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NARRATIVE REVIEW

Chemical Warfare Agent: Toxicity and Health Effects of Sarin Gas (GB)

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ABSTRACT

Chemical warfare agents (CWAs) are toxic substances used to cause harm, injury, or incapacitation to an adversary in the context of warfare and related military activities. Sarin stands as an exemplar among agents, embodying some of the most potent compounds ever developed. This strength originates from its ability to permanently inhibit the acetylcholinesterase (AChE) enzyme, leading to the accumulation of acetylcholine (ACh) at synaptic junctions, which, in turn, induces stimulation of muscarinic and nicotinic receptors. The main objective of the current article is to summarize the negative influence of sarin gas on health and its role in the incidence of several pathological conditions in people who's exposed to the gas. From this point of view, the clinical features of sarin exposure (health effect and related diseases) and the influence of nerve agents on deactivation of cholinesterase were the main area covered in this article. Furthermore, and for better understanding of the gas behavior and its toxicity, it was important to discuss the features of the gas, discovery, mechanism of toxicity, and pharmacological management. Lately, various approaches have also been reported with esteem of sarin detection, destruction, attacks, and treatment approaches after sarin poisoning.

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Historical background

Throughout history, chemical and biological hazardous materials have been utilized as weaponry and tools for homicide since prehistoric times. Historical records indicate

instances of their deployment in warfare during ancient Greek and Roman eras, although their effectiveness was constrained by the limited knowledge available during those periods [1]. Numerous instances of chemical use in warfare and armed conflict can be traced back to the fourth century BC. Early human societies were pioneers in employing chemical compounds for both hunting and military engagements. The earliest application of chemical weapons might haveinvolvedusingsmokefromfires to displaceanimals or adversaries from caves. Additionally, distant human ancestors used naturally occurring substances derived from plants, insects, or animals, which were identified as causing illness or death, in efforts to establish or sustain dominance[2].

The initial applications of chemicals paved the way for the development of more potent chemical weapons. For instance, during the fourth century BC, sulfur-containing smoke was deployed in the conflict between Sparta and Athens. Simultaneously, Chinese manuscripts from the same era document the use of arsenical-based compounds in warfare [3]. During their siege of Kirrha in 600 B.C., the Athenians successfully polluted water sources with the roots of Helleborus. The use of CWAs has persisted sporadically in battlefields, reaching its peak during World War I (WWI). The French were the first to deploy ethyl bromoacetate during this conflict. Subsequently, a range of substances such as o-dianisidine chlorosulphonate, chloroacetate, chlorine, phosgene, hydrogen cyanide, chlorine, diphenylchloroarsine, ethyl- and methyldichloroarsine, and sulphur mustard were employed, resulting in approximately a million casualties and almost 10,000 fatalities [4]. In 1937, Gerhard Schrader devised the universal formula for all organophos- phorus compounds and synthesized the nerve agents tabun (GA) and sarin (GB). This was promptly succeeded by the development of additional agents [5].

The initial documented battlefield deployment of nerveagents GA and GB occurred during the Iran-Iraq War, followed by their use against Kurdish populations [6,7]. The 1987-1988 deployment of sarin against Iranian military personnel and civilians in Halabja marked the first verified battlefield use of nerveagents. Research indicates that chemical warfare during the Iran-Iraq conflict resulted in approximately 100,000 casualties. Nerve agents demonstrated significantly higher lethality compared to other chemical warfare agents and played a substantial role in Iraqi missile operations during this conflict[5]. Subsequent incidents involving nerve agents occurred in Japan, with the 1994 Matsumoto incident resulting in seven fatalities and approximately 200 casualties requiring medical intervention. he following year, a sarin release in Tokyo's transit system caused 12 fatalities and necessitated medical treatment for over 5,000 individuals [8]. More recently, the United Nations confirmed the deployment of sarin in Damascus's Ghouta district in August 2013 during the Syrian civil conflict[9].

Chemical warfare agents (Nerve agents)

Chemical warfare, commonly referred to as chemical warfare agent (CWA), involves using the harmful properties of chemical substances in the context of warfare and other military activities. In warfare, CWAareclassified into various types, including nerveagents, vesicants (blistering agents), blood agents (cyanogenic agents), choking agents (pulmonary

agents), riot-control agents (tear gases), psychomimetic agents, and toxins [4]. Nerve agents (NAs) are significant CWA due to their severity and hazardous nature. They are categorized as a subset of organophosphorus (OP) compounds, and over recent decades, they have been deployed as tactical weapons and for terrorist activities. Furthermore, their applications extend to serving as additives in petroleum and as pesticides [10]. NAs are regarded as the most deadly substances among chemical warfare agents, being potentially fatal during the acute phase of poisoning[11].

Nerve agents and pesticides comprise phosphorus (V) compounds with a terminal oxide and three singly bonded substituents (two alkyl substituents and an additional substituent known as "leaving group") **(Figure 1)** [12]. CWAs that are widely recog- nized are distinguished by both their chemical nomenclature and two-letter codes assigned by the North Atlantic Treaty Organization (NATO). These agents are clas- sified into two series: the G series, including GB (Sarin), GD (Soman), GA (Tabun), and GF (Cyclosarin); and the V series, consisting VE (S-2-diethylaminoethyl O-ethylethylphophonothioate), VG (2-diethoxyphosphorylsulfanylN, N-diethylethanamine), VM (2-ethoxy-methylphosphoryl sulfanyl N, N-diethylethanamine), and VX (S-2 diiso-propylamino O-ethylmethylphosphonothioate). The designation "G" signifies the country of origin, Germany, while "V" potentially indicates "Venomous." Due to their phospho-rylating mode of action arising from the organophosphonate structure, nerve agents are considered the most hazardous synthetic chemical derivatives. Specifically, the pivotal factor contributing to their peril lies in their mammalian toxicity when contrasted with closely related species [12]. Furthermore, nerve agents are dangerous both in liquid and vapour form, and they can be lethal within minutes of exposure, especially in mild climates where they are present in liquid form. When distributed, the more volatile types simul-taneously appear as liquid and vapour hazards, while the less volatile types mainly pose a liquid hazard. The G-agents are more volatile than VX. GB (Sarin) is the most volatile, but evaporates less readily than water[13].

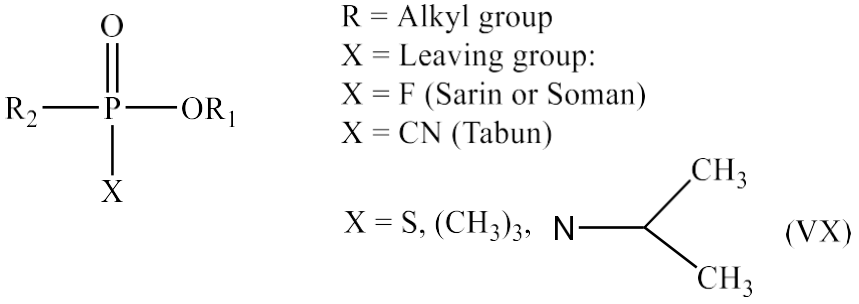


Figure 1: General Structure of Nerve Agents. Adapted fromreference[13].

Sarin gas (GB)

Sarin, an organophosphate nerve agent with non-persistent characteristics, was initially identified in 1938 within the research facilities of Dr. Gerhard Schrader. Its discovery occurred unintentionally during Dr. Schrader's exploration of novel insecticides, where he

also serendipitously uncovered tabun (GA), marking the initial characterization of nerve agents. Sarin, the second G-series nerve agent to be identified, was named in recognition of its discoverers: Schrader, Ambros, Rüdiger, and Van der Linde. It was designated as GB due to its sequential position as the second nerve agent within the G-series to be identified[14]. The synthetic nerve agent sarin (C4H10FO2P) is classified as an organophosphate chemical weapon, characterized by its distinctive carbon-phosphorus covalent bond structure **(Figure 2)** [15].

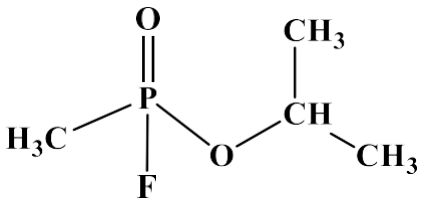


Figure 2 : Depicts the chemical structure of sarin. Adapted and reproduced from reference[15].

Chemical and Physical properties of Sarin

Sarin exhibits volatility characteristics comparable to water and demonstrates the highest vapor pressure among organophosphate nerve agents. The compound's persistence and volatilization rate are fundamentally influenced by environmental temperature conditions and substrate characteristics upon which the agent is deposited. Due to its molecular mass and density, sarin vapor possesses a higher specific gravity than air, resulting in gravitational accumulation in topographical depressions, including valleys, trenches, and subterranean structures [8,12,16]. Table 1 summarize the chemical and physical properties of sarin gas.

Table 1. 1: Chemical and Physical Properties of Sarin.

Chemical name	Isopropyl methyl phosphonofluoridate
State	Liquid
Oder	None
Molecular weight	140.1 g/mol
Appearance	Clear colorless; tasteless
Liquid Density	1.09 g/ml at 25^{o}C
Vapor Density (air = 1)	4.8
Volatility	22,000 mg/m^3
Solubility inwater solvent	Miscible
Solubility in other solvents	Soluble
Melting point	-56 ^{o}C
Boiling point	158 ^{o}C
Lethal concentration-time (LCt)$_{50}$	100 mg(min)/m^3
Topical LD$_{50}$ *	1700 mg
Vapor pressure	2.10 mm Hg at 20^{o}C

* Topical LD$_{50}$ represents the individual topical dosage that would kill one half of an unprotected population. Adapted from references[7,17–19].

Sarin Toxicity

The primary source of sarin's toxicity lies in its rapid absorption through the skin, eyes, and respiratory tract, with inhalation representing the most hazardous mode of exposure. Adverse effects from exposure to sarin vapor or aerosols manifest within a brief timeframe, typically ranging from seconds to five minutes following inhalation[14]. Elevated exposures to sarin at substantial levels can result in fatality within minutes to hours. Sarin can be inhaled in its vapor state or absorbed in its liquid state through the skin, eyes, or mucous membranes. Due to its exceptional potency, sarin has the capacity to cause lethality in 50% of individuals exposed, with a dosage of 100 mg applied across the skin or an inhalation exposure level ranging from 50 to 100 mg/min/m^3 [20]. The four most widely recognized symptoms of sarin toxicity comprise miosis, hypersecretions, bradycardia, and fasciculations. Notably, acute respiratory insufficiency emerges as the predominant factor contributing to immediate fatality [21–25].

Table2. 2: Toxicological Effects and Exposure Parameters of Sarin. Adapted from references [14,20–22]

Parameter	Details	Time Frame	
Exposure Routes			
Primary Routes	• Skin • Eyes • Respiratory tract	-	14
Most Hazardous Route	Inhalation	-	14
Lethal Dosage			
Dermal LD50	100 mg	Minutes to hours	20
Inhalation LC50	50-100 mg/min/m^3	Seconds to 5 minutes	20
Physical States			
Vapor	Inhalation exposure	Immediate effects	14,21
Liquid	Absorption through: Skin, Eyes Mucous membranes	Variable	21,22
Principal Symptoms			
Primary Effects	• Miosis •Hypersecretions Bradycardia • Fasciculations	Variable	21,22
Fatal Outcome	Acute respiratory insufficiency	Minutes to hours	21,22

Notes: LD50: Lethal dose causing 50% mortality
LC50: Lethal concentration causing 50% mortality
Time frames vary based on exposure route and concentration

Metabolism and pharmacokinetics of sarin

Despite its high toxicity, sarin exhibits a brief duration of residence within the body. Upon entry into the organism, sarin undergoes rapid metabolism and subsequent excretion. The principal metabolite is isopropyl methylphosphonic acid, a pharmacologically inert hydrolysis product[23,24]. This metabolic byproduct undergoes rapid elimination via urine. In the case of rats subjected to subcutaneous injection with sarin, 59% and 91% of the administered dose were expelled from the body after 4 and 24 hours, respectively. Subsequently, the sarin metabolite became non-detectable in urine within a two-day period. These findings led to the estimation that sarin possesses a terminal half-life of 3.7 ± 0.1 hours in rat urine. Additionally, pharmacokinetic investigations have been conducted in guinea pigs, which are regarded by some as a highly indicative model for human exposure[24–26]. The study demonstrated that a dosage equivalent to 0.1 times the lethal concentration for 50% of the population (LC_{50}) of sarin in guinea pigs resulted in a half-life of 56.39 minutes in the plasma and 923 minutes in red blood cells (RBCs) [26].

One major source of variation in pharmacokinetics is the cytochrome P450 enzymatic system, which comprises intracellular heme-binding enzymes present in all living cells [27]. The P450 enzymes are intracellular proteins associated with cell membranes, primarily located on the endoplasmic reticulum, and to a lesser extent, they are also found on plasma membranes and mitochondria [28]. Their localization within the human body exhibits variations across diverse tissues and organs, with the liver containing the majority of the primary enzymatic activity [29]. One of the two steps in the detoxification process of sarin involves the bioactivation of the parent compound by the cytochrome P450 system, followed by the hydrolysis of the resulting oxygenating metabolite (oxon) by serum and liver paraoxonase (PON1)[30].

CHOLINESTERASE ENZYMES

Before starting with the health problems accompanied sarin gas exposure, which is the main goal of this review, it was necessary to give a detailed characterization of AChE such as structure, active site, catalytic efficiency, mechanism of action, its role in normal nerve transmission, inhibition of the enzyme and loss of biological activity. The reason behind this detailed explanation is mainly due to two reasons: firstly, the main toxic mechanism of nerve agents involves the inhibition of acetylcholinesterase, and secondly, all these pathological conditions are directly linked to the gas's impact on the properties and efficacy of the enzyme. Secondly, the therapeutic approach is aimed at counteracting the consequences of cholinergic overstimulation. It involves blocking the effects of ACh on muscarinic receptors, as well as reactivating phosphorylated AChE by disrupting the covalent bond formed between the nerve agent and AChE. This process restores the physiological function of the enzyme[31].

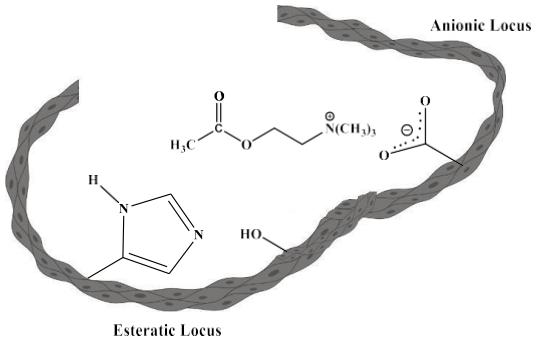
The human brain contains AChE in both neurons and glial cells, and its physiologi- cal function is well-established. It plays a pivotal role in facilitating the transmission of nerve impulses, predominantly through its interaction with cholinergic receptors situated in both the central and peripheral nervous systems [32]. The mechanism of ACh-mediated neurotransmission is essential for survival; its sudden disruption can be fatal, and its grad-

ual decrease is linked to the progressive decline of cognitive and neuromuscular abilities, such as in Alzheimer's disease. However, AChE transcends its role as a mere enzyme in the cholinergic nervous system; it appears tobeinvolved in various biologicalprocesses, including neuritogenesis, cell adhesion, differentiation, and the formation of amyloid fibers [33–35].

AChE structure, active sites and catalytic efficiency

According to AChE's three-dimensional structure, the active centre is situated at the bottom of a small gorgethat is roughly 20 Å deep [36]. It is also worth noting that the AChE active center encompasses four distinct sites: the catalytic triad (comprising Glu334, His447, Ser203), the acetyl pocket (involving Phe295, Phe297), the choline subunit (including Trp 86, Glu 202, Tyr 337), and the peripheral site (encompassing Trp 286, Tyr 72, Tyr 124, Asp 74) [37]. The active site of AChE can be classified into three areas, according to Quinn and as illustrated in (**Figure 3**): (i) an esteratic subsite, which is home to the catalytic triad's serine and histidine and binds to the acyl group of ACh; (ii) an anionic subsite, which is made up of negative charges and interacts with ACh's quaternary ammonium group; and (iii) a hydrophobic region situated in proximity to the esteratic and anionic subsites, crucial for the binding of arylic substrates [38].

Figure 3: AChE Active Sites



Mechanism of ACh hydrolysis by AChE

The primary function of AChE activities centers on the hydrolysis of the neurotransmitter ACh. This process is characterized by nucleophilic additions and acid-base reactions, predominantly relying on the involvement of the catalytic residues within the triad. The suggested mechanism, which is consistent with the experimental results, involves a series of two nucleophilic attacks and two proton transfers, resulting in the formation of a covalent acyl enzyme intermediate. Within AChE, the withdrawal of a proton from Ser-203 by His-447 induces the formation of a nucleophilic Ser–O, which subsequently initiates an attack on the ACh molecule, leading to the creation of a tetrahedral adduct as an intermediate. The stability of the protonated state of His-447 is facilitated by Glu-334, and this stabilization of charges within the transition state plays a pivotal role in augmenting the extraordinary catalytic efficiency of AChE. Glu-334 stabilizes the protonated state of His-447, and this chargestabilization within the transitionstatesignificantly enhances thecatalytic potency of AChE [39,40]. Thecatalytic activity of AChE involves considerable mobility of His-447[41], and

precise positioning of this residue is crucial for attaining maximum catalytic efficiency [42,43]. Within the esteratic subsite, acetylcholine ACh undergoes hydrolysis, resulting in the production of acetate and choline. The carboxyl ester hydrolysis generates an acyl-enzyme and free choline. Subsequently, theacyl-enzyme experiences a nucleophilic attack facilitated by a water molecule, with assistance from the histidine group. This process liberates acetic acid and restores the free enzyme **(Figure 4)**[44].

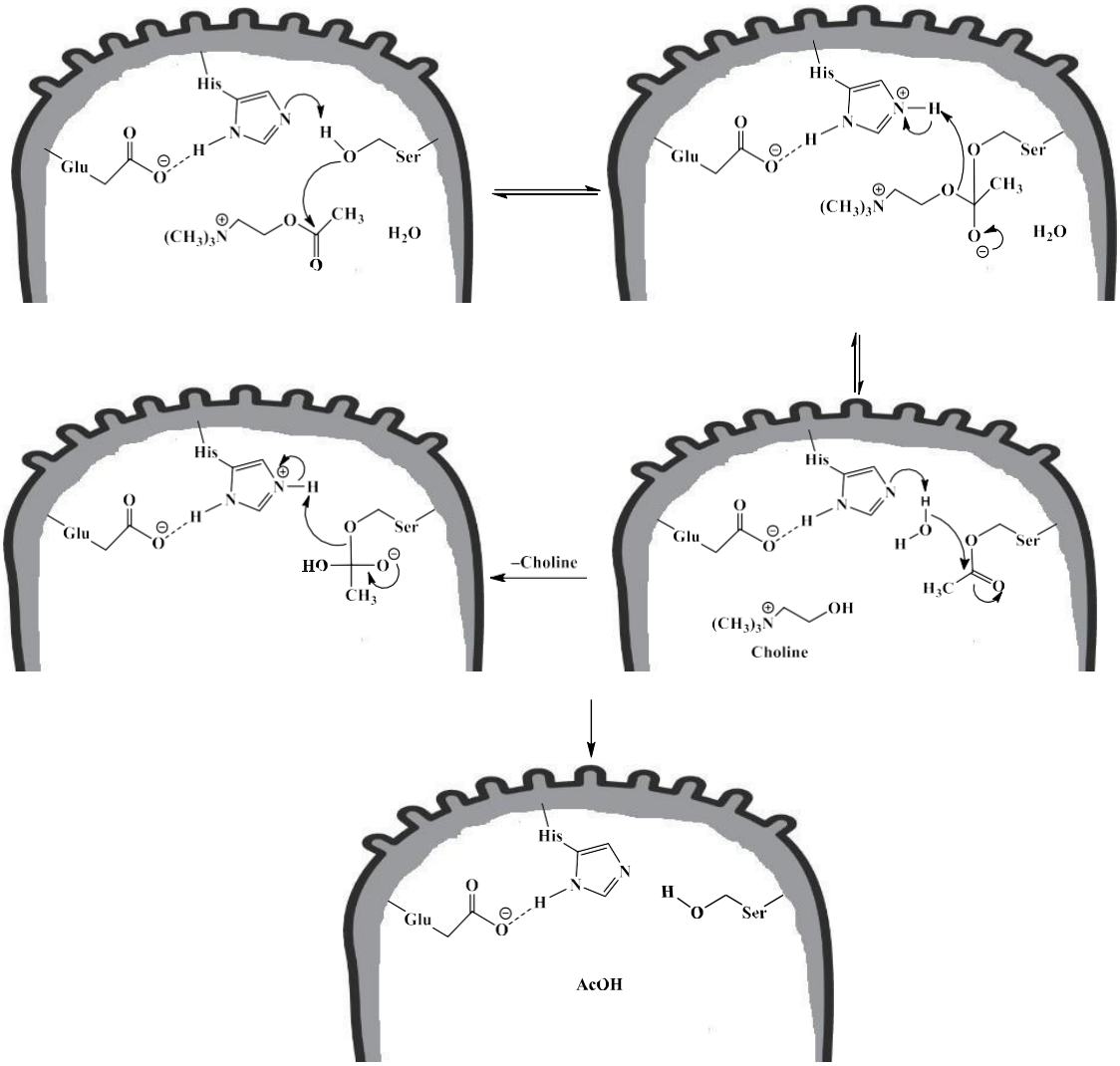


Figure 4: illustrates the mechanism of ACh hydrolysis facilitated by AChE. Adapted and reproduced from reference [38].

The role of AChE in normal nerve transmission

AChE is a main and principal form of cholinesterase in human body, which referred to as "true cholinesterase". This enzyme normally hydrolyzes the neurotransmitter ACh and participate in the normal nerve transmission[45]. The mechanism of normal nerve transmission started with the releasing of acetylcholine from a nerve terminal and subsequently attaches to the acetylcholine receptor (AChR) in the muscle and the organs and a depolarization wave is transmitted. When this happened, acetylcholine is hydrolyzed by AChE before the next nerve transmission take place **(Figure 5)**[46].

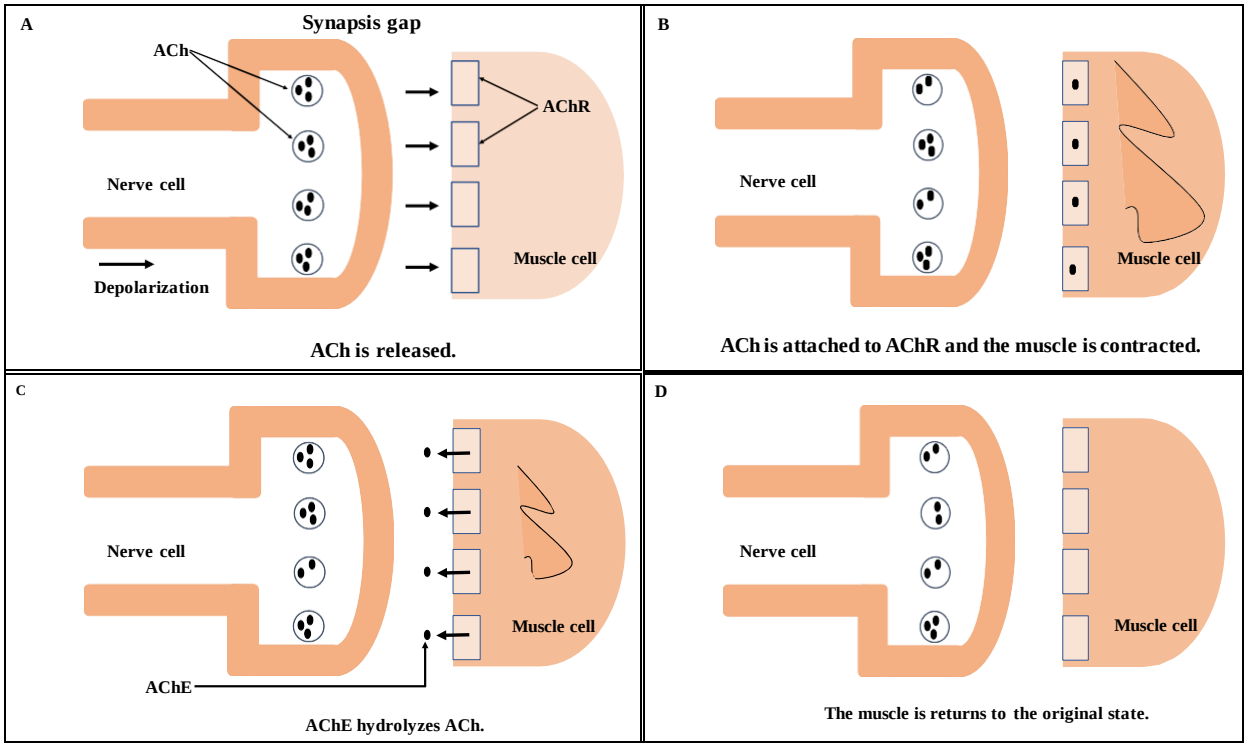


Figure 5: Mechanism of normal nerve transmission.

Acetylcholine Esterase (AChE) Inhibition

Sarin gas operates by attaching to serine residues situated at the active site of AChE, rendering acetylcholine unable to detach from the receptor and resulting in muscle spasms [47]. The profound toxicity of sarin and other nerve agents stems from their irreversible inhibition of AChE. The clinical manifestations of sarin gas exposure predominantly arise due to AChE inhibition, preventing the degradation of acetylcholine. This inhibition leads to an accumulation of acetylcholine, resulting in cholinergic overstimulation in target tissues. While the nerve gas serves as a potent inhibitor of acetylcholinesterase, preventing the hydrolysis of acetylcholine, the unhydrolyzed acetylcholine persists at the AChR. This persistence induces repetitive firing of a depolarization wave in the muscle and organs, ultimately resulting in dysfunctions of both the muscle and organs **(Figure 6)**. The inhibitory mechanism encompasses a quick interaction between sarin and the hydroxyl group of serine within the active site of AChE, resulting in the formation of a phosphate or phosphonate ester. The enzyme, once phosphorylated, undergoes a slow regeneration process, rendering it inaccessible for its physiological substrate, acetylcholine[48,49].

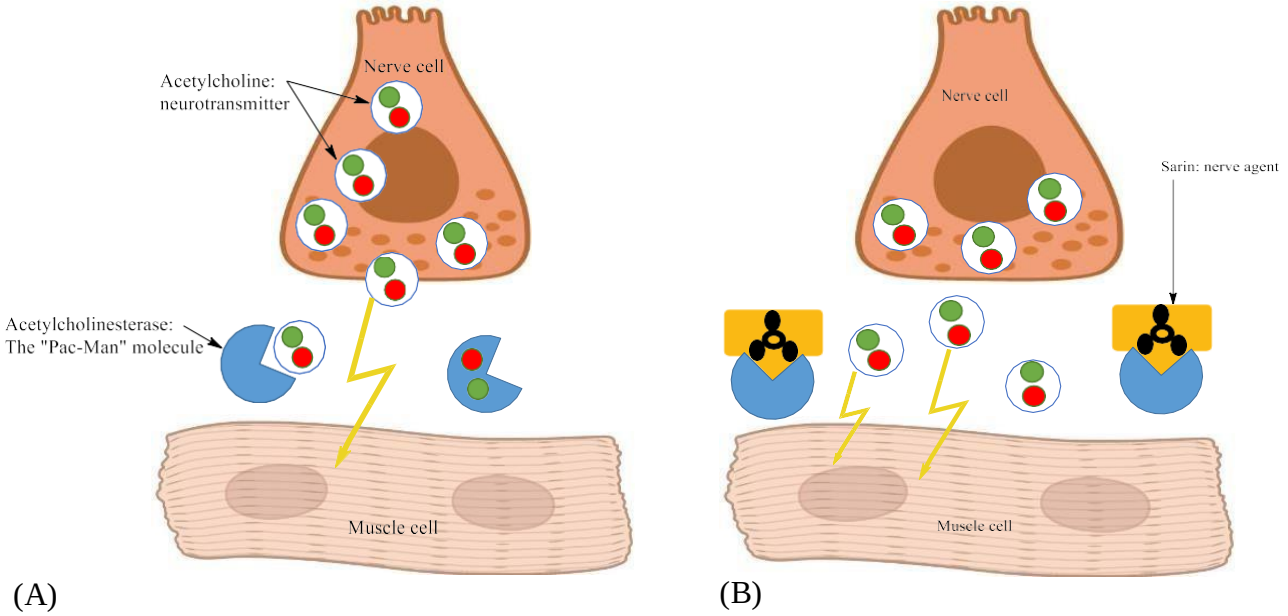


Figure 6 : depicts the molecular-level impact of Sarin. (A) the neurotransmitter initiates a signal to the muscle cell, followed by its breakdown by the AChE enzyme, allowing for muscle relaxation. (B) Sarin obstructs the enzyme, resulting in the continuous transmission of signals by the neurotransmitter, persistent breakdown of the transmitter, and constant muscle contraction.

HEALTH EFFECT OF SARIN AND ACHE INHIBITION-RELATED DISEASES

Sarin has the capability to permeate the skin barrier, eyes, and respiratory system through inhalation or absorption via the digestive system. Exposure to this agent has been associated with various health issues in individuals [50]. The majority of the patients who had sarin poisoning exhibited notable miosis and reduced serum AChE activity [51]. The muscarinic effects include visual symptoms (dizziness, blurred vision), discharge fromthe nose, pulmonary manifestations (bronchoconstriction, increased secretion of bronchi), digestive symptoms (vomiting, cramping in the abdomen, diarrhoea), along with sweating, salivation, and cardiovascular impacts (bradycardia and hypotension)[52]. Meanwhile, the nicotinic effects involve muscular fasciculation and paralysis. Effects of the CNS can include paralysis, coma, slurred speech, ataxia, and confusion[14]. Taken together, exposure to sarin gas affects various organs and may result in numerous severe health defects, as detailed below:

Central nervous system

Various research inquiries have explored the direct consequences of sarin on the nervous system. AChE is ubiquitously distributed in both the CNS, encompassing the brain and spinal cord, and the peripheral nervous system (PNS), which includes ganglia and nerve fibers establishing connections between the CNS and the body [53]. The principal focus of the parasympathetic nervous system lies in the preservation and replenishment of energy. It operates to slow down the heartbeat, reduce blood pressure, promote gastrointestinal motility and secretion, shield the eyes from excessive light, and facilitate the emptying of the urinary bladder and rectum. The inhibition of AChE induced by sarin exacerbates all of these physiological functions [54].

Based on research by Sidell and Boraky (1992), the acute manifestation of the cholinergic syndrome linked to sarin is observed when AChE is inhibited by approximately 75–80%. Exposure at lower levels has the potential to induce a reversible suppression of cholinergic systems, accompanied by various non-cholinesterase effects. Sarin's inhibition of AChE enzymes shows that the specific species and dosage are important factors [16]. Several studies have documented the outcomes experienced by individuals subsequent to incidents of sarin poisoning. For instance, a study by Nishiwaki et al. (2001) found that police officers and rescue workers in Tokyo continued to show deficits in their memory function three years after the sarin poisoning incident[55]. Moreover, in Tokyo, toxic exposure has been shown to have delayed effects on psychomotor function, as documented by Yokoyama et al. (1998a, b). Following sarin exposure, the researchers reported various symptoms, including ocular fatigue and abnormal sensations in the extremities [56]. In order to study the effects of sarin, Murata et al. (1997) performed neurophysiological research on eighteen people who had been exposed to sarin in Tokyo. The results of their study indicate that sarin exposure can cause symptoms that remain in the visual and upper nervous systems. This implies that sarin may have neurotoxic effects in addition to its inhibitory effects on brain ChE[57].

Sarin effects on vision: ocular system

The most common eye symptom is miosis, which is particularly noticeable after individuals have been exposed to vapour. The duration of miosis ranges from a few days to as extended as nine weeks [58]. An additional consequence of exposure to sarin is the occurrence of acute or aching ocular pain resulting from ciliary spasm, often accompanied by headaches [59]. Another prevalent characteristic resulting from exposure to sarin includes compromised visual acuity, tearing, and a redness of the eyes, attributed to subconjunctival vascular dilation[16]. Further symptoms associated with the effects of sarin include blurry vision and obscurity of the vision. Furthermore, "Peripheral dimness" was reported by two of six subjects after exposure to sarin vapors [60,61].

Respiratory system

Intoxication with anticholinesterase agents, such as sarin compounds, induces profound hyperpnea, which eventually halts the respiratory system. The significance of bronchoconstriction, neuromuscular blockade, and central respiratory depression differs depending on the species, anticholinesterase compounds, and administration strategies [62]. Studies have indicated that rhinorrhea is commonly attributed to local irritation resulting from sarin exposure, although it can also manifest as a consequence of systemic toxicity. The discharge associated with sarin-induced rhinorrhea surpasses that observed in instances of hay fever or cold, and its intensity correlates with the dosage administered[63]. Furthermore, substantial exposure to sarin vapor may result in ventilator malfunction[64]. Research has demonstrated that untreated cases of acute organophosphate exposure in humans lead to fatality within 24 hours, whereas treated cases may succumb within a span of 10 days [65]. Increased secretion of bronchi, pulmonary edoema, bronchospasm, bronchoconstriction, central apnea, and paralysis of the respiratory muscles connected to the medullary respiratory centre are usually the combination of events that fatally result in death[66]. Sarin has the capacity to engage with cholinergic elements within the central nervous system's respiratory centers, critical for the regulation of breathing. These components comprise the dorsolateral nucleus tractus solitarius, ventrolateral medulla, and the pneumotaxic center. Furthermore, sarin induces an elevation in the production of glycine and gamma-aminobutyric acid (GABA), leading to respiratory rate depression and a decrease in phrenic nerve activity [67]. Inhaling sarin at concentrations nearing the lethal concentration can result in elevated hypoxia-inducible factor-1α levels, bronchoconstriction, and heightened pro-inflammatory cytokine release. These alterations may have an effect on the lung epithelium, exacerbate bronchosecretions, and even be lethal[68].

Cardiovascular system

The anticipated impact of sarin on thecardiovascular system includes alterations in heart rate and blood pressure, as well as the potential occurrence of arrhythmias [69]. Additionally, it can cause an increase in vagal tone, which could lead to atrioventricular block and bradycardia. Notably, the heart rate may paradoxically increase due to the accumulation of ACh in sympathetic ganglia and at the adrenal medulla, or in response to the patient's fear and anxiety [70]. While ventricular arrhythmias are uncommon, they can occur as a result of sarin exposure [71]. In the fifteen cases of accidental sarin poisoning reported by Ludomirsky et al. (1982), Q-T interval prolongation was observed in 14 individuals, while malignant tachyarrhythmia occurred in 6 patients [72].

Skin and mucosal membrane

In the context of risk assessment, it is essential for individuals in the field, including both casualties and care providers, to prioritize skin protection alongside measures taken to prevent respiratory-related risks [73]. After dermal exposure to sarin gas, various systemic

signs and symptoms may manifest approximately two to three hours later. Significantly, the skin-penetrating capabilities vary among NAs, with VX demonstrating an absorption rate through the skin nearly eight times faster than other NAs. Moreover, the skin absorption of NAs undergoes a substantial increase with rising ambient temperatures, especially between 18 and 46°C [74]. Widespread perspiration is a prevalent complication that frequently occurs after prolonged exposure to sarin, whether through the dermal or inhalation route [75]. However, the more volatile the agent, the larger the topical dose required to produce toxicity [76]. Sulfur mustard and VX chemicals rapidly permeate the skin, resulting in serious and enduring damage, and sometimes even fatalities. In contrast, sarin is primarily absorbed through inhalation into the respiratory system[77,78].

Gastrointestinal system

Increased secretory activities and increased motility are associated with elevated ACh levels in the gastrointestinal tract. Acetylcholine overactivity is characterized by excessive segmenting and propulsive contractions throughout the tubular gastrointestinal (GI) tract. Acetylcholine's effects on smooth muscle M subtypes' muscarinic receptors are the main cause of this increased motor activity. Furthermore, acetylcholine activates M1 and M3 muscarinic receptors, which causes an increase in secretory functions in the intestinal, pancreatic, gastric, and salivary regions [79]. The excessive consumption of toxic acetylcholinesterase inhibitors prompts the release of a substantial quantity of fluid and electrolytes into the intestinal cavity, resulting in the onset of profuse, watery diarrhea often accompanied by intense cramping [80]. Among the initial indicators, nausea and vomiting manifest, often as a consequence of dermal exposure and potential complications in the neurological system. In a study of 111 patients assessed following the Tokyo sarin attack, 60.4% reported experiencing nausea, 36.9% noted occurrences of vomiting, and diarrhea was observed in merely 5.4% of the individuals [74].

Genitourinary system

The urinary system substantially facilitates the elimination of nerve agents through excretion[81]. Numerous investigations have proposed that both the renal circulation and the excretion of electrolytes are subject to partial cholinergic regulation, implying that exposure to cholinesterase inhibitors has the potential to impede regular renal function. Empirical evidence has indicated that sarin exposure often results in pathological damage to the kidneys, including cases of acute tubular necrosis in human patients [82–85]. According to a study conducted by Ballantyne et al. (2017), the impact of OP on renal function can be attributed to secondary issues such as hypotension or dehydration resulting from cholinesterase inhibition[86]. Exposure to organophosphates can also lead to additional consequences such as seizures and musclefasciculation, which, inturn, mayresult in rhabdomyolysis, myoglobinuria, and acute renal failure, as observed in patients exposed to pesticides [87]. Myoglobinuria is one of the symptoms that might exacerbate or reveal the usually subtle nephrotoxicity

associated with ChE inhibition alone. Specifically, kidney cells may be more susceptible to the harmful effects of OPs due to their lipophilic nature, which may allow OPs to cross plasma membranes and get direct access to organelles and intracellular space[88].

Intermediate syndrome

In the late 1980s, the phenomenon known as the intermediate syndrome was initially documented in the country of Sri Lanka [89]. From a clinical perspective, the syndrome differs from acute cholinergic syndrome in that it does not exhibit muscarinic symptoms or signs. Additionally, following exposure to sarin, the development of symptoms characteristic of acute cholinergic syndrome precedes the onset of intermediate syndrome symptoms [90]. Intermediate syndrome was caused by muscle fiber necrosis after an acute cholinergic crisis and was developed by weakness of the proximal limb muscles, motor cranial nerves, respiratory muscles, and neck flexors [91]. Although there is little information available about the incidence of intermediate syndrome after NAs have been exposed to, some reports indicate that intermediate syndrome can appear 24–96 hours after exposure to nerve agents or organophosphate insecticides. After that, recovery usually starts 4 to 18 days later[92–94].

Induction of delay neuropathy

Delay neuropathy presents as progressive onset of weakness, diminished reflex responses, and peripheral tingling, constituting a sensory and motor disorder of the peripheral nervous system that emerges 2-4 weeks following sarin exposure [95]. The development of the organophosphate-induced delay neuropathy (OPIDN) is caused by the suppression of a CNS enzyme known as neuropathy target enzyme (NTE) [96]. The likely cause of OPIDN is the degeneration of myelin and axons, coupled with the inhibition of NTE. About 30% of individuals may develop cholinergic irritation 1-4 weeks after exposure, which manifests as pharyngitis, laryngitis, increased salivation, and nasal secretion. This phase is succeeded by paralysis of the leg muscles, which endures for 1–2 months but does not result in alterations to sensory innervation. Subsequently, denervation and atrophy of the leg muscles may also be observed[93].

Brain damage

In the context of neurological impact, sarin gas has the capacity to induce ongoing and enduring harm to the central nervous system [97]. Nerve agent exposure can cause significant and long-lasting neurological and neuropsychiatric abnormalities. The impairment of neuronal excitotoxicity and irreversibly suppressed AChE is linked to the brain damage [51,98]. The neurological impact of sarin exposure exhibits dose-dependent characteristics, often resulting in extensive brain damage that commonly affects regions such as the piriform cortex, hippocampus, amygdala, and thalamus [99–101]. In each of the aforementioned instances,

apoptosis represents the initial potential mechanism for neuronal cell death[102]. Follow- ing exposure to organophosphates, apoptotic neurons have been observed in the brain tissue of rats [103,104]. Rat models of Alzheimer's, Parkinson's, Huntington's disease, stroke, and amyotrophic lateral sclerosis (ALS) have also been shown to exhibit apoptotic neu - rons [104]. Another form of neuronal cell demise attributable to the impact of sarin is necrosis. This is characterizedbycellular swelling, dilationof diversecellular organelles, aggregation and random degradation of nuclear DNA, widespread plasma membrane endocytosis, and autophagy followed by inflammation[104]. Serious physiological conditions, such as hypoxia, ischemia, exposure to toxins, sudden temperature changes, and nutritional restriction, generally lead to necrotic celldeath[105].

DETECTION OF SARIN

Detection and identification hold significant importance in the implementation of countermeasures against the use of CWAs [106]. The principal techniques utilized to detect sarin and other CWAs involve the analysis of their metabolites and breakdown byproducts. Ensuring precision with minimal instances of false positives and negatives is paramount, especially within the challenging conditions of a battlefield environment[107]. The primary focus of academic research on diagnostic methods for NAs exposure has centered on utilizingreadilyavailablesurvivor samples, suchas blood(includingserum, plasma, wholeblood, or red cells) and urine. Since sarin remains intact within the body for only a short duration, blood samples should ideally be collected within a few hours following exposure to sarin. Therefore, intact chemicals do not appear to besuitable targets for retrospective detection of exposure [108,109]. When it comes to determining appropriate markers and detection limits, biomedical samples such as blood and urine often pose the greatest challenges. Alkylated hemoglobin[110], alkylated DNA [111], and urinary metabolites [112] have all emerged as distinctive biological indicators in instances of poisoning in both humans and animals. Black's study in 1999 endeavored to identify appropriate biomarkers for validating the utilization of the organophosphorus nerve agents, including sarin and soman, through an exploration of their interaction with plasma proteins [113].

Over the past sixty years, different techniques and detection equipment have been used to detect organophosphorus compounds such as gas chromatography (GC) [114], liquid chromatography (LC) [115], ion mobility spectrometry (IMS) [116] and Fourier transform infrared spectrometry (FTIR) [117] . Some other techniques utilized in the detection of sarin include atmospheric pressure and chemical ionization (APCI), as well as flame photometric detection[107]. Moreover, an analytical method such as enzymatic inhibition has been employed for assessing sarin and its metabolites in both biological and environmental samples. Measurement of AChE inhibition, for instance, stands as the prevailing approach for detecting exposure to Nas [118] . In their research undertaken in the year 2000, Lee and colleagues employed an enzymatic assay that involved measuring AChE inhibition to identify the existence of sarin within aqueous samples. Notably, their methodology achieved a detection

with a threshold of 8 pg (100 pm) [119] . Liquid chromatography-tandem mass spectrometry (LC-MS) stands as one of theanalytical techniques devised for quantifying the levels of Isopropyl Methyl phosphonic acid (IMPA) in blood and urine [109]. Gas chromatography with flame ionization detection (FID) is another technique employed by Hui and Minami (2000) to monitor fluorine levels in the urine of Japanese patients as an indication of sarin gas exposure [57]. Furthermore, the gas chromatography method with flame photometric detection (GC-FPD) can be utilized for the analysis of hydrolysis products in both plasma and urine [120]. At the late of the nineteenth century, many researchers have devoted attention to GC–MS, owing to its high sensitivity and selectivity[121].

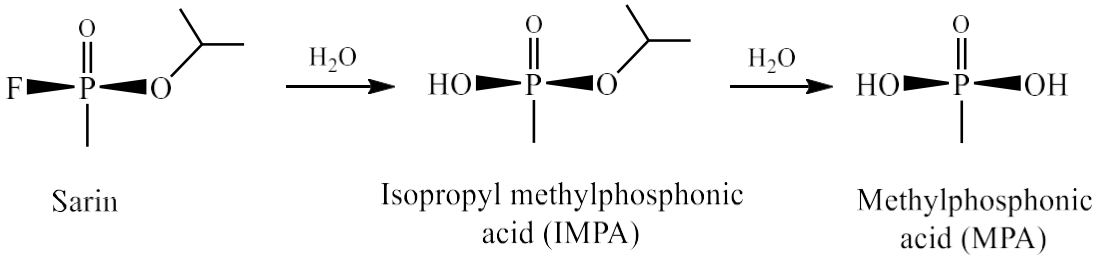
DESTRUCTION OF SARIN GAS

The rapid and safe elimination of CWAs is essential to ensure no unintended releases or secondary effects occur. Consequently, it becomes essential to employ methods that ensure the swift neutralization of CWAs within typical timeframes. The importance of these approaches in efficiently disposing of stockpiles containing both chemical and biological agents becomes pivotal, especiallyinscenarios where CWAgases or aerosols areemittedasa consequence of elevated temperatures [122]. Within the framework of the Chemical Weapons Convention (CWC), the disposal of all stockpiles containing CWAs is mandated, presenting significant challenges. These challenges encompass the substantial expenses associated with destruction, ensuring the safety of workers involved, as well as safeguarding neighboring populations and the environment. Additionally, legal and political considerations further compound the complexities inherent in this process [123]. In the past, the predominant disposal techniques for CWAs encompassed land burial [124], sea dumping [125], detonation, and open-pit burning [126]. However, all these approaches presented considerable environmental hazards and potential health risks to nearby communities [127]. Remarkably, the documented techniques for eliminating CWAs can be categorized broadly into three groups: thermal decomposition[128], chemical degradation[129], and catalytic decontamination[130]. Thermal decomposition is accomplished through either incineration or pyroly- sis [131]. CWAs are transported to the demilitarization facility as an integral component of the incineration process, during which automated machinery is employed to extract the chemical agent from both munitions and bulk containers. Consequently, employee exposure to CWAs is minimal at the demilitarization factory [4]. However, alkaline solutions and oxidants can lessen and frequently eliminate the toxicity of chemical agents, rendering them useful tools for reducing the toxicity of CWAs through chemical degradation process [131]. Another approach for the destruction of CWAs is known as catalytic decontamination, a process that utilizes catalysts to convert them into harmless chemicals [131]. The two techniques that can also take place within the gas phase, thermal breakdown and catalytic decontamination, arecrucial for comprehending and explaining the several CWAquick defeat procedures that rely on the temperature and materials produced by the fireball. Given the rise in temperatures typically associated with a fireball, thermal decomposition is consistently considered

a significant process for rapid neutralization[129,130,132]. Thefollowing aresometechnologies that are mostly used for destruction of sarin.

Destruction of sarin by hydrolysis

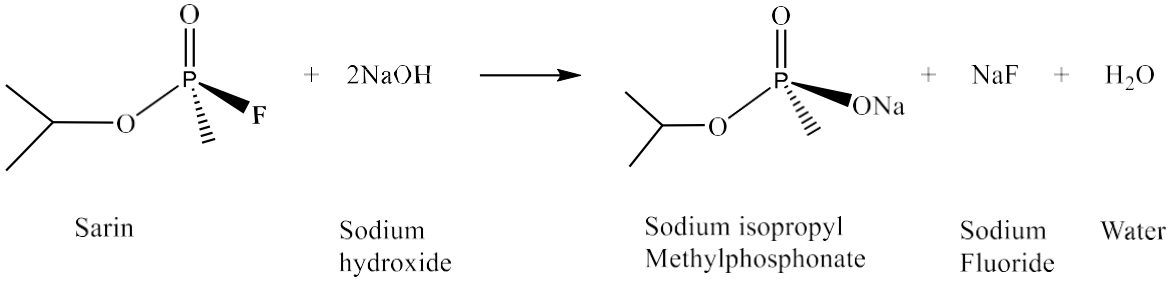
An appealing method for sarin degradation involves chemical hydrolysis, wherein sarin reacts with water to yield less toxic byproducts. This outcome is attributed to the acidic nature of the reaction products. Typically, a base such as lime or sodium hydroxide is employed to neutralize the acidity of these products, hence the commonly used term 'neutralization' to describe this process in a generic sense [133]. The investigation of OPs hydrolysis has been extensively explored through experimental and computational approaches over time. These studies indicate that nerve agents hydrolyze by an addition-elimination mechanism, resulting in the formation of a stable intermediate of penta-coordinated phosphorus. The process of hydrolysis plays a crucial role in the metabolism of G-agents, primarily orchestrated by enzymes termed A-esterases. Consequently, this enzymatic pathway results in the generation of metabolic derivatives, namely O-alkyl methylphosphonic acids, particularly observed in the instance of sarin (**Scheme 1**).



Scheme 1: Hydrolysis of sarin to methyl phosphonic acids (MPA)

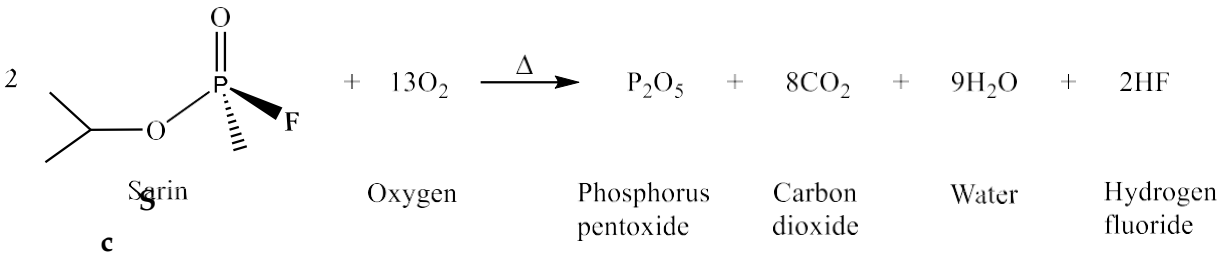
Similar to other OPs, sarin[f1] [ZA2] hydrolysis has undergone thorough investigation. The utilization of aqueous sodium hydroxide (NaOH) at room temperature for the neutralization of G Series agents enables the effective destruction of substantial quantities of sarin[133]. When sarin reacts with aqueous sodium hydroxide, it generates an aqueous solution comprising inorganic salts alongside the organic degradation product (**Scheme 2**). The material undergoes packing into drums before being deposited into a hazardous waste landfill. Prior to atmospheric discharge, the water vapor undergoes a scrubbing process. The wastewater is then conveyed to an industrial sump or lagoon for disposal[134].

Scheme 2: Hydrolysis of sarin to sodium isopropyl methylphosphate and aqueous solution of inorganic salts



Destruction of sarin by incineration technology

Incineration constitutes a thermal method for managing waste, characterized by a controlled combustion process aimed at reducing volume and harnessing energy from the waste stream[135] . In 1982, the National Research Council (NRC) designated incineration technology as the ”baseline” system and officially approved it as the preferred method. This technology has proven highly effective in disposing of accumulated warfare agents and is presently extensively employed by the United States Army, as well as in Germany and the United Kingdom[17,133] .The incineration process for sarin is delineated as follows (**Scheme 3)**



Scheme 3: The combustion reaction of sarin to phosphorous pentoxide by incineration technology[f1] [ZA2] . Adapted from reference[130].

TREATMENT OF SARIN GAS POISONING

Addressing nerveagent poisoningposes a significant obstacle for medicalservices today, primarily due to the pronounced toxicity associated with these substances. Consequently, specific measures for self-protection are essential, such as the continuous utilization of full personal protective equipment, particularly when the possibility of contamination per- sists. The main source of risk linked with these substances arises from the abrupt emer- gence of potentially fatal cholinergic crises, emphasizing the critical necessity for an early commencement of therapy. Given that the fundamental detrimental mechanism of nerve agents is attributed to the inhibition of acetylcholinesterase, treatment strategies are primarily directed towards mitigating the impacts of cholinergic overstimulation. In order to reactivate suppressed acetylcholinesterase, antidotes for nerve agents must be promptly administered at appropriate dosages and for a duration corresponding to the expected reactivation period[136]. Thus, the treatment of sarin exposure victims involves prehospital management as well as the administration of antidotes. The upcoming sections will provide examples of nerve agent antidotes.

8.1.Nerve agents' antidotes

After prehospital management, antidote is another method for treatment of sarin nerve agent exposure which is frequently used to reduce the poising with this agent. The treatment regimen for nerve agent poisoning typically involves the administration of an antimuscarinic medication, an oxime compound that reactivates phosphorylated AChE, and, if deemed necessary, an anticonvulsant medication[137]. The management of acute nerve agent poisoning necessitates decontamination, respiratory assistance, administration of antidotes, and provision of anticonvulsant therapy [138]. The objectives of decontamination in cases of nerve agent exposure are twofold: to inhibit further absorption of nerve gas agents by affected individuals and to curtail the dissemination of nerve gas agents to others. Commencement of decontamination procedures should be initiated promptly, ideally preceding the transfer of victims to medical facilities [139]. Given that respiratory failure stands as the primary cause of fatality in instances of nerve agent exposure, the management of nerve agent toxicity initiates with the evaluation of airway, breathing, and circulation status [140,141]. The chemical structures of the antidotes are shown in **(Figure 7)**.

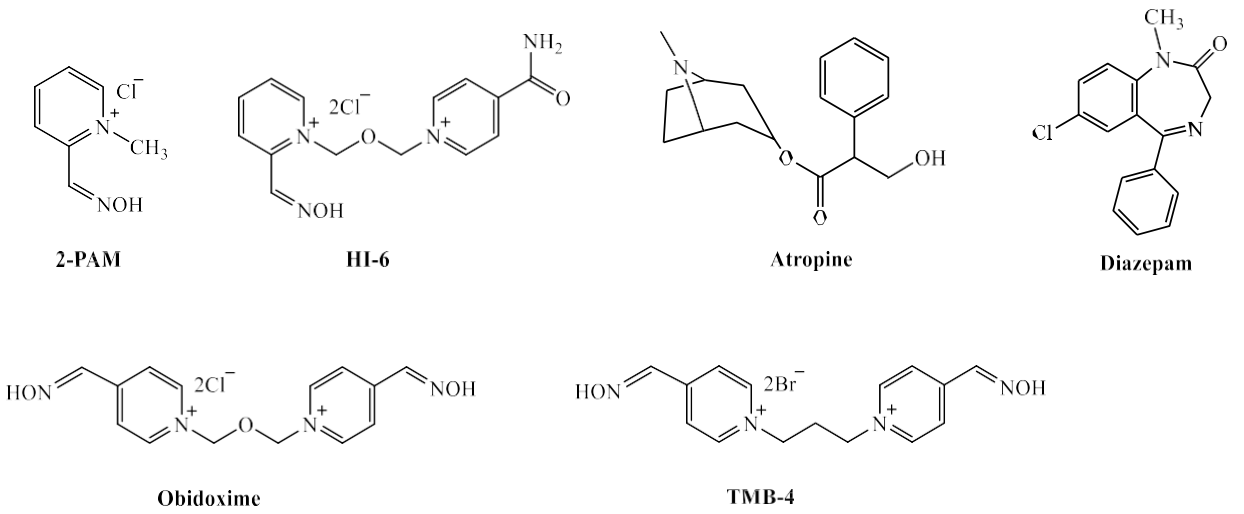


Figure 7 : Standard chemical structures of the antidotes

The detailed information of mentioned drugs and their mechanism of action are shown as follow:

Antimuscarinic drugs

In the 1930s, researchers embarked on investigations into therapeutic approaches for NA poisoning. Manifestations observed in affected individuals suggested the possible effi

cacy of atropine as a useful treatment. As a competitive antagonist of muscarinic receptors, atropine inhibits the actions of ACh specifically on muscarinic receptors, without affecting nicotinic receptors. Substances with anticholinergic properties, such as atropine sulfate, counteract the excessive stimulation of muscarinic receptors [142]. Atropine exhibits advantageous effects on both the CNS and the peripheral nervous system. It has consistently been prioritized as the primary therapeutic agent for addressing symptoms associated with NA poisoning, owing to its ability to effectively mitigate the potentially life-threatening muscarinic effects [143,144]. The proposed detoxification mechanism of sarin by atropine drug based on the idea that atropine is grounded in its classification as a cholinergic blocking agent, or an anticholinergic compound. Atropine demonstrates remarkable efficacy in inhibiting the actions of surplus acetylcholine at peripheral muscarinic sites, as illustrated in **Figure 8** [145]. In experimental settings, substantial quantities of atropine may potentially hinder certain cholinergic effects at nicotinic sites. However, these antinicotinic effects remain inconspicuous even at elevated clinical doses [146]. Administering small doses (2 mg) of atropine to individuals unaffected by nerve agent intoxication results in various physiological responses. These include mydriasis, reduction in secretions (including sweating), mild drowsiness, diminished gastrointestinal motility, and tachycardia [147].

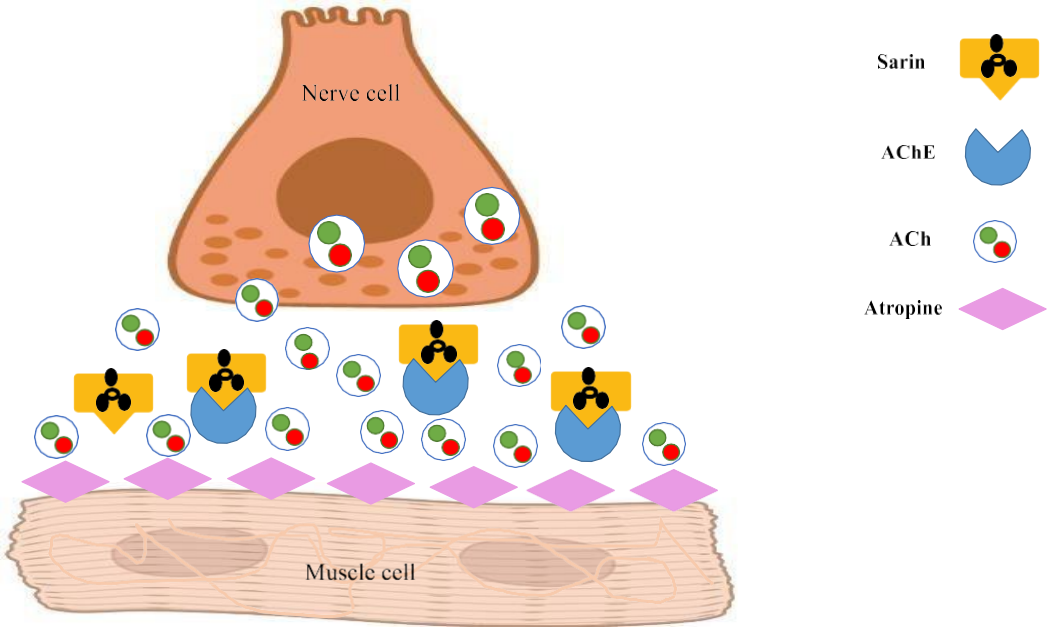


Figure 8 : Detoxification mechanism of sarin by atropine on a molecular level.

Reactivators

The inefficacy of atropine in addressing nicotinic effects and its failure to restore AChE activity necessitate a focused exploration into identifying supplementary com- pounds. Nucleophilic agents such as hydroxylamine, hydroxamic acid, and oximes present promising candidates, as they possess the potential to reinstate AChE activity [148]. These nucleophilic agents, oximes among them, act by breaking the covalent bond formed between the nerve agent and AChE, consequently reinstating the enzyme's physiological function[142,149]. The objective was to formulate a compound possessing nucleophilic characteristics conducive to displacing the phosphorus moiety attached to the catalytic serine residue of AChE, thereby reactivating the enzyme. In the early 1950s, Irwin B. Wilson and Sara Ginsburg embarked on this task, and their strategy involved utilizing the neurotransmitter ACh as a blueprint, ultimately leading to the synthesis of pyridine-2-aldoxime methiodide, commonly referred to as Pralidoxime (2-pyridine aldoxime methyl chloride) or 2-PAM [150]. 2-PAM has emerged as the primary reactivator effective against phosphorylated AChE, frequently utilized for the treatment of sarin and other nerve gases, and continues to be employed to date [151]. The detoxification mechanism of sarin by 2-PAM is attributed to its capability to bind to the nerve agent, such as sarin, which inhibits cholinesterase, and subsequently disrupt the bond between the agent and the enzyme, thereby restoring the enzyme's normal activity (**Figure 9**) [152]. In clinical settings, this is evident in organs containing nicotinic receptors, where aberrant skeletal muscle activity diminishes, resulting in the restoration of normal muscle strength[147].

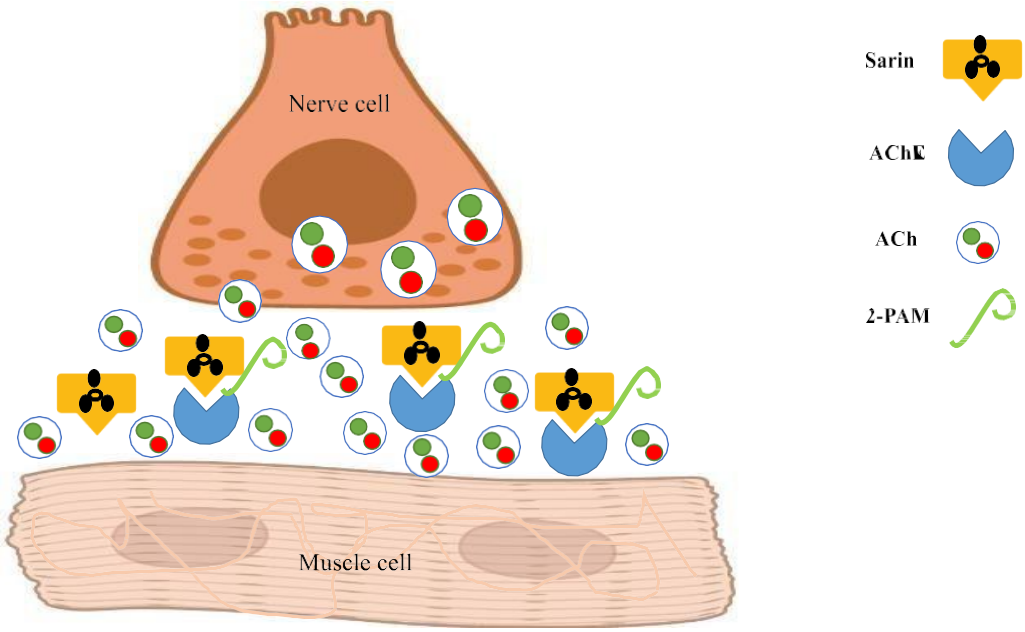


Figure 9: Detoxification mechanism of sarin by 2-pam on a molecular level.

Anticonvulsant Drugs

Electrographic seizures followed by motor convulsions are another characteristic of NA poisoning [153]. It is theorized that seizure development is primarily caused by hypoxia and overstimulation of cholinergic pathways [153]. Examples of effective treatments for sarin-induced seizures, which can minimize brain damage, include benzodiazepine anticonvulsants such as diazepam, lorazepam, andmidazolam[154].

CONCLUSION

In this review article, we have provided a concise summary of the historical usage of chemicals in warfare spanning from ancient times to the present day. The utilization of CWAs continues to pose a potential risk, notwithstanding the prohibition imposed by the CWC. Comprehensive understanding of these agents is crucial for devising an effective emergency response strategy. This review additionally provides a summary of the properties, toxicological aspects, and pharmacology of sarin. Moreover, the review explains the normal mechanisms of action of the acetylcholinesterase enzyme and its inhibition due to sarin exposure. Additionally, it discusses the potential effects of sarin on biochemical/-physiological systems and the resulting diseases or disorders following exposure to sarin gas. Most of the research is needed to examine the effects of sarin on the human body. In addition, this paper described the recent methods and technologies used for the detection and destruction of sarin gas. Finally, this review

ABBREVIATIONS

Ach: Acetylcholine, **AChE**: Acetylcholinesterase, **AChR**: Acetylcholine receptors, **ALS**: Amyotrophic lateral sclerosis, **APCI**: Atmospheric pressureand chemicalionization, **CNS**: Central Nervous System, **CWA**: Chemical Warfare Agent, **CWC**: Chemical Weapons Convention, **FTIR**: Fourier transform infrared spectrometry, **FID**: Flame ionization detection, **GA**: Tabun, **GB**: Sarin, **GC**: Gas chromatography, **GI**: gastrointestinal, **IMS**: Ion mobility spectrometry, **IMPA**: Isopropyl Methylphosphonic acid, **LD50**: Lethal Dose 50%, **LC**: Liquid chromatography, **LC-MS**: Liquid chromatography-tandem mass spectrometry, **NRC**: National Research Council, **NTE**: Neuropathytarget enzyme, **NAs**: Nerve Agents, **NATO**: North Atlantic Treaty Organization, **OPIDN**: Organophosphate-induced delay neuropathy, OP: Organophosphonate, PNS: Peripheral nervous system, **RBCs**: Red bloodcells, **2-PAM**: 2-Pyridine Aldoxime Methyl Chloride

DECLARATIONS

1. All authors contributed equally to the paper, with tasks divided collaboratively, including research and writing. Each author shares equal responsibility for the content and conclusions.
2. Conflict of interest

The authors declare no conflict of interest

3. Ethical Approval

(Institutional ethical approvals and informed consent)

This research does not conflict with our university's ethical standards, nor with any known ethical criteria.

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