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Diagnosing pesticide poisoning deaths

To the Editor: We would like to comment on the recent article by Dempster *et al.* titled 'Deaths from suspected mothball poisoning in children'.[1]

We applaud the authors' use of advanced analytical techniques to investigate unexplained poisoning deaths in children, and to determine the cause for future preventive efforts.

Toxicity-related deaths in South Africa must, by legislation, undergo formal medicolegal death investigations, with an authorised forensic medical practitioner determining the cause of death after consideration of all available evidence.[2,3] As suspected pesticide poisoning fatalities may have overlapping clinical presentations, we agree that postmortem investigations with toxicological testing are critically important, but results should be interpreted cautiously and holistically. The detection of a metabolite should generally be regarded as evidence of exposure rather than proof of poisoning, unless supported by consistent clinical, laboratory, pathological and circumstantial findings. We therefore urge caution in attributing the cause of death in these cases to naphthalene poisoning based primarily on the detection of a naphthalene-associated metabolite in liver tissue.

Bearing this in mind, we would like to focus on a few points.

Firstly, low-level exposure to naphthalene is ubiquitous through sources such as air pollution, exhaust emissions, cigarette smoke and certain types of food.[4] The parent compound and its metabolites distribute to lipid-rich tissues and are slowly released back into the circulation. It is well-recognised that naphthalene metabolites may persist and be detectable at low levels in blood, urine and tissues after chronic exposure.[5] As such, the presence of naphthalene-1,2-diol in the deceased children's liver tissue may indicate prior exposure, but does not confirm naphthalene poisoning.

Secondly, the clinical toxidrome of naphthalene toxicity is haemolysis, with or without methaemoglobinaemia, which leads to anaemia, haemoglobinuria and acute kidney injury.[6] While some of the nonspecific features described in the presented cases may be observed with naphthalene poisoning, the absence of clinical, laboratory, gross autopsy or histopathological evidence for haemolysis does not support the diagnosis of naphthalene poisoning.

Thirdly, while the available clinical histories and pathological findings may be consistent with poisoning-related deaths, these findings are largely nonspecific and do not provide clear support for naphthalene toxicity as the cause of death. Furthermore, histological findings described neither confirm nor exclude a specific cause of death, apart from a bilateral interstitial pneumonitis reported in case 2. As such, the interpretation of the detection of the naphthalene metabolite should be correlated with additional comprehensive toxicological findings to determine a definitive cause of death.

Fourthly, while there is growing utilisation of matrix-associated laser desorption/ionisation mass spectrometry (MALDI-MS) in forensic science,[7] these techniques may currently be regarded as supplementary in postmortem forensic toxicological investigations, rather than standalone confirmatory methods.[8,9] Limited information is provided in the article regarding the analytical panel scope (i.e. which pesticides and metabolites were included) and identification criteria, assessment of matrix effects or interferences, or validation parameters required for forensic toxicology applications. This is particularly important given the recognised susceptibility of MALDI-MS techniques to ion suppression, interferences and challenges associated with complex biological matrices.[10] Furthermore, liver tissue is not typically the preferred specimen for investigation of acute pesticide poisoning deaths, where blood and gastric contents often provide greater value.

We are concerned that attributing these deaths to mothball poisoning without sufficient evidence may inadvertently direct preventive efforts away from other highly hazardous pesticides such as organophosphates, paraquat and amitraz. As acute pesticide poisoning in children may have a confusing clinical presentation and management may be challenging, we encourage all healthcare workers to familiarise themselves with available resources, such as AfriTox, to optimise diagnosis and management, or call the Poisons Information Helpline of South Africa (0861 555 777) for complex cases. Notification of all pesticide poisonings, recently escalated to a category 1 condition, as highlighted by Mathee *et al.*[11] in the same issue of *SAMJ*, is a core aspect of management: not only does it aim to prevent further events by triggering a public health response, it also contributes to national toxicosurveillance data.

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Response to correspondence regarding 'Deaths from suspected mothball poisoning in children'

To the Editor: We thank the authors for their thoughtful engagement with our case series, and for highlighting important principles in the interpretation of toxicological findings.

We agree that postmortem toxicological results must be interpreted cautiously, and in conjunction with all available clinical, pathological and circumstantial information. We wish to clarify, however, that our report did not present the detection of naphthalene-associated metabolites as definitive proof of fatal naphthalene toxicity. The AP-MALDI-MSI findings were interpreted within the Child Health and Mortality Prevention Surveillance (CHAMPS) Determination of Cause of Death (DeCoDe) framework, which integrates clinical history, verbal autopsy, histopathology, microbiological investigations, molecular pathogen testing and multidisciplinary expert review.

We acknowledge that low-level naphthalene exposure may occur in the environment. However, the repeated detection of naphthalene-associated metabolites in three independent paediatric deaths, all presenting with acute features suggestive of poisoning and in whom infectious causes were excluded, makes incidental background exposure less likely. In addition, low-level exposure to toxins such as air pollution, exhaust emissions, cigarette smoke and certain types of food is unlikely to be above the limit of detection of mass spectrometry-based methods. Detectable mass spectrometry signatures are suggestive of high-dose exposure and/or bioaccumulation of metabolites with prolonged exposure.

We further note that while haemolysis is a recognised manifestation of naphthalene toxicity, it is not universally present. Clinical expression is variable and influenced by dose, timing of exposure and host susceptibility. In acute exposures where death occurs rapidly, classical haemolytic features may be absent, incomplete, or not readily appreciable on postmortem sampling. Importantly, the CHAMPS postmortem diagnostic platform does not include a dedicated haemolysis panel, and assessment is therefore limited, with histopathological examination of selected tissues and available antemortem clinical data. As such, the absence of documented haemolysis should not be interpreted as definitive evidence against naphthalene toxicity.

We agree that AP-MALDI-MSI should currently be regarded as an adjunctive rather than definitive forensic toxicology tool. This was precisely the rationale for its inclusion in our report: to highlight the potential value of novel screening approaches in resource-limited settings where conventional toxicology testing is frequently delayed or unavailable. We also demonstrate that AP-MALDI-MSI may provide a viable alternative screening method when assessing cases of suspected poisoning where the causative agent is unknown.

Importantly, our intention was not to divert attention from other highly hazardous pesticides, but rather to expand the differential diagnosis in unexplained paediatric poisonings, and strengthen toxicovigilance. The purpose of these findings was to demonstrate that surveillance in paediatric cases should expand beyond other highly hazardous compounds, and to highlight that there may be other toxic compounds that are overlooked. We share the authors' view that improved surveillance, timely toxicological testing and clinician awareness remain central to preventing childhood poisoning deaths.

We appreciate the opportunity to clarify these points, and welcome further discussion on strengthening paediatric toxicology diagnostics in South Africa.

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