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Review

Chemical warfare agent NOVICHOK - mini-review of available data

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ABSTRACT

The Cold War period is characterized by the infighting between the Western countries and the USSR in diverse areas. One of such fields was development of the weapons of mass destruction. Within various programs on both sides, a wide scale of different agents have been developed. However, information about some of them are still protected under the designation "top secret". Notwithstanding, in history several cases are known when such information beheld the daylight. One of such cases was the program FOLIANT and NOVICHOK. Both programs were developed by the USSR as a reaction to English/American invention of VX agent. If at least a part of available information is truthful, we can allege that these compounds belong among the most toxic synthetic agents ever. Within this contribution, we have reviewed available Eastern and Western data about the A-agents and their precursors, so-called NOVICHOKs, including their history, synthesis, physical-chemical properties, pharmacological characteristics and clinical manifestation.

1. Historical overview

Immediately after the World War I, nobody doubted that the next war would run without chemical warfare agents (CWAs). The more the conflict seemed to be realistic, the more intensive were the preparations of potential participants. Not only the experience rising from the previous usage of CWAs was thoroughly evaluated, but also searching for novel more effective substances gradually escalated(Halámek and Kobliha, 2011; Klement, 2011).

In 1934, a project on synthetic insecticides was launched at industrial corporation I. G. Farben (Germany) by Otto Bayer who assigned this research branch to the chemist Gerhard Schräder. In 1936, Schräder's interest turned to organophosphorus compounds. His systematic work on organophosphate (OP) insecticides led to the synthesis of more than 2000 compounds, including highly toxic ethyl dimethylphosphoramidocyanidate (tabun, GA, Trilon 83, Fig. 1)(Szinicz, 2005). Subsequently, Schräder and co-workers discovered a more lethal OP compound similar to tabun – propan-2-yl methylphosphonofluoridate (GB, Trilon 46, Fig. 1). They named this compound sarin in honour of the team members: Schräder, Ambros, Ritter and van der Linde (Coleman, 2005). Since 1935, an official decree required for all inventions possessing potential military application to be reported to the German Ministry of War. In 1937, the samples of tabun and sarin were sent to the German Army Weapons Office (Wa Prüf 9) where their value for military purposes had been immediately recognized and hence all patent applications concerning these agents were declared secret (Szinicz, 2005). Work on these compounds was carefully guarded and was realized under the code name Trilon. The discovery of tabun and sarin was further followed by the revelation of a pinacolyl analogue of sarin – soman (3,3-dimethylbutan-2-yl methylphosphonofluoridate, GD, Fig. 1) in 1944 by the Nobel laureate Richard Kuhn and Konrad Henkel(Tucker, 2006). Tabun, sarin and soman belong to the class of nerve agents (NAs) that are collectively termed "*G-agents*"; the *G* stands for *German* since German researchers discovered this group of compounds(Ledgard, 2006).

Until April 1945, almost 9000 tonnes of tabun, 1300 tonnes of sarin and 20 tonnes of soman were mass-produced by the Nazi regime, however, they were never used (Halámek and Kobliha, 2011). There has been a considerable debate about why the Germans did not use their chemical arsenal in the World War II. Several explanations include: i) personal negative experience of Adolf Hitler who was seriously affected by mustard gas during the World War I; ii) fear of retaliation, and iii) underestimation of German superiority in chemical weapons (Paxman and Harris, 2011; Pitschmann, 2014; Tucker, 2006).

After World War II, another chapter in the history of development and production of CWAs began. As Nazi resistance collapsed, the Soviet and Allied forces captured the NA production facilities and technologies of the Germans' including scientific archives and experts in this field. Both groups quickly reorganized the military potential of these agents and set to work at developing and stockpiling their own supplies

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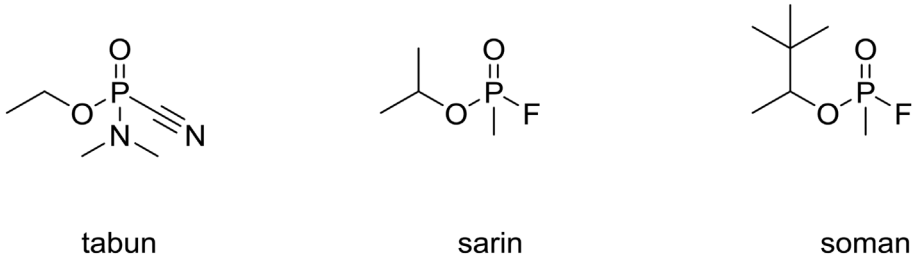

Fig. 1. Chemical structures of G-agents.

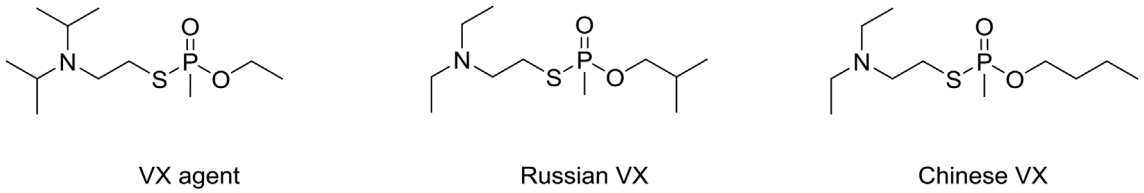

Fig. 2. Chemical structures of V-agents.

(Wiener and Hoffman, 2004). In 1949, British chemist Ranajit Ghosh discovered novel, military important group of OP esters derived from variously substituted 2-aminoethanethiole. Shortly after this discovery, the existence of these compounds had been reported to the British Chemical Warfare Establishment in Porton Down. VX agent (*S*-{2-[di (propan-2-yl)amino]ethyl} *O*-ethyl methylphosphonothioate, Fig. 2) has been selected as the most promising substance of the series(Szinicz, 2005). In a deal brokered between the British and the US governments, the British traded the VX technology for the thermonuclear weapons technology of the United States. Thereafter, full scale production of VX commenced in 1961 in the USA (Tucker, 2006). During the same period, the Soviet scientists developed independently of the UK and the USA an isomer of VX agent – the so-called Russian VX (VR, RVX, Substance 33, *S*-[2-(diethylamino)ethyl] *O*-(2-methylpropyl) methylphosphonothioate, Fig. 2) which later became a prototype for the series of NOVICHOK agents. Another structural analogue of VX known as Chinese VX (CVX, *O*-butyl *S*-[2-(diethylamino)ethyl] methylphosphonothioate, Fig. 2) was also developed and studied(Romano et al., 2007).

VX and its analogues belong to the class NAs that are collectively termed "*V-agents*"; the *V* stands for *venemous* because they are very toxic and the symptoms of their intoxication resemble the manifestation of snake venom poisoning(Tucker, 2006). These phosphonylated and phosphorylated thiocholine derivatives, lacking electron-withdrawing groups such as halogen or cyano group, are very reluctant to nucleophilic substitution and so to hydrolysis. This fact together with extremely low volatility ensure the resorption of these substances through unprotected skin into the bloodstream(Ellison, 2007; Wiener and Hoffman, 2004).

Until the 1950′s, the CWAs were unitary, i.e. the toxic agent was filled in the ammunition and then stored until its use. The problems resulting from the production, stockpiling of unitary CWAs as well as from requirement for expensive disposal of defective or expired chemical ammunition, disagreement of local population, activities of various ecological organisations and last, but not least from the absence of novel CWAs with desirable stability within the process of storage launched in the USA the project denoted Binary Lethal Weapons System. For the purpose of this project two NAs were selected – sarin and VX (Fig. 3) (Gupta, 2015; Halámek and Kobliha, 2011). Such technology involves two or more non-toxic chemical precursors physically separated from each other. The final step of synthesis of the toxic agent from above-mentioned precursors is performed immediately before or in the process of firing of the ammunition(Wiener and Hoffman, 2004). Therefore, binary weapons (BWs) prevent unintentional toxicity to those handling, transporting or disposing the weapons. The complications associated with BWs involve complicated construction of ammunition, smaller cartridges where the precursors are imposed and lower yields of the final step.(Halámek and Kobliha, 2011).

Initially, the Soviets had very reserved attitude to BWs. They were convinced that this type of ammunition is generally less efficient and due to complicated construction more expensive comparing to weapons filled with unitary agents. The Soviets perceived the BW program as a way of the USA how to circumvent the upcoming Chemical Weapons Convention (CWC) (Halámek, 2008). Such negative attitude of the USSR was probably determined by huge amounts of stockpiled unitary CWAs but also by relatively low age of chemical arsenal. Not negligible was also the fact that the USSR did not puzzle over the disposal of expired or defective ammunition. However, with the progress of the time all these arguments lost importance since signing of the CWC was drawing nearer as well as the Soviet chemical arsenal was gradually expiring.(Halámek, 2008).

At the time, when in the US binary weapon program was at its peak, several long-term research projects took place also in the USSR. Among them, the most important in the field of chemical sciences were FLUORINE (in Russian "*FTOR*") and PHOSPHORUS (in Russian "*FOSFOR*"). These projects were of high priority not only from the point of view of national economy but also of the military sector. Particular attention was paid to compounds with strong biocidal effect(Halámek, 2008; Vásárhelyi and Földi, 2007).

Moreover, it was found that within the storage process Russian VX was very sensitive to moisture. The necessity of RVX stabilization together with development of its thickened version or even conversion to the binary form led to initiation and escalation of the top secret Soviet project FOLIANT between 1973 and 1976. The knowledge obtained within FLUORINE and PHOSPHORUS projects was incorporated into the FOLIANT program as well. The main aim of this project was synthesis of the third generation of NAs with higher toxicity compared to V-agents that will be undetectable using NATO standard chemical detection equipment(Halámek, 2008; Halámek and Kobliha, 2011; Vásárhelyi and Földi, 2007). More than 200 chemists and engineers were involved in the FOLIANT program. According to available sources, at least three unitary chemical weapons were synthesized (A 230, A 232 and A234, Fig. 4). Structures of so-called A-agents have been never published. Over the last few years, the information that these compounds are derivatives of dihaloformaldoxime started to appear. This assumption was based on published works of Soviet chemists who probably participated on the FOLIANT program(Kruglyak et al., 1972a, 1972b; Malekin et al., 1972; Martynov et al., 1969; Petrov et al., 1967;

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