












CASE SERIES

Deaths from suspected mothball poisoning in children

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Childhood poisoning is a significant health concern in South Africa (SA), especially in densely populated informal housing settlements where children are frequently exposed to various household poisons. Poisoning accounts for 4 - 5% of paediatric hospital admissions in SA. The most common causes are fuels, pesticides and medicines, although many cases have unidentifiable causes. In this case series, three children, aged 3 - 5 years, were declared dead upon arrival at a public healthcare facility. Prior to death their symptoms included vomiting of a foam-like substance and distress (crying, shaking, fatigue). Postmortem fine-needle liver biopsies were obtained and underwent atmospheric pressure matrix-assisted laser desorption/ionisation mass spectrometry imaging (AP-MALDI-MSI) analysis. MSI analysis identified the presence of naphthalene-associated metabolites, the active component in household mothballs, suggesting death due to accidental ingestion. These cases highlight the urgent need for novel toxicology screening tools to accurately determine causes of death and guide targeted preventive strategies. Strategic efforts are needed to reduce childhood poisoning through robust toxicovigilance to monitor and regulate the sale of toxic substances and enhance access to toxicology testing.

Keywords: childhood poisoning, household poisoning, naphthalene, mothballs, toxicovigilance, mass spectrometry imaging

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Globally, childhood poisoning is a major public health concern, contributing significantly to hospitalisation, disability and mortality.^[1] The Institute for Health Metrics and Evaluation reported 1.88 million cases of poisoning globally in 2019, of which 830 000 occurred in persons <20 years.^[2] The epidemiology of childhood poisoning varies across different geographical regions, largely driven by socioeconomic status.^[3] In South Africa (SA), poisoning accounts for 4 - 5% of paediatric hospitalisations, with case fatality rates ranging from 0.4 - 9.8% depending on the type of poison.^[4,5] Overall, in 2021, poisoning accounted for 0.13% of deaths in children <5 years in SA.^[2] Common causes of poisoning in children hospitalised at the Red Cross War Memorial Children's Hospital in Cape Town, SA, included pharmaceutical poisoning (49%), followed by industrial products (22%), household products (11%) and pesticides (11%), with naphthalene accounting for 2% and unspecified pesticides for 14%.^[6] At Chris Hani Baragwanath Academic Hospital, Johannesburg, the main causes of poisoning were organic solvents (including paraffin) (37.6%), pharmaceuticals (32.9%) and pesticides (17.5%), with unspecified and other poisons cumulatively at 10.2%.^[4] Similarly, at a regional hospital in KwaZulu-Natal Province, the main types of poisoning included pharmaceuticals (45.2%), hydrocarbons (23.4%) and pesticides (10.2%).^[5]

In most parts of SA, there is limited access to laboratory services that have the capacity to identify the poison in children hospitalised with suspected toxicity. Toxidromes (a constellation of clinical signs that infer a type of poison) are used by clinicians to guide management

of children where a history of the type of poison is not forthcoming. Online toxicology programmes (such as AfriTox: <https://www.afritox.co.za/>) and call centres are available to support clinicians in SA. However, toxidromes may be incomplete, and not sensitive or specific, and many poisons overlap in clinical presentation.^[7] Furthermore, in children who have died from unknown causes or suspected poisoning, there are markedly prolonged delays in obtaining postmortem toxicology testing results, and families are often not provided with closure.^[8-10] Therefore, the need for effective toxicovigilance to identify and manage cases of poisoning, and to inform targeted public health strategies to reduce childhood mortality and morbidity, is evident.

As part of the Child Health and Mortality Prevention Surveillance (CHAMPS) study in Soweto, SA, minimally invasive tissue sampling (MITS) was undertaken to determine the cause of death in children whose parents consented to the study. As part of a pilot collaboration, liver biopsy samples were analysed using atmospheric pressure matrix-assisted laser desorption/ionisation (AP-MALDI) mass spectrometry imaging (MSI) to identify possible toxins in a child whose death was suspected to be from poisoning. Here we present three cases in which naphthalene, a substance commonly found in mothballs, was identified.

The CHAMPS and MITS-lite studies were approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (ref. nos M210893 and M200265, respectively) and the CHAMPS Soweto Health and Demographics Surveillance System Community Advisory Board.

Case series

The CHAMPS Network was established in 2016 to conduct standardised surveillance for causes of child mortality in high-mortality, sentinel sites in sub-Saharan Africa and Asia. CHAMPS, an ongoing study, identifies and analyses causes of death in children <5 years old from samples taken for histopathology, molecular and microbiological diagnostics and clinical data abstraction and verbal autopsies.^[11] Findings are reviewed by the determination of cause of death (DeCoDe) panel for each case. The multidisciplinary panel consists of paediatricians, microbiologists, obstetricians and pathologists who review clinical, antemortem and postmortem data to determine the cause of death (CoD). The CoD is then classified into the underlying conditions initiating the events leading to death, the immediate condition directly resulting in death and any comorbid conditions in the pathway to death.^[12] The findings are communicated to families of the deceased children, and aggregated data are shared with a range of local, national and international stakeholders.

Between December 2020 and October 2021, three children who were declared dead on arrival at healthcare facilities, and where the DeCoDe panel assessed that the CoD was possibly poisoning, had a liver specimen sent for AP-MALDI MSI toxicological investigation (Table 1).

Case 1

A 4-year-old male child presented with a history of vomiting and suspected poisoning. From the verbal autopsy, the mother reported that the child had been well until the day of death, when the child ate some food, after which he began to vomit. She reported that he vomited a foam-like substance, and it seemed as though he had been poisoned, and the child was rushed to the nearest healthcare facility. On gross examination of the corpse, there were no significant findings. The forensic provisional report indicated that the history preceding death was consistent with aldicarb poisoning. CHAMPS histopathology of the liver noted mild sinusoidal inflammation with a finding of sinusoidal leucocytosis, while the lungs and heart histology were unremarkable.

Case 2

A 3-year-old female child with no past medical history presented on the day of death with vomiting, continued to vomit until a foam-like substance started to appear and was then rushed to the local primary healthcare facility, where she was assessed as having died before arrival. From the clinical history and gross autopsy findings, the death was assessed as possible aldicarb poisoning. CHAMPS histopathology of the liver noted extramedullary haematopoiesis, and interstitial pneumonitis of the right and left lung was noted, with no other findings or diagnosis noted.

Case 3

A 3-year-old female child presented with a history of being 'shaky' and wanting to sleep after playing with other children outside. On examination at the primary healthcare clinic, a fine white powder was noted on the patient. The formal forensic report noted that the brain was swollen, with a small subarachnoid haemorrhage in the cerebellum with a spiderweb appearance of blood vessels. At the nose, there was oozing dried brownish mucus, and both kidneys appeared congested. There were no other abnormalities detected. The stomach contained ~100 mL of partially digested food mixed with green granules, and the report concluded that the death may be consistent with aldicarb poisoning. The CHAMPS histopathology examinations of the liver and lungs were unremarkable.

Investigations

From the MITS procedures performed, for all three cases, polymerase chain reaction screening of up to 116 pathogens on a custom-designed syndromic TaqMan Array cards (Thermo Fisher Scientific Inc., USA) and standard postmortem cultures showed no significant infectious CoD. During the DeCoDe panel, the underlying cause of death was suspected to be poisoning for all three cases.

For all three cases, liver biopsy samples were prepared and analysed using AP-MALDI MSI. An untargeted MSI analysis approach was used to detect a wide range of biomolecules of interest. This technique may provide a novel screening tool for the rapid identification of toxins, and has been identified as a method to aid forensic toxicology.^[13]

For the mass spectrometry imaging analysis, frozen liver biopsies were embedded in a 250 mM sucrose solution and sectioned to a thickness of 12 µm using a Leica CM1860 cryostat (Leica Biosystems, Germany).

AP-MALDI MSI provides the unique advantage of being able to detect drugs, metabolites and biomolecules in their native state without the need for labelling or chemical modification. In this study, we were able to detect naphthalene-1,2-diol.

Naphthalene, an aromatic hydrocarbon, and its metabolites were detected in all three liver samples. Additionally, bile-associated metabolites and a high number of different lipid species, suggesting possible dysfunctional lipid metabolism, were identified.

Discussion

The recent spike in and media awareness around childhood poisoning has highlighted this public healthcare crisis in SA. The deaths of the three young children in the present case series, likely from accidental ingestion of mothballs (naphthalene), emphasises the breadth of the concern. Mothballs are a household item that are sold without restrictions in supermarkets and by street vendors in SA. Their shape and colour resemble a hard candy, and they can easily be ingested by an unsupervised child.^[14] Although not frequently reported, previous studies have shown that naphthalene toxicity may occur after ingestion, inhalation or dermal exposure, and may be fatal.^[15,16] There is no known toxidrome for naphthalene poisoning. However, clinical manifestations of naphthalene poisoning include headache, vomiting, diarrhoea, abdominal pain and altered mental state.^[15,16] The fatal dose of naphthalene in children is unknown, and although uncommon, there are reports of death following ingestion of naphthalene.^[15-17]

There is a paucity of data describing the histological features in children with fatal naphthalene poisoning. In a single report of a child poisoned with ~5 g of moth balls, at autopsy there was congestion, oedema and haemorrhage of the lungs. Naphthalene has been previously detected in liver tissue.^[18,19] Similar to the case series findings, histopathology of the liver showed infiltration of polymorphonuclear leucocytes and lymphocytes as well as lipid metabolomic changes.^[17] In naphthalene poisoning cases, pathological manifestations are thought to be driven by the production of oxygen free radicals, resulting in lipid peroxidation and subsequent DNA damage. The increased oxidative stress leads to the formation of methaemoglobin, an oxidised form of haemoglobin that does not bind oxygen and increases the affinity of oxygen for the partially oxidised portion of haemoglobin. This process impairs the delivery and release of oxygen, leading to tissue hypoxia. Oxidative and mechanical trauma to red blood cells results in the release of free haemoglobin into plasma, which is filtered in the kidney

Table 1. Summary of cases

Case	Age	Gender	Symptoms	Forensic report	DeCoDe underlying CoD	AP-MALDI findings
1	4 years	Male	Sudden onset of vomiting, foam-like substance	Consistent with aldicarb poisoning	Poisoning	Naphthalene metabolites
2	3 years	Female	Sudden onset of vomiting, foam-like substance	Possible aldicarb poisoning	Poisoning	Naphthalene metabolites
3	3 years	Female	Sudden onset of crying, shaking, fatigue	Consistent with aldicarb poisoning	Poisoning	Naphthalene metabolites

DeCoDe = determination of cause of death; CoD = cause of death; AP-MALDI = atmospheric pressure matrix-assisted laser desorption/ionisation.

Table 2. Clinical features of naphthalene and aldicarb poisoning

Affected system	Naphthalene	Aldicarb
Circulatory system	Tachycardia	Bradycardia, hypotension, tachycardia
Digestive system	Diarrhoea, nausea/vomiting	Diarrhoea, nausea/vomiting
General	Excessive sweating	Excessive sweating, loss of appetite
Mental state	Confusion/aggression	Anxious/frightened/agitated
Nervous system	Depressed level of consciousness/coma, seizures	Ataxia, depressed level of consciousness/coma, hypoactivity, hypotonia/weakness/paralysis, involuntary movements/tremor, muscle fasciculation, seizures
Pain	Abdominal pain, headache, painful micturition	Abdominal pain, headache
Respiratory system	Difficulty in breathing, shallow respiration	Difficulty in breathing, respiratory muscle paralysis, rhinorrhoea
Skin colour	Generalised pallor, jaundice	Generalised pallor
Urinary system	Oliguria/anuria, pink/orange colour of urine	Urinary incontinence

and dissociates into haem and globin. The increased levels of intracellular haem are cytotoxic, and lead to acute kidney injury by direct cytotoxicity, decreased renal perfusion and intratubular cast formation.^[15-17] Afritox provides guidelines on management. These include triage, decontamination and supportive management, and are often symptom-based, including transfusion of packed red blood cells for anaemia, monitoring of fluid and electrolyte balance and administration of alkalis in the presence of haemoglobinuria to prevent renal damage.^[15-17,20]

In this case series, all three cases were attributed to aldicarb poisoning by the forensic pathologist, but this was in the absence of formal toxicology testing and was based on clinical history and gross autopsy findings. From the history, the first two cases had a history of vomiting and the third had an altered mental status. The manifestations of naphthalene poisoning are not specific and heterogenous, and it is unlikely that a clinician or pathologist will be able to differentiate between naphthalene poisoning v. other toxidromes. Notably, aldicarb was not identified in any of these cases using AP-MALDI MSI testing. Table 2 lists the signs and symptoms and system involvement for naphthalene and aldicarb poisoning. Notably, similarities in the clinical presentation of the toxins warrants investigations to be performed.^[20]

This case series has some limitations. For the MSI analysis, frozen temperatures render enzymes metabolically inactive, and therefore time from sampling to freezing should be minimised. In our study, the time to freezing was not documented. Another limitation is that we were unable to detect the parent compound of naphthalene, but only its biologically active metabolite.

Conclusion and recommendations

In the present study, naphthalene was detected in liver tissue using AP-MALDI MSI. In addition, histopathology findings for the three cases noted possible dysfunctional lipid metabolism, consistent with naphthalene poisoning.^[15-17]

Childhood poisoning is preventable. Children are vulnerable to accidental poisoning owing to their natural curiosity, mobility,

mouthings behaviours and limited hazard awareness. The risk of poisoning is further increased by diminished supervision in the home, increased access to potential poisons due to inadequate storage, accidental ingestion when being mixed with food for pest control, and 'look-alike' poisons that appear similar to candy or foods.

Underreporting of fatalities due to naphthalene because of a lack of specific toxin testing has consequences. The assumption that this is a rare cause of accidental poisoning leads to mismanagement of cases, and missed opportunities during public health interventions to prevent it. Mothball poisoning is likely to be of greater public health concern than reported. In settings where this household item is still commonly used, and supervision of children may be limited owing to social circumstances, this toxin should be suspected in children with suspected poisoning.

This case series highlights the importance of toxicological testing in instances of suspected poisoning, to enable accurate feedback to families and to inform surveillance and preventive strategies. Novel detection methods are necessary to identify and target interventions in children with suspected poisoning. The application of AP-MALDI MSI aids the identification of poisons, and has the potential to assist strategic efforts in reducing childhood poisoning rates through robust toxicovigilance.

Data availability. N/a.

Declaration. None.

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Author contributions. KS, SvdM, OL and MD were responsible for sample collection and contributed to the initial CHAMPS research, including study oversight. LE and SJ provided background information

and conducted the analysis of public health impact. AMEM and SB performed the mass spectrometry testing, including the application of the AP-MALDI technique, and provided technical expertise and analytical insight. SGL, SAH and ZD contributed technical guidance and support with statistical analysis. MD, SJ, LE, SGL, SAH and ZD contributed to manuscript preparation and revision. MD had primary responsibility for the final content.

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Conflicts of interest. None.

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