



Investigation of a Methemoglobinemia Outbreak Caused by Eating Sausages with High Concentrations of Nitrates and Nitrites in Trang Province, Thailand, January 2022

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Abstract

In late January 2022, a cluster of methemoglobinemia cases across five provinces of Thailand was notified to the regional public health authorities. A joint investigation was conducted aiming to describe characteristics of the outbreak in one of the provinces, traceback the suspected food, and recommend prevention and control measures. We conducted a cross-sectional descriptive study, interviewing the cases, reviewing their medical records, and interviewing their parents and treating physicians. An active case finding was conducted. A probable case was defined as a person who presented with acute central cyanosis with oxygen saturation less than 92% by pulse oximetry. Suspected food samples were collected for nitrates and nitrites testing. Three cases (2 males, 1 female) were identified and there was no death. Their ages ranged from 8–12 years. The sausages came from the same source and were found to have high concentrations of nitrates (1,270.8–1,690.0 mg/kg) and nitrites (3,554.5–3,776.2 mg/kg). The sausages were identified as a likely cause of the outbreak. Government regulation, product liability laws, and food safety concerns among food retailers and customers are important to reduce the impact of consuming unsafe foods.

Keywords: methemoglobinemia, sausages, nitrates, nitrites, Trang

Introduction

Methemoglobinemia is a rare disorder associated with oxidation of divalent ferro-iron of hemoglobin to ferric iron of methemoglobin (MetHb), resulting in hypoxia due to impaired oxygen release to the tissue.¹⁻³ The normal level of MetHb in human blood is less than 1%. There is a direct correlation between MetHb levels and clinical signs and symptoms. Values less than 10% are associated with low pulse oximeter levels, alteration of the skin color and being asymptomatic. Values between 10–30% are associated with cyanosis, dark brown blood, and being asymptomatic and confused. Values between 30–50% are associated with dyspnea, dizziness, syncope, confusion, chest pain, palpitation, headache and fatigue. Values between 50–70% are associated with metabolic acidosis, arrhythmias, seizure, delirium and coma, while MetHb values above 70% are considered potentially lethal.³⁻⁴ Acquired

methemoglobinemia is mainly due to the exposure to oxidizing agents such as drugs or substances that cause oxidation of the hemoglobin.³ There are numerous drugs that can cause methemoglobinemia including sulfonamides, dapsone, aniline derivatives, and nitrites. The most common causative drugs are benzocaine and lidocaine.⁵⁻⁷ Nitrates and nitrites contaminating water supplies or used as preservatives in foods can also be triggering agents.⁸ Among 62 food-related methemoglobinemia studies in which oxidizing agents were identified, nitrates and nitrites were the predominant suspected agent.⁹

During 28–30 Jan 2022, the situation awareness team of the Office of Prevention and Control Region 12 Songkhla (ODPC12) was notified of a cluster of methemoglobinemia cases in Kalase Subdistrict, Sikao District, Trang Province. Three cases were referred to Trang Provincial Hospital with acute central cyanosis

and hypoxemia after all had eaten a particular type of sausage. During the same period, another five methemoglobinemia cases from Chiang Mai, Kanchanaburi, Saraburi and Phetchaburi Provinces were notified by the Ramathibodi Poison Center (RPC). A smoked chicken sausage purchased on the internet was the suspected cause of the outbreak. Staff from ODPC12 joined the Trang Provincial and District Health Offices to investigate the outbreak during 31 Jan–2 Feb 2022. The objectives were to verify the diagnosis, describe characteristics of the outbreak, traceback the suspected food, and recommend prevention and control measures.

Methods

ODPC12, in collaboration with Trang Provincial Health Office, Trang Hospital, Sikao District Health Office and Kalase Health Promotion Hospital, conducted a descriptive cross-sectional study. Face-to-face interviews were conducted with the cases, their parents and the treating physicians. Medical records of the cases and informal reports from the RPC were reviewed. Data collected included demographic characteristics, clinical history, treatment, outcomes, consumption of suspected food, and other potential risk factors. An active case finding was performed using a network of Trang Hospital's physicians and public health personnel using a software application (Line groups). Trang Provincial Health Office communicated an official order document including the active case finding guideline and a case definition to all hospitals and district health offices in Trang Province. A probable case of hemoglobinemia was defined as a person who visited a hospital or a health promotion hospital in Trang Province during 20 Jan–7 Feb 2022 and presented with acute central cyanosis and blood oxygen saturation less than 92% by pulse oximetry without cardiogenic, pulmonary or central nervous system causes and had at least one of the following two inclusion criteria: (i) blood drawn was chocolate-brown color; (ii) had history of consuming preserved food such as sausages or Vietnamese pork sausages within 4 hours before developing symptoms. A confirmed case was defined as a probable case who had a blood MetHb concentration exceeding 2%. Family members of the cases were interviewed eliciting demographic data, amount of suspected food consumption, and relevant clinical history.

Laboratory Study

Two of the three probable methemoglobinemia cases had available whole blood specimens in an EDTA tube.

The specimens were collected on the date of onset and kept at a temperature of 2–8 °C. Measuring the methemoglobin concentration and confirming a diagnosis of methemoglobinemia was done by CO-oximetry at the Clinical Chemistry Laboratory Unit, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital. Leftover sausages and those from the same lot eaten by the cases were collected for nitrates and nitrites testing at Trang Medical Science Center by high performance liquid chromatography technique.

Suspected foods were traced back after we performed in-depth interviews with the cases' parents, shopkeepers and a food dealer. Data collected consisted of the geographic distribution of sausage packages from the suspected lot, number of remaining packages in Trang Province, information of the source, and other potential risk factors. Multiple organizations from both the provincial and national level jointly conducted the investigation as the outbreak occurred in many regions of Thailand. We reported the results of our investigation to the Division of Epidemiology, Department of Disease Control and the Thai Food and Drug Administration (Thai FDA) in order for our results to be linked with other events and to broaden the search for the causative food source.

Results

Descriptive Epidemiology

Among the cluster of clinically suspected methemoglobinemia cases detected and notified by the RPC during 28–30 Jan 2022, eight were hospitalized and there were no deaths. Five were female and three were male, and their ages ranged from 1–12 years (median 7.5 years). The first case, from Kanchanaburi Province, developed symptoms on 20 Jan 2022 followed by a second case, from Trang Province, who developed symptoms on 26 Jan 2022. The last two cases, also from Trang Province, both developed symptoms on 29 January. The geographical distribution of cases by province is shown in Figure 1. All cases presented with acute central cyanosis and hypoxemia within 15 minutes to 2 hours (median 90 minutes) after eating packaged sausages. The range of oxygen saturation was 79–90% (median 85%). The packaging and labelling of the sausages varied by province. In Trang Province, the label on the package mentioned only the brand of the sausage, whereas in three other provinces, the label read "Smoked footlong chicken sausages, 1,000 grams". In one province, there was no label on the package.



Figure 1. Geographic distribution of reported cases of clinically suspected methemoglobinemia cases by province, 28–30 Jan 2022

In Trang Province, three patients from two separate families met the case definition; one confirmed case and two probable cases were epidemiologically linked and no additional cases were identified by the active case finding. The first case, a 12-year-old boy, developed symptoms on 26 Jan 2022 and the remaining two cases, an 8-year-old boy and a 9-year-old girl, developed symptoms on 29 Jan 2022 (Figure 2). The incubation periods ranged from 15 minutes to 1 hour. All cases developed acute central cyanosis,

acute peripheral cyanosis, and nausea/vomiting. Other presenting symptoms are shown in Table 1. The level of oxygen saturation on arrival to the emergency room ranged from 79–90%. All cases were managed in the pediatric intensive care unit with 10–15 liters per minute (LPM) supplemental oxygen by a non-rebreather mask and other supportive care including fluid and electrolyte correction. The duration of hospital stay was 1–3 days and all three recovered.

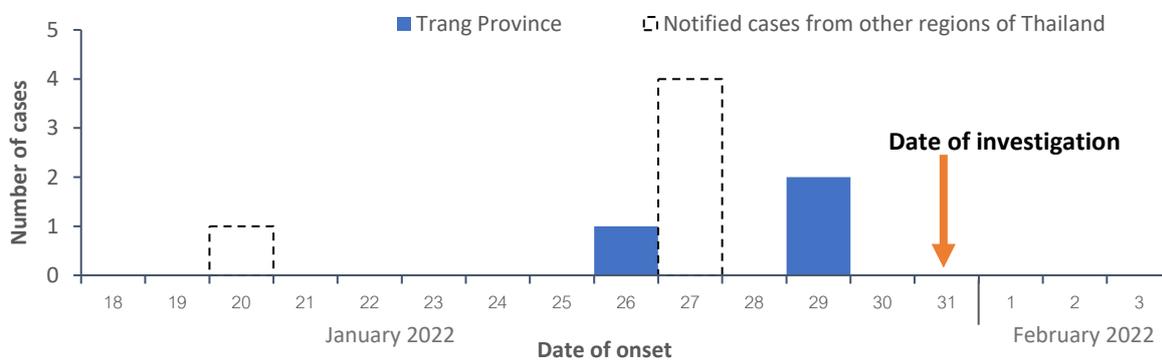


Figure 2. Number of methemoglobinemia cases by date of onset during 20 Jan–7 Feb 2022

Family 1: A 12-year-old boy with no underlying disease presented with acute central cyanosis, peripheral cyanosis, dizziness and weakness 30 minutes after eating 8 pieces of sausage. The boy's symptoms were noticed by his mother, who immediately took him to Sikao District Hospital. At the emergency room, his blood oxygen saturation was 79%. He received oxygen supplementation and was referred to Trang Provincial Hospital with the

provisional diagnosis of acute central cyanosis, cause unspecified. His pulse oximetry showed that his blood oxygen saturation level was 86%. His blood was taken and showed a chocolate-brown color. He was promptly diagnosed with methemoglobinemia based on his clinical presentation and history of sausage consumption. The laboratory at Trang Provincial Hospital has no capability to test for MetHb. The RPC was consulted for a second opinion. The boy received

10–15 LPM of supplemental oxygen via a non-rebreather mask with close monitoring in the pediatric intensive care unit. On 28 Jan 2022, his clinical cyanosis recovered and his oxygen saturation level was 96% and he was discharged from the hospital. On interviewing the boy's mother, the consumed sausages were bought from a shop in the village and were fried before eating. The boy's mother had no symptoms after consuming only half of one sausage and neither did the boy's elder sister who ate one small piece.

Family 2: On 29 Jan 2022, an 8-year-old boy and his 9-year-old elder sister developed acute central cyanosis, peripheral cyanosis, chest pain, nausea/vomiting and dyspnea after eating 6 and 2 pieces of sausages, respectively. The boy's incubation period was 15 minutes while for the girl it was 1 hour. Both were with their mother when symptoms developed and they were

promptly taken to Wangwiset District Hospital in Trang Province, blood oxygen saturation at room air of the boy and the girl was 85% and 90%, respectively. The attending physician consulted the RPC and referred the siblings to Trang Provincial Hospital. After receiving supplemental oxygen, their blood oxygen saturation was 90% and 95%, respectively. The provisional diagnosis was methemoglobinemia by clinical presentation, history of sausage consumption, and chocolate-brown blood color. Supportive treatment was given via 10–15 LPM of supplemental oxygen by a non-rebreather mask. Both recovered and were discharged on 31 Jan 2022. The suspected food was a sausage which was bought from a community market and fried before being served. The sausages were the same brand as those eaten by the first case but the characteristics of the sausages and the package label differed.

Table 1. Characteristics and clinical presentation of methemoglobinemia cases, Trang Province, 20 Jan–7 Feb 2022

Characteristics	Case 1 (family 1)	Case 2 (family 2)	Case 3 (family 2)
Type of case	Probable	Confirmed	Probable
Age (years) / gender	12 / male	8 / male	9 / female
Date of symptoms onset	26 Jan 2022	29 Jan 2022	29 Jan 2022
Time from ingestion to symptoms onset	30 minutes	15 minutes	1 hour
Implicated food	Sausage brand X	Smoked sausage brand X	Smoked sausage brand X
Sausages consumed (pieces)	8	6	2
Clinical presentation			
Acute central cyanosis	Yes	Yes	Yes
Acute peripheral cyanosis	Yes	Yes	Yes
Nausea/vomiting	Yes	Yes	Yes
Dizziness	Yes	No	Yes
Chest pain	No	Yes	No
Weakness	Yes	No	No
Facial pallor	Yes	No	No
Dyspnea	No	Yes	No
Oxygen saturation by pulse oximetry (%)			
At the first hospital (room air)	79	85	90
After administration of oxygen	86	90	95
Blood MetHb concentration (%)	Not done	10.0	0.3
Sample collection date	-	29 Jan 2022	29 Jan 2022
Laboratory receiving/testing date	-	2 Feb 2022	2 Feb 2022
Reporting date	-	3 Feb 2022	3 Feb 2022
Type of oxygen therapy	Oxygen 10–15 LPM by a non-rebreather mask		
Methylene blue prescribed	No	No	No
Outcome	Recovered	Recovered	Recovered

Note: First arterial blood gas results at the provincial hospital

Laboratory Results

Of these three cases, the two from the second family had leftover blood specimens available for collecting on the day of symptoms onset. The MetHb concentration

of these two cases were 10.0% and 0.3% (Table 1). As shown in Table 2, there was a high concentration of nitrates and nitrites in sausages obtained from the same lot as those consumed by the first case and in leftover sausages uneaten by cases 2 and 3.

Table 2. Laboratory results of suspected foods in a methemoglobinemia outbreak, Trang Province, 20 Jan–7 Feb 2022

	Sample weight (g)	Sample collection date	Laboratory testing date	HPLC results (mg/kg) ^a	
				Nitrite ^a	Nitrate ^b
Case 1					
Leftover sausages	NA	NA	NA	NA	NA
The same lot of sausages	2,000	31 Jan 2022	31 Jan 2022	3,554.5	1,690.0
Cases 2 and 3					
Leftover sausages	100	31 Jan 2022	31 Jan 2022	3,776.2	1,270.8
The same lot of sausages	NA	NA	NA	NA	NA

Note: HPLC: High-performance liquid chromatography. NA: Not available. ^aNotification from the Ministry of Public Health in 2016: the maximum amount should not be more than 80 mg/kg. ^bProhibited in all preserved meat products

Traceback of Suspected Food by Multi-Organizations

Figure 3 shows a flow diagram of the traceback process of the suspected sausages. The sausages consumed by the three cases in Trang Province came from the same source. The lot, consisting of 80 packs of sausages, were sent to a wholesale shop in Thungsong District, Nakhon Si Thammarat Province and then distributed

to retailers in Sikao District. Fifty-two packs of sausages from this lot remained, 20 in the wholesale shop and 32 in the retail shops. Each pack weighed 500 grams and contained 12 sausages. This information was reported to the Thai FDA and the Division of Epidemiology, Department of Disease Control on 31 Jan 2022.

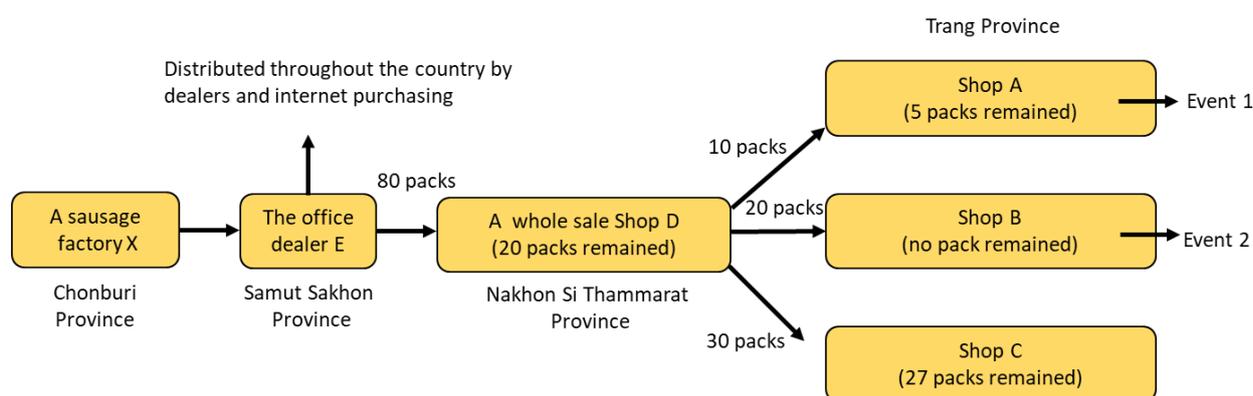


Figure 3. Traceback of suspected food in a methemoglobinemia outbreak, Trang Province, 20 Jan–7 Feb 2022

On 2 Feb 2022, the Thai FDA together with the Consumer Protection Police Division and the Division of Epidemiology, Department of Disease Control identified the production site, which was located in Chonburi Province. The site did not have a production license and the production process did not have a standard method of measurement of the chemical contents. Nitrates and nitrites were poured in manually and their amounts were not measured accurately.

Discussion

This study investigated a methemoglobinemia outbreak after cases had consumed packaged sausages with high nitrates and nitrites content. All cases were clinically diagnosed by their presentation of unexplained acute central cyanosis and hypoxemia with chocolate-brown colored blood and a history of sausage consumption. One case was confirmed with high blood MetHb concentration of 10% by CO-oximeter test, which is a non-invasive measurement method and

gold standard for detecting the fraction of methemoglobin in the blood.⁹ Due to clinical signs and symptoms of the cases including dizziness, dyspnea, chest pain and weakness, MetHb estimate levels may range from 30–50%. Delays in sending laboratory specimens may have resulted in a lower MetHb concentration than would have been detected had the specimens been sent sooner. MetHb is unstable as it can be converted enzymatically to hemoglobin and becomes oxyhemoglobin if measurement is delayed. A past study found that MetHb is stable for up to 2 hours in dipotassium EDTA, lithium heparin or potassium oxalate as anticoagulants.¹⁰

Methemoglobinemia is a rare but life-threatening condition. Severe methemoglobinemia is fatal due to persistent hypoxemic injury and multiple organ failure despite treatment with maximal ventilator support, especially when specific treatment such as methylene blue, ascorbic acid or blood transfusion is not delivered in time.^{3,11–12} The severity depends on the MetHb level and access to appropriate treatment. A large

systematic review of food-induced methemoglobinemia during 1936–2020 found that there were 568 cases with 35 deaths resulting in an overall case fatality rate of 6.2%. The majority of cases survived, even with severe methemoglobin levels of up to 89%, provided that methylene blue was administered.⁹

Most of the community and provincial hospitals in Thailand, including Trang Provincial hospital, have no capability to perform MetHb tests. Methemoglobinemia should be considered in cyanosis patients without cardiopulmonary disease who are unresponsive to oxygen therapy. A useful clinical sign is chocolate-brown colored blood. The attending doctor assessed the toxic severity by repeated evaluation of clinical hypoxemia and regular monitoring with pulse oximetry and arterial blood gas. The RPC in Thailand has consulting specialists available 24 hours a day and, during our investigation, gave the treating physician confidence in the diagnosis and treatment plan. Methylene blue from a nearby tertiary hospital was prepared and available for use if required. The recommendation for asymptomatic cases is regular monitoring without additional treatment. Oxygen supplementation should be added as needed.^{3,13} The first-line treatment for symptomatic cases with a high MetHb level is methylene blue with a starting dose of 1–2 mg/kg of 1% methylene blue. Administration can be repeated up to a cumulative dose of 5.5 mg/kg if there is no response after 30 minutes. Ascorbic acid can be added as an adjunctive therapy. Patients who do not respond to first-line therapy should undergo blood transfusion or hyperbaric oxygen therapy. A high MetHb level is defined as a level more than 10–30%, with higher than 20% being the most reported level in the literature.³

Sodium nitrate and sodium nitrite are widely used to retard bacterial growth and to preserve the color of lean meat. Many previous studies reported that methemoglobinemia occurred after consumption of food containing high concentrations of nitrates or nitrites.^{14–18} In 2016, the Ministry of Public Health prohibited the addition of nitrates in all preserved meat products and prohibited the addition of nitrites in smoked sausages. The maximum level of nitrites allowed to be added to preserved meat products, such as sausages, bologna, Chinese sausages (Kuncheing) or Northeastern Thai sausages, should not exceed 80 mg/kg of the product. The sausages produced at the factory in Chonburi contained 44–47 times more nitrites than the level allowed. Although the sausages from this lot were distributed to many customers in Trang, we could not identify additional cases by active case finding. Methemoglobinemia cases who have

blood MetHb concentrations lower than 10% may be asymptomatic.³ As the blood MetHb concentration is directly related to the amount of food consumed, those who consumed a small amount of sausage from the affected lot, for example the mother of the first case and the elder sister of the second case, reported no symptoms and therefore did not go to the hospital for further examination.

The suspected sausages came from the same source and were distributed to many provinces through dealers and internet purchases. This study presented many points needed for consideration concerning food safety. We found that the sausage factory did not have a production license and the production process did not have a standard method of measuring the chemical contents. The somewhat careless purchasing behavior of retailers and customers was also an important risk factor. Labels on food products should always be inspected to see if important information such as the serial number of the Thai FDA, date of manufacture and expiry date, name and location of the manufacturer, key ingredients and nutrition detail is included. None of this information was found on the packages of the suspected sausages. Recognition of the health dangers of unsafe food purchased on the internet is very important to the public's health.¹⁹

Public Health Actions and Recommendations

The Trang Provincial Health Office promptly communicated to the public about the risks of methemoglobinemia, advised them on their selection of sausages and preserved food that have the Thai FDA logo marked on the label with the ingredients and expiry date clearly visible. All remaining sausages from the same lot of suspected sausages in Trang were traced and prohibited to be sold. The shop owners were warned about the dangers of methemoglobinemia if these sausages were eaten and they agreed to return the remaining packs to the dealer to receive a refund. The Consumer Protection Group of Trang Provincial Health Office surveyed the preserved foods in the markets to assess the risk and give advice to the shop owners.

We notified the surveillance and rapid response team in Thungsong District, Nakhon Si Thammarat Province to conduct an active case finding in that area. The Division of Epidemiology, Department of Disease Control disseminated the surveillance information and investigation guidelines of methemoglobinemia to all local public health agencies throughout the country on 3 Feb 2022.

Regular monitoring of preserved foods in factories and markets according the Thai FDA guideline is needed

to reduce the risk of excess chemicals in preserved foods. The government regulations must be enforced so that food factories follow standard operating procedures. Penalties must be given to factories that violate these regulations. Use of product liability laws also influences the practices of food businesses, and the consumer's right to seek compensation from the factory that allowed the food to become unsafe. Food retailers and customers should refuse products that fail to have standardized labels attached to the package. Regular monitoring of preserved foods in the factory and market according to the Thai FDA guideline.

Limitations

The patients' blood samples were taken on the date of symptom onset for other laboratories but the investigators could not promptly send the specimens to be examined for MetHb concentration. Therefore, the laboratory results may not accurately reflect the situation at the time of symptoms onset. In this outbreak investigation, we actively searched only symptomatic cases who visited a hospital or health promotion hospital, so the magnitude of the problem may be underestimated. Some asymptomatic or mild cases may have been missed.

Conclusions

Sausages with high nitrates and nitrites content were identified as the most likely cause of a hemoglobinemia outbreak in Trang Province in late January 2022. Three cases were identified with one having a laboratory confirmed methemoglobin level of 10%. All cases were children aged 8–12 years and all recovered after being treated with 10–15 liters/min of supplemental oxygen via non-rebreather mask. The high level of nitrates and nitrite concentration of the suspected sausages stemmed from the lack of standard operating procedures at the factory which produced the sausages. The factory also did not perform a proper measurement of the chemical contents of the sausages prior to distributing them to the wholesalers. Improved government regulations and product liability laws, and food safety concerns of food retailers and customers are important issues that can reduce the impact of consuming unsafe foods.

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Suggested Citation

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