

CBRN NEWS

Tropane alkaloids and the potential for accidental or non-accidental mass outbreaks of anti-cholinergic toxidrome

David J Heslop¹¹ School of Population Health, University of New South Wales, Sydney, Australia

Abstract

In December 2022 a large outbreak of anti-cholinergic toxidrome was reported in Australia associated with contamination of baby spinach leaves with *Datura stramonium*. Over 100 individuals around Australia experienced symptoms consistent with intoxication with the primary plant derived tropane alkaloids scopolamine, hyoscyamine and atropine. Tropane alkaloids are part of a wider group of incapacitating chemical substances that includes the chemical weapon BZ that results in the characteristic anti-cholinergic toxidrome. Human food production and manufacturing processes are prone to accidental and non-accidental contamination with tropane alkaloids, and food quality standards and measures are essential to protecting food security where incorporation of tropane alkaloids is possible. While mass non-accidental contamination of human food production and manufacture is a possibility, historically exposure scenarios involving tropane alkaloids have usually been limited to small scale poisoning events dating back to antiquity. This article summarises the risks of accidental and non-accidental exposure to tropane alkaloids with particular focus on the potential for mass exposure events.

Keywords

Atropine, Scopolamine, Hyoscyamine, Tropane Alkaloids, CBRNE, Anti-cholinergic Toxidrome, Mass poisoning

Background

On 17 December 2022, Food Standards Australia and New Zealand issued a consumer alert and product recall notice for products containing potentially contaminated baby spinach (1–3). As of 19 December 2022, over one hundred individuals in Australia have presented to health facilities with symptoms consistent with anti-cholinergic toxidrome (4). Common symptoms were reported as hallucinations, delirium, and unusual behaviour, with the age of the affected population ranging from children through to older adults across a number of Australian States and Territories. At the early stages of the investigation, contamination of the baby spinach production or supply chain with “toxic plant material” was identified as the cause of the mass poisoning event. Australia and New Zealand have extremely stringent controls in place to protect manufacturers and consumers in the food supply chain from food borne illnesses (5). On 22 December 2022, Food Standards confirmed that the cause for the poisonings was contamination of the spinach crop with *Datura stramonium*, also colloquially also known as Jimsonweed, Angel’s Trumpet, Devil’s Weed, Thorn Apple, Moonflower or simply *Datura*.

While these indications suggest that this event was accidental and potentially due to substandard farming practices, only a comprehensive and systematic public

health investigation that includes consideration of various causes can exclude a non-accidental event. A number of historical instances of deliberate contamination of foodstuffs have been reported in the past. Deliberate attacks on food security are a key vulnerability of human society, are difficult to detect, and their impacts are felt “democratically” across the population (6). Of these, the most well-known occurred in the United States in the 1980’s. *Salmonella spp.* was developed into a bioweapon and used on the local population by a religious cult in the United States of America. This organisation applied the pathogen to food products at points in the supply and distribution of certain foods in supermarkets and restaurants and resulted in the mass poisoning of individuals in The Dalles. This mass food poisoning event was not known to be a deliberate exposure event, even after cult members provided admissions. Nearly a year later the FBI accidentally discovered the bioweapons laboratory on the cult’s ranch (7,8).

Food production, manufacture and supply are particularly vulnerable to intentional or unintentional threats to food quality and safety (9). In Australia, deliberate insertion of needles into strawberries occurred in 2018 (10). Microbial contamination of food remains commonplace with considerable potential morbidity and mortality, most commonly due to food being stored under inappropriate

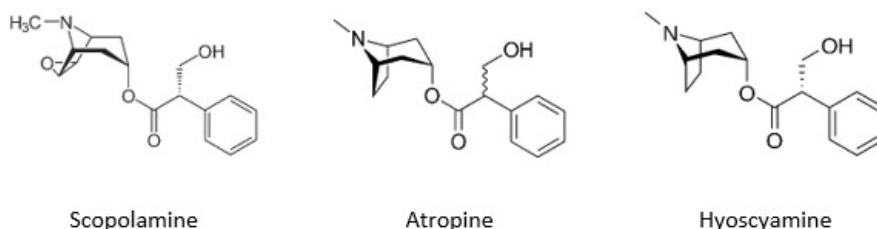
conditions or handled in ways that lead to significant contamination and growth of pathogenic bacteria or viruses (11). Less commonplace, but equally important, is contamination of foods with toxic plant or animal derived chemicals. For example, many plants produce substances that then are used to make important pharmaceutical products (e.g. opium, digitalis etc). Common food products require careful cultivation, harvesting and processing techniques to monitor for and minimise potentially toxic contaminants that can enter the food chain if co-harvested with a target food crop (12,13). Many plant-derived substances can cause poisoning in animals and humans, with the Tropane Alkaloids (TAs) being a common cause and present in a wide variety of plant species. Plant derived TAs have a long history of being the cause of both accidental and non-accidental poisoning in humans and animals (14–18).

This paper will provide an overview of the risks posed by plant derived tropane alkaloids, with particular focus on the risks of contamination of food for human consumption during production, harvest, processing, and supply and distribution. The potential for non-accidental or accidental mass exposure events will be discussed.

Plant derived tropane alkaloids (TAs)

Tropane alkaloids (TAs) are a diverse group of compounds found mainly within plants of the Solanaceae species. Principle genera of the Solanaceae group which contain TAs are *Datura*, *Scopolia*, *Atropa*, *Hyoscyamus*, *Duboisia*, *Mandragora*, and *Burgmansia* (19), however ingestion of numerous other plant species is also able to cause anti-cholinergic syndrome. TA concentration varies across genera and is influenced also by the species, growing environment, geographic location, temperature, moisture, and cultivation technique (20). The major tropane alkaloids are hyoscyamine and scopolamine, with many other minor tropane alkaloids present in some species (Figure 1). However, hyoscyamine and scopolamine predominate and can account for up to 90 percent of total alkaloid content in most TA containing plants with the remaining TA content being mainly made up of close chemical variants (21–23). Subvariants of *D. stramonium* have also been found to have significantly increased concentrations of hyoscyamine and scopolamine compared to *D. stramonium*.

Figure 1. Chemical structures of the primary plant derived Tropane Alkaloids (Public Domain).



There are a wide variety of psychoactive compounds produced by plants, many of which have traditional and medicinal qualities. Some are economically important agricultural crops, with widespread recreational use in many societies such as nicotine and caffeine. Others have a longstanding history of use in herbal and traditional medical practices, use in religious and spiritual contexts, or for recreational purposes. Most, if not all, of these substances are associated with morbidity and mortality when individuals are exposed to a high dose.

Anticholinergic toxidrome and the toxicology of TAs

The tropane alkaloids (TAs) atropine, hyoscyamine and scopolamine cause a characteristic anticholinergic toxidrome following ingestion (19,24–27). The typical features of anticholinergic toxidrome are outlined in Table 1 and include peripheral nervous system effects by firstly competitively blocking muscarinic cholinergic receptors in various effector organs and synapses such as the sinoatrial node, sudomotor system, and the enteric nervous system. The effects of

atropine in the central nervous system are less well understood but are profound. There also appears to be dose dependent opposing effects of atropine on cardiac function, presumably from differential central effects (19,25). Studies in animals have shown significant behavioural changes following atropine exposure, and there is extensive evidence of behavioural changes associated with accidental therapeutic overdose with atropine consistent with central effects.

Contamination of food and food production processes with TAs

Contamination of food products at any point through the production, manufacturing, and supply and distribution phases is a major economic threat to many industries due to the potential for both humans and also economically important livestock to become poisoned. Recent advice from the Food and Agriculture Organisation (FAO) of the World Health Organisation to producers and manufacturers of grain products made recommendations for the maximum safe level of contamination of various plant crops and

products with TAs (13). Most particularly, safe levels of seed contamination of products were defined as seeds can contaminate a wide variety of food stuffs, are toxic in small amounts, and are difficult to detect in mass production process. Prior to these recommendations only a small number of countries had defined precise limitations on grain and seed contamination with TA containing plant materials.

Most contamination incidents involving foods are the result of seed contamination of grain, seed and legume stocks. For example, multiple incidents of mass TA poisoning have been reported around the

world due to seed contamination of flour, or the inclusion of small amounts of seeds of TA containing plants. Contamination of buckwheat flour in Slovenia caused TA poisoning in around 73 persons in 2003 (28), along with many other examples of contamination of staple food products in Europe and North America (29). In 2019, a mass poisoning event in Uganda involving humanitarian relief food contaminated with TA containing plant materials resulted in hundreds of casualties and a number of deaths (18).

Table 1. Clinical features of the anticholinergic toxidrome (19,24).

Eponymous statements reflecting key toxidrome features	Corresponding clinical findings	Presumptive physiological action of TAs
Mad as a hatter	Delirium, confusion, agitation, hallucinations	Central Nervous System effects
Red as a beet	Dermal flushing, Fever	Cardiac effects (hyperdynamic) Peripheral vasodilatation
Dry as a bone	Reduced sweating, Dry mucous membranes	Decreased sudomotor activity
Blind as a bat	Mydriasis (dilated pupils)	Effect on sphincter pupillae
Hot as a hare	Fever	Decreased sweating Impaired thermoregulation High cardiac output
Full as a flask	Urinary retention	Inability to relax urethral sphincter
Additional signs and symptoms	Tachycardia Cardiac arrhythmias Absent bowel sounds	

Figure 2. *Datura stramonium*, in flower (work of H. Zell, 2009 CC by attribution)



Contamination of edible fresh foods such as mixed salad leaves, in contrast to contamination of food products with seeds, is less commonly reported in the literature and probably reflects a lower frequency of occurrence. Cases of individuals who have mistakenly collected the leaves of TA containing plants for consumption have been reported (20,30), but reports of mass contamination events are rare (31). This may be due to the relatively unpalatable and bitter taste of the leaves of the Solanaceae family when compared to other species with edible leaves (20). It would be reasonable to presume that, unless unpalatability or bitter taste was a desirable characteristic, individuals would naturally self-limit consumption of the leaves of Solanaceae species in the case of plant product contamination. The recent contamination of baby spinach leaves with *D. stramonium* in Australia appears to be unusual since the taste and shape of *Datura* leaves would differ substantially from a product that was intended to contain only baby spinach leaves (Figure 2). However, it is possible that the taste of *Datura* could have been masked by some methods of preparing the contaminated product for consumption. The affected farm had been accused of poor weed control in 2018 (32).

Finally, the contamination of product during the processes involved in processing, packaging, supply and distribution of baby spinach leaves is possible, but equally unlikely to be explanatory. Bulk packaged spinach leaf production involves a process where leaves undergo multiple sequential washes, visual and automated inspection, size sorting and quality control steps. Contamination of product during process steps, such as contamination of wash water with high concentration of TAs (in other words, effectively washing the leaves with TA “tea”), is unlikely to be able to result in significant concentrations of TAs on the surface of the final product that the consumer could ultimately ingest. Additionally, many consumers routinely conduct further washes of loose salad products immediately prior to consumption as a routine part of domestic food safety practices particularly in warm climates like Australia.

Deliberate contamination of food with TAs

The most common reason for ingestion of TAs is for recreational purposes. This practice has, unfortunately, frequently been associated with high morbidity and mortality (14,17,19,27). Morbidity and mortality is particularly high when exposure occurs in young persons, with multiple case reports of mortality in young persons. There is substantial variability in the concentration of TAs across different species and different crops of TA containing plants (14,20). There is also variability between different parts of the plants in terms of the concentration of TAs present, for example between the leaves, root and seeds. Ingestion is the usual route of exposure, mostly achieved by including parts of the plant as part of a food product,

or by brewing “herbal tea” using plant components containing a high TA content. TAs are generally heat stable, and the resultant concentration of TA is impossible to accurately determine and can vary substantially. Consequently, the home preparation and deliberate ingestion of TA containing foods is associated with an extremely high risk of inadvertent poisoning.

While there is a longstanding history of deliberate intoxication or poisoning of individuals with TAs dating back to antiquity, deliberate mass exposure of populations with TAs has not been seen as commonly. However, mass poisoning with compounds that produce the anti-cholinergic syndrome is possible by both ingestion but also by the inhalational route. There have been reports of the use of TA like incapacitants prohibited under the Chemical Weapons Convention (CWC) on populations (33). Allegations of the use of various chemical weapons, one of which was likely to be 3-quinuclidinyl benzilate (QNB, codenamed BZ), by Serbian forces near Srebrenica against an evacuating civilian population have been made (34). QNB is a substance very similar in chemical structure to atropine, and which exposure causes the characteristic anti-cholinergic toxidrome. Accounts of survivors of the Srebrenica march describe being attacked with munitions that resulted in dispersal of smoke that flowed across the land. Exposure to the smoke resulted in delirium, hallucinations, delusions with unusual and sometime aggressive and homicidal behaviour (34). This is consistent with airborne exposure to a substance with anti-cholinergic properties.

Inhalational exposure to many types of TAs is possible. Experiments conducted during the 1960s in the United States at Edgewood Arsenal demonstrated the effectiveness of inhalational exposure to various TAs, both synthetic and naturally derived such as QNB which was first formulated at Edgewood. Airborne dispersal of QNB and other TAs would firstly require preparation in a suitable form for airborne dispersal, followed by employment in a suitable delivery system. The airborne dispersal of QNB and similar compounds would likely disperse with a high concentration gradient resulting in a range of exposures and diversity in resultant toxidromes (33), although the combination of TAs with other incapacitants is highlighted as a particular concern.

Conclusion

Tropane Alkaloids – namely atropine, hyoscyamine and scopolamine – are produced in significant concentrations in a variety of plant species. The most well genera are the Solanaceae which include the well-known deadly nightshade, henbane, and *Datura*. Contamination of food for human consumption with TAs is a common problem for plant primary producers and minimising the presence of TA containing plant materials requires a disciplined

approach to cultivation with strict monitoring and other controls. Non deliberate mass TA poisoning through the ingestion of contaminated food is most likely to have its causative event at the food production or early stages of food processing. Small amounts of seed contamination in grains undergoing milling can result in difficult to detect contamination and profound health impacts for consumers. The recent mass poisoning with *Datura stramonium* plant materials in Australia appears to be an unusual example of poisoning through accidental ingestion of the plant material itself and possibly represents a breakdown in agricultural production standards. Deliberate mass poisoning through airborne exposure to TAs or similar compounds has been suspected in the Balkans in the late 1990s, however has not otherwise been reported in the literature. Despite this, the deliberate use of TAs could represent a significant threat to populations and has the potential to generate significant events with high morbidity and mortality.

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