CBRNE Def. Stud. 1(1), June 2026, 25-32

CBRNE Defense Studies

Journal homepage: https://journal.solusiriset.com/index.php/cds

Review Article

Chemical warfare agent toxicology at the intersection of science and defense: a review of sarin and lewisite

Thessa Octavia Joyetta Tarigan[1,2], Tiara Rizki Yulita[1,2], Robith Alzamzami[1,2], Zidni Aghna Haqina[1,2], Cinta Cornelia Damai Santi[1,2], Rahmat Basuki[1,2]*, Nugroho Adi Sasongko[3,4,5]

[1]*Department of Chemistry, The Republic of Indonesia Defense University, Bogor 16810, Indonesia*

[2]*League of Geniuses and Innovative Cadets (L.O.G.I.C), The Republic of Indonesia Defense University, Bogor 16810, Indonesia*

[3]*Research Center for Sustainable Production System and Life Cycle Assessment, National Research and Innovation Agency (BRIN), Banten 15314, Indonesia*

[4]*Energy Security Graduate Program, The Republic of Indonesia Defense University Bogor, 16810, Indonesia*

[5]*Murdoch University, 90 South St, Murdoch Western Australia 6150, Australia*

https://doi.org/10.55749/cds.v1i1.187
Received: 29 May 2026; Revised: 20 Jun 2026; Accepted: 22 Jun 2026; Published online: 24 June 2026; Published regularly: 30 Jun 2026

Abstract—Chemical warfare agents (CWAs) remain a significant threat to military personnel, civilian populations, and public health systems due to their high toxicity and potential for mass casualties. This review compares the toxicological characteristics of sarin, a representative organophosphorus nerve agent, and Lewisite, an organoarsenic vesicant agent. Sarin exerts its toxicity primarily through irreversible inhibition of acetylcholinesterase, resulting in excessive accumulation of acetylcholine at cholinergic synapses and the development of acute cholinergic crisis characterized by miosis, bronchoconstriction, muscle fasciculations, seizures, respiratory failure, and death. In contrast, Lewisite induces cellular injury through the interaction of arsenic moieties with sulfhydryl-containing enzymes and proteins, disrupting essential metabolic pathways and leading to oxidative stress, tissue necrosis, vesication, respiratory injury, and systemic organ damage. The review discusses the physicochemical properties, toxicokinetics, biochemical mechanisms, clinical manifestations, diagnostic approaches, and medical management strategies associated with both agents. Historical incidents involving sarin and Lewisite are also examined to illustrate their operational significance and the challenges they pose to emergency preparedness and disaster response. Despite differences in their molecular targets and pathophysiological effects, both agents present substantial risks due to their rapid onset of toxicity and potential to overwhelm healthcare systems during large-scale exposures. A comprehensive understanding of these mechanisms is essential for improving risk assessment, clinical management, medical countermeasure development, and preparedness against chemical threats.

Keywords— *Sarin and Lewisite, Chemical warfare agents, Toxicology, Chemical terrorism, Medical countermeasures*

1. INTRODUCTION

Like other weapons of mass destruction, chemical warfare agents are lethal and highly incapacitating. Although the use of chemical weapons constitutes a violation of international law and a grave violation of human rights, chemical weapons have been used in conflicts, wars, and acts of terrorism [1]. Among chemical weapons, nerve agents, such as sarin, have caused serious illness and fatalities among civilians, military personnel, police, security personnel, and healthcare workers in past wars and terrorist attacks. The mechanism of toxicity of nerve agents involves inhibiting the vital enzyme acetylcholinesterase, leading to widespread symptoms and signs of cholinergic hyperactivity [2].

In the post-Cold War era, few countries are immune to the threat of terrorism, in which nerve agents may be chosen as a means of indiscriminate attack. If used as an offensive weapon under certain meteorological conditions, nerve agents can cause massive casualties [3]. The number of casualties could be very high and exceed the capacity of local medical resources. The malicious use of nerve agents could have a significant impact on emergency medical systems on an unprecedented scale. Therefore, healthcare workers need to understand the toxicology, assessment, management, and prevention of diseases caused by these agents [1]. In this article, the Sarin and Lewisite were summarized the current state of knowledge regarding nerve agents based on a review of the literature in the fields of toxicology and disaster epidemiology related to nerve agents.

***Corresponding author**.
Email address: rhmtbsq@gmail.com (R. Basuki)

1.1. Background

Toxicology is the branch of science that studies the harmful effects of chemical substances on living organisms. It is a multidisciplinary field, as it encompasses pharmacology, biochemistry, chemistry, physiology, and pathology; and although it is sometimes considered a branch of some of these fields, toxicology is actually a distinct discipline [4]. Toxicology can be considered the science of poisons [5]. However, the scientific foundations of toxicology were laid by Paracelsus (1493–1541), and this approach was continued by Orfila (1787–1853). Nevertheless, the development of toxicology as a distinct science has been slow, especially when compared to fields such as pharmacology and biochemistry, and toxicology has a far more limited academic foundation. This may partly reflect the nature of the field, which has developed as a practical art, as well as the fact that many practitioners are more interested in descriptive studies for screening purposes or to meet legal requirements [6].

1.2. Scope

This review focuses on the toxicological characteristics of sarin as a representative nerve agent. The discussion covers physicochemical properties, mechanisms of toxicity, routes of exposure, clinical manifestations, diagnosis, medical countermeasures, and implications for public health. Additionally, historical incidents involving sarin are reviewed to illustrate the challenges associated with emergency preparedness and the management of mass casualties following a chemical attack.

In addition to nerve agents, the class of chemical warfare agents also includes blister agents, which have a different mechanism of toxicity. One of the best-known compounds in this class is lewisite ($C_2H_2AsCl_3$), an organoarsenic compound developed as a chemical weapon due to its ability to cause rapid tissue damage and high systemic toxicity. Unlike sarin, which acts by inhibiting acetylcholinesterase, lewisite induces biological damage through the interaction of its arsenic atom with the sulfhydryl (-SH) groups on various cellular enzymes and proteins. This interaction disrupts vital metabolic processes, triggering oxidative stress, cell membrane damage, tissue necrosis, and dysfunction of various organs [7].

1.3. Biochemical Basis of Nerve Agent Toxicity

Nerve agents are highly toxic organophosphorus compounds that exert their biological effects primarily through irreversible inhibition of acetylcholinesterase (AChE), an enzyme responsible for terminating cholinergic neurotransmission [8]. Under normal physiological conditions, AChE rapidly hydrolyzes acetylcholine (ACh) at synaptic junctions. Exposure to nerve agents such as sarin results in phosphorylation of the active site serine residue of AChE, leading to enzyme inactivation and excessive accumulation of acetylcholine at muscarinic, nicotinic, and central nervous system receptors [9].

The resulting cholinergic overstimulation produces a characteristic toxidrome that includes miosis, excessive secretions, bronchoconstriction, muscle fasciculations, seizures, respiratory failure, and potentially death [10]. The severity of poisoning depends on the absorbed dose, route of exposure, and the rapidity of medical intervention. Following inhibition, the nerve agent–AChE complex may undergo an aging process, during which dealkylation stabilizes the bond between the agent and the enzyme. Once aging occurs, oxime reactivators become ineffective, making timely treatment critical [11].

In addition to direct cholinergic toxicity, experimental studies have demonstrated that nerve-agent exposure induces cascading oxidative stress, neuroinflammation, mitochondrial dysfunction, and structural neuronal injury, which heavily contribute to long-term neurological sequelae observed in survivors of acute poisoning [12]. Furthermore, the toxicokinetics of these agents—encompassing their rapid systemic absorption, lipophilic distribution, hepatic metabolism, and pathways of elimination—influence the absolute magnitude and duration of these toxic effects by determining precise tissue exposure and target-organ vulnerability [13].

2. CLASSIFICATION OF CHEMICAL WARFARE AGENTS

Most nerve agents were initially produced for the development of insecticides; however, due to their extremely high toxicity, these compounds were subsequently evaluated for military use. These compounds are classified as phosphorus-containing organic compounds, which are chemically similar to organophosphate pesticides. They produce biological effects by inhibiting the enzyme acetylcholinesterase, which normally functions to deactivate acetylcholine, a neurotransmitter. Consequently, the accumulation of acetylcholine at receptor sites causes acute cholinergic crisis. Death can occur due to respiratory depression within seconds to minutes after exposure if no treatment is provided [3].

Sarin (**Figure 1**) was first used on the battlefield during the First Gulf War in 1984–1987. There is circumstantial evidence that the Iraqi military used sarin against Kurdish villagers in 1988 and during the Iran-Iraq War. In 1988, Iraq used various chemical and cluster bombs, including sarin and other toxic nerve agents, injuring approximately 70,000 people and killing more than 5,000. The poison gas attack on the city of Halabja, Iraq, was the largest-scale chemical weapons attack against a civilian population in the modern era [14,15]. The Halabja attack involved various chemical agents, including the nerve agents sarin, tabun, and VX, as well as mustard gas. Estimates of the number of victims from nerve agents during the Iran-Iraq War range from 20,000 to 100,000. In 1994 and 1995, the Japanese religious sect Aum Shinrikyo used sarin in two terrorist attacks in Matsumoto and Tokyo. Additionally, sarin is known to be part of the military stockpiles of several countries, including the United States [1].

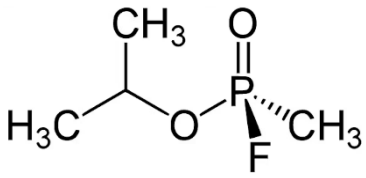

Figure 1. Chemical structure of Sarin

Although sarin is one of the most well-known nerve agents and has been used in various armed conflicts and acts of terrorism, the threat posed by chemical weapons is not limited to nerve agents alone. Another group that also poses a high level of danger is vesicant agents, or blister agents, which operate through a different mechanism of toxicity and can cause both local tissue damage and serious systemic effects [16].

One of the most well-known vesicant agents is Lewisite (**Figure 2**), an organoarsenic compound developed for military purposes due to its ability to cause rapid tissue injury and significant systemic toxicity. This compound causes biological damage by interacting with sulfhydryl (-SH) groups on cellular enzymes and proteins, thereby inhibiting important metabolic functions [17]. These disruptions can trigger cellular dysfunction, oxidative stress, tissue necrosis, and even multi-organ failure. Exposure to Lewisite can occur through inhalation, skin contact, or eye contact, resulting in various clinical manifestations such as acute pain, skin irritation, blister formation, eye damage, respiratory tract injury, and systemic poisoning. This is due to its highly toxic nature and its ability to cause rapid injury to living tissue [18].

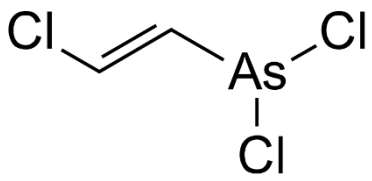

Figure 2. Chemical structure of Lewisite

2.1. Historical Sarin Attack

In 1994, sarin was used in a chemical terrorist attack in Matsumoto, Japan. Matsumoto, located 250 km northwest of Tokyo, is a medium-sized city with a population of approximately 200,000 and 80,000 households. A religious cult released impure sarin using a heater and a fan from a truck for about 10 minutes. Approximately 600 people were exposed to sarin; 7 people died; 58 were hospitalized, and more than 200 sustained injuries. Due to secondary sarin contamination from the initial exposure, 35% of rescue workers also sustained injuries. All of these workers had begun rescue operations within 5 hours of the sarin release. In follow-up health examinations over a two-year period, patients who suffered severe poisoning still experienced some symptoms, such as occasional seizures, palpitations, dyspnea, and mild fever [19].

The sarin attack in Matsumoto demonstrated the effects of a nerve gas attack in an open environment. Contrary to previously reported characteristics of sarin, the gas's lethal effects appear to remain potent even in open environments, as seven (1.2%) of the 600 people exposed died from sarin vapor in the city [20]. When the cult group sprayed the diluted sarin, the weather was humid (95%) with light rain and a gentle breeze (0.5 m/s) on an early summer night (20.4°C). These conditions may have allowed the sarin vapor to maintain its lethal concentration. Additionally, all of the victims who died had their windows open at the time of exposure [21].

Nine months after the sarin attack in Matsumoto, one of the largest acts of chemical terrorism occurred in Tokyo during the Monday morning rush hour, known as the Tokyo subway sarin attack. Twelve passengers were killed and approximately 5,500 people were injured. Five members of the same religious sect released sarin by piercing plastic bags containing the liquid with the tips of their umbrellas. They carried 10 bags containing about 600 ml of sarin liquid diluted to 35% strength onto five different commuter trains on three intersecting subway lines [22].

2.2. Historical Development and Military Use of Lewisite

Lewisite, chemically identified as dichloro(2-chlorovinyl)arsine, is an arsenic-containing blister agent (vesicant) that exhibits distinct physical and field-persistence characteristics compared to nerve agents like Sarin [23]. Historically, Lewisite was first synthesized and developed for chemical warfare by an American military chemist, Winford Lee Lewis, in 1918. In its purest form, Lewisite is a colorless, oily liquid; however, impurities in munitions-grade production typically alter its appearance into a yellowish dark-brown or violet fluid [24]. Unlike Sarin, which is notoriously odorless and non-persistent, Lewisite can be readily detected by its organoleptic properties, emitting a characteristic faint geranium-like odor [25].

The operational behavior of Lewisite in the field is largely governed by its low volatility and vapor pressure. At a ambient temperature of 20° C, Lewisite exerts a vapor pressure of only 0.395 mmHg and a corresponding volatility of 4,480 mg/m^3. In stark contrast, Sarin exhibits a highly volatile nature, with a vapor pressure ranging between 2.1 and 2.9 mmHg and an atmospheric volatility of approximately 22,000 mg/m^3 under identical environmental conditions [26]. This disparity implies that while Sarin vaporizes rapidly and disperses into the air as a non-persistent cloud, Lewisite tends to settle on terrains and surfaces as a liquid hazard, presenting long-term contact risks. Nevertheless, its field persistence is chemically compromised by ambient moisture; Lewisite undergoes a rapid hydrolysis reaction upon contact with water, degrading into non-volatile arsenical solids and hydrochloric acid [27].

3. THE TOXICOLOGICAL MECHANISMS OF SARIN AND LEWISITE

3.1. Mechanism of Sarin (Nerve Agent)

At the molecular level, the extreme toxicity of Sarin (O-isopropyl methylphosphonofluoridate) stems from its ability to cause irreversible inhibition of the vital enzyme acetylcholinesterase (AChE) via a

phosphorylation process. Under normal physiological conditions, AChE rapidly terminates nerve signal transmission by hydrolyzing the neurotransmitter acetylcholine (ACh) into acetate and choline within the synaptic cleft. The catalytic triad of AChE consists of Serine (Ser203), Histidine (His440), and Glutamate (Glu327) [28].

When Sarin enters the biological system, it mimics the natural substrate of AChE and targets the nucleophilic hydroxyl group of the Ser203 residue at the enzyme's esteratic site. The phosphorus atom in Sarin undergoes a nucleophilic attack by the Ser203 hydroxyl group, leading to the displacement of the fluorine leaving group [29]. This reaction results in the formation of a stable, covalent phosphonylated enzyme complex (E-P complex), completely blocking the enzyme's catalytic activity.

Following the initial inhibition, the phosphonylated AChE can undergo a secondary non-enzymatic process known as "aging" (*dealkylation*) [30]. During aging, the isopropyl alkoxy group attached to the phosphorus atom is enzymatically cleaved, leaving a negatively charged phosphonyl oxygen. This negative charge electrostatically stabilizes the phosphonyl-enzyme bond, rendering the enzyme permanently inactivated and completely refractory to oxime-mediated reactivation therapies. Consequently, the profound inhibition of AChE leads to a massive and continuous accumulation of ACh at both nicotinic and muscarinic receptor sites, triggering an acute and potentially fatal cholinergic crisis [31].

3.2. Mechanism of Lewisite (Blister Agent)

Unlike nerve agents, the toxicological cascade of Lewisite (dichloro(2-chlorovinyl)arsine) is driven by the high affinity of its trivalent arsenic As^{3+} moiety toward vicinal dithiols, specifically targeting the sulfhydryl/thiol (-SH) groups of cellular enzymes and structural proteins [32]. The primary molecular target of Lewisite is the lipoic acid cofactor within the pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase complexes, which are critical rate-limiting components of mitochondrial metabolism [33].

The arsenic atom in Lewisite binds covalently to the two neighboring sulfhydryl groups of dihydrolipoamide, forming a highly stable, cyclic five-membered dithiaarsolane ring. This binding deactivates the lipoamide cofactor, effectively halting the conversion of pyruvate into Acetyl-CoA, thereby completely disrupting the tricarboxylic acid (TCA) cycle—commonly known as the Krebs cycle. The arrest of the Krebs cycle abruptly shuts down mitochondrial oxidative phosphorylation, leading to a catastrophic depletion of cellular adenosine triphosphate (ATP) and acute metabolic energy failure [34].

In addition to metabolic shutdown, the inhibition of mitochondrial respiratory enzymes triggers an immediate electron leakage from the transport chain, converting molecular oxygen into reactive oxygen species (ROS), such as superoxide radicals and hydrogen peroxide. This surge in ROS induces severe oxidative stress, causing extensive lipid peroxidation of mitochondrial and plasma membranes, intracellular calcium homeostasis disruption, and structural degradation of cellular macromolecules [35]. Deprived of ATP and subjected to compounding oxidative damage, the structural integrity of the cell collapses completely. This bioenergetic and structural ruin culminates in acute tissue necrosis, clinically manifesting as rapid inflammation, immediate excruciating pain, and extensive vesicle (blister) formation upon dermal or systemic exposure [36].

4. CLINICAL MANIFESTATIONS AND HEALTH EFFECTS

The physiological anomalies induced by Sarin and Lewisite reflect their distinct underlying molecular pathophysiologies. While Sarin drives systemic cholinergic overstimulation, Lewisite acts as an immediate cytotoxic vesicant, causing severe rapid localized tissue destruction.

4.1. Clinical Manifestations of Sarin

The clinical presentation of Sarin exposure varies depending on the route and dose, but it is universally characterized by an acute cholinergic crisis [37]. When considering localized effects, direct ocular contact with Sarin vapor causes rapid, intense miosis due to localized inhibition of AChE in the pupillary constrictor muscle, which is frequently accompanied by conjunctival hyperemia and severe ocular pain. Similarly, localized inhalation immediately stimulates the airway's secretory glands, presenting as severe rhinorrhea and acute bronchoconstriction [38]. On the skin, direct contact with liquid Sarin induces localized diaphoresis and focal muscle fasciculations restricted to the site of exposure.

On a systemic level, as Sarin enters the bloodstream, it triggers widespread parasympathetic hyperactivation often summarized as the SLUDGEM syndrome, which includes massive salivation, lacrimation, gastrointestinal hypermotility, and severe bronchorrhea. At the neuromuscular junctions, systemic accumulation of acetylcholine drives initial muscle twitching and widespread fasciculations that rapidly progress to flaccid paralysis [39]. Because Sarin readily crosses the blood-brain barrier, high-dose systemic exposure results in severe central nervous system disruption, leading to an immediate loss of consciousness, status epilepticus, central respiratory depression, and ultimately, death from asphyxia within minutes [40].

4.2. Clinical Manifestations of Lewisite

In contrast to the delayed onset seen in other blister agents such as Sulfur Mustard, Lewisite exposure produces an immediate, catastrophic clinical onset upon contact with biological tissue. This immediate, excruciating pain is a unique diagnostic hallmark of Lewisite, driven by rapid cell necrosis and direct chemical irritation of peripheral nerve endings by the trivalent arsenical compound [26]. When the eyes are exposed to either liquid or vapor forms of Lewisite, victims experience immediate blepharospasm, severe burning pain, and massive eyelid edema, which can rapidly

progress to extensive corneal necrosis and irreversible retinal damage.

Dermal exposure demonstrates rapid pathology, where intense erythema and edema develop within minutes, progressing over 2 to 12 hours into large, tense, fluid-filled blisters. Furthermore, inhalation of Lewisite vapor causes immediate, severe damage throughout the respiratory tract, manifesting initially as aphonia and severe coughing. As the agent moves deeper into the respiratory tree, it triggers extensive pseudomembranous inflammation and necrosis of the bronchial mucosa, culminating in hemorrhagic pulmonary edema and terminal respiratory failure [17] In contrast to the delayed onset seen in other blister agents such as Sulfur Mustard, Lewisite exposure produces an immediate, catastrophic clinical onset upon contact with biological tissue. This immediate, excruciating pain is a unique diagnostic hallmark of Lewisite, driven by rapid cell necrosis and direct chemical irritation of peripheral nerve endings by the trivalent arsenical compound [26]. When the eyes are exposed to either liquid or vapor forms of Lewisite, victims experience immediate blepharospasm, severe burning pain, and massive eyelid edema, which can rapidly progress to extensive corneal necrosis and irreversible retinal damage.

Dermal exposure demonstrates rapid pathology, where intense erythema and edema develop within minutes, progressing over 2 to 12 hours into large, tense, fluid-filled blisters. Furthermore, inhalation of Lewisite vapor causes immediate, severe damage throughout the respiratory tract, manifesting initially as aphonia and severe coughing. As the agent moves deeper into the respiratory tree, it triggers extensive pseudomembranous inflammation and necrosis of the bronchial mucosa, culminating in hemorrhagic pulmonary edema and terminal respiratory failure [17].

5. CHALLENGES AND FUTURE PERSPECTIVES

5.1. Challenges Toward Advanced Sarin Countermeasures

Despite extensive research on sarin toxicity, several challenges remain. Current understanding is largely focused on acetylcholinesterase (AChE) inhibition, while the mechanisms underlying delayed neurological effects, such as neuroinflammation and neurodegeneration, are not fully understood [41].Existing biomarkers are mainly useful for acute exposure assessment and provide limited information on long-term outcomes [42]. The effectiveness of current antidotes is also constrained by AChE aging and poor blood–brain barrier penetration of many oximes [43]. In addition, field decontamination remains difficult during large-scale incidents, rapid detection in public settings is still limited, and the long-term storage stability of antidotes such as atropine and pralidoxime presents logistical challenges [44].

Future research should focus on elucidating the molecular pathways involved in chronic neurological injury following sarin exposure. Advanced omics technologies, including genomics, proteomics, and metabolomics, may facilitate the discovery of novel biomarkers for early diagnosis and long-term monitoring [45]. The development of next-generation oximes with improved blood–brain barrier permeability, catalytic bioscavengers, and neuroprotective agents also represents an important research priority [46]. In addition, artificial intelligence and computational toxicology could accelerate antidote discovery and improve predictive models of sarin-induced toxicity. Research efforts should also prioritize the development of portable biosensors capable of rapid and real-time sarin detection in public settings, as well as environmentally friendly decontamination materials that exhibit fast reaction kinetics, high neutralization efficiency, and minimal ecological impact.

5.2. Challenges Toward Advanced Lewisite Countermeasures

Compared with sarin, the toxicological mechanisms of lewisite remain less thoroughly characterized. Although its acute vesicant and arsenical effects are well known, information regarding chronic toxicity and long-term health outcomes remains limited [33]. The lack of specific biomarkers for distinguishing lewisite exposure from other arsenic sources further complicates diagnosis. Moreover, British Anti-Lewisite (BAL, **Figure 3a**), the primary antidote, is associated with adverse effects and limited efficacy against secondary issue damage [47]. Challenges also persist in rapid field dete. Challenges also persist in rapid field detection, effective decontamination, and antidote storage and deployment.

BAL has a 3-carbon backbone with two sulfhydryl (-SH) groups and a hydroxyl group (**Figure 3a**). Early research into the mechanism of effectiveness of BAL came from work with arsenic and sulfur groups in hair protein. It was surmised at the time that metals bind to the sulfhydryl groups of various enzymes as a mechanism for their significant toxicity. The Oxford Group had been testing glutathione ($C_{10}H_{17}N_3O_6S$ a polypeptide of glycine, cystine, and glutamic acid) with one sulfhydryl group in the treatment of arsenic poisoning without much success. Using the human hair with abundant thiol groups they were able to elucidate the mechanism for BAL. As time progressed it was found that the sulfhydryl groups of lipoic acidwas the target for arsenic poisoning. Lipoic acid is a key component of two important enzymes: pyruvate dehydrogenase (PDH) and alpha-ketogluterate dehydrogenase (KDH). PDH converts the end product of glycolysis to acetyl coenzyme A, which can then enter the tricarboxylic acid (TCA) cycle. KDH is an enzyme with the TCA cycle. Lipoic acid is an 8-carbon dithiol that is covalently linked to one subunit of the PDH and KDH complex (**Figure 3b**). In the presence of arsenic, the two sulfhydryl groups bind with arsenic to form a six-membered ring (**Figure 3c**). BAL presents two sulfhydryl groups to the bound arsenic-lipoic acid and forms a more stable five-membered ring (**Figure 3d**) thereby freeing PDH and KDH from arsenic inhibition. As mentioned previously, other metals also form complexes with sulfhydryl groups. The most stable complexes between BAL and metal ions are formed with Class B metals (arsenic, mercury, and gold). Lead is a Class A metal and chelation is best accomplished by adding a second

chelator such as meso-2,3-dimercaptosuccinic acid (DMSA) or ethylenediaminetetraacetic acid (EDTA).

Future studies should aim to clarify the molecular and cellular pathways involved in arsenic-mediated toxicity using advanced systems toxicology approaches. The identification of lewisite-specific biomarkers, including protein adducts and metabolomic signatures, may improve exposure assessment and clinical diagnosis. Research efforts should also focus on the development of safer and more effective chelating agents, as well as combination therapies incorporating antioxidant, anti-inflammatory, and regenerative strategies [48]. Furthermore, the development of highly selective biosensors for rapid field detection and environmentally sustainable decontamination systems capable of efficiently neutralizing arsenical compounds represents an important area of future investigation. The application of organoid models, three-dimensional tissue cultures, and nanotechnology-based detection platforms may provide more clinically relevant insights and enhance preparedness against arsenical chemical threats [49].

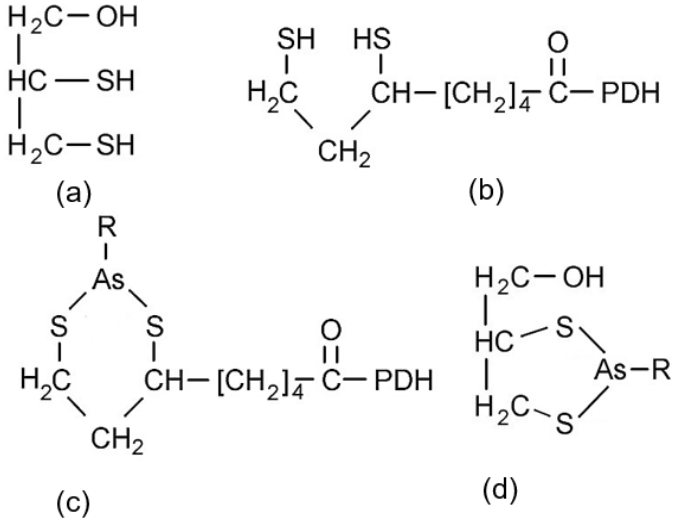

Figure 3. (a) Chemical structure of BAL; (b) Lipoic acid attached to pyruvate dehydrogenase (PDH); (c) Six-membered ring formed by arsenic and lipoic acid; (d) Favored 5-membered ring of BAL and arsenic

5.3. Emerging Directions in Chemical Warfare Toxicology

Several common challenges remain for both sarin and lewisite, including limited human exposure data, incomplete understanding of long-term health effects, and insufficiently sensitive diagnostic tools. Effective field decontamination, rapid public-area detection, and the stability and availability of medical countermeasures also continue to hinder emergency preparedness [50]. Future advances in chemical warfare toxicology will likely rely on the integration of omics technologies, artificial intelligence, computational modeling, nanotechnology, and biosensor platforms. These approaches may improve biomarker discovery, enable real-time detection, and accelerate the development of safer antidotes and eco-friendly decontamination systems [51]. Continued international collaboration through organizations such as the Organisation for the Prohibition of Chemical Weapons will remain essential for strengthening global preparedness against chemical threats [52]. Despite extensive research on sarin toxicity, several challenges remain. Current understanding is largely focused on acetylcholinesterase (AChE) inhibition, while the mechanisms underlying delayed neurological effects, such as neuroinflammation and neurodegeneration, are not fully understood [41]. Existing biomarkers are mainly useful for acute exposure assessment and provide limited information on long-term outcomes [42]. The effectiveness of current antidotes is also constrained by AChE aging and poor blood–brain barrier penetration of many oximes [43]. In addition, field decontamination remains difficult during large-scale incidents, rapid detection in public settings is still limited, and the long-term storage stability of antidotes such as atropine and pralidoxime presents logistical challenges [44].

6. CONCLUSION

In summary, chemical warfare agents (CWAs) such as Sarin and Lewisite represent catastrophic instruments of mass destruction and asymmetrical terrorism, each operating through fundamentally distinct biochemical and physiological pathways. Sarin, a highly volatile organophosphorus nerve agent, targets the nervous system by selectively phosphorylating the catalytic serine residue of acetylcholinesterase, leading to a systemic cholinergic crisis characterized by neuromuscular paralysis and central respiratory arrest. Conversely, Lewisite is a non-volatile, persistent arsenical vesicant that exerts severe localized and systemic cytotoxicity through its high affinity for sulfhydryl groups, effectively shutting down the mitochondrial Krebs cycle via pyruvate dehydrogenase inhibition and triggering extensive tissue necrosis, immediate excruciating pain, and pulmonary destruction.

Despite these divergent toxicological routes, both agents pose unprecedented challenges to public health and emergency response infrastructure, demanding an integrated and rapid medical countermeasure strategy. Effective mitigation requires immediate, simultaneous deployment of field decontamination, aggressive respiratory support, and systemic antidotal interventions, such as oximes for nerve agents or specialized chelating therapies for arsenical poisoning. Ultimately, a comprehensive understanding of these molecular biochemical pathways, combined with robust medical preparedness, enhanced detection technologies, and multinational scientific collaboration, forms the definitive cornerstone for neutralizing the threat and minimizing the catastrophic impacts of chemical terrorism in the future.

7. AUTHOR'S DECLARATION

7.1. Supporting Information

This manuscript does not include supplementary materials. All methods, analytical procedures, and results necessary for understanding and evaluating the study are contained within the main article. Access to the qPCR data supporting the findings may be provided by the authors upon reasonable request.

7.2. Acknowledgements

The authors sincerely acknowledge the financial support provided by the Department of Chemistry, The Republic of Indonesia Defense University.

7.3. Conflict of Interest

The authors have no conflict of interest in this publication.

7.4. Author Contributions

TOJT, TRY, RA, ZAH, CCDS performed the writing original draft, review & editing. RB and NAS performed the conceptualization, investigation, and methodology. All authors were collaborated on revising the manuscript. All authors read and approved the final version of the manuscript.

7.5. AI Statement

Gemini AI was utilize to generate graphical abstract. The Trinka AI was utilized exclusively to support language refinement and the preparation of graphical materials. The literature evaluation, synthesis of information, critical analysis, and all scientific interpretations presented in this review were conducted independently by the authors.

8. REFERENCES

[1] Chai, P.R., Boyer, E.W., Al-Nahhas, H. and Erickson, T.B. 2017. Toxic chemical weapons of assassination and warfare: nerve agents VX and sarin. *Toxicol. Commun. 1*(1). 21-23. Doi: https://doi.org/10.1080/24734306.2017.1373503

[2] Abou-Donia, M.B., Siracuse, B., Gupta, N. and Sobel Sokol, A. 2016. Sarin (GB, O-isopropyl methylphosphonofluoridate) neurotoxicity: critical review. *Crit. Rev. Toxicol. 46*(10). 845-875. Doi: https://doi.org/10.1080/10408444.2016.1220916

[3] Costanzi, S., Machado, J.H. and Mitchell, M. 2018. Nerve agents: what they are, how they work, how to counter them. *ACS Chem. Neurosci. 9*(5). 873-885. Doi: https://doi.org/10.1021/acschemneuro.8b00148

[4] Gundert-Remy, U., Barth, H., Bürkle, A., Degen, G.H. and Landsiedel, R. 2015. Toxicology: a discipline in need of academic anchoring—the point of view of the German Society of Toxicology. *Arch. Toxicol. 89*(10). 1881-1893. Doi: https://doi.org/10.1007/s00204-015-1577-7

[5] Hayes, A.W. and Dixon, D. 2017. Cornerstones of toxicology. *Toxicol. Pathol. 45*(1). 57-63. Doi: https://doi.org/10.1177/0192623316675768

[6] Pognan, F., Beilmann, M., Boonen, H.C., Czich, A., Dear, G., Hewitt, P., Mow, T., Oinonen, T., Roth, A., Steger-Hartmann, T. and Valentin, J.P. 2023. The evolving role of investigative toxicology in the pharmaceutical industry. *Nat. Rev. Drug. Discov. 22*(4). 317-335. Doi: https://doi.org/10.1038/s41573-022-00633-x

[7] Shiek, S.S., Sajai, S.T. and Dsouza, H.S. 2023. Arsenic-induced toxicity and the ameliorative role of antioxidants and natural compounds. *J. Biochem. Mol. Toxicol. 37*(3) 23281. Doi: https://doi.org/10.1002/jbt.23281

[8] Voros, C., Dias, J., Timperley, C.M., Nachon, F., Brown, R.C. and Baati, R. 2024. The risk associated with organophosphorus nerve agents: from their discovery to their unavoidable threat, current medical countermeasures and perspectives. *Chem. Biol. Interact. 395*. 110973. Doi: https://doi.org/10.1016/j.cbi.2024.110973

[9] Walczak-Nowicka, Ł.J. and Herbet, M. 2021. Acetylcholinesterase inhibitors in the treatment of neurodegenerative diseases and the role of acetylcholinesterase in their pathogenesis. *Int. J. Mol. Sci. 22*(17). 9290. Doi: https://doi.org/10.3390/ijms22179290

[10] Lagacé, F., Schmitt, A., Martrille, L., Benassi, J. and Adalian, P. 2020. Using histomorphometry for human and nonhuman distinction: A test of four methods on fresh and archaeological fragmented bones. *Forensic. Sci. Int. 313*. 110369. Doi: https://doi.org/10.1016/j.forsciint.2020.110369

[11] Bernardo, L.B., Borges, C.V., Buitrago, P.A., Kuča, K., Cavalcante, S.F., Sousa, R.B., Lima, A.L. and Kitagawa, D.A. 2024. Synthesis and in vitro assessment of the reactivation profile of clinically available oximes on the acetylcholinesterase model inhibited by A-230 nerve agent surrogate. *Arch. Toxicol. 98*(10). 3397-3407. Doi: https:// doi.org/10.26434/chemrxiv-2024-xkp1w

[12] Meyer, C. and Thippeswamy, T. 2025. Organophosphate Chemical Nerve Agents, Oxidative Stress, and NADPH Oxidase Inhibitors: An Overview. *Int. J. Mol. Sci. 26*(19). 9313. Doi: https://doi.org/10.3390/ijms26199313

[13] Cao, C., Wang, L., Zhang, J., Liu, Z., Li, M., Xie, S., Chen, G. and Xu, X. 2022. Neuroligin-1 plays an important role in methamphetamine-induced hippocampal synaptic plasticity. *Toxicol. Lett. 361*. 1-9. Doi: https://doi.org/10.1016/j.toxlet.2022.03.007

[14] Huber, C. 2019. A war of frustration: Saddam Hussein's use of nerve gas on civilians at Halabja (1988) and the American response. *Senior Honors*. *6*(03) .2022. Doi: https://commons.lib.jmu.edu/honors201019/683

[15] Etemad, L., Moshiri, M. and Balali-Mood, M. 2018. Delayed Complications and long-term management of sulfur mustard poisoning: a narrative review of recent advances by iranian researchers part ii: clinical management and therapy. *Iran. J. Med. Sci. 43*(3). 235.

[16] Romero Martínez, M.A., Ramos Alonso, E., López Muñoz, F., Ríos, C.D.L., Egea, J., Gil Martín, E., Pita Pita, R., Torrado Durán, J.J., Serrano López, D.R. and Juberias, A., 2021. Toxicology of Blister Agents: Is Melatonin a Potential Therapeutic Option?. *Diseases*. *9*(2). 27. Doi: https://doi.org/10.3390/diseases9020027

[17] Li, C., Srivastava, R.K. and Athar, M. 2016. Biological and environmental hazards associated with exposure to chemical warfare agents: arsenicals. *Annals Ann. N.Y. Acad. Sci. 1378*(1). 143-157. Doi: https://doi.org/10.1111/nyas.13214

[18] Li, C., Srivastava, R.K. and Athar, M. 2016. Biological and environmental hazards associated with exposure to chemical warfare agents: arsenicals. *Ann. N. Y. Acad. Sci. 1378*(1). 143-157. Doi: https://doi.org/10.1111/nyas.13214

[19] Muzaffar, S., Khan, J., Srivastava, R., Gorbatyuk, M.S. and Athar, M. 2023. Mechanistic understanding of the toxic effects of arsenic and warfare arsenicals on human health and environment. *Cell Biol. Toxicol. 39*(1). 85-110. Doi: https://doi.org/10.1007/s10565-022-09710-8

[20] Sugiyama, A., Matsuoka, T., Sakamune, K., Akita, T., Makita, R., Kimura, S., Kuroiwa, Y., Nagao, M. and Tanaka, J. 2020. The Tokyo subway sarin attack has long-term effects on survivors: A 10-year study started 5 years after the terrorist incident. *PloS one*. *15*(6). 0234967. Doi: https://doi.org/10.1371/journal.pone.0234967

[21] Socher, M., Romanek, K., Zilker, T., Fromme, H. and Wildner, M. 2025. Assaults with Highly Toxic Substances in Public Spaces: Preparedness in Lessons Learnt from Precedent Cases. Doi: https://doi.org/10.5772/intechopen.1011887

[22] Baker, D.J. and Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. *Hum. Exp. Toxicol. 15*(5). 369-375. Doi: https://doi.org/10.1177/096032719601500501

[23] Makhaeva, G.F., Rudakova, E.V., Sigolaeva, L.V., Kurochkin, I.N. and Richardson, R.J. 2016. Neuropathy target esterase in mouse whole blood as a biomarker of exposure to neuropathic organophosphorus compounds. *J. Appl. Toxicol. 36*(11). 1468-1475. Doi: https://doi.org/10.1002/jat.3305

[24] Srivastava, R.K., Muzaffar, S., Khan, J., Bansal, M., Agarwal, A. and Athar, M. 2025. Common molecular profile of multiple structurally distinct warfare arsenicals in causing cutaneous chemical vesicant injury. *Sci. Rep. 15*(1). 6505. Doi: https://doi.org/10.1038/s41598-024-83513-1

[25] Milatović, D., Jokanović, M. and Gupta, R.C., 2009. Handbook of

toxicology of chemical warfare agents.

[26] Gorbatyuk, M., Sinha, N.R., Kumar, R., Zhylkibayev, A., Athar, M., Patrick, M. and Mohan, R.R. 2025. Current progress in research on ocular injury caused by exposure to vesicants. *Prog. Retin. Eye. Res. 109*. 101413. Doi: https://doi.org/10.1016/j.preteyeres.2025.101413

[27] Nair, A., Yadav, P., Behl, A., Sharma, R.K., Kulshrestha, S., Butola, B.S. and Sharma, N., 2021. Toxic blister agents: Chemistry, mode of their action and effective treatment strategies. *Chem. Biol. Interact*. 350. 109654. Doi: https://doi.org/10.1016/j.cbi.2021.109654

[28] Allgardsson, A., Berg, L., Akfur, C., Hörnberg, A., Worek, F., Linusson, A. and Ekström, F.J. 2016. Structure of a prereaction complex between the nerve agent sarin, its biological target acetylcholinesterase, and the antidote HI-6. *PNAS. 113*(20). 5514-5519. Doi: https://doi.org/10.1073/pnas.1523362113

[29] Abou-Donia, M.B., Siracuse, B., Gupta, N. and Sobel Sokol, A. 2016. Sarin (GB, O-isopropyl methylphosphonofluoridate) neurotoxicity: critical review. *Crit. Rev. Toxicol. 46*(10). 845-875. Doi: https://doi.org/10.1080/10408444.2016.1220916

[30] Zhuang, Q., Franjesevic, A.J., Corrigan, T.S., Coldren, W.H., Dicken, R., Sillart, S., DeYong, A., Yoshino, N., Smith, J., Fabry, S. and Fitzpatrick, K. 2018. Demonstration of in vitro resurrection of aged acetylcholinesterase after exposure to organophosphorus chemical nerve agents. *J. Med. Chem. 61*(16). 7034-7042. Doi: https://doi.org/10.1021/acs.jmedchem.7b01620

[31] Aroniadou-Anderjaska, V., Apland, J.P., Figueiredo, T.H., Furtado, M.D.A. and Braga, M.F. 2020. Acetylcholinesterase inhibitors (nerve agents) as weapons of mass destruction: History, mechanisms of action, and medical countermeasures. *Neuropharmacology*. *181*. 108298. Doi: https://doi.org/10.1016/j.neuropharm.2020.108298

[32] Harper, L.K. and Bayse, C.A., 2015. Modeling the chelation of As (III) in lewisite by dithiols using density functional theory and solvent-assisted proton exchange. *J. Inorg. Biochem. 153*. 60-67. Doi: https://doi.org/10.1016/j.jinorgbio.2015.10.004

[33] Nurchi, V.M., Buha Djordjevic, A., Crisponi, G., Alexander, J., Bjørklund, G. and Aaseth, J. 2020. Arsenic toxicity: molecular targets and therapeutic agents. *Biomolecules*. *10*(2). 235. Doi: https://doi.org/10.3390/biom10020235

[34] Lyczko, M., Lyczko, K., Majkowska-Pilip, A. and Bilewicz, A. 2019. 1, 2-Benzenedithiol and Toluene-3, 4-dithiol Arsenic (III) Complexes—Synthesis, Structure, Spectroscopic Characterization and Toxicological Studies. *Molecules*. *24*(21). 3865. Doi: https://doi.org/10.3390/molecules24213865

[35] Yu, F.L., Zhang, M.Y., Song, G.W., Ning, Y.S., Wu, X. and Gao, Y., 2025. The effect of arsenic on mitochondrial fatty acid metabolism via inhibition of carnitine palmitoyltransferase 1B and choline kinase beta in C2C12 cells. *Plos one*. 20(5). e0320557. Doi: https://doi.org/10.1371/journal.pone.0320557

[36] Turkington, R.E., Hukriede, N.A., Ho, J., Jayasundara, N. and Sanders, A.P. 2025. Metal mechanisms of mitochondrial toxicity: recent review of arsenic, cadmium, and lead-induced nephrotoxicity. *Environ. Sci. Pollut. Res. 32*(24). 14439-14451. Doi: https://doi.org/10.1007/s11356-025-36538-6

[37] Jett, D.A., Sibrizzi, C.A., Blain, R.B., Hartman, P.A., Lein, P.J., Taylor, K.W. and Rooney, A.A. 2020. A national toxicology program systematic review of the evidence for long-term effects after acute exposure to sarin nerve agent. *Crit. Rev. Toxicol. 50*(6). 474-490. Doi: https://doi.org/10.1080/10408444.2020.1787330

[38] Lee, T.J. and Borgman, M.A. 2022. Toxic Inhalations. In *Management of Chest Trauma: A Practical Guide*. 367-385. Cham: Springer International Publishing. Doi: https://doi.org/10.1007/978-3-031-06959-8_31

[39] Hatfill, S.J. 2019. Chemical warfare: nerve agents. *J. Am. Phys. Surg*. *24*(1). 19-24.

[40] Howard Jr, J.F. 2018. Toxic neuromuscular transmission disorders. In *Myasthenia gravis and related disorders*. 275-298. Cham: Springer International Publishing. Doi: https://doi.org/10.1007/978-3-319-73585-6_17

[41] Andrew, P.M. and Lein, P.J. 2021. Neuroinflammation as a therapeutic target for mitigating the long-term consequences of acute organophosphate intoxication. *Front. Pharmacol. 12*. 674325. Doi: https://doi.org/10.3389/fphar.2021.674325

[42] John, H. and Thiermann, H. 2021. Poisoning by organophosphorus nerve agents and pesticides: an overview of the principle strategies and current progress of mass spectrometry-based procedures for verification. *J. Mass Spectrom. Adv. Clin. Lab*. *19*. 20-31. Doi: https://doi.org/10.1016/j.jmsacl.2021.01.002

[43] Norrrahim, M.N.F., Razak, M.A.I.A., Shah, N.A.A., Kasim, H., Yusoff, W.Y.W., Halim, N.A., Nor, S.A.M., Jamal, S.H., Ong, K.K., Yunus, W.M.Z.W. and Knight, V.F. 2020. Recent developments on oximes to improve the blood brain barrier penetration for the treatment of organophosphorus poisoning: a review. *RSC Adv*. *10*(8). 4465-4489. Doi: https://doi.org/10.1039/C9RA08599H

[44] Labaška, M., Gál, M., Mackuľak, T., Švorec, J., Kučera, J., Helenin, J., Svitková, V. and Ryba, J. 2024. Neutralizing the threat: A comprehensive review of chemical warfare agent decontamination strategies. *J. Environ. Chem. Eng. 12*(6). 114243. Doi: https://doi.org/10.1016/j.jece.2024.114243

[45] Dai, X. and Shen, L. 2022. Advances and trends in omics technology development. *Front. Med. 9*. 911861. Doi: https://doi.org/10.3389/fmed.2022.911861

[46] Mohamed, R.A., Ong, K.K., M. Kasim, N.A., A. Halim, N., M. Noor, S.A., Knight, V.F., Ab. Rahman, N.N. and W. Yunus, W.M.Z. 2021. Transitioning from oxime to the next potential organophosphorus poisoning therapy using enzymes. *J. Chem. 2021*(1). 7319588. Doi: https://doi.org/10.1155/2021/7319588

[47] Balali-Mood, M., Eizadi-Mood, N., Hassanian-Moghaddam, H., Etemad, L., Moshiri, M., Vahabzadeh, M. and Sadeghi, M. 2025. Recent advances in the clinical management of intoxication by five heavy metals: Mercury, lead, chromium, cadmium and arsenic. *Heliyon*. *11*(4). Doi: https://doi.org/10.1016/j.heliyon.2025.e42696

[48] Bjørklund, G., Oliinyk, P., Lysiuk, R., Rahaman, M.S., Antonyak, H., Lozynska, I., Lenchyk, L. and Peana, M. 2020. Arsenic intoxication: general aspects and chelating agents. *Arch. Toxicol. 94*(6), 1879-1897. Doi: https://doi.org/10.1007/s00204-020-02739-w

[49] Kosnett, M.J. 2013. The role of chelation in the treatment of arsenic and mercury poisoning. *J. Med. Toxicol. 9*(4). 347-354. Doi: https://doi.org/10.1007/s13181-013-0344-5

[50] Calvano, C.J., Enzenauer, R.W. and Johnson, A.J. eds. 2019. *Ophthalmology in Military and Civilian Casualty Care*. No. 168443. Springer. Doi: https://doi.org/10.1007/978-3-030-14437-1

[51] Singh, A.V., Bhardwaj, P., Laux, P., Pradeep, P., Busse, M., Luch, A., Hirose, A., Osgood, C.J. and Stacey, M.W. 2024. AI and ML-based risk assessment of chemicals: predicting carcinogenic risk from chemical-induced genomic instability. *Front. Toxicol*. *6*. 1461587. Doi: https://doi.org/10.3389/ftox.2024.1461587

[52] Hartung, T. 2023. Artificial intelligence as the new frontier in chemical risk assessment. *Front. Artif. Intell. 6*, p.1269932. Doi: https://doi.org/10.3389/frai.2023.1269932