Wageningen Academic Publishers

# Tropane alkaloids in food: poisoning incidents

**P. Adamse, H.P. van Egmond, M.Y. Noordam, P.P.J. Mulder and M. de Nijs**

*RIKILT – Wageningen UR, P.O. Box 230, 6700 AE Wageningen, the Netherlands; paulien.adamse@wur.nl*

Received: 16 July 2013 / Accepted: 30 September 2013


**REVIEW ARTICLE**

## Abstract

A large number of wild and cultured plants produce secondary metabolites that can be toxic to humans and animals. The present study aims to provide insight into the routes of (un)intentional poisonings of humans by tropane alkaloids. Poisonings of humans by tropane alkaloids occur as unintended ingestions (contamination, mislabelling: thirteen reports; mistaken identity: eleven reports) or intended ingestions (overdoses: nine reports). Contamination of food occurs when toxic plant (parts) are accidentally mixed with edible plants during harvest or processing. Concentrations are usually highest in roots and seeds. Intended ingestions can be the result of consumption for recreational purposes (hallucinogenic effects) or for medical properties (e.g. treatment of arthritis, use as anaesthetic), or homicides and suicides. Carry-over of plant toxins in feed into food products of animal origin does not appear to be a relevant source of exposure. There are several analytical methods available for monitoring tropane alkaloids in food and feed but no regulatory limits have been set. The toxic doses are often not clear due to the lack of analytical data in the cases reported. Human foods that potentially contain tropane alkaloids are herbal teas, herbal preparations, blue- or black berries and edible flowers. Contamination has also been found in beans, buckwheat, soybean and linseed.

**Keywords:** contamination, exposure, human, overdose, tropane alkaloids

## 1. Introduction

A large number of wild and cultured plants produce secondary metabolites in concentrations that can harm human health when ingested. Accidental or intentional mixing of these plant (-parts) with food will expose the consumers to the toxins. While the risks of abuse of several plant toxins are well known, such as for ricin used in assassination attempts, insight in the relevance for day-to-day human health of most plant toxins is poor. Among the plant toxins of potential health concern to humans are various groups of alkaloids, including the tropane alkaloids (TAs). Recent incidents with intoxications by TAs in humans have pointed out the need for more information on the relevance for humans. This includes more information on the routes of exposure. The aim of this review is to study the incidents in humans in which TAs play a role to identify the main risks for human exposure in Europe and the possible ways to reduce risks. Background information on TAs is given to enable understanding of the incidents.

### Tropane alkaloids

TAs are a class of alkaloids that contain a tropane ring in their chemical structure (Figure 1). Over 200 compounds in this class are known (EFSA, 2008; Koleva *et al.,* 2011). Well known TAs are L-hyoscyamine and L-scopolamine (Figure 1). Atropine is often mentioned as an important TA as well. In pharmacology it is the racemic mixture of the L- and D-enantiomers of hyoscyamine, with L-hyoscyamine as the pharmaceutically active and toxicologically relevant form. Since most methods of analysis cannot separate the enantiomers, atropine is often used as a general indicator for L- (and D-)hyoscyamine, to express the toxic content of plants or preparations, without stating the enantiomeric composition.

Other TAs are known stimulants, such as cocaine and cocaine-related alkaloids. These will not be discussed in this review as these compounds are drugs of abuse and not related to food.

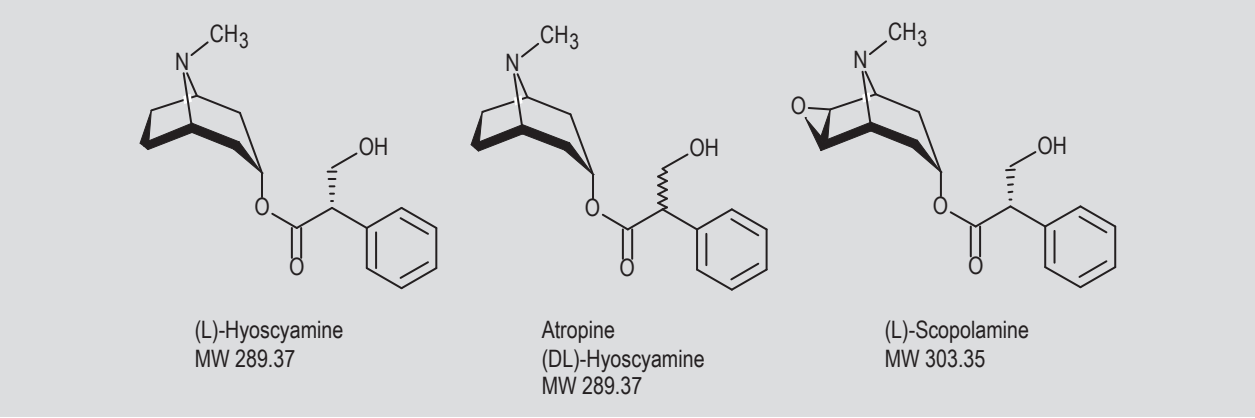


**Figure 1. Chemical structure of hyoscyamine, atropine and scopolamine.**

A novel group of very polar TAs, calystegines, was discovered in deadly nightshade (Biastoff and Dräger, 2007; Goldmann *et al.* 1990). Calystegines are synthesised by the plant partially by the same biosynthetic pathways as the scopolamine and hyoscyamine. However, no toxicological data are available for this group of compounds and for this reason they are not further discussed here. This paper will focus on scopolamine and atropine (L- and D-hyoscyamine).

## Plants containing tropane alkaloids

The TAs scopolamine and hyoscyamine naturally occur in plants of the families *Erythroxylaceae* (e.g. coca) and *Solanaceae* (e.g. mandrake, henbane, deadly nightshade, *Datura*, potato, tomato), *Proteaceae*, *Euphorbiaceae, Rhizophoraceae, Convolvulaceae* and *Cruciferae* (Table 1). Scopolamine and hyoscyamine are produced in significant amounts only in species of the *Solanaceae* family.

Various TAs can occur in the plant simultaneously and in all parts of the plants. Concentrations are usually highest in roots and seeds (Wagner and Keim, 2009). The concentration of each alkaloid present varies with species, season, geographic location, and part of plant. An extensive review on chemotaxonomy and geographical distribution of TAs has been presented by Griffin and Lin (2000). Few studies exist on lethal doses of TAs. In a study using seeds of jimsonweed obtained from different locations in the USA average concentrations of 2.3 and 0.5 mg/g seed of atropine and scopolamine, respectively, were detected (Russel *et al.,* 2010). Other sources (cited in EFSA, 2008) indicate levels of atropine, scopolamine or TAs in general between 1 and 9 mg/g seed. One jimsonweed seed weighs approximately 8 mg (EFSA, 2008), which means that approximately 100 seeds could contain up to 7 mg atropine.

## Effects of atropine and scopolamine in humans

The main effect of TAs is that they prevent binding of acetylcholine to its receptor. Since acetylcholine is an important neurotransmitter, this results in effects on heart rate, respiration and the central nervous system (anticholinergic poisoning). Both scopolamine and hyoscyamine are responsible for the toxic effects (Council of Europe, 2011).

## Medical uses

Both atropine and scopolamine have a long history of use as medicine (in non-toxic doses) against a variety of ailments worldwide. This varies from pupil dilation to treatment of nausea and motion sickness and treatment of intestinal cramping, heart problems and respiratory problems (Encyclopedia of chemistry; http://www.chemeurope.com/en/encyclopedia). For example, the name belladonna in *Atropa belladonna* (deadly nightshade) means beautiful woman, and refers to the past use of this plant in European medicine to dilate the pupils for aesthetic reasons (MedlinePlus, 2013). Thorn apple leaves used to be a component of 'asthma cigarettes' (Beltman *et al.*, 1999). Atropine is recommended in traditional Chinese medicine to treat arthritis (Lin and Chen, 2002).

## Toxic effects

While TAs administered in low doses can be beneficial for medical treatment, severe unwanted toxic effects can occur in case of overdosage. The effects described in the literature studied for this paper are presented in Tables 2-4. Effects most often reported on humans caused by toxic doses include dizziness, blurred vision, pupil dilation, dry mouth, red skin, vomiting, clouded consciousness, muscle spasms, low body temperature, hallucinations, delirium, tachycardia, and even death. Toxic effects usually occur within 60 minutes after ingestion and sublethal clinical symptoms may persist for up to 24 to 48 hours (Spina and Taddei, 2007).

**Table 1. Plants containing tropane alkaloids. The plant parts are sometimes mistaken for other (non-toxic) species and used in food and medications.**

| Plants | Tropane alkaloid | Plant parts |
|---|---|---|
| *Atropa belladonna* (deadly nightshade) | scopolamine, hyoscyamine, atropine | berry: resembles edible berries like *Vaccinium* (e.g. bilberry, blueberry, cranberry, huckleberry); leaf: resembles *Malva sylvestri*s (mallow); used in salads, soups or stuffed with bulgur or rice; root: generally the most toxic part (Biastoff and Dräger, 2007) |
| *Datura stramonium* (jimsonweed, devil's weed, thorn apple, tolguacha, Jamestown weed, stinkweed, datura, moonflower) | scopolamine, hyoscyamine, atropine | leaf: resembles Jew's mallow (Goto *et al.,* 1996 cited by Namera, 2005), nettle (*Utica*) (Scholz *et al.,* 1980), mallow (*Malva*) (Awang and Kindack, 1989), *Symphytum officinale* (comfrey) (Awang and Kindack, 1989, Oberlies *et al.,* 2004); used as tea; root: burdock (*Arcticum*) (Bryson *et al.,* 1978 cited by Awang and Kindack, 1989); root tea used traditionally as blood purifier, diuretic, curing skin problems; seed: mistaken for sesame; flower: resembles *Paulownia* (e.g. foxglove tree) (Houghton, 2004); used in salads (Van de Bovenkamp *et al.,* 2009) |
| *Datura suaveolens* (*Brugmansia suaveolens*, angel's trumpet) | scopolamine, hyoscyamine | leaf, flower, seed (CDC, 1984; Smith *et al.*, 1991) |
| *Datura tatula, metel* (jimsonweed, thorn apple). | ca. 0.1 mg atropine/seed. | leaf, flower, seed (Friedman and Levin, 1989) |
| *Duboisia myoporoides* (corkwood, leaves collected in New Caledonia) | scopolamine, atropine | leaf (Dufva *et al.* 1976) |
| *Erycibe henryi* Prain ('Ting Kung Ten'), a species of *Convolvulaceae* medicinal herb | tropane alkaloid | leaf, flower, seed (Lin and Chen, 2002) |
| *Hyoscyamus muticus* | scopolamine, hyoscyamine | extract from hairy roots (Häkkinen *et al.,* 2005) |
| *Hyoscyamus niger* (black henbane, stinking nightshade) | scopolamine, hyoscyamine, atropine | leaf, flower, seed (Van de Bovenkamp *et al.,* 2009) |
| *Latua pubiflora* (*Solanaceae*, Chile) | scopolamine, hyoscyamine | berry, leaf (Munoz and Casale, 2003) |
| *Lycium barbarum* (wolfberry, matrimony vine, Duke of Argyll's tea plant, goji berry) | atropine | berry (the content is below toxic levels, max. 19 µg/kg) (Adams *et al*., 2006) |
| *Mandragora officinarum* (mandrake) | scopolamine, hyoscyamine, atropine | root, berry (Griffin and Lin, 2000, Van de Bovenkamp *et al.,* 2009) |
| *Nicotiana tabacum* | scopolamine, hyoscyamine | extract from hairy roots (Häkkinen *et al.,* 2005) |
| *Scopolia carniolica* Jacq. | scopolamine, hyoscyamine, atropine | leaf, root (Ştefănescu *et al.,* 2006; Van de Bovenkamp *et al.,* 2009) |

Recommended antidotal treatments (counteracting the effects of a poison) are activated charcoal, benzodiazepines and physostigmine (Wagner and Keim, 2009).

### Presumed toxic levels of tropane alkaloids

Information on sub-lethal or lethal dosages of TAs in humans is, almost without exception, obtained in an indirect way via assumptions on ingested amounts of seeds/plant and concentrations of TAs in the seeds/plants. In addition, individuals may vary in susceptibility to TAs (http://www.medicinescomplete.com/mc/martindale/current/). The toxic effects also depend upon whether and when an antidote has been administered. Martindale (http://www.medicinescomplete.com/mc/martindale/current/) reports lethal atropine dosages to be 100 mg or less for adults and 10 mg for children, when not treated with an antidote such as physostigmine to reverse the anticholinergic toxicity. Bracher *et al* (2011) report lethal dosages of atropine sulphate of 100 mg (equivalent to 83 mg atropine) for adults and 2 mg for children when administered orally. However, Marquardt and Schäfer (2004) estimate that the lethal doses for orally administered atropine ranges from 10 to 20 mg/kg body weight for adults and from 1 to 10 mg/kg b.w. for children. Based on adult weight of 60 kg, this means a lethal dosage of atropine of 600-1,200 mg per adult. According to

**Table 2. Cases of human poisoning due to contamination or mislabelling of foods and medication with plants containing tropane alkaloids (TAs).**

| Reference | Country, date (product, contamination/ mislabelling, plant part) | Incident |
|---|---|---|
| RASFF[1]; Finland Times (2013) | Finland, 2013 (vegetable-bean-seed, contamination, seed) | *Datura* seeds in frozen vegetable-bean-seed mix from Belgium, with raw material from Spain. Poisoning of several people in Finland after consuming the frozen vegetable product. |
| Department of Health (2012) | Hong Kong, 2012 (medication, mislabelling) | Patients were given toxic *Flos Daturae Metelis* (dried flowers of *Datura metel*) instead of benign *Flos Campsis* (dried flowers of *Campsis grandiflora*). |
| Shea (2012) | Hong Kong, 2011 (medication, mislabelling and contamination) | Using toxic *Strobilanthes forrestii* Diels instead of benign *Cyathula officinalis* Kuan by herbalist due to the similar Chinese nomenclature. *S. forrestii* Diels was contaminated with TAs during processing. |
| Department of Health and Sports (2010) | France, 2010 (beans, contamination, bud) | *Datura stramonium* in canned green beans. Poisoning of three people after consuming the preservatives contaminated with buds of *D. stramonium*. |
| Fretz *et al.* (2007) | Austria, 2006 (flour, contamination, seed) | Millet-carrots balls containing *D. stramonium* seeds (50 seeds/kg of grain). Eight persons suffered an intoxication mimicking *Bacillus cereus* food poisoning. |
| Perharič (2005); Perharič *et al.* (2013) | Slovenia, 2003 (flour, contamination, seed) | Contamination of buckwheat flour with seeds from *D. stramonium*. In September 2003, cases of domestic food poisoning with a typical syndrome of TA toxicity occurred. The whole buckwheat grain contained up to 190 *D. stramonium* seeds/kg of grain. After further investigation it was estimated that 0.7-137.6 µg atropine/kg body weight and 0.4-63.5 µg scopolamine/kg bw had been ingested. |
| Ramirez *et al*. (1999) | Venezuela, 1999 (honey, contamination, plant part unknown) | Wasp honey contaminated with TAs. Fifteen persons developed atropine poisoning after consumption of wasp honey. TA poisoning was established due to typical clinical signs, antidotal response and the presence of *Datura* plants near the wasp nests. |
| CDC (1995b) | USA, 1994 (tea, contamination, plant part unknown) | Commercial Paraguay tea (*Ilex paraguariensis*) containing TAs. Seven cases of anticholinergic poisoning in 3 families were reported. |
| Routledge and Spriggs (1989) | Great Britain, 1989 (tea, contamination, plant part unknown) | Atropine as possible contaminant of comfrey (*Symphytum*) tea which was recommended as cure for flatulence. |
| Galizia (1983) | Great Britain, 1983 (tea, contamination, plant part unknown) | Atropine (through *Datura*) as possible contaminant of comfrey tea. |
| Awang and Kindack (1989) | Canada, 1981, 1984 (berries, contamination, plant part unknown) | Mallow (*Malva sylvestris*) poisoning due to presence of berries of *Atropa belladonna* (deadly nightshade). |
| Scholz *et al.* (1980) cited by Awang and Kindack (1989) | Austria, 1980 (tea, contamination, plant part unknown) | Nettle (*Urtica*) tea poisoning. One person was intoxicated after drinking stinging nettle tea supposedly contaminated with elements of 'belladonna' (*Atropa belladonna*). |
| Bryson *et al.* (1978) cited by Awang and Kindack (1989) | USA, 1978 (tea, contamination, plant part unknown) | Burdock (*Arcticum*) root tea poisoning. One person suffered acute atropine-like poisoning after drinking burdock tea. |
| Van der Heide (1988) | Germany, 1988 (tea, mislabelling, leaves) | Tea from *D. stramonium*. A 10 year old girl was intoxicated after drinking tea prepared from dried *D. stramonium* (thorn apple) leaves. The product was intended for inhalation (asthmatic cigarettes) but was mislabelled as tea. |

[1] Rapid Alert System for Food and Feed, an online searchable database from DG SANCO. Available at: https://webgate.ec.europa.eu/rasff-window/portal/.

**Table 3. Cases of poisoning due to mistaken identity of plants and plant parts containing tropane alkaloids (TAs).**

| Reference | Country, date (product, plant part) | Incident |
|---|---|---|
| NVWA (2013) | Netherlands, 2013 (tea, root) | Dried root of *Atropa belladonna* (deadly nightshade) was mistaken for marshmallow root tea (*Althaea*). Four persons were admitted to the hospital after drinking what they thought was marshmallow root tea (one sample contained 1,100 mg/kg hyoscyamine). |
| Papoutsis *et al.* (2012) | Greece, 2012 (cooked vegetables, leaves) | Seven individuals were admitted to a hospital after consumption of cooked vegetables (blites) also containing similar looking Datura innoxia. |
| Amini *et al.* (2012) | Iran, 2008-2011 (product unknown, flowers) | Intoxication by *Datura stramonium*. Nineteen patients were hospitalised during this time period after ingesting *D. stramonium*. Children suffered more severe effects than teenagers and poisoning in adults was rare. All of the children ingested the plant accidentally. |
| Tsiligianni *et al.* (2009) | Greece, 2009 (meal, plant) | Two adults were poisoned after eating a meal which accidentally contained Mandragora officinarum instead of the commonly used Borago officinalis. |
| Russell *et al*. (2010) | USA, 2008 (stew, leaves) | Supposedly *Datura* leaves in stew. A family of six was poisoned after eating stew contaminated with jimsonweed (*D. stramonium*). The leaves for the stew were picked from the backyard. |
| Houghton (2004) | China, before 2004 (product unknown, flowers) | Tropane alkaloid poisoning due to prescription of the wrong herb. *Datura metel* flowers had been supplied instead of flowers from *Paulownia* species (foxglove tree). |
| Chang *et al*. (1999) | Taiwan, 1999 (product unknown, leaves) | Poisoning by TAs from *Datura* leaves. *Datura* leaves were used as edible wild vegetables. |
| Goto *et al.* (1996) cited by Namera (2005) | Japan, 1996 (root, seeds) | Intoxications by TAs in various plant parts of *Datura*. *D. metel* was mistaking for Jew's mallow; its root was consumed instead of burdock and the seeds were mistaken for sesame seeds. |
| Kimura (1995) cited by Namera (2005) | Japan, 1995 (product unknown,leaves) | Intoxication after preparing *Datura* leaves as vegetable. A 71-year-old female mistook *Datura* for Jew's mallow. The same plant as that eaten by her was examined by a specialist and proved to be *Datura tatula*. |
| Pereira and Nishioka (1994) | Brazil, 1994 (product unknown, leaves) | Poisoning by the use of *Datura leaves* in a homemade toothpaste. |
| CDC (1984) | Canada, 1983 (product unknown, seeds) | Intoxication after consumption of *Datura* seeds. In preparing hamburgers the cook had mistakenly seasoned the patties with seeds from Angels' Trumpets (*Datura suaveolens*) laying to dry over the stove. |

a Morbidity and Mortality Weekly Report of the Centers for Disease Control (CDC) the estimated lethal dose of atropine in humans is 10 mg and 2-4 mg of scopolamine (CDC, 1995b). The European Medicines Agency (EMA, formerly EMEA) reported in 1998 that the intake of 2 to 5 berries of deadly nightshade by children and 10 to 20 berries by adults could be lethal (EMEA, 1998).

Only a few cases are reported where TA levels were determined after the intoxication. An 18-year-old male died after ingesting an unknown number of atropine tablets containing 30 mg per tablet. The atropine concentration in his whole blood was 0.2 µg/ml (Baselt and Cravey, 1995 cited by Namera, 2005). A 6-year-old boy died 8 hours after ingesting an unknown amount of *Datura stramonium* seeds (Al-Shaikh and Sablay, 2005). His blood concentrations of hyoscyamine and scopolamine were 1.1 and 0.2 µg/ml, respectively; in his urine only hyoscyamine at 14.2 µg/ml was found (Boumba *et al*., 2004).

### Routes of contamination

The most often reported route of ingestion by humans is as a tea, although ingesting seeds or other plant parts and smoking dried leaves also are common (Beltman *et al*., 1999). Jimsonweed (or Jamestown weed) is named for a case of human poisoning in 1676 in Jamestown, VA, USA, when soldiers were accidentally poisoned by eating the plant in a salad. They subsequently suffered delirium and hallucinations (Beverly, 1705). Also toothpaste mixed with the leaves and flowers of *Datura sp.* (Pereira and Nishioka, 1994) and homemade wine with *Datura sp*. have been reported as vehicles of intoxication (Smith *et al.,* 1991).

### Exposure through animal products

Theoretically, humans may be exposed to TAs through animal product such as milk and meat. Contamination of these products results from occurrence of TAs in

**Table 4. Cases of poisoning due to overdoses of plants containing tropane alkaloids.**

| Reference | Country, date | Incident |
|---|---|---|
| Nikolaou *et al.* (2012) | Greece, 2010 | An adult male was intoxicated after consuming 5 berries of *Mandragora officinarum* to enhance his sexual performance. |
| Wagner and Keim (2009) | USA, 2005 | None of the 975 anticholinergic plant poisonings reported to the American Association of Poison Control Centers in 2005 were fatal. |
| Al-Shaikh and Sablay (2005) | Kingdom of Saudi Arabia, 2005 | Intoxication by ingestion of seeds of *Datura* plant by a 6 year old boy. |
| Boumba *et al.* (2004) | Greece, 2004 | Lethal intoxication after intentional consumption of *Datura* seeds for hallucinogenic purposes by a 19-year old male. |
| Lin and Chen (2002) | Taiwan, 2002 | Intoxication after ingestion 30 g of raw stem of 'Ting Kung Teng' (*Erycibe henryi* Prain) he picked from a hillside, as recommended in traditional Chinese medicine to treat arthritis. |
| Tiongson and Salen (1998) | USA, 1998 | Approximately 50 *Datura stramonium* seeds caused hallucinations for 36 hours in an 18-year-old adolescent. |
| Koevoets and van Harten (1997) | the Netherlands, 1997 | Intoxication after intentional consumption of thorn apple seeds for hallucinogenic purposes by a 20-year old male. |
| Baselt and Cravey (1995) cited by Namera (2005) | USA, 1995 | A pharmacy college student (male) ingested about 1 g of atropine together with alcohol; he was sent to a hospital and survived. His blood atropine concentration was 0.13 µg/ml. |
| Baselt and Cravey (1995) cited by Namera (2005) | USA, 1995 | Lethal intoxication of an 18-year-old male after ingestion of atropine tablets (30 mg per tablet, unknown number). The atropine concentration in his whole blood was 0.2 µg/ml. |
| CDC (1995a) | USA, 1994 | Lethal intoxication of two young adolescents after drinking tea brewed from a mixture of roots from a jimsonweed plant and alcoholic beverages. |
| Smith *et al.* (1991) | USA, 1991 | Intoxication by scopolamine due to unlikely high levels present. *Datura suaveolens*, Angel's trumpet, was intentionally used for making wine. The filtered wine contained an estimated 29 mg scopolamine/ml, which resulted in an estimated ingested dose of 435 mg scopolamine from three tablespoons of wine (15 ml). No atropine was detected. |

animal feed. There are a few examples of carry-over after feeding animals feed supplemented with scopolamine and hyoscyamine or after injecting the animals with scopolamine. The EMEA (EMEA, 1997) reports a rapid depletion of residues of scopolamine (butylscopolaminium bromide) in tissues and milk from horses, pigs and cattle. After feeding hens for three months with a standard diet supplemented with scopolamine and hyoscyamine only traces of the compounds were found in the eggs (Kovatsis *et al.*, 1994). No information is available on metabolites.

## Effects of processing

TAs are relatively heat stable. The baking process used in making bread of wheat contaminated with jimsonweed seeds (*D. stramonium*) reduced the TA concentration with 0-28% (Friedman and Levin, 1989). On the other hand, boiling of contaminated buckwheat flour to prepare žganci, a porridge-like meal made of buckwheat, reduced the concentration of atropine and scopolamine with 60 and 40%, respectively (Perharič *et al.*, 2013).

## Methods of analysis

Numerous methods are available for detecting TAs in plant materials and food. Some of those methods are applicable for biological samples (eggs, blood serum and urine) as well. Most described methods are based on High-performance liquid chromatography (HPLC), gas-chromatography or capillary electrophoresis separation techniques in combination with utraviolet, mass spectrometry (MS) or tandem mass spectrometry (MS/MS) detection (Aehle and Dräger, 2010; Beyer *et al.,* 2009; Caligiani *et al.*, 2011; Cataldi and Bianco 2008; Dräger, 2002; EFSA, 2008; Mateus *et al.,*1999; Munoz and Casale, 2003; Namera, 2005; Perharič *et al.*, 2013; Steenkamp *et al.,* 2004). TAs are extracted from the matrix with aqueous or organic solvents at acidic or alkaline pH (Dräger, 2002; Namera *et al.*, 2002). Liquid-liquid or solid phase extraction is sometimes applied for additional purification and concentration (Dräger, 2002; Mroczek *et al.,* 2006). The L- and D-enantiomers of hyoscyamine in atropine can be separated by using chiral HPLC columns (Adams *et al.*, 2006; Aehle and Dräger, 2010; Breton *et al.*, 2005; Cieri, 2005; Mateus *et al.*, 2000; Wedig and Holzgrabe, 1999). LC-MS/MS for the determination of TAs (atropine and scopolamine) in grains and in (compound) animal feeds is one of the currently favoured techniques. The limits of

quantification reported are between 0.001 and 0.1 µg/ml in human serum (e.g. Aehle and Dräger, 2010, Namera *et al*., 2002). A dipstick method has been developed for hyoscyamine and scopolamine with a target level of 800 µg/kg for the sum of both components (Van Egmond *et al.*, unpublished data).

### Legislation on tropane alkaloids in the European Union

There is currently no EU-legislation on the TA levels in food. EU Directive 2002/32/EC states that animal feed is allowed to contain weed seeds and unground and uncrushed fruits containing alkaloids, glucosides or other toxic substances separately or in combination with a maximum level of 3,000 mg/kg, including *Datura sp.* with a maximum level of 1000 mg/kg (EC, 2002). The Netherlands has placed the *Datura* plants on a 'forbidden herbs' list, excluding it from use in food (commodities act decree on herbal preparation [in Dutch: warenwetbesluit kruidenpreparaten], Ministry of Health, Welfare and Sport, 2001). EFSA is currently (2013) preparing an opinion on TAs in food and feed. This may result in an advice on need for regulation on the TA levels in food.

## 2. Tropane alkaloid poisoning incidents

Scientific literature was reviewed for described cases of TA poisoning in humans. Literature was only included when the original article could be accessed. However, in a few cases when the original reference was not accessible anymore the scientific paper citing from this reference has been included. This is noted in the reference.

### Human intoxications with tropane alkaloids due to contamination of food or through mislabelling of food

There are various reports on cases of human poisoning due to contamination or mislabelling of foods with plants containing TAs (Table 2). In the thirteen reports studied, covering the period 1988 to 2012 and ten countries, at least five of these intoxications were caused by contaminated or mislabelled tea. Contamination with TAs has also been found in buckwheat (Perharič, 2005; Perharič *et al.*, 2013). Buckwheat is mainly used for human consumption in flour for yeast dough, pancakes or pasta, or broken as buckwheat groats. In health food stores buckwheat is also sold as kernels. Buckwheat is often recommended in diets for celiacs since it does not contain gluten. Roasted buckwheat grains are also known as 'kasha' and are known from the Eastern European cuisine. The European Commission has created a database containing all notifications from the control authorities of all Member States regarding serious health risks deriving from food or feed, the Rapid Alert System for Food and Feed (RASFF). Between 2006 and the first half of 2013 eleven alerts and notifications were reported on the presence of *D. stramonium* seeds in millet, canned green beans, frozen vegetables-bean-seed mix and sunflower seeds intended for food or feed (EFSA, 2008). Also bulk commercial commodities, such as soybeans, linseed and wheat, may be contaminated by impurities, including jimsonweed seeds, which may coexist with the harvested crop (Friedman and Levin, 1989).

### Poisoning due to mistaken identity

Intoxications due to mistaken plant identity when preparing food or homemade medicines are presented in Table 3. A total of eleven reports have been studied, covering the period 1984 to 2013 and nine countries. Intoxications were due to ingestion of prepared leaves, roots, berries or seeds of *Datura* that were mistaken for fox glove tree or Jew's mallow (leaves), burdock (root) or sesame (seeds) and of leaves from *Mandragora officinarum* erroneously taken for the commonly used edible *Borago officinalis*.

### Poisoning due to intentional ingestion

Plants containing TAs are sometimes ingested to experience their hallucinogenic effects, presumed medicinal effects or to commit suicide (Table 4). Of the nine reports studied, covering the period 1991 to 2005 and five countries, at least two reported fatalities.

## 3. Conclusions and recommendations

Exposure of humans to TAs (poisoning) can be caused by unintended ingestions (contamination, mistaken botanical identity, carry-over), intended ingestions (medical use), and poisoning due to abuse of plant material (overdoses).

Unintended ingestions often occur in children or from a mix-up of plants and mushrooms in adults. They are usually caused by mistaken identity or mislabelling of commercially available products. The mislabelling of pure *Datura* tea or medicine can cause serious health problems and might be lethal. Increasingly common is the abuse of plants for hallucinogenic reasons, 'recreational use' (Beyer *et al,.* 2009). Carry-over from feed to animals products does not seem to be a relevant route of exposure of humans.

Secondary metabolites in wild and cultured plants can be toxic to humans and animals. Due to accidental or intentional mixing of these plants in food or feed the consumers of these products will be exposed to the toxins. Based on the incidents described in this paper it is to be expected that foods potentially (and unintentionally) containing TAs would be herbal teas, herbal preparations, traditional Chinese or Ayurvedic medicines (Van de Bovenkamp *et al.,* 2009), blue- or blackberries (either fresh or dried) and edible flowers. Contamination with TAs has also been found in buckwheat (for human consumption), soybean and linseed (animal feed) (EFSA,

2008; Perharič, 2005). It can be expected that TAs occur in low concentrations when bulk food is contaminated. Plants containing TAs have also been used in homemade products like wine and toothpaste, but these products are not likely to be sold commercially.

It is advised to monitor buckwheat and millet for TAs to prevent accidental exposure of humans. Tea should be at a higher level of control since mislabelling may result in exposure to extremely high doses of TAs. Methods to determine levels of TAs in blood and urine should be improved and implemented. With appropriate biomarkers potential TA-exposure could be monitored.

## Acknowledgments

This work was carried out within the RIKILT project 'Method development and analysis of mycotoxins and plant toxins in food (1207272001)' with financial support of the Netherlands Food and Consumer Product Safety Authority of the Ministry of Economic Affairs.

## References

Adams, M., Wiedenmann, M., Tittel, G. and Bauer, R., 2006. HPLC-MS trace analysis of atropine in *Lycium barbarum* berries. Phytochemical Analysis 17: 279-283.

Aehle, E. and Dräger, B., 2010. Tropane alkaloid analysis by chromatographic and electrophoretic techniques: an update. Journal of Chromatography B 878: 1391-1406.

Amini, M., Khosrojerdi, H. and Afshari, R., 2012. Acute *Datura stramonium* poisoning in East of Iran - a case series. Avicenna Journal of Phytomedicine 2: 86-89.

Al-Shaikh, A.M. and Sablay, Z.M., 2005. Hallucinogenic plant poisoning in children. Saudi Medical Journal 26: 118-121.

Awang, D.V.C. and Kindack, D.G., 1989. Atropine as possible contaminant of comfrey tea. The Lancet 334: 44.

Beltman, W., Van Riel, A.J.H.P., Wijnands-Kleukers, A.P.G., Vriesman, M.F., Van den Hengel-Koot, I.S., De Vries, I. and Meulenbelt, J., 1999. Smartshops – Smart shops: a survey of products, claimed effects and medical-toxicological relevance. RIVM report 348802 017 [in Dutch]. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands.

Beverly, R., 1705. The history and present state of Virginia, in four parts (University of North Carolina). Book II. The natural product and conveniencies in its unimprov'd state, before the English went thither. p. 24. Available at: http://docsouth.unc.edu/southlit/beverley/beverley.html.

Beyer, J., Drummer, O.H. and Maurer, H.H., 2009. Analysis of toxic alkaloids in body samples. Forensic Science International 185: 1-9.

Biastoff, S. and Dräger, B., 2007. Calystegines. In: Cordell, G.A. (ed.) The alkaloids, volume 64. Academic Press, New York, NY, USA, pp. 49-102.

Boumba, V.A., Mitselou, A. and Vougiouklakis, T., 2004. Fatal poisoning from ingestion of *Datura stramonium* seeds. Veterinary and Human Toxicology 46: 81-82.

Bracher, F., Heisig, P., Langguth, P., Mutschler, E., Rücker, G., Scriba, G., Stahl-Biskup, E. and Troschütz, R., 2011. Kommentar zum Europäischen Arzneibuch [Commentary to the Pharmacopoeia Europaea]. Atropini sulfas, Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany.

Breton, D., Buret, D., Clair, P. and Lafosse, M., 2005. Chiral separation of atropine by high-performance liquid chromatography. Journal of Chromatography A 1088: 104-109.

Caligiani, A., Palla, G., Bonzanin, F., Bianchi, A. and Bruni, R., 2011. A validated GC-MS method for the detection of tropane alkaloids in buckwheat (*Fagopyron esculentum* L.) fruits, flours and commercial foods. Food Chemistry 127: 204-209.

Cataldi, T.R. and Bianco, G., 2008. Capillary electrophoresis of tropane alkaloids and glycoalkaloids occurring in *Solanaceae* Plants. Methods in Molecular Biology 384: 171-203.

Centers for Disease Control (CDC), 1984. *Datura* poisoning from hamburger-Canada. Morbidity and Mortality Weekly Report 33: 282-283.

Centers for Disease Control (CDC), 1995a. Epidemiologic notes and reports jimson weed poisoning – Texas, New York, and California, 1994. Morbidity and Mortality Weekly Report 44: 41-44.

Centers for Disease Control (CDC), 1995b. Anticholinergic poisoning associated with a herbal tea – New York City, 1994. Morbidity and Mortality Weekly Report 193-195.

Chang, S.S., Wu, M.L. and Deng, J.F., 1999. Poisoning by *Datura* leaves used as edible wild vegetables. Veterinary and Human Toxicology 41: 242-245.

Cieri, U.R., 2005. Identification and estimation of the levo isomer in raw materials and finished products containing atropine and/or hyoscyamine. Journal of AOAC International 88: 1-4.

Department of Health, 2012. Anticholinergic poisoning. Poisoning Watch 5, number 1. Available at: http://www.chp.gov.hk/files/pdf/poisoning_watch_vol5_eng_20121231.pdf.

Department of Health and Sports, France, 2010. Presence of *Datura stramonium* in canned green beans [in French]. Available at: http://www.sante-sports.gouv.fr/rappel-de-produits-presence-de-datura-stramonium-dans-des-conserves-de-haricots-verts-des-marques-u-et-notre-jardin.html.

Dräger, B., 2002. Analysis of tropane and related alkaloids. Journal of Chromatography A 978: 1-35.

Dufva, E., Loison, G. and Holmstedi, B., 1976. Native antidote against ciguatera poisoning. Toxicon 14: 55-64.

European Commission (EC), 2002. Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. Official Journal of the European Union L 140: 10.

European Food Safety Authority (EFSA), 2008. Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on tropane alkaloids (from *Datura sp.*) as undesirable substances in animal feed. The EFSA Journal 691: 1-55.

European Medicines Agency (EMEA), 1997. Butylscopolaminium bromide summary report. EMEA/MRL/244/97-Final. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500011136.pdf.

Council of Europe , 2011. European pharmacopoeia, 7th Ed. Council of Europe, Strasbourg, France. Available at: http://online.edqm.eu/EN/entry.htm.

European Medicines Agency (EMEA), 1998. *Atropa belladonna* summary report. EMEA/MRL/540/98-Final. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500010731.pdf.

Finland Times, 2013. Sale of toxic Valio product also banned; 3 more poisoned by Rainbow toxic vegetables. Available at: http://www.finlandtimes.fi/national/2013/05/24/1155/Sale-of-toxic-Valio-products-also-banned/print.

Fretz, R., Schmid, D., Brueller, W., Girsch, L., Pichler, A.M., Riediger, K., Safer, M. and Allerberger, F., 2007. Food poisoning due to jimson weed mimicking *Bacillus cereus* food intoxication in Austria, 2006. International Journal of Infectious Diseases 11: 557-558.

Friedman, M. and Levin, C., 1989. Composition of jimson weed *(Datura stramonium*) seeds. Journal of agricultural and food chemistry 37: 998-1005.

Galizia, E., 1983. Clinical curio hallucinations in elderly tea drinkers. British Medical Journal 287: 979.

Goldmann, A., Milat, M.L., Ducrot, P.H., Lallamand, J.Y., Maille, M., Lepingle, A., Charpin, I. and Tepfer, D., 1990. Tropane derivatives from *Calystegia sepium*. Phytochemistry 29: 2125-2127.

Griffin, W.J. and Lin, G.D., 2000. Chemotaxonomy and geographical distribution of tropane alkaloids. Phytochemistry 53: 623-637.

Häkkinen, S.T., Moyano, E., Cusidó, R.M., Palazón, J., Pinõl, M.T. and Oksman-Caldentey, K-M., 2005. Enhanced secretion of tropane alkaloids in *Nicotiana tabacum* hairy roots expressing heterologous hyoscyamine-6b-hydroxylase. Journal of Experimental Botany 56: 2611-2618.

Houghton, P., 2004. UK needs greater expertise in TCM. The Pharmaceutical Journal 273: 125.

Koevoets, P.F. and Van Harten, P.N., 1997. Thorn apple poisoning [in Dutch]. Netherlands Tijdschrift voor de Geneeskunde 141: 888-889.

Koleva, I.I., Van Beek, T.A., Soffers, A.E., Dusemund, B. and Rietjens, I.M., 2011. Alkaloids in the human food chain--natural occurrence and possible adverse effects. Molecular Nutrition and Food Research 56: 30-52.

Kovatsis, A., Kotsaki-Kovatsi, V.P., Nikolaidis, E., Flaskos, J., Tzika, S. and Tzotzas, G., 1994. The influence of *Datura ferox* alkaloids on egg-laying hens. Veterinary and Human Toxicology 36: 89-92.

Lin, C.C. and Chen, J.C., 2002. Medicinal herb *Erycibe henri* Prain ('Ting Kung Teng') resulting in acute cholinergic syndrome. Journal of Toxicology – Clinical Toxicology 40: 185-187.

Marquardt, H. and Schäfer, S., 2004. Lehrbuch der Toxikologie, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany.

Mateus, L., Chekaoui, S., Christen, P. and Veuthey, J.-L., 1999. Capillary electrophoresis-diode array detection – electrospray mass spectrometry for the analysis of selected tropane alkaloids in plant extracts. Electrophoresis 20: 3402-3409.

Mateus, L., Chekaoui, S., Christen, P. and Veuthey, J.-L., 2000. Enantioseparation of atropine by capillary electrophoresis using sulphated β-cyclodextrin: application to a plant extract. Journal of Chromatography A 868: 285-294.

MedlinePlus, 2013. Belladonna. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/natural/531.html.

Ministry of Health, Welfare and Sport, the Netherlands, 2001. Decree herbal preparations BWBR0012174. [in Dutch: Warenwetbesluit Kruidenpreparaten] Availabe at: http://wetten.overheid.nl/BWBR0012174/.

Mroczek, T., Glowniak, K. and Kowalska, J., 2006. Solid-liquid extraction and cation-exchange solid-phase extraction using a mixed-mode polymeric sorbet of *Datura* and related alkaloids. Journal of Chromatography A 1107: 9-18.

Munoz, O. and Casale, J.F., 2003. Tropane alkaloids from *Latua pubiflora*. Zeitschrift für Naturforschung 58: 626-628.

Namera, A., 2005. Tropane alkaloids. In: Suzuki, O. and Watanabe, K. (eds.). Drugs and poisons in humans, a handbook of practical analysis. Springer, Berlin, Heidelberg, Germany, pp. 509-517.

Namera, A., Yashiki, M., Hirose, Y., Yamaji, S., Tani, T. and Kojima, T., 2002. Quantitative analysis of tropane alkaloids in biological materials by gas chromatography-tandem mass spectrometry. Forensic science international 130: 34-43.

Netherlands Food and Consumer Product Safety Authority (NVWA), 2013. Herbal tea Jacob Hooy possibly contaminated with poisonous herb. Press release from NVWA [in Dutch]. Available at: http://www.nvwa.nl/actueel/nieuws/nieuwsbericht/2029501/kruidenthee-jacob-hooy-waarschijnlijk-verontreinigd-met-giftig-kruid.

Nikolaou, P., Papoutsis, I., Stefanidou, M., Dona, A., Maravelias, C., Spiliopoulou, C. and Athanaselis, S., 2012. Accidental poisoning after ingestion of 'aphrodisiac' berries: diagnosis by analytical toxicology. Journal of Emergency Medicine 42: 662-625.

Oberlies, N.H., Kim, N.-C., Brine, D.R., Collins, B.J., Handy, R.W., Sparacino, C.M., Wani, M.C. and Wall, M.E., 2004. Analysis of herbal teas made from the leaves of comfrey (*Symphytum officinale*): reduction of N-oxides results in order of magnitude increases in the measurable concentration of pyrrolizidine alkaloids. Public Health Nutrition 7: 919-924.

Papoutsis, I., Nikolaou, P., Athanaselis, S., Stefanidou, M., Pistos, C., Spiliopoulou, C. and Maravelias, C., 2010. Mass intoxication with *Datura innoxia*-case series and confirmation by analytical toxicology. Clinical Toxicology 48: 143-145.

Pereira, C.A.L. and Nishioka, S. de A., 1994. Poisoning by the use of *Datura* leaves in a homemade toothpaste. Journal of Toxicology – Clinical Toxicology 32: 329-331.

Perharič, L., 2005. Mass tropane alkaloid poisoning due to buckwheat flour contamination. Clinical toxicology 43: 413.

Perharič, L., Koželj, G., Družina, B. and Stanovnik, L., 2013. Risk assessment of buckwheat flour contaminated by thorn-apple (*Datura stramonium* L.) alkaloids: a case study from Slovenia. Food Additives and Contaminants, Part A 30: 321-330.

Ramirez, M., Rivera, E. and Ereu, C., 1999. Fifteen cases of atropine poisoning after honey ingestion. Veterinary and Human Toxicology 41: 19-20.

Routledge, P.A. and Spriggs, T.L.B., 1989. Atropine as possible contaminant of comfrey tea. The Lancet 333: 963-964.

Russel, J., Edwards, C., Jordan, C., Luckman, E., Chu, A., Blythe, D. and Krick, J., 2010. Jimsonweed poisoning associated with a homemade stew – Maryland, 2008. Morbidity and Mortality Weekly Report 59: 102-104.

Scholz, H., Kascha, S. and Zingerle, H., 1980. Atropin-poisoning from 'health tea' [in German]. Fortschritte der Medizin 98: 1525.

Shea, Y.-F., Chow, T.-Y.A., Chiu, P.K.-C., Chan, C.-K., Mak, T.W.L. and Chu, L.-W., 2012. Delirium due to herbal tea contaminated with tropane alkaloid. Journal of Clinical Gerontology and Geriatrics 3: 110-112.

Smith, E.A., Meloan, C.E., Pickell, J.A. and Oehme, F.W., 1991. Scopolamine poisoning from homemade 'moon flower' wine. Journal of Analytical Toxicology 15: 216-219.

Spina, S.P. and Taddei, A., 2007. Teenagers with jimson weed (*Datura stramonium*) poisoning. Canadian Journal of Emergency Medicine 9: 467-469.

Steenkamp, P.A., Harding, N.M., Van Heerden, F.R. and Van Wyk, B.-E., 2004. Fatal *Datura* poisoning: identification of atropine and scopolamine by high performance liquid chromatography/photodiode array/mass spectrometry. Forensic Science International 145: 31-39.

Ştefănescu, C., Deliu, C., Vlase, L., Tămaş, M. and Leucuţa, S., 2006. Studies on *Scopolia carniolica* Jacq. from the spontaneous flora and *in vitro* cultures. In: Proceedings of the 3rd conference of the Medicinal and Aromatic Plants of Southeast European Countries. September 5-8, 2004. Nitra, Slovak Republic. Available at: http://www.amapseec.org/Proceedings_Nitra.pdf.

Tiongson, J. and Salen, P., 1998. Mass ingestion of jimson weed by eleven teenagers. Delaware Medical Journal 70: 471-476.

Tsiligianni, I.G., Vasilopoulos, T.K., Papadokostakis, P.K., Arseni, G.K., Eleni, A. and Lionis, C.D., 2009. A two cases clinical report of *Mandragora* poisoning in primary care in Crete, Greece: two case report. Cases Journal 2: 9331.

Van de Bovenkamp, M., Jeurissen, S.M.F., Pelgrom, S.M.G.J., Spijkerboer, H.N., Van Riel, A.J.H.P., De Kaste, D., Baars, A.J. and Pronk, M.E.J., 2009. Evaluation of the health risks associated with so-called banned herbs. RIVM report 320011002 [in Dutch]. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands.

Van der Heide, R.M., 1988. Poisoning with 'Hustentee' [in Dutch]. Nederlands Tijdschrift voor Geneeskunde 132: 1993.

Wagner, R.A. and Keim, S.M., 2009. Tropane alkaloid poisoning. Available at: http://emedicine.medscape.com/article/816657-diagnosis.

Wedig, M. and Holzgrabe, U., 1999. Enantioseparation of tropa alkaloids by means of anionic cyclodextrin-modified capillary electrophoresis. Electrophoresis 20: 1555-1560.