Episode 58: Marzipan, Almonds and Cyanide - A Toxicology Christmas Special

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Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week it's a very festive episode, very special. We're at that time of year where everything's winding down for Christmas, decorations are up and, importantly, Rebecca, you have the Christmas snacks in.

I have some Christmas snacks. I've not done my like full Christmas snack haul yet. What are your favourite Christmas snacks? Ooh, I do love them, it's pie.

Okay, festive pie. I mean any of the chocolate selection boxes, I think Heroes are probably my favourite. Okay. Or Lindor.

Lindor, good. Lindor is good, but it's not really a selection, that's just one great thing. We're not sponsored by Lindor yet. What about you?

Have you got your Christmas snacks in? I try not to eat too much Christmas snacks. That's sad times. But Christmas cheese is definitely a thing.

Oh yeah, Christmas cheese. But how do you feel about marzipan? I quite like marzipan, I feel like I'm in the minority on that one. I like marzipan too.

Marzipan is pretty divisive. My wife absolutely hates marzipan, she can't stand anything almond flavour. But it is very, very Christmassy. I mean, we don't just have it at Christmas, it is something that happens throughout the year.

But in particular at Christmas, there's a lot of it around, isn't there? Traditional English Christmas cakes with marzipan between the fruitcake and the icing, German stollen. In the Netherlands, they eat marzipan shaped potatoes and things like that. Marzipan shaped potatoes.

I was Googling it this morning, apparently it's a thing. It's not just potatoes, it's like marzipan that looks like other food. I feel like I need to see this. Yeah, definitely go do some Googling.

But the question is, what is the connection between marzipan and toxicology? And we're going to be exploring that a bit this week. Before we jump into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn. And for those of you who don't use social media, but still want to get in touch with episode suggestions or comments about episodes, you can email us at thetoxlab@gmail.com.

And I can't believe it's already here. But this is our last episode for 2025. So we can take a couple of weeks off, and we'll be back with a brand new episode on the fifth of January. So what is the relationship between marzipan and toxicology?

Well, it's a little bit of a journey. Marzipan is mostly made of sugar and almonds. Almonds actually come in two different varieties. The variety that we all know and love is what we call a sweet almond.

But the same trees that produce sweet almonds can occasionally carry a recessive genetic trait that leads them to produce what we call bitter almonds. And bitter almonds have got a bit of a history.

They were used as early medicines. They were used to treat a range of conditions in Greco-Roman times, including digestive complaints as a mild sedative.

Medical texts used to say, don't exceed X number of kernels, don't give to the young and weak, things like that. And it's because, crucially, bitter almonds contain very high levels of a compound called amygdalin. Amygdalin is what we call a cyogenic glycoside. It's essentially a sugar molecule attached to a cyanide molecule.

And if you eat bitter almonds, as part of the breakdown, it releases cyanide. And I rabbit holed really hard on this subject this morning on the bus. What does cyanide smell like? Almonds.

Everybody says cyanide smells of almonds. And almonds clearly smell of almonds. But the smell of almonds is actually from a compound called benzaldehyde. And benzaldehyde is also released from amygdalin when amygdalin is broken down.

Benzaldehyde is really simple. It's a benzene group and then an aldehyde attached. It's probably the simplest of the aromatic aldehydes. And it's got this really distinctive almond flavor.

Artificial benzaldehyde is used a lot in baking. Most modern marzipan now contains artificial benzaldehyde because marzipan, reasonably, is made from sweet almonds, not bitter almonds for toxicity reasons. And so they then add the almond flavor back to make it taste more like a bitter almond. And it's also in cherry coke.

Interesting. Cherry coke has a cherry and inverted commas flavor. Drink it now and think of almonds. And it will taste a bit like almonds because it's that same compound.

I'm gonna have to go buy some now. So does cyanide smell of almonds? Or do almonds smell of cyanide and benzaldehyde? And I couldn't really answer this question.

So there are people that have been exposed to cyanide through elemental exposures to cyanide. So potassium cyanide salts added to acid produces hydrogen cyanide. No benzaldehyde in sight. And yet people claim it smells of almonds.

Some people can't smell cyanide. This is recognized that there's a genetic trait that says some people can't smell cyanide, but yet they can still smell benzaldehyde. So does cyanide smell of almonds? Or is it just this association that we have made?

Or do they both smell of almonds and it's a coincidence? I'm not a smell scientist, but if there are any smell scientists out there that can comment on this, I would really love to hear from you. Because I think this is a fascinating intersection between poisons and the senses. It's not just bitter almonds that actually contain amygdalin.

Lots of plants contain amygdalin. And we'll explore this a little bit after our first case. But cherries, apricot pips, apple pips even contain small amounts. Lots of fruit seeds contain amygdalin.

And so our first case is going to be looking at bitter almonds and cyanide. Before we jump into this case and the other papers we're going to discuss today, these papers do touch on suicide. So if that's something you don't want to be listening to, please click off this episode, listen to some of our other content or another podcast entirely, we won't be offended. So this first case report comes out of Iran and involves a 36 year old woman with a history of suicide attempts and no significant drug history who presented to the emergency department complaining of vomiting.

She had an almond orchard that had trees which produced bitter almonds and she had ingested approximately 40 of these one hour prior to admission in an attempt to end her life. 20 minutes after

ingesting these she began vomiting. Upon admission to hospital she was confused with the GCSF9 and was tachycardic and hypertensive with bilateral dilated pupils. Two hours after her admission she became hypotensive and four hours after the admission she became unconscious.

Her blood pressure and heart rate dropped and she was subsequently intubated and given norepinephrine. Blood gas analysis showed a severe metabolic acidosis with a pH of 6.92 and a bicarbonate of 8.6 millimoles per litre. Due to the lack of laboratory facilities the patient's blood cyanide levels could not be measured but based on her clinical and other lab observations along with her confirmed history of ingesting bitter almonds she was diagnosed with acute cyanide poisoning as a result of ingesting amygdalene containing food.

An ECG was performed which showed zynostachycardia and a gastric lavage and activated charcoal were administered to try and reverse the poisoning. The patient also received sodium bicarbonate infusions in an attempt to address the metabolic acidosis that were seen and the patient was transferred to the referral center for poisoning due to a lack of antidote at the local hospital. Upon arrival her GCS had dropped to six and she had a blood pressure of 90 over 60 with a heart rate of 80 beats per minute and her ECG showed a normal sinus rhythm.

She was then admitted to intensive care and was given 300 milligrams of sodium nitrite which is an antidote for cyanide poisoning. The patient then became hypotensive and was given an infusion of norepinephrine and sodium bicarbonate infusions continued to be administered to correct the acidosis and four hours after her admission to this specialist hospital a blood gas result showed that the acidosis had corrected and all her levels were now within the normal range.

The following day the patient had regained consciousness and was successfully extubated and then just stepped down to the ward before being transferred to a psychiatric center for further care. So let's quickly talk about cyanide then. Cyanide is a poison I'm sure many people have heard of and how does cyanide work? Well essentially it stops cells being able to utilize oxygen.

So cyanide acts by binding to the heme center in an enzyme called cytochrome c oxidase and this is part of complex four of the electron transport chain which is needed for oxidative phosphorylation which is required to produce ATP so it's basically how the body produces energy. When this enzyme doesn't work the cells then can't use oxygen to respire which then leads to hypoxia and the production of lactate as a result of the switch to anaerobic glycolysis.

So clinically people resemble this hypoxic state a state without oxygen except there's plenty of oxygen in their blood it's just the cells can't use it because that step in the chain is blocked and this has some clinical effects that we saw in that case we saw a rise in lactate which is what you typically see in anaerobic respiration.

There's a couple of other signs of cyanide toxicity as well I'm not sure if they were mentioned in this case people could appear red and the reason that this is noticeable is because normally the blood in your veins is deoxygenated but because the oxygen hasn't been utilized at the tissue level you end up with oxygenated blood in your veins and that's why people look redder or pinker than usual. The other thing I want to look at here then is the source of this cyanide these cyanogenic glycosides present in bitter almonds and bitter almonds in particular are very high in amygdalin much higher than other fruits.

Apricot pips do contain a reasonable amount bitter almonds contain the equivalent of about one to six milligrams of hydrogen cyanide per bitter almond. Apricot kernels lower but can be similar up to about three milligrams but crucially it really varies between different varieties of apricot so some can be really low some can be really high. Apple pips also contain amygdalin contain trace levels so you'd

need to be eating hundreds of apple pips to get serious toxicity.

They're often unfairly demonized yes they contain cyanide but really really low levels and in terms of hydrogen cyanide sort of dosing a fatal dose of hydrogen cyanide can be about 50 to 200 milligrams of hydrogen cyanide so we're looking at maybe 10 to 20 bitter almonds could potentially be fatal. So let's look more generally then at cyanide and sources of exposure of cyanide. We found a paper looking at poison control data didn't we? So this paper is from the UK national poison information service and its aim was to describe the sources of exposure clinical features investigations and choice of antidote when cyanide was implicated.

So this is a retrospective analysis of the UK poisons information database from the 1st of January 2008 to the 31st of December 2019 and from this data they identified cases where cyanide or a cyanogenic compound was either a potential causative agent or recorded in the medical history. Encounters were excluded where the history and or the clinical picture were not consistent with possible cyanide poisoning or if the request was general rather than related to a specific patient. So over the 12 years they had 1421 encounters to work with.

169 of these were excluded because they were unlikely to be related to cyanide exposure or they were duplicate cases. This left 1252 cases and in this data the median age of individuals was 32 years with a male to female ratio of 1.5 to 1. Out of all these exposures 77% of them were accidental, 35% of exposures were from plants, 32% involved combustion, cyanide salts were implicated in 18% of cases and cyanogenic compounds were implicated in 11% of cases. 14% of the total cases involved children under the age of five and the majority of these exposures were the result of accidental exposure to a cyanogenic plant.

So cyanogenic plant was similar to what we were talking about weren't we? Bitter almonds but also apricot pips, cherry seeds. This is poison control data so possibly there were phone calls relating to apple seeds although unlikely to have been significant nonetheless it's entirely possible poison control were contacted. Inhalation of products of combustion was the most common source of all age groups over 20 years old and in case of intentional exposure which was 8% of cases the most common source of exposure was cyanide salts.

So fire is a big one when certain things burn, modern plastics things like that. Cyanide release is a real risk in house fires and it can often be a complicating factor in somebody who's admitted to hospital after smoke inhalation. It's not just the air damage and the smoke to the lungs but also cyanide can be a significant contributor to the morbidity and mortality. In terms of reported symptoms 37% of patients reported no symptoms at all.

Of those that did the most common symptoms reported was a headache in 6%, dizziness in 5% and nausea in 5%. Other signs included elastic acidosis in 13% of cases which we saw in the first case study we looked at, coma in 8% and a general acidosis in 6%. Hypotension, coma and cardiac arrest were the signs most likely to be associated with the fatal outcome and 21 patients over this time period did go into cardiac arrest with a survival rate of 52%. Poisoned severity scores reported in 1209 of these cases with 38% being classified as none, 35% minor, 10% moderate, 13% severe and 3% were fatal.

93% of patients exposed to cyanogenic plant material had either minor or no symptoms and products of combustion exposure was the most common cause of a severe poisoning severity score. Cyanide salts and products of combustion exposure were also the most common cause of exposure leading to a fatal outcome. Serum lactate was measured in 362 patients within this time period with a median serum lactate concentration increasing for the different poisoning severity outcomes ranging from a median of one minimals per litre in those without symptoms to a lactate of 14 minimals per litre in those with a fatal outcome.

And this was quite a nice correlation graph wasn't it showing that the higher your lactate is the more severely poisoned you are essentially and therefore worse outcomes. They also created rock curves which gave optimal cutoff values for predicting poisoning severity score based on lactate results. So results for the lactate of greater than two minimals per litre had a minor severity score or higher greater than 5.8 minimals per litre for a moderate or higher score greater than 7.5 minimals per litre for a severe or higher score and greater than 11 minimals per litre for a fatal score.

But in 243 patients a carboxyhemoglobin measurement was carried out and all of these individuals were exposed to products of combustion. 25% of them had a carboxyhemoglobin result of 30% or more and this indicated severe toxicity and was associated with the fatal outcome. So a massive chunk of the patients who were exposed to cyanide in fires were also exposed to carbon monoxide. Out of this massive data set only nine patients had cyanide concentrations measured.

Four results had a cyanide concentration of less than one milligrams per litre indicating mild toxicity. Two had a cyanide concentration between one and three milligrams per litre indicating moderate toxicity and three had severe toxicity and a cyanide concentration of greater than three milligrams per litre. This is a big gap actually isn't it there's not readily available certainly in this country cyanide measurements and certainly not to the degree that would let you manage an acutely unwell patient who's just been pulled out for fire or anything like that.

So often the treatment of people from fires is to assume a degree of cyanide exposure and given antidote. So in 110 cases which was approximately 9% antidotes were given. In 50 cases this was given prior to contact with NPIS and clinicians were advised by NPIS to give an antidote in 56 cases. In the remaining four cases NPIS advised other tests to be performed egolactate before giving an antidote.

51 cases received hydroxycobalamin, 42 received sodium thiosulfate, 9 received dicobol EDTA, 7 received sodium nitrite and sodium thiosulfate and only one case had an adverse outcome when an antidote was used and this occurred in a patient from a house fire who developed hypotension following dicobol EDTA. So in terms of the types of exposure where antidotes were given, 92 cases involved products of combustion exposure, 10 were cyanisole ingestions, 6 were cyanogenic plant ingestions and one was a cyanogenic compound exposure.

In terms of the severity score where an antidote was administered, 2% had a minor score of 15% moderate, 39% severe and 53% were fatal cases. So antidotes were much more likely to be used in fire exposures than cyanogenic plant exposures and cyanogenic compound, I'm assuming that's something like acetonitrile, cyanide containing solvent, something like that. I don't think they say, do they? They do that as mentioned that that's one potential cause of a cyanogenic compound exposure, but they don't like list them all.

So why don't we talk then a bit about how some of the antidotes work? So the four main antidotes that are mentioned in the poison control data. So we'll start with nitrite, which works by producing methemoglobin, which is hemoglobin with iron in its three plus oxidative state rather than its two plus. And this can then compete with cytochrome C oxidase for the free cyanide and helps mop it up that way.

It's also possible to use volatile organic nitrate compounds. So poppers essentially, so compounds like amyl nitrate and these can be inhaled and again produce that methemoglobin. You've got to be a little bit careful of course, cause methemoglobin cannot carry oxygen. So it in itself can be toxic.

So you do need to get a balance between detoxifying with cyanide and also producing too much methemoglobin, which could impair your blood's ability to carry oxygen. One of the other antidotes was hydroxycobalamin, wasn't it? This is a form of vitamin B12 and vitamin B12 can exist in a few

different forms. And one of those is cyanocobalamin.

It forms a cyanobond and it can be used again to detoxify cyanide because hydroxycobalamin reacts with the cyanide and forms cyanocobalamin. Sodium thiosulfate was another antidote that we touched on. And this acts as a sulfur donor, which increases the conversion of cyanide to thiocyanate by the enzyme rhodonese, which can then be eliminated by the kidneys. And that's our typical cyanide excretion pathway.

Dicobalt EDTA was another one and this contains cobalt, which can form stable complexes with cyanide to form cobalt cyanides, which can then be really excreted. But these can be highly toxic, leading to seizures, hypotension, shortness of breath, chest pain, vomiting, and rashes when given, especially in case with cyanide was not involved as not the sort of treatment that you can give, unless you're pretty sure that cyanide was involved. So from this poison control data, only 10% of cases had follow up data with the mean period to follow up of 6.7 days and the range was 1 to 35 days.

61 patients had recovered completely, 40 patients died, and 18 demonstrated ongoing symptoms ranging from generalized weakness to hypoxic brain injury. So in conclusion then, there is a link between marzipan, bitter almonds, and cyanide. But probably if you go to the shop and buy some marzipan, you're not going to be exposed to significant amounts of cyanide. So is it possible therefore to be poisoned by marzipan?

Because it's Christmas, we've got one bonus case for you this week and we dug in the archives and we have found a marzipan poisoning case. So this is from an article that was published in 1994 about a case that occurred in December 1992. So a 26 year old female received 12 marzipan balls from an unknown admirer who had sent her an anonymous letter several months prior as she decided to share these with her three friends. They managed to eat no more than one marzipan ball each before throwing them away due to an unpalatable taste.

The following day the four friends complained of GI symptoms including abdominal cramps, constipation, diary, and vomiting. Two of the individuals who had eaten an entire marzipan ball presented the emergency department two days later after the initial ingestion complaining of pain in their hands and feet that made worse when they were touched and they were unable to walk due to the extreme pain in their feet. They also went on to develop chest pain and chest pain was also seen in the two other individuals who didn't present to the emergency department.

Based on these symptoms the hospital suggested this might be thallium poisoning and a blood and urine sample was sent for confirmation. Four to eight days after ingestion saw the two patients in hospital develop hypertension and tachycardia with T wave changes on an ECG and eight to fifteen days after saw hair loss develop in three of the patients a GI bleed in one and insomnia was also recorded. They used radiography to look at the marzipan balls to see whether they contain any metal and there were areas of radio opacity which supported thallium as this is radio opaque.

And I do recommend people go and check out the photo in the article for this. The idea of using an x-ray machine to x-ray some balls of marzipan and see which ones were radio opaque and which ones weren't is really quite something to admire. It was really cool. Atomic absorption spectroscopy was then used to measure the levels of thallium in the marzipan balls and this showed that they contained approximately one gram of thallium each although the dicing between them was quite variable.

In the early 50 for thallium is between eight and twelve milligrams per kilogram and so therefore consuming as little as one of these could potentially be fatal. Three days after the ingestion a spot urine thallium result showed levels of thallium at 10,837 micrograms police it in one patient and 9,569 micrograms police it in the other and these were the two individuals that are most severely affected.

So let's dive in a little bit quickly then about how thallium is poisonous so thallium is a heavy metal it's nestled between mercury and lead on the periodic table.

What's interesting about thallium is it's toxic because it mimics potassium in the body and despite the fact that thallium and potassium are quite a way apart on the periodic table remarkably thallium ions have got a similar atomic radii to potassium and so they get taken up into cells in the same way that potassium does and thallium has a very high affinity to sulfur ligands and so any enzymes or proteins that contain cysteine thallium will bind to and disrupt and so it disrupts then cellular enzymes which are necessary for cellular functions and so you end up with this generalized toxicity and one of those symptoms that's a little bit characteristic of thallium is the hair loss and interestingly hair follicles undergo quite a lot of cellular reproduction and therefore they take up a reasonable amount of potassium and so they are particularly sensitive to thallium and that's why the hair loss occurs because it's hair follicles being preferentially affected by the thallium poisoning.

An interesting fun fact thallium was actually used as a hair removal product in the early 20th century. Okay obviously quite a bit of systemic toxicity it didn't last very long on the shelves but it was used for that reason. So individuals were treated with multiple doses of activated charcoal and a potassium chloride infusion. As we've mentioned potassium has been shown to increase thallium elimination as it has similar atomic radius and child to thallium.

Prussian blue and dialysis were also given so thallium undergoes entropathic reseculation so it travels from the liver back to the intestines where it's then reabsorbed and returned back to the liver and the prussian blue traps and binds thallium in the intestine which prevents its reabsorption back into the bloodstream. And prussian blue is the same prussian blue that's used by artists worldwide. I don't know if you've ever seen it it's an absolutely beautiful pigment. Are you familiar with the Japanese artist Takusai?

I don't think so. He painted the great wave off Kamigawa. Oh yes yeah I know that painting. Okay that that blue that is all prussian blue he used a lot of prussian blue.

It's an interesting segue to test for cyanide there's a test called the prussian blue test where cyanide is reacted with iron salts in an acidic solution and this forms this prussian blue pigment and that's a way of detecting cyanide. And this was a really really interesting case wasn't it we found the academic case first but we were able to find a little bit more context in a local newspaper at the time. And the context for this case is that these people were all students from Europe visiting the US.

One of them had already received a letter described as non-threatening from an anonymous suitor and then a few months later an anonymous box of marzipan came through the post. Possibly a little moral of the story here. Don't eat sweets sent to you in the post by anonymous strangers but I'm not sure certainly I can't find any evidence to suggest that they ever found the culprit. I don't think they did.

So it is possible to be poisoned by marzipan unlikely for that poisoning to be cyanide poisoning but possibly although unlikely again could be thallium poisoning. In summary then there is a link between almonds marzipan cyanide. Cyanide is a real thing and exposure risk is real probably not through marzipan. Marzipan can be a hidden delivery mechanism for non-cyanide poisons and maybe if you sent anonymous marzipan in the post maybe don't eat it.

Solid advice. Well I hope you've all enjoyed listening this week and I want to give you all a massive thank you not just for listening today but actually listening throughout the last year as we kind of go into our festive break that we have. Yeah just thank you all for being here. Thank you all for being part of this little community that we've built over the last year or so.

Hope you all have a wonderful festive season and we'll see you on the 5th of January. Bye!