

Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

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Novichok nerve agent returns in the attempted assassination of Russian opposition figure Alexei Navalny

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Introduction- On August 20, 2020 prominent Russian political dissident Alexei Navalny was on a flight bound to Moscow when he was suddenly wracked with severe pain and was unable to breathe. In response, the pilots conducted an emergency landing in the nearby Siberian city of Omsk where the previously healthy 44-year-old was quickly hospitalized. There, he was stabilized by being put into a medically induced coma and placed on a ventilator. After extensive testing, Russian clinicians stated he likely had a severe bout of hypoglycemia and that no toxic substances were found in his system. Deeply concerned about possible poisoning and his death, German officials were allowed to fly Navalny to their country two days later. Upon becoming aware of this bizarre incident, members of Navalny's team rushed to the Tomsk Siberian hotel he had been staying and collected everything that could be used as possible crime evidence.

Shortly after being admitted to a German hospital, biological samples taken from Navalny were sent to the Bundeswehr Institute of Pharmacology and Toxicology. Their analysis of his blood and urine revealed trace amounts of a Novichok nerve agent which was publicly announced on August 24. This shocking claim was independently confirmed by labs in France

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and Sweden. Interestingly, just two years earlier the first known use of the mysterious Novichoks occurred in the attempted assassination of ex-Russian spy Sergei Skripal in England. While it failed, over 20 innocent bystanders were poisoned, and one died (1). Most experts felt that this poisoning was directed by the senior Kremlin leadership.

Nerve agents and the Novichoks- The Novichoks are a subclass of organophosphorus (OP) nerve agents, distinct from traditional agents such as sarin, soman and VX. All nerve agents rapidly bind critical amino acids found in the active site of acetylcholinesterase (AChE, EC 3.1.1.7) preventing it from degrading its substrate, the neurotransmitter acetylcholine. This results in the neurotransmitter accumulating in neuronal synapses that can cause an array of clinical manifestations collectively called the cholinergic toxidrome. If left untreated it can cause death, typically due to paralysis of the diaphragm resulting in asphyxiation (2). The mnemonic DUMB BELSS is often used to remember the most commonly observed effects. It stands for Diarrhea, Urination, Miosis, Bradycardia, Bronchoconstriction/ Bronchorrhea, Emesis, Lacrimation, Sweating and Salivation.

These OP nerve agents are some of the most toxic substances known to man. A dermal exposure of just 10 mg of VX can be lethal to an adult human. A summer 2019 *Therapeutics and Toxins News* article provides a comprehensive review on the relatively unknown Novichok agents and their use in the 2018 Skripal attempted assassination (1). The traditional nerve agents were reviewed in the winter 2016 issue of this journal which has sections that discuss laboratory test methods and current treatments (3).

The Novichok class of nerve agents represent the latest, most lethal, generation of chemical weapons. They were covertly developed by the Russians at the end of the Cold War with four main objectives: 1) to be undetectable to current chemical detection tests 2) to breach NATO military chemical protective gear 3) to be safer to handle and 4) to bypass the Chemical Weapons Convention that bans chemical agents. It was likely assumed these weapons could be used with impunity against Russia's enemies.

As with most nerve agents, the Novichoks reportedly can be delivered as a liquid, aerosol or gas and may be dispersed as an ultra-fine powder by adsorbing the liquid onto a solid carrier (4). Reports indicate that seven Novichoks have been adopted as weapons by the Russian military (4). The right panel of Figure 1 shows the proposed chemical structures of four different Novichoks (5). There are no documented incidents of these agents being used on the battlefield and Russia is the only country known to have developed them.

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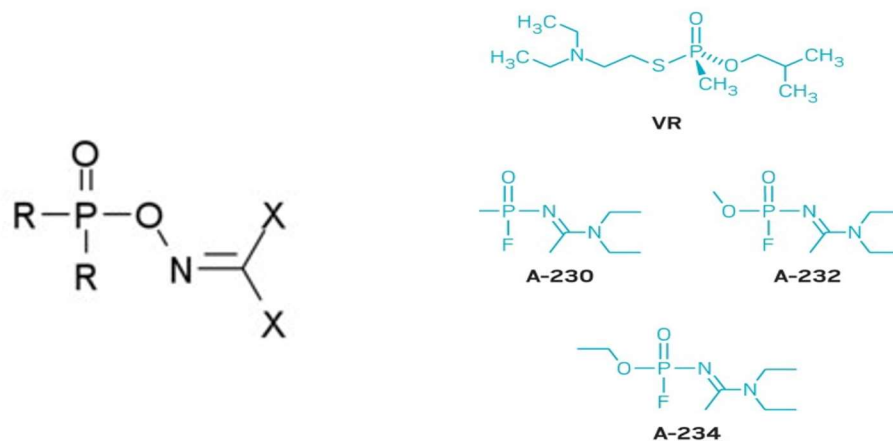


Figure 1. Left- the presumed generic chemical structure of Novichok nerve agents. R= alkyl, alkoxy, alkylamino or fluorine and X is a halogen (F, Cl, Br) or a pseudohalogen like a nitrile group. Right- the proposed chemical structures of four Novichok agents (5).

The post-Cold War global concern over the development and use of chemical weapons led to the 1997 Chemical Weapons Convention (CWC). This international agreement effectively bans chemical weapons production and mandates scheduled destruction of existing declared stockpiles (6). There are currently 193 state signatories to include Russia and the US. The Organization for the Prohibition of Chemical Weapons (OPCW) provides an unbiased 3rd party lab confirmation testing and serves as the CWC's global watchdog. In 2017, the OPCW confirmed that VX nerve agent had been used to brazenly assassinate Kim Jong Nam at the busy Kuala Lumpur Airport; he was the half-brother of North Korean dictator Kim Jong Un (7). In 2018, the OPCW unequivocally confirmed Novichok was used in the Skripal attack in England (1).

International intrigue: what we currently know- Alexei Navalny is an internationally prominent political adversary to Russian President Putin. Soon after graduating from law school, he entered politics and was focused on anti-corruption and pro-democracy. He has been described as the person Putin fears the most. He currently has over six million YouTube followers and at least two million Twitter followers (8). He has led multiple public protests highlighting the corruption of the Putin administration, some had up to 50,000 participants. Navalny's actions have resulted in at least 13 different arrests. In 2018, he attempted to run

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against Putin in the Russia presidential election but was banned due to his prior criminal convictions, that most consider to be illegitimate (8).

On the 7th of September 2020 Navalny came out of the coma and 16 days later was discharged from the Berlin hospital. He then received extensive physical therapy to regain his strength. On October 6, 2020, the OPCW confirmed the results of previous labs that a Novichok agent was found in Navalny's blood and urine. It was not publicly disclosed as to which Novichok(s) were identified. German Chancellor Angela Merkel stated, "he was meant to be silenced and I condemn this in the strongest possible manner." She further stated there are "serious questions that only the Russian government can answer- and must answer."

It was first presumed that Navalny was poisoned just prior to his Moscow flight as he had not consumed anything that morning but a cup of hot tea at the airport. However, the German scientists revealed on September 17 that a water bottle recovered from his hotel room had detectable levels of Novichok on it. This clearly indicated he was poisoned prior to the airport. The trace Novichok detected was likely left there by Navalny's lips after he had already been poisoned.

Multiple independent investigative journalist groups claim to have evidence a team of Russian Federal Security Service (FSB) agents had trailed Navalny for years and were in Tomsk near his hotel before he was poisoned. Their conclusions are based on phone and flight records as well as leaked passport data that showed the team's movement. This was fully corroborated by Navalny on December 21st when he released a video showing him impersonating a Russian official to speak with a scientist who he thought was responsible for the poisoning. This FSB agent stated the poison was put on Navalny's clothing with extra placed in his underwear and that he would have died if not for the plane's emergency landing and rapid medical intervention.

The European Union (EU) has stated the "attempted assassination of Navalny was part of systemic effort to silence dissident voices in Russia." In response, the Russians have tried to deflect blame by claiming the positive test results are inaccurate and that it is an elaborate anti-

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Russian plot to impede their country's development. The EU, UK, NATO, and US have imposed sanctions targeting senior Russian officials.

It is noteworthy that following the 2018 Skripal poisoning incident, the Novichoks were added to the list of chemicals regulated under the CWC. Now there can be no misunderstanding about potential legal loopholes to circumvent the treaty. Novichok production, storage and use is strictly prohibited. This new Navalny incident strongly suggests that Russia is again in breach of the CWC that they signed. After fully recovering from the nerve agent attack, Navalny flew back to Russia on January 17, 2021 and upon disembarking was met by authorities and jailed. This was allegedly due to him not reporting to Russian police while convalescing in Germany. Recently he was sentenced to serve a minimum of 2.5 years in a labor colony.

Conclusion- It is quite distressing that there is another high profile attempted murder that involved using a nerve agent to target a political rival. Just as an evidential smoking gun led back to Russia's role in the 2018 Sergei Skripal poisoning, so too again does the Novichok presence leads to Russia's involvement in this attempted assassination of Alexei Navalny. There is no plausible explanation that this incident was accidental but instead clearly appears to have involved deliberate targeting to silently kill. Hopefully repeated and unified international condemnation with major economic consequences will stop these tragic events from reoccurring.

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Editor's Corner: Division News

Dear Readers,

It has been over a year that we have all been all suffering through the COVID 2019 pandemic; worldwide, over 154 million people have contracted the virus with over 3 million deaths. The pandemic can be tamed only with diligent social distancing measures, precautions, and especially with vaccination. Unfortunately, the pandemic currently roars in the Indian subcontinent, where vaccination was insufficient and appropriate social distancing was ignored. Complicating the pandemic has been the appearance of multiple mutants; some may be more infectious, able to evade detection by most tests, while others have reduced response from current therapies, cause higher morbidity and mortality, and have ability to evade natural or vaccine induced immunity. Most vaccines, RNA or modified adeno virus, generate immunity against the spike protein of the virus. Like everything else, AACC National Meeting has also been affected. In 2020, it was all virtual; this year it is expected to be in person in Atlanta (GA, USA) during Sept 26-30. Airline flights are banned now from India to various parts of the world. Networking and learning, meeting speakers and colleagues has all been on hold for more than a year, but we hope that social distancing, vaccination, and smart preventative measures can keep cases low so that we can attend this year. Good luck, enjoy the summer, and stay safe!

Pradip Datta, Editor.

AACC TDM TOX Web Resources:

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

Upcoming Conferences/Courses

Most have been postponed.

AACC National Meeting

Sept 26 to 30, 2021

Atlanta, USA

International Federation of Clinical Chemistry

Nov 28 to Dec 02, 2021

Munich, Germany

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Announcements:

1. We need your ideas and article contributions for this newsletter. It is a good opportunity to put authorship in resume. Please contact Dr. Pradip Datta at pradip.datta@siemens.com.
2. *Don't forget to vote next month in Division elections! Voting will be open June 14 – July 2. The link will be posted on the Artery and sent out via email.*