lycium barbarum* fruit.

9. Presence of tropane alkaloids in food, RASFF alerts

The European Union's Rapid Alert System for Food and Feed (RASFF) has 67 events (alerts, information, rejections at the border) related to tropane alkaloids between 2006 and the beginning of August 2022 **[82]**. The vast majority of affected foods are cereal products: millet (golden, brown) flour and products, sorghum, buckwheat, as well as foods for young children (cereal flakes), maize (flour, popcorn), spinach, cumin seeds, peppermint, muesli, oat and soy flakes, herbal teas, crisps ***(Figure 7)***. In all cases, tropane alkaloids were present as impurities in the products. In most cases, the source of tropane alkaloids was jimson weed (*Datura stramonium*) and black nightshade (*Solanum nigrum*), but in most cases only the presence/amount of atropine and scopolamine was reported in the RASFF database.

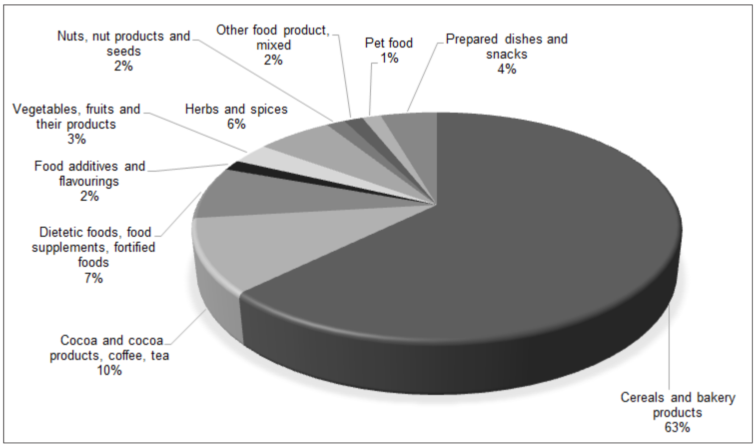

Figure 7 Distribution of food types in the European Union's RASFF system for tropane alkaloid notifications, 2006-2022 July

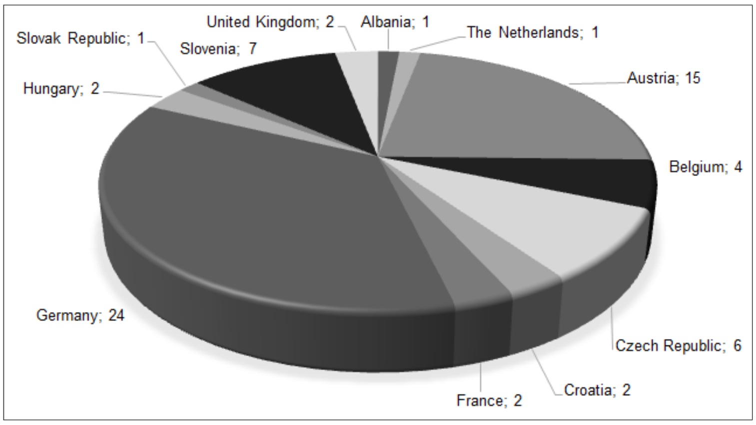

Figure 8. Distribution of RASFF cases involving tropane alkaloids by reporting country (2006-2022)

Most of the notifications came from Germany (24) and Austria (15) ***(Figure 8)***, but contaminated food reached more than 40 countries, affecting almost all EU Member States, but also China, Japan, Senegal, Bahrain, Switzerland, South Africa, Andorra, Bosnia and Herzegovina, etc. The highest number of notifications of tropane alkaloids was in 2015 ***(Figure 9)***, with Germany and Austria reporting 4-4 products and the Czech Republic reporting one case to RASFF.

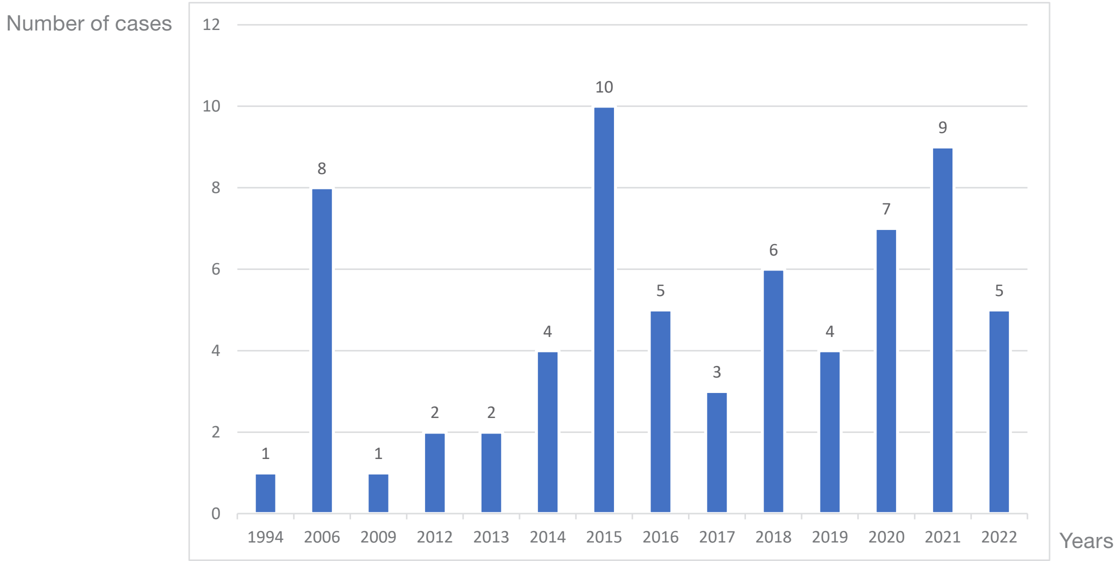

Figure 9 Number of RASFF notifications on tropane alkaloids by year, 1994, 2006-2022

Of the 67 incidents, 22 involved Hungary, either because the raw material originated from Hungary (11 cases) or because the product was or could have been placed on the Hungarian market (11 cases). Hungary has notified two cases of food contaminated with tropane alkaloids to the RASFF system. One of the foodstuffs is the caraway seed contaminated with jimson weed, which received a lot of press coverage in 2018, which was clearly reported on the RASFF portal as the source of contamination was a Hungarian product (2018.0774). The other Hungarian notification relates to a Polish oatmeal, in which the Hungarian authority also found jimson weed (2020.5838). Frozen yellow beans containing jimson weed seeds produced and marketed by different companies, which appeared on the website of the National Food Chain Safety Office (NFCSO) and in several press releases in 2021-2022, are not included in the RASFF.

In 2006, *Datura* seeds (130 seeds/kg) were found in organic millet from Hungary and Austria (2006.0833), and seeds of jimson weed were also found in red millet for animal feed in 2009 (2006.BYZ). In 2009, Slovenia reported to RASFF 110 µg/kg atropine and 47 µg/kg scopolamine in buckwheat flour from Hungary (2009.0558). In 2104, German authorities found atropine (46 µg/kg) and scopolamine (25 µg/kg) in brown millet (*Uroclora ramosa*) flour from Austria, where the raw material originated in Hungary and the Netherlands (2014.1652). In March 2015, three consecutive alerts were released from Austria included Hungarian raw material, with 481 µg/kg atropine and 533 µg/kg scopolamine in organic puffed millet, 384 µg/kg atropine and 388 µg/kg scopolamine in puffed millet and 304 µg/kg atropine and 358 µg/kg scopolamine in millet balls (2015.0338, 2015.0339, 2015.0399). In 2016, atropine (23.5 µg/kg) and scopolamine (9.5 µg/kg) were again detected in millet flour (2016.1298). The year 2018 was about caraway seeds (see later), in 2021 the German authorities detected atropine (100 - 238 µg/kg) in organic flaxseed meal from Hungary (2021.6052), in 2021 also the German authorities reported the presence of tropane alkaloids in Hungarian parsley in RASFF (2021.3836), but no specific measurement results are available in the database.

Tropane alkaloid contamination of products entering Hungary was reported in RASFF in 2006 in organic millet flours (2006.0737, 2006.0833), in 2014 in two cases in cereal-based baby foods from Germany (2014.1694, 2014.1596), in 2015 in brown millet and in a maize flour-based product (2015.0203, 2015.0210). In 2018, atropine and scopolamine were detected in vegetable source material from Poland (exact composition unknown) (2018.2009), in popcorn from France (2018.1447) and in organic Austrian muesli ((2018.2695) also marketed in Hungary. In 2020, Polish oatmeal contaminated with jimson weed seeds (2020.5838) and organic soybean meal containing atropine and scopolamine (2020.0366) were sold market. In 2022, multi-flavoured corn chips from Germany were sold in Hungary (2022.3840) (tropane alkaloid measurement results are not available on the RASFF website until the manuscript is closed).

According to the information on the RASFF site, the Member States concerned have recalled the contaminated products from the market, and there is no information on poisoning or adverse health effects.

It is also worth noting that in the last few years (between 2018 and 2022), the Hungarian authorities have reported and alerted consumers to the presence of tropane alkaloids and jimson weed in various foods, but these cases were not reported in the RASFF. In 2016, the Hungarian food safety authority (NFCSO) withdrew two extruded millet balls (gluten-free, extruded organic millet balls, peanut flavoured, from controlled organic farming, 75 g; lightly salted, gluten-free, extruded millet balls from controlled organic farming, 150 g), most likely produced domestically, due to high atropine and scopolamine content **[83]**. In 2020, muesli bars of different flavours from Germany were recalled from the market following a manufacturer's self-check **[84]**. In 2021-2022, the presence of jimson weed seeds was detected by the national authority in 1000 g of quick-frozen yellow beans marketed under different brands by different distributors **[85, 86]**[1] .

10. Presence of tropane alkaloids in catering

Based on available literature and RASFF alert data, the most frequently contaminated processed foods with tropane alkaloids are those where cereals (wheat, maize, rye, oats, rice, millet), pseudo-cereals (buckwheat, teff, amaranth), legumes are used as raw materials. Unfortunately, they are often found in products for vulnerable groups such as baby foods, cereal-based foods for young children, breakfast cereals. Contamination of herbs with weed seeds may also occur. Due to confusion with certain herbs, health products and food supplements may also be potential sources of tropane alkaloids. Fortunately, the presence of tropane alkaloids in food of animal origin (mainly meat, but also milk, dairy products, eggs) is not expected, given that feed contaminated with tropane alkaloids tastes bad, is not consumed by the animal, is not absorbed by the digestive tract and is not absorbed by the body.

The above-mentioned foods and food ingredients are inevitably present in catering, so potential adverse health effects in this area also need to be addressed. If we look at the public news reports on tropane alkaloid poisonings from 2006 to 2022, the RASFF data, or the warnings and alerts of the national food safety authority (NFSCO) we can see that the most publicised of these was the following caraway seed event in 2018.

Based on press reports, it is known that in April 2018, consumers (mostly foreign tourists) were hospitalised with acute poisoning symptoms after eating food at a restaurant **[87]**. Based on the symptoms and after a systematic examination of the patients, it became clear that it was atropine poisoning. According to an article in the Hungarian journal Gastronomy Magazine, a few months earlier, in December 2017, a similar poisoning had occurred in a restaurant, and the authorities had come across a food, specifically a spice, caraway seed, which could have been responsible for the consumers' symptoms **[87]**. The food that had been implicated in the poisoning was goulash soup, which was (also) seasoned with caraway seeds in accordance with the traditional recipe **[88]**. Following the first case in December 2017, the authority drew the attention of consumers and the catering industry to the presence of caraway seeds contaminated with tropane alkaloids in several batches marketed by companies **[89, 90]**. The Hungarian authorities forwarded the results of the tests to the RASFF system, where the alert is listed with the reference number 2018.0774, and specific measurement data for whole caraway seeds are also available for atropine (16177.6 μg/kg) and scopolamine (4658.3 μg/kg). The interesting thing is that the RASFF alert identified Hungary as the origin of the product, but the press reports suggest that the spice may have reached the restaurants where the poisoning occurred via several points of entry (importer, trader, milling and packaging company, distributor), but the possible origin is more likely Egypt, but no confirmation is available on the NFSCO website or on the RASFF portal. It is also worth noting that a Hungarian baby food company has recalled an own product spiced with caraway seeds that may have been affected by the contamination, thus also complying with the principle of business liability. The authority, with the involvement of the distributors concerned, recalled the products still on the market, so that there were no further reports of poisoning, although the contaminated spice may have reached private households.

After the 2018 caraway seed poisonings, a summary presentation was given by a NFCSO staff member at the Hungalimentaria 2019 conference in 2019, in which the results of measurements were presented **[90]**. An average of 721 mg/kg (688-745 mg/kg) atropine and 237mg/kg (232-244 mg/kg) scopolamine were detected in ground spice caraway, 15.8 mg/kg (16.2-15.4 mg/kg) atropine and 4.5 mg/kg (4.3-4.6 mg/kg) scopolamine in whole caraway. In variously prepared wheat protein products, an average of 145 μg/kg atropine and 124 μg/kg scopolamine were present, while in baby food both tropane alkaloids were present in amounts below 10 μg/kg. Although the data have so far not been confirmed in any scientific publication, data published in this presentation certainly indicate that the batches of spice mixtures tested by the Hungarian food safety authority contained a significant proportion of jimson weed contamination. The contamination is visible to the naked eye in the whole crop, while in ground spices the weed seeds are obviously no longer recognisable.

As in the general food sector, organic, vegan, raw vegan and free-from products are becoming increasingly

[1] The NFSCO's product recall page only provides data for the last 6 months, so product recalls issued earlier can only be referred to on the basis of press releases.

popular in the catering sector. Organic vegetable ingredients may be contaminated with weed seeds, including tropane alkaloid seeds, due to the ban on the use of herbicides. In order to keep with tradition, a number of dishes made from cereals and pseudo-cereals (maize, millet, sorghum, buckwheat) are increasingly appearing on restaurant menus. Vegan products made from pure plant ingredients and products free of wheat and other gluten-containing ingredients offered to gluten-sensitive individuals can also be a source of plant contaminants, and therefore businesses in the food industry and catering sector should be aware of this potential risk.

11. Tropane alkaloid contamination of organic products

At present, under European legislation, a number of herbicides can be used in crop production under specific conditions to prevent the emergence and further growth of weeds in various crops. However, the use of chemicals is generally prohibited in organic farming, so farmers must also use methods other than chemical treatment to kill weeds. Given that alkaloid-containing weeds of tropane often appear in areas where various grain and legume crops and cereals are grown, in the absence of herbicides, weeds are often found in the harvested crop itself or in their seeds among the useful seeds.

The presence of weed seeds would not pose a risk if there were a significant difference in size, colour or specific weight between the seeds of the useful crop and the weed, since in these cases the seeds could be separated by using different cleaning devices. However, the seeds of millet, buckwheat, flaxseed, soybean and some other grain crops and herbs are very similar to the seeds of jimson weed in colour, size and thus no suitable technology is currently available to effectively remove weed seeds from the crop **[48]**. In non-organic farming, chemical weed control prevents the weed from germinating, while in organic farming, only time-consuming manual weed control and/or post-harvest laboratory control is an option, which is however complicated and costly to varying degrees depending on the method used, and therefore in most cases this is not an real option. Although there are few test results to support this claim, the fact that organic products are often found in RASFF alerts does indicate a higher risk of possible contamination of organic products with weed seeds. One publication is available in the literature on this topic. Cirlini et al. analysed 26 buckwheat products (flour, pasta, pastry) from organic, i.e. chemical-free production for tropane alkaloid content. Contamination was found in three samples (13.9-83.9 μg/kg atropine and 5.7-10.4 μg/kg scopolamine), with the highest levels found in one buckwheat flour at 83.9 μg/kg atropine and 10.4 μg/kg scopolamine **[52]**. Thus, tropane alkaloid contamination from weed seeds should be mentioned among the potential food safety risks of organic foods.

12. Summary

The contamination of certain food groups with tropane alkaloids from weed seeds poses a significant food safety risk and it is therefore recommended that the testing of relevant food raw materials, semi-finished and finished foods should be carried out in larger samples than is currently the case, either in official or service laboratories.

13. Update

In the first three months of 2023, three new tropane alkaloid alerts were added to the RASFF system. All three were reported by Germany, two were originated from the Netherlands and one from Poland. Organic hulled milled (2023.0140) contained 29 μg/kg atropine and 23 μg/kg scopolamine, popcorn (2023.1822) contained 16.7 μg/kg atropine and 2.3 μg/kg scopolamine and organic teff flour (2023.1823) contained 190.4 μg/kg atropine and 60.2 μg/kg scopolamine. The latter product was placed on the market in Hungary, NFCSO drew the attention of consumers to the contamination of the product in a press release and recalled the product from the market **[91]**.

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