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Novichok nerve agent and public health

Reza Afshari, MD, MPH, PhD, Environmental Health Services, BC Centre for Disease Control, BC. Reza.Afshari@bccdc.ca

What are nerve agents?

Chemical warfare agents include a wide range of agents. Nerve agents are a group of highly toxic organophosphorus compounds that have been developed over the past 80 years.[1] Mithridates VI or Mehrdad VI "Persian; gift of Mithra[God]" (113 [?] – 63 BCE) was the king of Pontus (in eastern modern Turkey), Old Persia and Greece who first used grayanotoxin containing honey or mad honey in 67 BCE against the troops of Pompey the Great. This event is the first recorded use of a biotoxin (a nerve agent) in warfare.[2]

Nerve agents are colourless liquids that affect mainly through direct contact with the skin (less volatile e.g. VX) and respiratory system (e.g. easy volatile water soluble Sarin).[3]

Main known nerve agents include:

- Tabun, GA: (CH3)2N-P(=O)(-CN)(-OC2H5)[3]
- Sarin, GB: CH3-P(=O)(-F)(-OCH(CH3)2) [3]
- Soman, GD: CH3-P(=O)(-F)(-CH(CH3)C(CH3)3[3]
- GF: CH3-P(=O)(-F)(cyclo-C6H11) [3]
- VX: CH3-P(=O)(-SCH2CH2N[CH(CH3)2]2)(-OC2H5) [3]
- Novichok

Toxicity of the nerve agents is related to volatility and water solubility.[3] Characteristics of the most well-known nerve agents are presented below.

	LCt_{50} Inhalation mg·min/m³	LD_{50} Skin mg/individual
Tabun	70	4000
Sarin	35	1700
Soman	35	300
VX*	15	10

*: LCt^{50} value is for the aerosolised form

Evolving the use of nerve agents

The use of nerve agents have been evolved in particular in the past four decades. It seems that the uses of nerve agents as chemical warfare agents (CWA) expanded to terrorism acts (TA), political assassinations (PA) and even accidental exposure (AE). The use of CWA for any reason is politically charged including claims and counter claims. Therfore it would be rare if an accident is being proven in an international count of law.

Most well-known or popularised VWA events include:

- 1984–1988; CWA, *Iraq* in the Iran–Iraq war [4]
- 1988*;* CWA*, Iraq*, Al-Anfal against its own Kurdish population[5]
- 1994-1995; TA, *Japan*, a few occasions e.g. Sarin in Matsumoto and Tokyo
- 1995; PA, *Russia,* on Ivan Kivelidi and Zara Ismailova, - Novichok
- 2013*;* CWA*, Syria*, Ghouta, Sarin,
- *2017; CWA, Syria, Khan Sheikhoun, Sarin*
- *2017; PA, Malaysia, Kim Jong-nam (the North Korean leader's half-brother)*
- *2018; PA, England, Salisbury, assassination of Sergei (ex-spy) and Yulia (his daughter) Skripal - Novichok*
- *2018; AE England, Wiltshire accidental exposure of Charlie Rowley and*
- *Dawn Sturgess*

Eye balling this list suggests that the pattern of use in higher income countries has been shifted CWA use towards terrorism, political assassination and accidents. It also implies a troublesome trend in the use of chemical agents by various rogue groups in civilian settings.[6]

What is Novichok?

Novichok means newcomer (Новичо́к) in Russian and was first developed as a fourth generation nerve agent. Novichok category includes many compounds including better known Novichok 5 and 7.[7] It is very stable with a slow evaporation rate and can remain dangerous for years once deployed. Novichok nerve agents are described in the literature as up to eight times more toxic than nerve agent VX.

Novichok was recently used in England in an assassination attempt of Sergei (ex-spy) and Yulia (his daughter) Skripal, who both survived. Later, Charlie Rowley and Dawn Sturgess were accidentally exposed, leading to their death.[8] The finding of Novichok received extensive media coverage.[9] [10] [11] [12]

The Organisation for the Prohibition of Chemical Weapons (OPCW) confirmed that analysis of samples nerve agent used in the Salisbury attack was military-grade Novichok.[11]

Certain reasons have been given to support the theory that Russia was behind this attack. Russia has the technical means, operational experience and motive for the attack according to the UK's National Security Adviser, Mark Sedwill.[13] Russia has categorically denied their involvement.

Clinical findings

Nerve agents including Novichok are organophosphate acetylcholinesterase inhibitors. Upon exposure, acetylcholine concentrations increase at neuromuscular junctions and cause involuntary contraction of all skeletal muscles (cholinergic crisis). This in turn leads to respiratory and cardiac arrest as heart and diaphragm muscles cannot function normally. The respiratory centre of the central nervous system is also affected. Death happens due to heart failure or suffocation as abundant fluid secretions fill the lungs. *Victims drown in their own body's water.*

Nerve agents at very low doses cause headache, contracted pupils (miosis), increased production of saliva (sialorrhea), running nose, nausea and a feeling of pressure on the chest. *Water runs from everywhere.*

At higher doses clinical manifestations are dramatic including (i) respiratory bronchoconstriction and secretion of mucous in the respiratory system that leads to difficulty breathing and coughing, (ii) gastrointestinal effects such as cramps and vomiting, involuntary discharge of urine and defecation, (iii) general weakness, local tremors, loss of consciousness, hallucination and convulsions. [1] [3] [14] [5]

Treatment

Treatment is out of the scope of this article. Mass-casualty triage system is essential. The use of a fast-acting peripheral anticholinergic drugs such as *atropine* along with a Hagedorn oxime such as pralidoxime, obidoxime,

TMB-4, or HI-6, reactivates acetylcholinesterase inactivated by phosphorylation by an organophosphorus nerve agent.[5]

Public Health consideration & lessons to be learned

"In 2016 alone, there were more than 13,400 terrorist attacks globally, killing more than 34,000 people."[6]

Recent public interest

Media rapidly disseminated news about these chemical attacks, and consequently public interest in Canada has increased, as a co-inside indicator (Figure 1). Graphically speaking, public involvement during the 2nd attack (accidental) was more focused on the term Novichok itself to the same extent of the first assassination attempt.

Searches for "nerve agent", which is probably secondary to searches for Novichok and perhaps related to more detailed or scientific information gathering, was not triggered to a high extent during the second incident. It is plausible that the public is more concern about accidental exposure. In the case of the fentanyl tragedy in British Columbia, the Media started reporting on middle class people, recreational use and teenagers dying of overdoses in Vancouver.[15] In the public view, the population at risk widened. We see a similar pattern here.

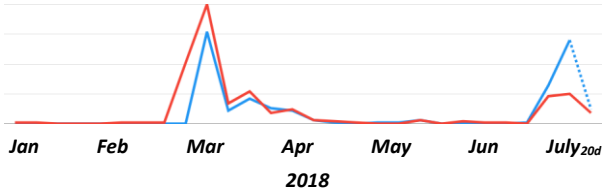

Figure 1. Public interest in "nerve agent" (🟥) and "Novichok" (🟦) in Canada (adapted from Google trends) in light of recent events in England.

Breakdown of public interest in "nerve agent" (🟥) and "Novichok by subregion from January to July 20 2018 are presented in Figure 2. Relatively speaking, Novichok was more of a public concern in BC and ON as compared to other provinces in this period. Searching for "nerve agent" was more popular in other provinces.

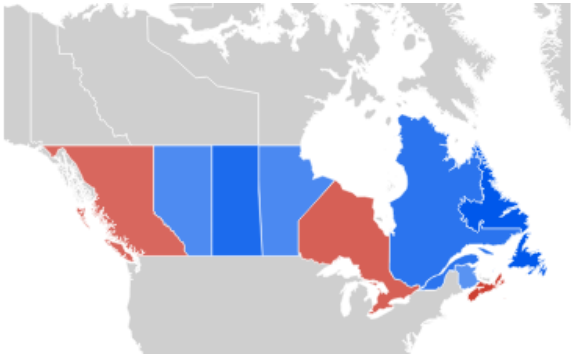

Figure 2. Public interest in "nerve agent" (🟥) and "Novichok" (🟦) in Canada in light of recent events in England; Compared breakdown by subregion, January to July 20 2018 (adapted from Google trends).

Public sentiments

"Real and perceived risks of toxic exposures in potential terrorist attacks are real and should be taken seriously. However, they may be combined with a proportion of psychologically based symptoms and become complexed and may lead to hysteria."[16]

Media involvement

Media tries to make a good story, potentially leading to mass hysteria, which has a contagious nature. Dealing with the Media should be managed carefully.

Organisational partnership

It is important to develop inter-organisational and public-professional partnerships. Releasing the news should be joint work.[16]

Toxicology tests

Extensive testing of most environments may reveal substances that can be harmful, but may also be artefactual. Specific accurate tests should be referenced.

Exposed cases

It is important to evaluate the subjective and objective manifestation of a toxic exposure. Time interval and proximity to the situation are important determinants.

Accidental exposure

In the Salisbury and Amesbury events Public Health England defined the risk to the public as low but, as a precaution, recommended members of the public to not to pick up items such as syringes, needles, cosmetics or similar objects made of materials such as metal, plastic or glass.[8]

Safe and Effective Response (protecting respondents)

Safety at the scene of the attack (proper use of personal protective equipment) must be the priority for all responders. First rapidly identify the presence of a chemical agent and then determine hot (contaminated), warm, and cold (uncontaminated) zones. Decontamination units can be staged in warm zone.[6]

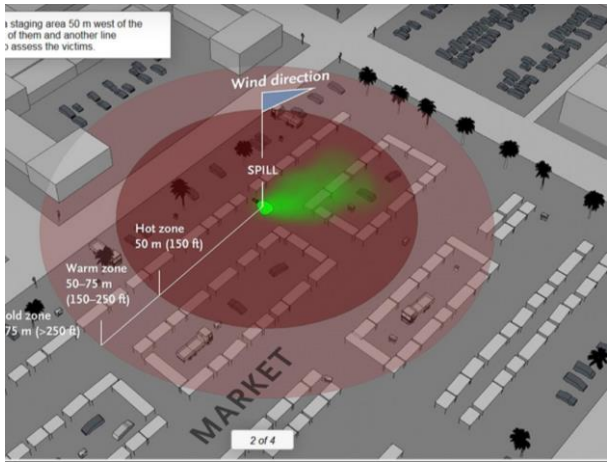

Figure adopted from.[6]

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