

Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

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- *VX Nerve Agent – in the News!*

International intrigue: alleged VX nerve agent assassination

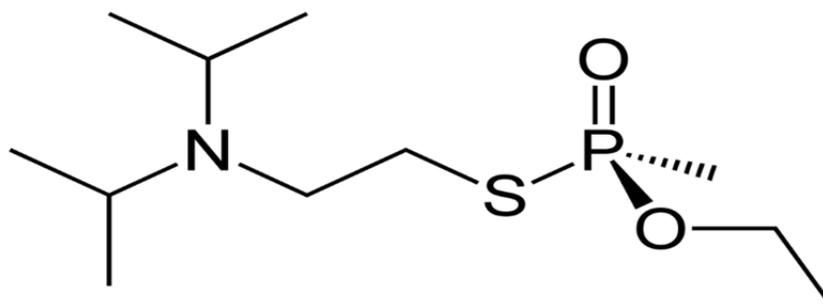
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Introduction- In mid-February 2017, an alarming international incident occurred at Kuala Lumpur airport where two women allegedly used VX to publicly assassinate a middle-aged man. Coincidentally, this man happened to be Kim Jong Nam, the estranged half-brother of North Korean dictator Kim Jong Un. Security video footage show the women approaching the unsuspecting victim from behind and then swiping his face with a “wet cloth” before fleeing while he sought aid. Shortly thereafter Kim Jong Nam died in transit to a nearby hospital.

VX is an organophosphorus nerve agent, which are some of the most toxic chemicals known to man and classified as weapons of mass destruction. This short article will primarily focus on describing VX as well as the current scientific evidence and possible motivations behind this bizarre event. For those seeking to learn more about nerve agents please consult the February 2016 issue of *Therapeutics and Toxins News* where I coauthored a review on the topic with two military pathology residents (1).

Figure 1. Chemical Structure of VX



VX (C₁₁H₂₆NO₂PS):

Ethyl ((2-bis(isopropylamino)ethyl)sulfanyl)(methyl)phosphinate

Background- VX is an odorless, tasteless compound that may appear amber in color or be transparent. Like the original G-series nerve agents, VX was accidentally discovered by industrial chemists attempting to make more potent insecticides. It was synthesized in the early 1950s by the British chemical company Imperial Chemicals Limited which determined it to be an effective insecticide but far too toxic to humans (2). They discontinued production and notified the British military which then shared this discovery with their allies. Soon thereafter the U.S. military decided it would make a good addition to their existing nerve agent chemical arsenal. They dubbed the compound VX, short for short for venomous agent X. Its chemical structure, formula and IUPAC name are shown in Figure 1.

VX and all other nerve agents specifically target the critical enzyme acetylcholinesterase (AChE). They bind in the active site thereby preventing AChE from degrading the neurotransmitter acetylcholine in neuronal synapses (3). The accumulation of acetylcholine causes extensive clinical manifestations collectively called the cholinergic toxidrome. If left untreated this can lead to death, usually due to the extended contraction of the diaphragm muscle and asphyxiation.

Compared to the G nerve agents, VX has some unique properties. Foremost, it is much less volatile and more viscous, having the consistency of motor oil at room temperature (Table 1). Unlike the other nerve agents, VX is much more readily absorbed through dermal contact making it primarily a contact hazard (2). In addition, it is also more resistant to degradation making it tactically useful as an “area denial” agent. Research has shown that VX can persist in soil from 2 - 6 days (2). Relative to the other nerve agents, VX has much bulkier side groups attached to its phosphorus center. Thus, when it first weakly binds to the AChE active site it takes considerably longer to form an irreversible covalent bond (i.e. to age). *In vitro* studies indicate that VX has an aging half-life of ~48 hours which allows a long window for oxime treatments to dissociate the VX-AChE complex (Table 1).

Despite this extended aging time VX is highly potent, less than a drop on human skin is considered sufficient to kill an adult human within a few minutes. The estimated LD50 of VX is only 10 milligrams (2). Shortly after contact, the victim will experience diaphoresis and localized fasciculation of underlying muscles. This is often followed by feeling nauseated and having headaches, miosis, tightness in the chest and potentially seizures. Eventually flaccid paralysis of all muscles in the body can occur and the sustained paralysis of the diaphragm leads to an inability to breathe and death.

There are no documented incidents of VX being used on the battlefield; however, one renowned military accident occurred in 1968. In March of that year, a VX cloud drifted out of a U.S. Army test area in Utah during an aerial spraying experiment. Ultimately, over 6,000 sheep grazing downwind in Skull Valley died from this accidental exposure (2). The Iraqi government under Saddam Hussein claimed to possess large stores of VX, however this was never substantiated.

There has been only one reported use of VX by terrorists. In the 1990s, the Japanese Aum Shinrikyo cult reportedly used it to kill one of their own members after spritzing the agent onto his neck from a syringe. Seven months after his murder, three VX metabolites were found in his blood; ethyl methylphosphonate, diisopropyl-2-(methylthio) ethylamine and methylphosphonic acid (4). These events occurred prior to the cult's sensational 1995 sarin subway attack in Tokyo which resulted in over one thousand innocent civilian casualties.

In the 1990s, nearly all countries recognized the eminent danger posed by chemical weapons. This collective concern resulted in the Chemical Weapons Convention (CWC), an international agreement effectively banning chemical weapons production and mandating destruction of existing stock piles (5). To date, 192 states are signatories of the CWC and it is estimated that ~93% of the world's declared chemical weapons stockpiles have been safely destroyed. Both the U.S. and Russia have spent considerable resources supporting this endeavor. However, three countries are not CWC signatories that are thought to have chemical weapons; North Korea, Egypt, and South Sudan. While Israel is a signatory they have yet to ratify the treaty, and are also thought to have maintained a chemical arsenal. The North Koreans allegedly have an extensive chemical stockpile that includes from 2,500 to 5,000 tons of nerve agent including VX (2). In addition, they may have assisted the Syrian government to build a nerve agent stockpile despite the tight international control of precursor chemicals.

International intrigue: what we currently know- Immediately after the incident at Kuala Lumpur airport, Kim Jong Nam found aid and complained of face pain as well as dizziness. Soon thereafter he had seizures and died within 15 - 20 minutes while in transit to the hospital. Malaysian authorities conducted an autopsy and their laboratory identified VX on his face and eyes (6). This identification does seem to reasonably fit the symptoms shown by Kim Jong Nam. Immediately after the incident the two alleged female operatives ran into the nearest bathroom to wash their hands where one vomited. Both were apprehended.

While the Malaysian government is adamant that VX was found on the decedent, these allegations need further investigation. Samples should be sent to an internationally recognized, unbiased third party where the results can be confirmed or refuted. The North Koreans have asked that the Organization for the Prohibition of Chemical Weapons (OPCW) perform this analysis. They are the designated enforcement arm of the CWC and have several labs capable of performing this analysis. Alternative options include the British military's laboratories at Porton Down or the U.S Army's Medical Research Institute of Chemical Defense.

In mid-March Malaysian authorities publicly stated they had confirmed that the victim was indeed Kim Jong Nam despite North Korean authorities vehemently stating it wasn't (7). This identification involved matching DNA from a son who was residing in China. Additionally, there were matching fingerprints left by Kim Jon Nam from 2001 when he

attempted to enter Japan to visit Disneyland. To date, the body has not been released to any relatives and the remains are being held at the Kuala Lumpur morgue.

While the scientific allegations at present seem to be founded, the motives for this apparent assassination remain unclear. Prior to this incident, the North Koreans had friendly relations with Malaysia. One interesting hypothesis is that the North Korean dictator feels threatened by others in his family lineage that he can't directly control. His family has ruled North Korea since the country's inception in the 1950s. Kim Jong Nam was his eldest brother and his greatest threat based on family lineage. Prior to the incident, Kim Jong Nam was living in exile in China. The Chinese government may have sheltered him in case something happened to the North Korean dictator. Kim Jung Un has previously murdered political rivals, to include close relatives, but always within the boundaries of his reclusive and increasingly isolated country. This public assassination may also have been an attempt to shift attention away from their rapidly developing intercontinental ballistic missile and nuclear weapons programs.

Hopefully, an outside unbiased laboratory can soon confirm or refute the Malaysian's scientific conclusions. If the VX allegations are founded, it seems likely there would be new, tougher international sanctions on the world's most reclusive nation.

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Editor's Corner: Division News

Division Lunch meeting at AACC National Meeting in San Diego is on July 31, 2017
Monday in Marriott Hotel.

AACC TDM TOX Web Resources:

<https://www.aacc.org/community/divisions/tdm-and-toxicology/toxin-library>

Upcoming Conferences

[American Pain Society](#)

May 17-20
Pittsburgh, PA

[AACC/ASCLS](#)

July 30-August 3
San Diego, CA

[ASCP](#)

September 6-8
Chicago, IL

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