Poisoning due to tutin in honey—a report of an outbreak in New Zealand

Michael Beasley, Dell Hood, Philippa Anderson, John Reeve, Robin J Slaughter

ABSTRACT

AIM: In autumn 2008, an outbreak of toxic honey poisoning was identified. The outbreak was not recognised initially until three cases from one family group presented to hospital, with a common factor of recent consumption of locally produced honey. The aim of this study was to investigate potential cases of this honey poisoning and determine which toxin was involved.

METHOD: The incident was investigated retrospectively by Waikato District Health Board’s Population Health unit and the New Zealand Food Safety Authority (NZFSA). Identified patients were followed up by questionnaire to gather case information. HortResearch (now Plant and Food Research) tested honey samples for toxins.

RESULTS: The causative agent was identified as tutin, which comes from the New Zealand native plant tutu (Coriaria arborea) which has long been known as a potential source of contamination of honey produced in the warmer parts of New Zealand. Retrospective case investigation identified a total of 22 possible or probable cases, based on a clinical case definition. The spectrum of toxic effects reported were broadly similar to those previously described for tutin, derived either directly from the plant itself or indirectly from honey. There were 13 samples of honey, linked to symptomatic individuals, which were available for testing. Of these, 10 were positive for tutin and its hydroxy metabolite hyenanchin (hydroxytutin) and one was positive for hyenanchin alone.

CONCLUSION: Toxic honey production is a significant risk in parts of New Zealand. Beekeepers and health professionals need to be informed of this risk and know how best to manage it. Due to this poisoning incident, public and professional awareness of honey poisoning has been substantially enhanced. This incident led to development of new food safety standards for New Zealand honey.

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toxic honey is a well-defined phenomenon that has been described since the time of the ancient Greeks. Poisoning from toxic honey occurs when phytotoxins from plant species are present in honey, usually via direct transfer in nectar or pollen. Because none of New Zealand’s native bees produce honey, the eating of locally produced honey did not begin until after the introduction of the honeybee Apis mellifera by missionaries in Northland in 1839. However, it was not until some decades later, in the late 1880s, that vomiting, headache and delirium was reported after eating locally produced honey from both managed hives and wild honey bees. Outbreaks of toxic honey have continued to occur sporadically in New Zealand over the last 130 years.

In a detailed review of honey poisoning in New Zealand published in 1965, Palmer-Jones records both the history of clinical recognition of the syndrome and the sequence of events which finally solved the mystery of how tutin, the toxin known to be present in the native plant Tutu (Coriaria arborea), was transferred to honey where it could then produce human toxicity.

Tutu is a native shrub or small tree which is common throughout New Zealand. It has distinctive flowers, berries and foliage (Figures 1 and 2). It is an early coloniser of cleared land, with seeds spread by birds. All parts of the plant are toxic, other than the fleshy petals around the seeds. These were used as a sweet flavouring and medicine by Māori, who knew that eating the entire
berry resulted in poisoning and sometimes death. Serious and sometimes fatal human poisoning from eating the berries was formally documented by European settlers.3

The first attempt to isolate the toxin in tutu was around 1870,3 and experimental studies were underway by ~1890,4 and continued through the early 1900s to better characterise its toxicity.5–7 Tutin is also found in Coriaria species in South America, and the related toxin coriamyrtin in species in the western Mediterranean,4 mainly in France, Spain and Morocco. However, there appears to be little evidence to suggest that these species have been responsible for honey poisoning, which is more explicitly reported in association with New Zealand.8–10

The symptom spectrum of toxic honey poisoning was noted to be similar to tutu poisoning,2 so this plant became a major suspected source. However, tutu flowers do not contain nectar and the toxin tutin is not present in pollen, which bees take for its protein. Therefore a mechanism of transfer was unclear. The toxin was known to be present in the sap, leaves and seeds.2,3

The transfer of tutin to honey was noted to occur only where an insect, Scolypopa australis, the passion vine hopper or ‘lace wing’ was also present. This pest insect, which was accidentally introduced from Australia around 1870, sucks sap from young green shoots. When it is feeding on tutu plants, the sticky intestinal secretions (‘honeydew’) which it excretes contain tutin.2 This insect is found only in warm regions, and this explains why honey poisoning has only been described in the warmer parts of New Zealand (particularly the northern half of the North Island and Marlborough), even though tutu grows throughout the country.

Figure 1: Tutu berry. © Used with permission. Photo Credit: Trevor James.

Figure 2: Tutu mature foliage. © Used with permission. Photo Credit: Trevor James.
At the time of the incident, it was believed that bees took honeydew only when their normal foods were in short supply, but subsequent investigation has revealed that bees take some honeydew at any time. In the areas in New Zealand from where toxic honey poisoning has been reported, flowers of native vegetation usually provide sufficient nectar and pollen, but it is likely that bees consume more of this toxic honeydew in drought conditions.

The major risk to human health is the consumption of honey directly from the comb, which avoids the usual dilution when honey is separated from the comb and large volumes from different sources are mixed.

As well as tutin, the less toxic hyenanchin (also known as hydroxytutin or mellitoxin) is typically also present in toxic honey. Tutin and hyenanchin are similar compounds; their chemical structures are presented in Figure 3. Hyenanchin is produced by the vine hopper’s metabolism of tutin.\(^2\(^1\)

**Method: outbreak investigation**

On 21 March 2008, a small rural hospital in Waikato, New Zealand reported that three people from a six-person family group had presented to their emergency department on two separate occasions with acute onset of vomiting and headache after eating locally produced comb honey. Two of the three had grand mal seizures. The association of the illness with the ingestion of comb honey was recognised because the illness affected only those who ate the honey, and because the third case presented some hours later, having no other food intake in common and having eaten the implicated honey for the first time at a later meal. The outbreak was notified to the public health service within hours of the presentation of the third family member.

The beekeeper who produced the honey was contacted for information about the
source of his product, and the amount which had been distributed for sale. It then emerged that the beekeeper had himself experienced a very similar illness with gastrointestinal symptoms and seizures about five weeks earlier. Symptom onset was around three hours after he had eaten around 20ml of the same comb honey which he had harvested the previous day. He had eaten “a taste” of the honey at the time of harvest without incident. Although he had received care from the same hospital, the association with ingestion of comb honey had not been recognised by patient or clinicians.

The working diagnosis was that the honey was contaminated with tutin, a phytotoxin present in the native shrub tutu. Urgent retrieval of the implicated honey was initiated from the three outlets where it had been sold. Because the notification occurred at the beginning of the Easter holiday, media assistance was sought to advise the public not to eat any comb honey, and to return any uneaten product from the implicated producer. Publicity was used to identify further cases.

The New Zealand Food Safety Authority (NZFSA), at that time the statutory body responsible for food safety, managed food safety issues arising from this incident while Waikato District Health Board’s Population Health managed the outbreak investigation and control measures, in an inter-agency collaborative emergency response. NZFSA has subsequently implemented longer-term measures to ensure the safety of commercially produced honey in New Zealand. NZFSA has since merged into the Ministry for Primary Industries.

Media coverage of this poisoning incident allowed retrospective identification of 22 people who had consumed the implicated honey. As no other method of case finding was possible, additional cases may have occurred outside New Zealand, as retailers recalled selling some of the contaminated honey to international visitors returning home.

The questionnaire used to gather case information was hastily devised and was based on the few relevant published papers which could be obtained in a short time. (See Appendix) It was administered around the country by various public health staff, many without clinical training. The interpretation of some questions may have been variable.

Based on the information collected the final case definitions used were:

- **Possible case** = vomiting OR any neurological symptom within 24 hours of eating comb honey.
- **Probable case** = vomiting AND any neurological symptom within 24 hours of eating comb honey.
- **Confirmed case** = Possible or probable case where tutin or hyenanchin was detected in honey consumed by the case.

The flow chart used to categorise cases is depicted below (Figure 4).

The questionnaire included questions about the source and quantity of honey consumed. Unsold honey packages and any remaining honey were collected from cases’ homes. Analysis for tutin and hyenanchin (hydroxytutin) was carried out later at HortResearch, then a government-owned laboratory in Hamilton (HortResearch has since been incorporated into a new agency, Plant and Food Research). The method of analysis for tutin and hyenanchin was liquid chromatography–mass spectrometry (LC-MS/MS) after aqueous extraction and partitioning into solvent.

Fifty-three of the 300-gram individual comb packages of honey were sold, under two different product names identifying the two hive sites from where the honey had been harvested. Subsequent toxin analysis revealed that the honey from only one of these locations contained tutin. All but seven of the sold packages were traced, although not all could be recovered.
Results of outbreak investigation

Of the 22 “probable” or “possible” cases initially defined on clinical grounds, 11 fitted the definition of a confirmed case after the relevant honey samples had been tested (Table 1). Initially, 18 cases were defined as probable cases and there were 10 samples of honey from this group available for testing. Of these samples, nine were subsequently confirmed as testing positive for tutin and hyenanchin. Four cases were initially classed as possible cases and three of these had honey samples available for testing.

Two of these sample tested were confirmed as containing toxins. Overall, this gave 11 confirmed cases, nine probable cases and two possible cases (Figure 4).

The signs and symptoms which developed in the probable and confirmed cases are presented in Figure 5. The onset of the clinical effects ranged from 0.5 to 17h with a median of 7.5h. Nausea and vomiting were commonly observed and there were eight cases of seizures. The amount consumed ranged from a “smear” to up to 200g of honey. The majority of these patients were male (70%) with an age range of between 3 and 76 years (Table 1).


Table 1: The key features of confirmed and probable cases.

<table>
<thead>
<tr>
<th></th>
<th>Confirmed cases</th>
<th>Probable cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
<td>3–74</td>
<td>12–76</td>
</tr>
<tr>
<td>Percent male</td>
<td>64%</td>
<td>77%</td>
</tr>
<tr>
<td>Ingestion—symptom onset interval</td>
<td>Median 7.2 hours</td>
<td>Median 8 hours</td>
</tr>
<tr>
<td></td>
<td>Range 0.5–17 hours</td>
<td>Range 0.5–17 hours</td>
</tr>
<tr>
<td>Honey consumed</td>
<td>“smear” – ~70 grams</td>
<td>“smear” – ~200 grams</td>
</tr>
<tr>
<td>Hospitalised/hospital visit</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Saw GP only</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No medical attention</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Seizures</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 5: Signs and symptoms that developed in probable and confirmed cases.

Discussion

Both tutin and hyenanchin are structurally similar to picrotoxin (see Figure 3), the active principle of picrotoxin, found in plants of the Order Menispermacea. These compounds block the inhibitory actions of the neurotransmitter GABA (γ-aminobutyric acid) that are mediated via GABA$_{A}$ receptors at various sites in the body. This antagonising of inhibitory processes results in central nervous system stimulatory effects which characteristically include seizures, but can also involve increased activity of the vasomotor, respiratory and autonomic centres in the medulla and/or cortex. Early researchers had concluded that tutin increased the excitability of the “medullary centres”.

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Central nervous system stimulation was a prominent feature among this series of cases with 40% (8/20) of probable and confirmed cases suffering from one or more seizures. The effects observed correlate well with the observed symptoms of human tutin poisoning; after a characteristic delay of three to six hours, nausea and vomiting develop, often followed by tremor and/or grand mal seizures, which may be severe and recurrent. Nausea and vomiting can persist for many hours. Other effects can include tachycardia, tachypnoea, difficulty breathing, delirium, blurred vision, anxiety, agitation, excitement, weakness, dizziness, amnesia, stupor and coma. Death is usually due to respiratory arrest.3,14–16 There were no prolonged periods of unconsciousness or deaths associated with this cluster.

Drug- or toxin-induced seizures are typically of relatively short duration, usually manageable with standard treatments, including benzodiazepines as first line agents (which as GABA receptor agonists, would seem particularly appropriate for tutin and hyenanchin).3,14 With most toxins, one would not generally expect any major long-term neurological sequelae in the great majority of patients. However, seizures are a “hallmark” effect of picrotoxin-like compounds and might be more protracted in this context than with many other toxic causes. The two cases that had more than one seizure in this series were managed conservatively with initial restrictions on their driving. There are accounts of incomplete neurological recovery following tutu poisoning.3,5,6 The observation of amnesia in this series of cases is not new. It has been previously noted that tutu poisoning may result in loss of memory and “incapacity for work”.2,3

Tachycardia was also commonly reported in this series of cases, and likely arose in part from increased central sympathetic outflow. Experimental studies of the related picrotoxin found it could produce an initial short-lived phase of decreased heart rate and blood pressure, attributed to activation of central parasympathetic centres, followed by a second phase of sinus tachycardia and/or increased blood pressure, attributed to central sympathetic activation.17,18 At very high doses, early bradyarrhythmias and later ventricular tachyarrhythmias were noted, the latter thought due to coronary artery spasm.19 Indeed, some experimental similarities had been earlier noted with tutin itself with Fitchett and Malcolm commenting on tachycardia, arteriolar constriction and increases (or decreases) in blood pressure.5–7

The respiratory symptoms in the current cases were not classified in detail; however, increased respiratory rate and effort is well described with picrotoxin, where it is linked to stimulation of the respiratory centre.20 The same effect is described with tutu (and coriamyrtin) poisoning, followed however in severe cases by respiratory depression including apnoea, also noted experimentally.5,6

There are considerable similarities to the effects noted from poisonings from closely related plants in Chile and the Western Mediterranean, containing tutin and coriamyrtin respectively,8,21 but the constellation of factors leading to honey poisoning from tutu in New Zealand does not appear to occur with similar species elsewhere.

At the time of this outbreak, the kinetics of tutin (and hyenanchin) in humans were largely unknown. Even the experimental kinetic data was limited,3,5,6 though it (and that regarding picrotoxin)22 suggested these compounds have a relatively short half-life, probably a few hours at most. The data from this outbreak also suggest the duration of most adverse effects is relatively short, being a matter of a few days only, but it appears some effects can last for longer. A pharmacokinetic study performed following this outbreak in six healthy males given tutin-contaminated honey (tutin dose 1.8ug/kg) showed two peak plasma concentrations; the first at 0.9 hours and a higher peak at 15 hours. This double-peak effect may help explain the range of onset times for clinical effects (0.5 to 17 hours) found in this case series. Limited adverse effects were noted in this low-dose pharmacokinetic study with only mild transient headache developing in one subject and mild light-headedness developing in another. The half-life of tutin was determined to be 5.4 hours.11

Immediately after this episode, the then New Zealand Food Safety Authority (NZFSA) began reviewing policy and procedures related to beekeeping in New Zealand to refine existing safety measures in relation to tutu-related risks. Detailed discussion...
of these is beyond the scope of this report. The policy and food standards related to managing the risk of tutin in honey are available online at http://www.foodsafety.govt.nz/industry/sectors/honey-bee/tutin/index.htm. To support the review, NZFSA commissioned the purification of tutin and then several toxicity studies. These experimental studies identified the doses of tutin that cause no observable adverse effects, and that hyenanchin was essentially not toxic at amounts where tutin would cause death. Experimentally, the median oral lethal dose (LD$_{50}$) of tutin in mice is 4.7mg/kg body-weight.$^{23}$ The acute toxicity study of tutin demonstrated a “no observed adverse effect level” (NOAEL) of tutin in test animals of 0.25mg tutin/kg body weight$^{23}$ from which NZFSA derived an interim upper acceptable concentration of tutin in honey$^{24}$ (as mentioned NZFSA is now within the Ministry for Primary Industries). Subsequent to this interim standard, the human pharmacokinetic study$^{11}$ enabled a more robust maximum residue limit to be established and the maximum concentration of tutin in honey set in the Joint Australia New Zealand Food Standards Code is now 0.7mg/kg.

A 2016 New Zealand standard has been produced to ensure honey producers comply with the Food Standards Code. This 2016 standard requires that all honey be shown to comply with the Food Standards Code when packed, and there are five options to do this. Either the honey has to be tested and demonstrated to comply, or shown to be of low risk of non-compliance. The four options for showing that the honey is low risk are either the honey was proven to have been harvested outside of the time period when scolytopopa are present, or it has been shown that the honey was from hives stationed where there is no tutu present within bee foraging range, or from hives stationed south of 42 degrees south latitude, or after three years of targeted monitoring, the concentration of tutin in the extracted honey is always not more than 0.035mg/kg, or targeted honey has tutin concentrations not more than 0.01mg/kg if the honey is from comb honey for sale.$^{24}$

**Limitations**

This investigation was based on retrospective information, obtained in most cases by telephone interview, and sometimes undertaken by non-clinical staff. It is likely that the interpretation of the information provided by the cases varied. Where possible this was validated with clinical information, but only 13 of 22 cases had sought medical advice, and the treating clinicians had recognised the likely cause of the illness only in the last case to present. Additionally, the publicity given to this outbreak would have augmented existing recall bias. However, the symptoms reported by the confirmed and probable cases are generally consistent with other New Zealand cases reports of toxic honey ingestion, and from “direct” poisoning from ingestion of the tutu plant itself.$^{2,14,15}$

Dry summers in the area of distribution of the passion vine hopper in northern New Zealand are not uncommon, and given incontrovertible evidence that the risk management strategies for honey production in place until the summer of 2007–2008 were inadequate, it is highly likely that there have been other outbreaks of tutin poisoning. Dispersed outbreaks arising from a widely distributed common source are difficult to identify and may go unnoticed. Tutin poisoning may explain other cases of isolated seizures in adults without identified neurological abnormality.

**Conclusions**

Toxic honey production is a significant risk in parts of New Zealand if honey safety is not managed effectively. Poisoning can result from the ingestion of processed as well as comb honey. With amateur and professional beekeeping now burgeoning, the risk of consumption of toxic freshly harvested comb honey may increase. It is critical that beekeepers are informed of this risk and know how best to manage it. It is also important that clinicians consider the diagnosis of toxic honey ingestion in patients who present with nausea, vomiting and symptoms of central...
nervous system agitation. Extrinsic toxins had understandably not been considered in the differential diagnosis of any case seen by a medical practitioner prior to the presentation of the family cluster, although in retrospect, the association of CNS stimulation with nausea and vomiting is characteristic. Foodborne toxin ingestion needs to be considered as a possibility, particularly where prior risk of seizures was remote. This, however, may be difficult as tutin poisoning had had little or no publicity for many decades. As well as a generational loss of knowledge about tutin toxicity in New Zealand honey (given that the last previously documented outbreak occurred in 1974), many healthcare workers in this country are overseas trained, and thus less likely to be familiar with the toxicity of New Zealand native plants.

One of the undoubted outcomes from this episode is that public and professional awareness of this form of honey poisoning has been substantially enhanced.

Appendix

Questionnaire used in investigation

HOUSEHOLD HEADER INFORMATION

TOXIC HONEY POISONING OUTBREAK

NOTIFIER IDENTIFICATION

Name of reporting source ____________________________________________________________
Contact ph: __________________________________________________________
Date: _____/_____/____

CASE IDENTIFICATION

Name of Case: _______________________________________________________________________
Address of Case: _____________________________________________________________________
Phone numbers: home _________________ Work: ___________________ Other: ____________
NHI Number: ____________________________________________

CASE DEMOGRAPHY

Date of Birth: _________/_________/_______
OR
Age: __________ (days/months/years)
Sex: M/F Approx Weight* _________________
Ethnicity: NZ Māori / NZ European-Pakeha / Pacific Island / Other European/ Other: _________________
Occupation: __________________________________________________________
Place of work/school/pre-school: _______________________________________________________
*Either weight in kg or use descriptor – large adult etc

HONEY PRODUCT DETAILS

Form of Honey: Comb / Liquid / Creamed
PACK DETAILS:
Trade or Brand Name: ________________________________
Product size or weight: ________________________________
Any Date Mark or Batch Number: ________________________

PURCHASE DETAILS
Where purchased: ________________________________
Date purchased: ________________________________
Where/How the honey been stored since purchase: ________________________________

Is there any additional product: Y/N (ADVISE CUSTOMER TO SEAL THE LEFT-OVER PRODUCT AND HOLD. WE WILL ARRANGE COLLECTION)
What address this currently at: ________________________________

RELATED CASES/CONTACTS
Anyone else been unwell following honey consumption: Y/N
Anyone consumed the honey and not been sick: Y/N
Aware of anyone else may have received this honey (whether or not consumed): Y/N
N.B. Interviewer - If Y please complete the contact list

CONSUMPTION DETAILS
Date and time honey eaten: ________________________________

Amount eaten: ________________________________

SYMPTOMS
Date and time became ill: ________________________________
Visit Doctor: Y/N Name and address: ________________________________
Hospital Y/N
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<th>ONSET DATE/TIME</th>
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<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<td>Diarrhoea</td>
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<tr>
<td>Muscle spasms</td>
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<td>Muscle weakness</td>
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<td>Blurred vision</td>
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<td>Red eyes</td>
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<td>Respiratory problems</td>
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<td>Rapid heart beat</td>
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<td>Delirium</td>
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<td>Giddiness</td>
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<tr>
<td>Convulsions</td>
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<tr>
<td>Amnesia (memory loss)</td>
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<td>Other (describe):</td>
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Case is happy for information to go to NZFSA Y/N

ANY ADDITIONAL COMMENTS/INFORMATION:

NAME OF INTERVIEWER: __________________________________________________________

DATE AND TIME OF INTERVIEW: __________________________
Competing interests:
Nil.

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REFERENCES:
