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Toxic blister agents: Chemistry, mode of their action and effective treatment strategies

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ABSTRACT

Since their use during the First World War, Blister agents have posed a major threat to the individuals and have caused around two million casualties. Major incidents occurred not only due to their use as chemical warfare agents but also because of occupational hazards. Therefore, a clear understanding of these agents and their mode of action is essential to develop effective decontamination and therapeutic strategies. The blister agents have been categorised on the basis of their chemistry and the biological interactions that entail post contamination. These compounds have been known to majorly cause blisters/bullae along with alkylation of the contaminated DNA. However, due to the high toxicity and restricted use, very little research has been conducted and a lot remains to be clearly understood about these compounds. Various decontamination solutions and detection technologies have been developed, which have proven to be effective for their timely mitigation. But a major hurdle seems to be the lack of proper understanding of the toxicological mechanism of action of these compounds. Current review is about the detailed and updated information on physical, chemical and biological aspects of various blister agents. It also illustrates the mechanism of their action, toxicological effects, detection technologies and possible decontamination strategies.

1. Blister agents

Blister agents or vesicants, are human-made chemicals that can cause blisters or vesicles on skin and mucous membrane upon contamination. Exposure to these chemicals may occur through intentional release as Chemical Warfare Agents (CWA) or unintentionally at workplace. Among all blister agents, mustards and lewisites have been highlighted as potential CWAs [1]. These chemicals are particularly not very lethal as nerve agents, but can cause severe injury that may result in prolonged morbidity or casualty [2]. It has been seen during the World War I (WWI) that these agents caused more number of casualties compared with any other CWAs that were used at that time [3].

The blister agents are named so as they can cause severe chemical burns, resulting in bullae formation. These agents may be present in vapour, liquid, and semi-solid form, acting primarily on skin and other epithelial tissues. However, depending upon the route of exposure, the agents can also severely damage the eyes, respiratory tract and internal organs by interacting with various cellular organelles. The most likely routes of exposure to these agents are inhalation, ingestion, dermal, and ocular contact. Upon contact with the skin, these chemicals cause localised degeneration of the skin and mucous membranes, and induce inflammatory changes. This leads the cell to undergo apoptosis, thus causing the degradation of the basal membrane leading to the formation of blisters/bullae [4]. The vesicants are highly reactive chemicals that interact with proteins, DNA, and other cellular components, resulting in drastic cellular changes immediately after contamination [5,6].

The clinical effects after exposure may occur within seconds or manifest within 2–24 h, depending on the vesicant [7]. Based upon the route of exposure, clinical effects may be manifested in the dermal (blistering, skin erythema), respiratory (pharyngitis, cough, dyspnoea), ocular (blurred vision, conjunctivitis, blindness), gastrointestinal (nausea, vomiting, diarrhoea), etc. Exposure to higher doses can also cause cardiac arrest and affect the Central Nervous System (CNS)

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Abbreviations

BABE	1-(4, 7-bis (4-aminophenyl)-1*H*-benzoimidazole-2-yl) ethan-1-ol
TFPy	1, 3, 6, 8-tetrakis (4-formylphenyl) pyrene
CEES	2-chloroethyl ethyl sulphide
ATP	Adenosine Triphosphate
BAD	Bcl2 associated agonist of cell death
BAX	Bcl-2 associated X
BAL	Broncheoalveolar lavage
CBRN	Chemical Biological Radiological Nuclear
CWA	Chemical Warfare Agent
CWC	Chemical Weapons Convention
COF	Covalent Organic Frameworks
COX	Cyclooxygenase
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
GSH	Glutathione
AuNP	Gold Nanoparticles
HAZMATCAD	Hazardous Materials Chemical Agents Detector
IR	Infrared
IL	Interleukin
L	Lewisites
MMP-9	Matrix metalloproteinase-9
MOFs	Metal Organic Frameworks
MAPK	Mitogen-activated protein kinase
EDEA	N-ethyldiethanolamine
NAD	Nicotinamide adenine dinucleotide
HN	Nitrogen Mustard
MDEA	N-methyldiethanolamine
B–NF-κB	Nuclear factor kappa
OPCW	Organisation for the Prohibition of Chemical Weapons
PPE	Personal Protective Equipment
CX	Phosgene Oxime
Pt	Platinum
PARP	Poly (ADP-ribose) Polymerases
PCNA	Proliferative cell nuclear antigen
QCM	Quartz chemical microbalance
ROS	Reactive Oxygen Species
RNS	Reactive Nitrogen Species
HD	Sulfur Mustard
SAW	Surface Acoustic Wave
TiO_2	Titanium oxide
TEA	Triethanolamine
TNFR	Tumor Necrosis factor receptor
TNF	Tumor necrosis factor
WO_3	Tungsten Oxide
UV	Ultraviolet
UPR	Unfolded Protein response
UNODA	United Nations Office for Disarmament Affairs

causing the patient to experience convulsions, tremors or coma [8].

Blister agents were initially developed as an industrial chemical in 1822. The use of these agents against humans has been seen during WWI. However, initially choking agents were the important chemical warfare agent during that time. But, the exposure from these gases could be reduced by using gas-masks. Research on blister agents had started after the chlorine gas attack in 1915 by the Germans. The United States and Europe began to earnestly conduct research on the mass production of sulfur mustard, and tested its effects in the battlefield in the year 1917. These were the first agents to produce toxicological effects on masked soldiers by causing skin blisters and systemic effects due to cutaneous uptake. After WWI, different analogues of sulfur mustard were developed including nitrogen mustards. Nitrogen mustards were initially developed to remove warts and treat cancers but were replaced soon as warfare agents [9]. Massive production of nitrogen mustard was started by US and Germany. Further investigations on organic arsenicals were conducted by Germans during this period. They even used agents like ethyldichloroarsine, methyldichloroarsine, and ethyldibromoarsine in the battlefield. However, effects were less severe.

Due to the ghastly situations caused by the use of CWAs, the Geneva Protocol, prohibiting the use of chemical weapons in battlefield, was signed in 1925. However, there were a few loopholes in the Protocol, wherein, there was no prohibition for the development, production or stockpiling of chemical weapons. Moreover, the states that supported the Protocol possessed the rights to use these chemical weapons against states that were not in favour of the Protocol as stated by, UNODA, 1925. Hence, during World War II (WWII) the Nazi used poisonous gases in the concentration camps. During this period, sulfur mustard analogue bis-(2-chloroethylthioethyl) ether was also developed. This analogue turned out to be more persistent and was found to be three times more toxic than sulfur mustard [10]. In a research conducted by US, toxicity of lewisites had increased drastically but still remained lesser than sulfur mustards, and was later used as anti-freeze additives for sulfur mustards for storage. Sulfur mustards resulted in an exponential increase in the morbidity, earning it the moniker 'King of the Battle Gases'. The chemical compound went on to be used in the Japanese invasion of China (1937–1945), Iran-Iraq war (1980–1988) by the Iraq forces [11].

The Cold War period saw a significant development, manufacture and stockpiling of chemical weapons. By the year 1980, approximately 25 states were having active chemical weapon programmes. However, post-WWII, only few instances have reported the use of chemical weapons such as Iraq in the 1980s against the Islamic Republic of Iran and Halabja(1988). A brief timeline depicting the development of blister agents, to their use in different wars and major regulations undertaken have been illustrated in Supplementary Fig. 1 [10,12].

2. Classification of blister agents

2.1. Categorisation of blister agents

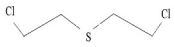
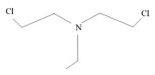
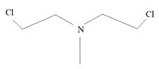
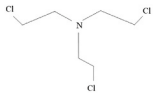
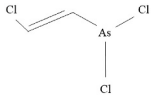
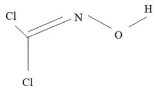
There are mainly three types of blistering agents that have the potential or have been used as CWAs-

2.1.1. Mustards

Mustard agents typically belong to the family of cytotoxic vesicating agents and are classified under Schedule 1, under 1993 Chemical Weapons Convention. The mustard agents can be classified further into subgroups- Sulfur mustards and Nitrogen mustards.

i) Sulphur mustard (2,2′-dichlorodiethyl sulfide)- Sulphur mustard can exist as vapour/aerosol and liquid forms. Sulfur mustards are denoted by HD. It can persist for 3 days to 1 week during summers and for around 3 weeks in winters. The rate of action of this agent is slow. The sulphur mustards have been known to primarily affect eyes, skin, and lungs [66]. These agents are clear yellow/brown oily liquids with a slight garlic or mustard odour and having low volatility. The IUPAC name, structure, synthesis, and a few relevant properties of these compounds have been illustrated in Table 1.
ii) Nitrogen mustards- Nitrogen mustards are compounds with chloroethylamine functional groups. Nitrogen mustards are denoted by HN. It can also persist for 3 days to 1 week during summers and for around 3 weeks in winters. The rate of action of nitrogen mustards is slow and it can exist in aerosol/vapour or liquid forms. Eyes, skin, and lungs are the primary site of contamination. Nitrogen mustards

Table 1
Description of Blister agents.

Blister Agent	IUPAC Name & Molecular Formula	Boiling Point	Melting Point	Mechanism of synthesis	Phase	Structure
Sulfur mustard (HD)	1-chloro-2-[(2-chlor-oethyl)sulfanyl] -ethane { $C_4H_8Cl_2S$ }	218 °C	14.4 °C	S_N1	Liquid; Vapour	
Nitrogen Mustard (HN)	HN1-2-Chloro-N-(2-chlor-oethyl)-N-ethyletha-n-1-amine { $C_6H_{13}Cl_2N$ }	HN1: 85.5 °C	HN1: 34 °C	S_N1	Liquid; Vapour	HN1: 
	HN2-2-Chloro-N-(2-chloroethyl)-N-methyleth-an-1-amine { $C_5H_{11}Cl_2N$ }	HN2-75 °C	HN2: 60 °C			HN2: 
	HN3- Tris(2-chloroethyl)a-mine { $C_6H_{12}Cl_3N$ }	HN3-143 °C	HN3: 3.5 °C			HN3: 
Lewisite (L)	2-chloroethenylarso-nous dichloride{ $C_2H_2AsCl_3$}	190 °C	−18 °C	S_N1	Liquid; Vapour	
Phosgene oxime (CX)	N-(dichloromethylidene)hydroxylamine{$CHCl_2NO$}	128 °C	40 °C	S_N1	Solid; liquid	

are colourless to yellow, oily liquids and are known to have variable odours. Some of the characteristics of nitrogen mustards have been highlighted in Table 1.

2.1.2. Lewisites

Lewisites are organoarsenic compounds, which were developed as a chemical weapon. These compounds act as blistering agents and are also widely known lung irritants. Lewisites are denoted as L. It can persist for about 1–3 days during summers and can extend to weeks during winters. They have a quick rate of action. The primary sites of contamination are eyes, lungs, skin, and mouth. Lewisites contain arsenic and are dark oily liquids with a slight odour of geranium. Some characteristics of lewisites have been stated in Table 1.

2.1.3. Halogenated oximes

Halogenated oximes are organic compounds developed as a potent chemical weapon. Phosgene oximes, denoted as CX, are prime examples of such compounds. It can persist for only a few days during summers or winters. The rate of reaction of these compounds is very quick. The primary targets are eyes, lungs, skin, and mouth. These are colourless solids or liquids and have an intense irritating odour. However, phosgene oximes are more aptly classified under nettle agents. Sometimes due to the similarity in the toxicity caused by phosgene oximes in the affected individual, they are also categorised as blister agents. A few characteristics of phosgene oxime have been shown in Table 1.

2.2. Route of synthesis

2.2.1. Sulfur mustards

These chemical compounds were the first of the blister agents developed. Although the compound was developed in the late 19th century, it was used as a chemical warfare agent only in the World War I. Sulfur mustard is described to be first developed by Despretz, in 1822, by a reaction of sulfur dichloride and ethylene, however, there is no description about the vesicating properties. After that, many methods have been utilized to develop the chemical. Interestingly, in the year 1886, Meyer treated 2-chloroethanol with aqueous potassium sulfide to form thiodiglycol, which he further treated with phosphorus trichloride, resulting in a highly purified yield of sulfur mustard. In 1913, however, Clarke modified the process mentioned by Meyer and replaced phosphorus trichloride with hydrochloric acid, creating a highly purified product with a higher yield [13]. The Clarke-Meyer method has been used since then as the gold standard for sulfur mustard production, as depicted in Fig. 1 [13,14].

Levinstein also developed a method for the production of sulfur mustard. In this method, sulfur dichloride was reacted with ethylene to form 2-chloroethanesulfonyl chloride. This compound is once again reacted with ethylene to form sulfur mustard. The levinstein method for the development of sulfur mustard has been shown in Fig. 1 [14].

Although sulfur mustards have the ideal physicochemical properties for a chemical warfare agent, they don't have a high freezing temperature (melting point 14 °C, pure). Its persistence for prolonged periods of time depends on the concentration and the state of the compound. Large liquid droplets tend to persist for a long time. This is due to the formation of oligomers at the air-liquid interface. The two electrophilic carbon atoms in the mustard agent react with water. Subsequently, the nucleophilic sulfur atom reacts with oxygen. Sulfur mustard reacts rapidly with water when present as a solution. However, due to low affinity for water (solubility 0.092 g/100 g at 22 °C) its degradation in the environment is quite limited.

2.2.2. Nitrogen mustards

Nitrogen mustards are similar to sulfur mustards except that tertiary amines substitute the 2—chloroethyl groups. Although they are low volatility liquids and have poor stability, these compounds tend to form more stable water soluble hydrochloride salts. The nitrogen mustards are industrially produced by chlorination of triethanolamine with thionyl chloride [15]. The nitrogen mustards have three majorly subtypes – HN-1, HN-2, and HN-3. The analogues, HN-1 and HN-2 have been found to be less stable than HN-3. With the boiling point of 143 °C, HN-3 is the most important, due to its higher vesicant activity. The compound is however, less volatile than sulfur mustard, but can be more hazardous under humid conditions. The nitrogen mustard analogue, HN-2 has also been used to treat a variety of cancers. Nitrogen mustards have also been prescribed in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, and against mycosis fungoides [102]. For the synthesis of nitrogen mustard, initially the carboxyl group of nicotinic acid is reacted with thionyl chloride to form nicotinoyl chloride. This compound

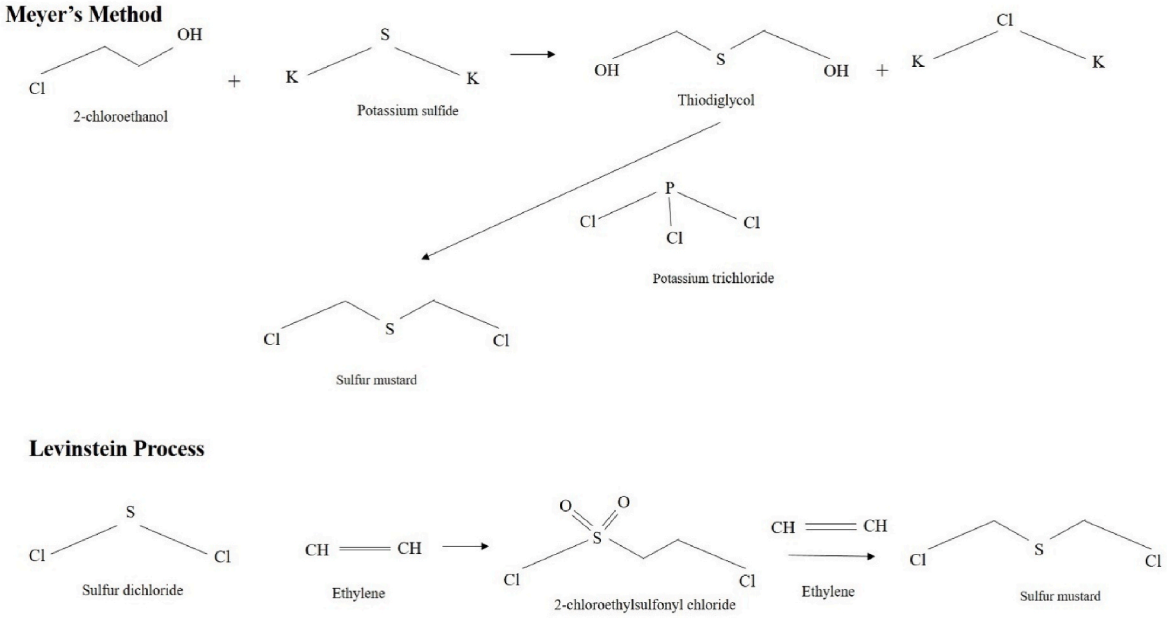


Fig. 1. Synthesis routes of sulfur mustard.

contains an activated carbonyl, which is reacted with triethanolamine to form 2-[bis (2-chloroethyl) amino] ethyl nicotinate. Further, a reflux reaction is carried out by adding thionyl chloride to form a nitrogen mustard compound. Fig. 2 was drawn by taking inspiration from the works of [16,17].

2.2.3. *Lewisites*

Lewisites were named after W.L. Lewis. The compound was primarily synthesized by adding arsenic trichloride to acetylene in hydrochloric acid solution, in the presence of mercuric chloride acting as a catalyst, as shown in Supplementary Fig. 2, which was inspired by the studies conducted by Ramesh et al. [5]. The arsenic chloride has a variety of vinyl chloride groups that can be mixed to form lewisites [18].Various experimental and computational studies have shown that lewisite exists mostly as *trans*-2-chlorovinylarsonous dichloride due to its high stability, as compared to the *cis* stereoisomer and the constitutional isomer (1-chlorovinylarsonous dichloride). Interestingly, the studies have also shown that the carbon-arsenic bond has a conformation in such a way that the lone-pair on the arsenic is approximately aligned with the vinyl groups. Lewisite remains a liquid at low temperatures and is persistent in

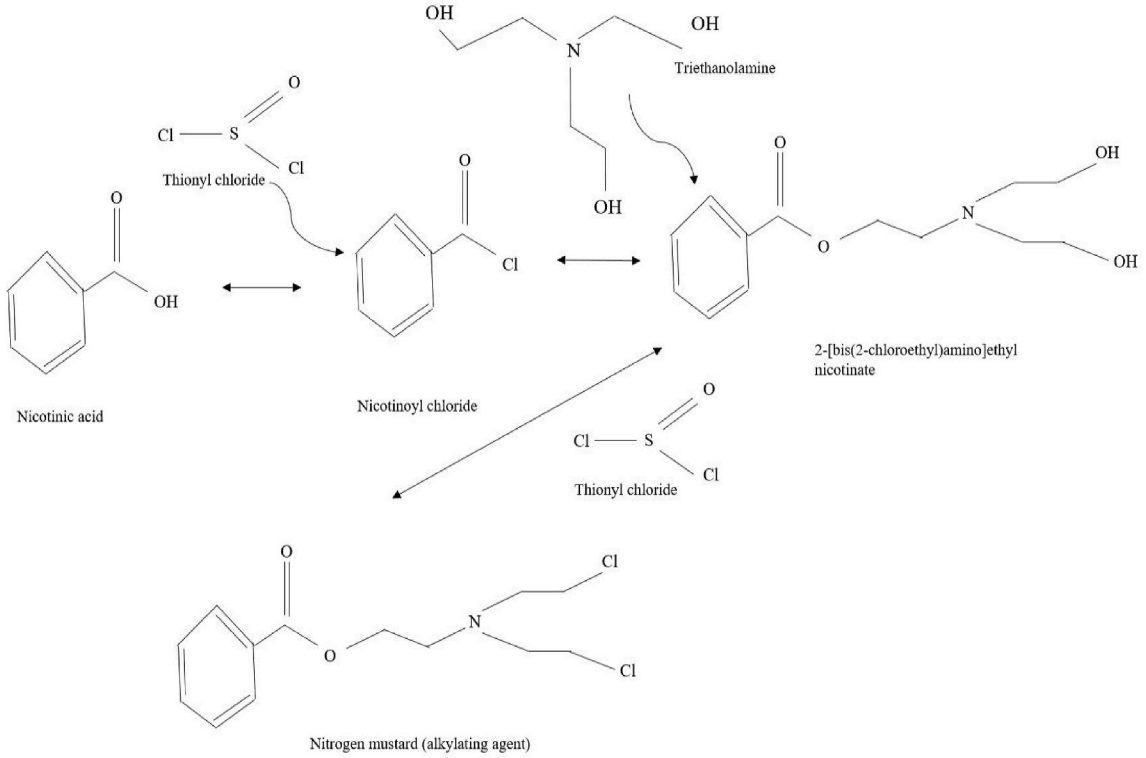


Fig. 2. Synthesis route of nitrogen mustard. . The illustration has been drawn by taking inspiration from the works of [16,17].

colder conditions. Lewisites have been found to increase the environmental persistence of sulfur mustard, causing a depression in its freezing point. However, the toxic effects of lewisites are lower than that of mustard agents.

2.2.4. Halogenated oximes

Phosgene oxime was developed in 1929 and was noted to be stockpiled during WWII. These compounds can be used solely or by mixing with other CWAs such as mustard agents or nerve agents. Phosgene oxime is usually prepared by reduction reaction of chloropicrin using a combination of tin metal and hydrochloric acid (used as the active hydrogen reducing agent) [19]. A violet colour is observed, which indicates the formation of trichloronitrosomethane (intermediate compound), as shown in Supplementary Fig. 3 [20]. The compound is susceptible to nucleophiles due to it being electrophilic. The compound produces a peppery/pungent odour on exposure. Phosgene oxime is highly soluble in water, and tends to corrode metals. The compound exists in a crystalline solid or liquid state. The compound can be mixed with lewisites, mustard agents etc., to enhance its toxicity. Phosgene oxime vapour is heavier than air, so it settles in low-lying areas.

2.3. Environmental effects and hazards

Sulfur mustards have been known to persist for days to weeks in the environment. Due to their persistence, they can cause many potential hazards in the environment by polluting water or the soil. The mustard gas degrades in soil via chemical hydrolysis, and the products undergo microbial utilisation. However, the mustard and the chlorine derivatives do not degrade completely and have been found to be present even after years of contamination [21]. The vesicant also tends to change the specific composition of soil microbes. Along with this, the compound has also been found to decrease the urease, dehydrogenase and invertase activities in the soil drastically, which in turn, could be correlated with the decrease in cellular-decomposing microorganisms. Mustard gases are heavier than water; hence settle down thus, contaminating the water and the aquatic life. Moreover, due to a rise in ambient temperature, the chemical can evaporate in the air causing an inhalation hazard.

Lewisites can undergo photo degradation if present in the atmosphere. The compound can undergo hydrolysis in both the aqueous and vapour phase. The hydrolysis of lewisites results in the formation of 2-chlorovinyl arsenious acid [22,23]. In the soil, lewisites undergo rapid volatilization to form lewisite oxides. These are then slowly hydrolysed in the soil. Microbial degradation occurs as a result of epoxidation of C═C bond and reductive dehalogenation, which finally results into toxic metabolites, with an epoxy bond and arsine group. There are low instances of bioaccumulation of these compounds in foods [24,25].

Halogenated oximes (phosgene oxime) are generally non-persistent in the atmosphere. Phosgene oximes are usually released in the air in its vapour form. However, the compound can easily be broken down in the atmosphere by various substances. Due to phosgene oxime not containing any functional group, it is photo-chemically degraded by hydroxyl radicals and ozone in the atmosphere [1]. Even the moisture present in the clouds can lead to breaking of the compound. Interestingly, phosgene oxime has a very short life span in water and is non-persistent in the soil. This is the reason for high instability of the phosgene oxime in the environment. In water, various bacteria can degrade the compound. Even in the soil, various bacteria or moisture break down the compound to carbon dioxide, hydrochloric acid and hydroxylamine hydrochloride, as a result of hydrolysis. However, small traces of phosgene oxime may seep in through the soil and contaminate the groundwater or even evaporate into the air. The agent does not volatilise in soil due to its partial existence as anions. However, the half-life of the agent was found to be 83 days at a certain pH and temperature [26,27]. Also, due to lack of chromophores, there is a very low chance of phosgene oxime undergoing photolysis in direct sunlight. The compound can also be hydrolysed via nucleophiles. On performing base hydrolysis of the compound by sodium hydroxide, the products formed are carbon dioxide, sodium chloride, water, and ammonium hydroxide. Hydrazine on the other hand converts phosgene oxime to cyanide and nitrogen. Moreover, phosgene oximes can be combined with other blister agents such as mustard agents or lewisites to increase their toxicity and environmental persistence.

3. Toxicological effects of blister agents on organs

3.1. Skin

When cells are exposed to a blister agent, such as sulfur mustard, it was observed that about 80% of the contaminant is able to enter the cells [28]. However, in occluded conditions, due to sweat or humidity, the penetration has been observed to increase. Around 15% of the agent that penetrates through skin binds to the macromolecules in the skin, the rest enter into the circulation and elicit systemic response. The agents affect mainly the outermost layer (epidermis). Within hours of exposure, the epidermis and dermis start to separate, turning the stratum corneum oedematous. The nuclear morphology of the basal layer is found to be pyknotic or karyolytic. The dermis starts undergoing discrete necrosis, along with a decrease in the number of fibroblasts and histiocytes. Interestingly, there is a massive cellular infiltration and due to capillary engorgement, thrombosis can be observed [106]. Alkylating agent induced damage to the skin, primarily in the basal keratinocyte layer is, therefore, characterised by oedema, inflammation, and cell death. Fig. 3 has been illustrated by drawing inspiration from the study conducted by Horwitz et al. [106].

It is also interesting to note that although the DNA tends to repair itself within 24 h of forming adducts, guanine adducts formed in a sulfur mustard contaminated individual were found even after 4 weeks of contamination. The reason for this could be that unhydrolysed alkylating agents get deposited in fat tissues or fat depots and get slowly released from there with time [29,30].

3.2. Lungs

Inhalation of blister agents affects the upper respiratory tract. In cases of severe exposure, severe pulmonary damage has been observed. In most of the scenarios, the formation of pseudomembranous laryngotracheitis is observed. Cell debris and fibrins derived from the infiltrating leukocytes and the epithelium undergoing necrosis form these pseudomembranes. The pseudomembranes formed are characterised by a diphtheria-like inflammation with fibrinous deposits. Exposure also results in a significant increase in the amount of mucus in the upper respiratory tract. The thick continuous membranous layer lining the uvula, tonsils, epiglottis, pharynx, larynx, and bronchi paranasal sinuses is affected with varying degrees. The epithelial lining of the upper respiratory tract undergoes necrosis [31]. After 3–6 h post-exposure, necrotic cells appear in the whole upper respiratory tract. Massive leukocyte infiltration is observed, which leads to bronchial obstruction. An interesting feature is the engorgement of the blood vessels. The alveoli also exhibit signs of emphysema [32,33]. The toxicological effects of blister agents on the respiratory system are schematically shown in Fig. 4 (drawn from the inspiration of the study conducted by Refs. [31,32].

3.3. Eyes

The lack of a stern barrier like the stratum corneum, blister agents can easily penetrate the ocular epithelia. This causes conjunctivitis and oedema in the cornea, and further slowly reduces the production of the conjunctival mucus. As a result of the endothelial damage, conjunctival vessels are occluded. Small vesicles start forming as a result of the corneal epithelium getting detached from the stroma [34]. Due to the high exposure limbal blood vessels can be destroyed, corneal necrosis

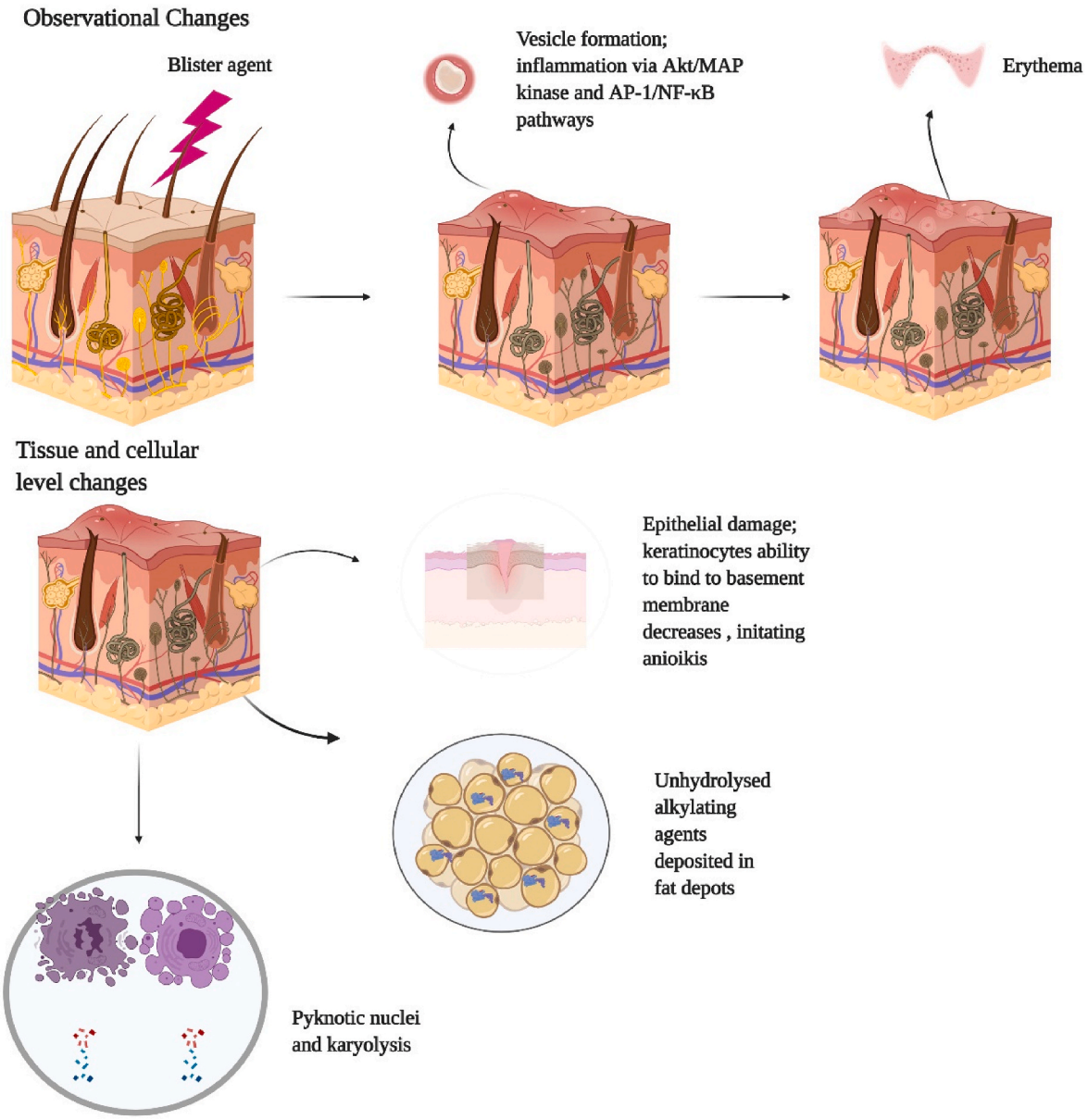


Fig. 3. Observational and tissue/cellular level changes as a result of blister agent toxicity on the skin. The image was inspired from the studies conducted by[106].

can occur. As a result of the epithelial lining of the cornea being more permeable than the stratum corneum of the skin, blistering agents can easily penetrate the barrier of the eye. As a result of the contamination, within hours the epithelial damage can be observed. Moreover, the corneal epithelium gets detached from the stroma. This leads to the formation of small vesicles in between the epithelium and the stroma. There is a significant destruction of the limbal blood vessels. Corneal oedema is observed within a day of exposure. An illustration of the ocular toxicological effects, as a result of blister agent exposure, is represented in Fig. 5.

4. Toxicological effects at cellular and molecular level

4.1. Mustards

4.1.1. Sulfur mustard

Among the three blister agents, sulfur mustard has been proven to have caused the formation of the largest and the earliest vesicles and was more severe than lewisites and nitrogen mustard. Sulfur mustard on exposure can affect the ocular, respiratory, cutaneous, and haematological tissues depending on the dosage and time of exposure. The compoundin liquid form, has more severe effects when exposed to the individual, due to higher concentration of the dose, causing severe lesions.

Once in contact with the skin, sulfur mustard readily penetrates the epidermal barrier due to its lipophilic properties. This could result in erythema and development of small vesicles on the skin. These vesicles can coalesce to form bullae (fluid filled blisters). These blisters increase in size and can change colours from yellow to tan. The toxic effect develops immediately after exposure to the skin [66]. As an alkylating agent, the highly reactive bi-functional sulfur mustard alkylates the DNA and the resident proteins. After the activation of sulfur mustard in the host, it forms cyclic ethylene sulfonium, which reacts with functional groups such as sulfhydryls, phosphates, ring nitrogens, and carboxyl groups. The compound forms monofunctional adducts and bi-functional crosslinks, which can persist for almost 3 weeks. This usually results in intrastrand crosslinks of cellular DNA which can induce DNA repair pathways. The alkylation of DNA can also cause breaks in the DNA, as a

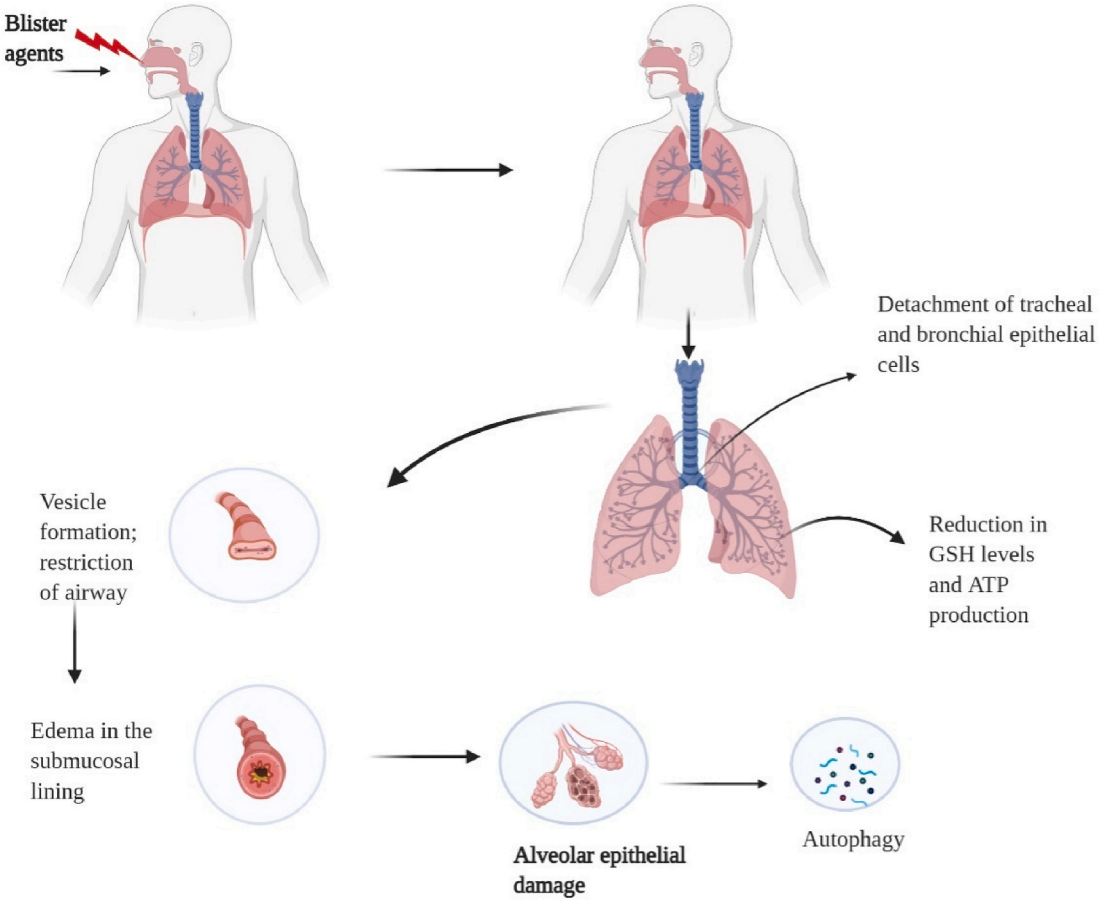


Fig. 4. Toxicological effects on lungs due to inhalation of blister agents.

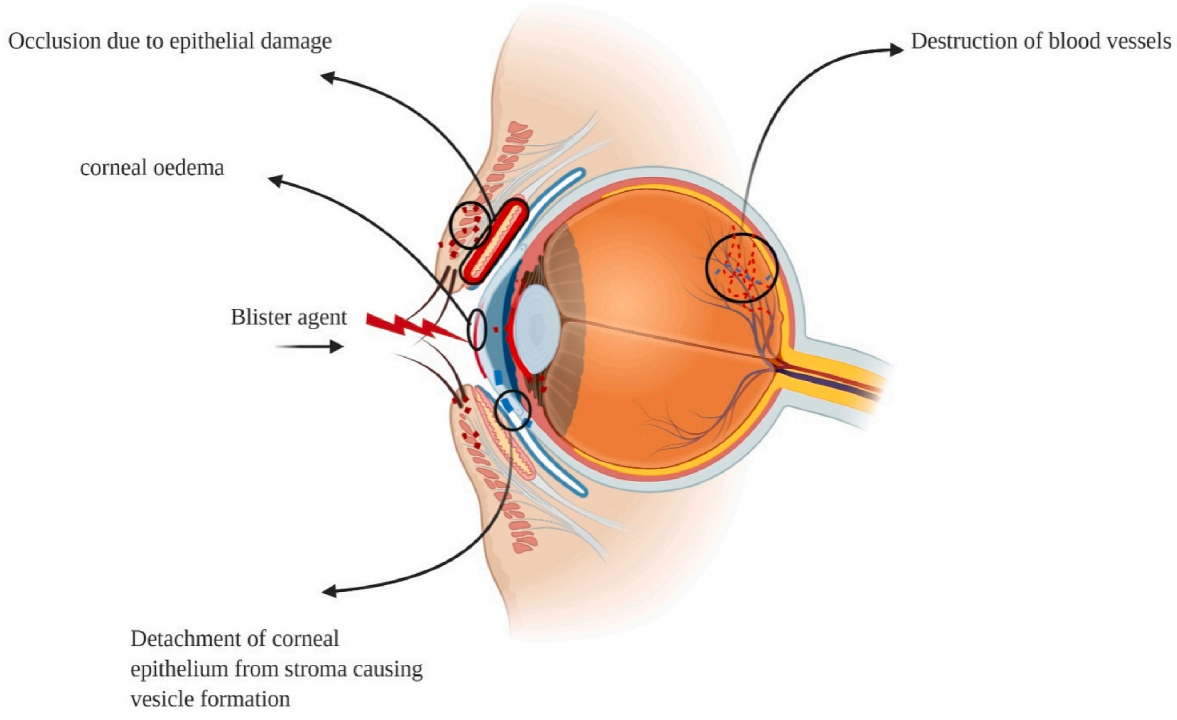


Fig. 5. Toxicological effects of blister agent on eyes.

result of depurination. This can trigger the activation of poly (ADP-ribose) polymerases (PARPs). Excessive PARPs can result in NAD + depletion, causing a decrease in ATP production [35]. This induces apoptosis, leading to necrosis of the infected cells. Apart from DNA alkylation, sulfur mustards are also known to cause oxidative stress. This occurs due to the depletion of glutathione in the cells, increasing the peroxide activity resulting in lipid peroxidation and other complications [36].

Further, there is an increase in the concentration of inflammatory cytokines such as TNFα, IL-1β, IL-6, and GM-CSF within hours of exposure. TNFα cascade is initiated as result of vesicant-induced lung injury. TNFα promotes oxidative metabolism in phagocytic leukocytes, which results in the increased concentration of ROS and RNS. This further leads to the synthesis of various proteases such as matrix metalloproteinase-9 (MMP-9), which causes the detachment of epithelial cells from the basement membrane [28]. Due to the oxidative stress, DNA damage, decrease in ATP production or reduced GSH, the cells undergo apoptosis. Due to the reduction in the GSH, there can be an increase in the Ca^{+} levels of the cells. Moreover, oxidative stress or increase in ROS can cause a disruption of mitochondrial membrane potential of the cell. This usually leads to the cell undergoing apoptosis through the intrinsic pathway. However, exposure to sulfur mustard also causes the activation of caspase-8, initiating the Fas-dependent death receptor pathway. Proteins like Bad, Bax, and PCNA increase due to the exposure to sulfur mustard. BAD and BAX are pro-apoptotic proteins (Bcl-2 family) that facilitate the cells to undergo apoptosis. Extenisve DNA damage occurs due to alkylation and disruption of DNA strands, resulting in an increase in the activity of Proliferative Cell Nuclear Antigen (PCNA). DNA damage causes the cells to undergo apoptosis and the proliferation of new cells to replace the dead cells. Further, due to DNA damage p53 (guardian gene) expression also increases. It arrests the cell cycle as a result of DNA damage or loss of cell integrity and promotes the cells to undergo apoptosis. The concentration of p38 MAP kinase and NF-κB also increases with the increase in the dosage of the blistering agent sulfur mustard, due to pro-inflammatory stimuli or cytotoxicity. Apart from the disruption of the epidermal cells, sulfur mustard directly alkylates the extracellular matrix proteins in the skin, decreasing the ability of the keratinocytes to adhere to the basement membrane, leading to basal cell detachment and initiates anoikis. The cellular mechanisms that follow the contamination with sulfur mustard is depicted in Fig. 6 [37,66]. Ocular tissues are also very sensitive to sulfur mustard with the effects observed within 2 h. The effects are not severe in low/acute exposure, with the individual developing conjunctivitis. As a result of exposure to higher doses, the corneal epithelium starts vesicating, which can lead to blindness. Corneal ulceration can also occur. Studies conducted have shown that there is an increase in hydration, separation in collagen fibril lattice, neovascularization, and other irregularities as a result of contamination via sulfur mustard. Neovascularization can result in oedema, corneal scarring etc. If exposed to the respiratory system, the symptoms start appearing in 8 h. The individual experiences irritation in the respiratory tract leading to difficulty in breathing. If the exposure is of high dosage, the mucosa undergoes necrosis with inflammation forming a grey membrane (similar to the one formed due to diphtheria) [37]. The airways can get obstructed due to the membrane and bullae formation. As a result, the individual can express respiratory distress and lead to death. Further, the tracheal and bronchial epithelial cells get detached from the basement membrane, cell debris, and fibrins deposit in the airway lumen and the submucosal lining starts showing oedema.

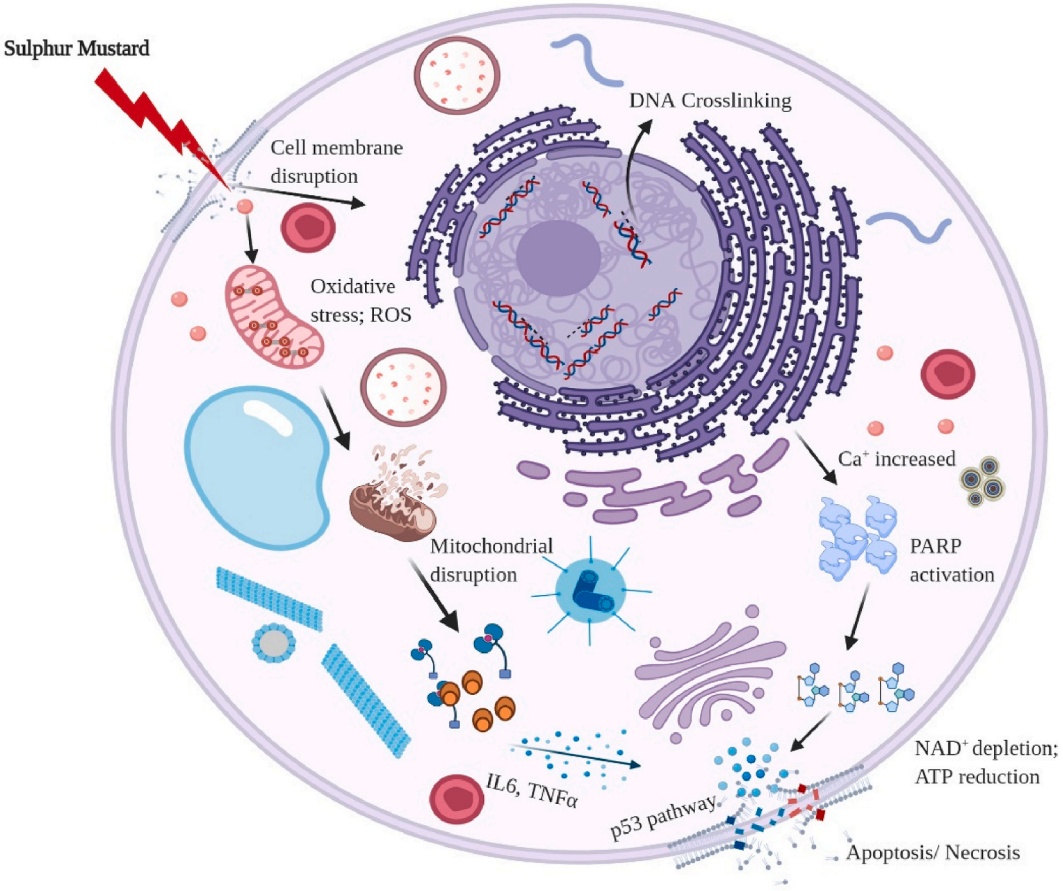


Fig. 6. Toxicological effects of sulfur mustard at molecular and cellular level. This diagram has been drawn by inspiration from the explanations of the studies by [66] and [37].

Following this, the tracheal epithelium starts forming blisters, columnar cells begin to shed, vacuolar degeneration can be observed and the inflammatory cells start to accumulate in the submucosa. The effects of mustards in the lower respiratory tract include thickening of alveolar septal walls along with perivascular oedema, thus, altering the integrity of the alveolar epithelial lining. Sulfur mustard has also been shown to induce autophagy. Sulfur mustard administration results in increased broncho-alveolar lavage surface tension, indicating alterations in pulmonary surfactants.

4.1.2. Nitrogen mustard

Nitrogen mustards like sulfur mustards are readily absorbed cutaneously or via mucous membranes. However, the toxicity of nitrogen mustards with respect to sulfur mustard is lower. Nitrogen mustards exhibit antineoplastic activity and have been used as anti-cancer drugs. Nitrogen mustards are derived from sulfur mustards, and portray similar toxic effects and pathophysiology. Nitrogen mustard also tends to get rapidly hydrolysed via active metabolites. Being an alkylating agent, nitrogen mustard primarily alkylates various nucleophilic binding sites, like, covalently binding to N-7 position of guanine [38]. The alkylation however, unlike sulfur mustard, is mediated by cyclic immonium ions in the case of nitrogen mustards. This causes cross linking within the DNA. Nitrogen mustard induces severe tissue necrosis in the contaminated site. Exposure to nitrogen mustard can cause dermatitis and hyperpigmentation, which can further lead to non-melanoma skin cancers. Although blister agents do not generally affect the central nervous system, nitrogen mustard at high doses can cause convulsions, ataxia, and coma. The compound causes bone marrow suppression leading to conditions like leukaemia, anaemia, etc. Toxic effects of nitrogen mustard also cause developmental problems and infertility. Like sulfur mustards, nitrogen mustards also cause metabolic dysfunction via PARP activation. However, it is interesting to note that unlike sulfur mustard which is fat soluble, nitrogen mustard requires a choline transport to cross the cell barrier. Although nitrogen mustard induces apoptosis at lower doses, at higher doses, the number of cells undergoing necrosis increases [39,40]. Apart from cutaneous injuries and lesions, nitrogen mustard also causes death of the cells in the intestinal epithelial lining, leading to severe dehydration. Nitrogen mustard, similarly to sulfur mustard, causes a significant reduction in leucocytes and upregulates the inflammatory mediators. Nitrogen mustard downregulates the creatine levels in kidneys leading to tissue catabolism. Pre-renal azotemia is highly probable, leading to death. The compound can damage the spleen indicating an immuno-compromised state [41]. The post contamination effect of nitrogen mustard toxicity is illustrated in Supplementary Fig. 4 [38].

4.2. Lewisite

Lewisite is a potent organoarsenic compound that acts as a quick acting blistering agent. Lewisite toxicity can lead to systemic effects leading to death of the exposed individual. Lewisites act at a much rapid rate than mustard gas, causing erythema followed by skin lesions within hours of contamination. Within minutes of contact, the compound produces a greyish area of dead epithelium, as a result of toxicity. Although blistering and major chemical burns are the primary effects, these effects are followed by severe fluid loss and hypovolemia as a result of capillary leakage. Like sulfur mustard, lewisites are also lipophilic in nature and use this to penetrate the skin rapidly [42]. Erythema is one of the primary symptoms. Like the mustard agents, lewisites also display toxic effects including glutathione reduction, dysregulation of calcium homeostasis, oxidative stress, lipid peroxidation, membrane damage, etc., finally leading to cell death [42]. Interestingly, due to arsenic group in the lewisites, the endoplasmic reticulum (ER) homeostasis may tend to get disrupted. This results in the accumulation of unfolded or misfolded proteins, causing a stress in the endoplasmic reticulum. As a result, unfolded protein response (UPR) signalling is activated, which further regulates the biosynthesis of chaperone proteins. The chaperone proteins bind to the misfolded or unfolded proteins and promote their folding, thus, reducing the ER stress. However, significant upregulation of such proteins can lead to inflammation and tissue damage. In this scenario, cell death occurs as a result of the UPR regulating proteins, in higher levels can be associated with neurodegenerative disorders, tumorigenesis and various metabolic disorders.

Although pro-inflammatory cytokines, such as IL6 and IL1β increase as a result of toxic effects, some inflammatory cytokines like TNFα and IL1α tend to get down-regulated. Moreover, lewisite contamination tends to produce a lewisitic shock and diffuses throughout the tissues contaminating a large area with a small dose. The eye is one of the most sensitive organs to lewisite exposure. When exposed, it causes instant irritation, pain, swelling, and tearing. When exposed to higher concentrations, inflammation along with oedema in the eyelids can be observed. Moreover, there is massive corneal necrosis, and in worst case scenario, the contamination can lead to blindness. These effects manifest primarily as a result of the breakdown of arsenous chloride into arsenic oxide, reaction with the sulfhydryls resulting in additional injuries, followed by liberation of hydrochloric acid. The excess release of hydrochloric acid can lower the pH of the eye causing superficial opacity. Arsenic also binds to lipoic acid (a dithiol 8-carbon component of the pyruvate dehydrogenase complex), resulting in accumulation of pyruvate and further in the inhibition of glycolysis [36]. Some other enzymes such as amylases, lipases, cholinesterase, etc., are also affected as a result. The enzyme inhibition characteristically hinders the formation of acetyl coenzyme-A from pyruvate, leading to necrosis of the cells. Moreover, the compounds also cause a reduction in the NAD + levels inside the cells, thus, reducing/inhibiting glycolysis. The inhibition of glycolysis could cause mitochondrial stress leading to apoptosis via the intrinsic pathway. Matrix metalloproteinases, for example- MMP-9, are the regulators of inflammatory and immune responses, hence, they play a significant role in degradation of extracellular matrix induced by lewisite exposure [43]. MMP-9 causes epithelial-stromal separation and inflammation in the cornea [44]. Neovascularization, resulting from vesicant exposure, is caused by the stimulation of an angiogenic factor, VEGF. The respiratory effects are similar to mustard gas, causing alveolar epithelial damage, leaking of capillaries, restricting airway tracts due to bullae formation etc. The toxicological effects of lewisites on cells have been illustrated in Supplementary Fig. 5.

4.3. Halogenated oximes

Halogenated oximes, generally categorised as nettle agents or urticants, sometimes have compounds that are classified as vesicants as well. Phosgene oxime is one such compound wherein the effects, although not as harsh as other blister agents, but, nevertheless are similar. Primarily, as an urticant, phosgene oxime causes irritation and corrodes the skin and mucous membranes. The contaminant causes blanching of the skin, erythematous ring formation, necrosis along with mild urticarial within minutes of exposure. Within 24 h, the blanched skin acquires a brown pigmentation. Following this, eschars are formed and within a week the eschar starts to slough. According to a study, within hours of exposure to phosgene oxime, hive-like formation of red areas (urticaria), along with wheal formation and necrosis was observed. Interestingly, there were also a few similarities to the parameters observed in the skin. The bi-fold thickness of the skin increases, oedema and erythema can be observed [45]. The increase in the thickness of the skin is a result of swelling in the cytoplasm due to condensation of nuclei and paranuclear clearing of the basal epidermal cells, which could suggest apoptotic death of the cells. The contaminant also causes an increase in the concentration of inflammatory cells such as neutrophils and mast cells in the area of exposure. Along with this, the number of dark pyknotic nuclei increases indicating an increase in apoptotic cell death. DNA damage occurs, which leads to the activation of the p53 pathway. Due to the uptake of phosgene oxime, the peripheral

vessels, including capillaries, sinusoids were significantly dilated. The RBCs congest to form red pulp like structures in the spleen. A large number of RBCs pool inside the alveolar capillaries in the lungs. The result of phosgene oxime exposure cutaneously can also cause an increase in the TNFα and COX-2 levels [103]. As one of the major sites of phosgene oxime toxicity is capillary beds, disruption, or loss of integrity in the capillaries can be seen. The peripheral vessels are dilated causing a surge in RBCs in vessels of almost all the vital internal organs [46]. This can further lead to fall in blood pressure, hypoxia, and finally death. Like all blister agents, phosgene oxime depicts cellular level toxicity as shown in Supplementary Fig. 6 [20].

5. Toxic industrial alkylating agents

Some compounds developed in the industry that are used for various day-to-day activities can also tend to show toxicity similar to blister agents; however, the potency or toxicity remains extremely low as compared to the conventional blister agent. Table 2 depicts a few toxic industrial chemicals that can cause toxicological effects on accidental or occupational exposure and the suggested treatment modalities.

6. Chemical simulants

Chemical simulants are those compounds which are similar to the actual CWAs but are less volatile and toxic. The simulants have characteristics that are similar to that of the actual agent. An ideal simulant should be characteristically similar, less toxic and can be studied without stringent monitoring. A list of a few chemical simulants with respect to the blister agents have been presented in Table 3.

7. Decontamination strategies

Formulations like EasyDECON™ have been developed as universal decontamination solutions against blister agents [54]. The EasyDECON™ has shown to reduce the amount of blister agents such as sulfur mustard, lewisite significantly on various inanimate surfaces [55,56]. Chelating agents such as DMSA™ (dimercapto succinic acid) have been proven to be effective decontamination formulations for use on the skins of exposed individuals [57,58]. Application of DMSA™, within 30 min of exposure has been proven to reduce the toxic effects of lewisites on the exposed skin. British Anti- Lewisite was developed as an effective antidote against lewisites [59]. Due to immediate uptake of phosgene oxime inside the contaminated individual, the timing of decontamination is very crucial. Systemic analgesics are administered, rather than topical anaesthetics, as the use of latter may increase the severity of corneal damage, in case of an ocular exposure. Dilution with milk or copious amounts of water is the preferred course of action as the primary means of treatment. A few decontamination formulations, along with their active ingredients and mechanism of action have been highlighted in Table 4.

7.1. Hydrolysis

Hydrolysis is a chemical reaction with water that causes a chemical compound to breakdown/degrade as a result of cleavage of chemical bonds, and addition of water or a hydroxyl ion. In living organisms, this reaction is performed by enzymes referred to as hydrolases.

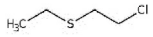
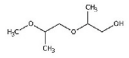
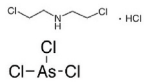
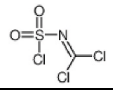
The solubility of sulfur mustards is higher in organic solvents than in water. Due to sulfur mustard being sparingly soluble in water, the hydrolysis of the chemical is fairly slow. However, when sulfur mustard is hydrolysed, a transient cyclic sulfonium cation (intermediate product) is formed. Following the formation of the intermediate product, a fast paced reaction ensues wherein the transient cyclic sulfonium cation reacts with water to form chloroethyl-2-hydroxysulfide and a hydrogen ion, in a fast-paced reaction. The reaction keeps repeating till the formation of dithioglycol. This is a quasi-monomolecular process with first-order kinetics that leads to the formation of dithioglycol and hydrochloric acid [64,65]. Interestingly, at higher concentrations, dissolution and hydrolysis take place simultaneously. In such a scenario, the initial product and the transient cyclic sulfonium cation react to form a dimericsulfonium cation. Another reaction process can occur via a transient dithiane disulfonium ion intermediate [66]. The temperature and the chloride ions determine the rate constant of hydrolysis. Chloride retards the hydrolysis rate without altering the reaction products. However, the pH and metal ions do not play a role in determining the rate of hydrolysis. Although sulfur mustard is not easily degradable, the products of hydrolysis however, are highly soluble in water and can be further degraded relatively easily. As inspired by the works of [64,66]; the hydrolysis reaction followed by sulfur mustard has been shown in Fig. 7.

Nitrogen mustards undergo hydrolysis to form ethanolamines. Different types of nitrogen mustards hydrolyse to form different products. The three derivatives, HN-1, HN-2, and HN-3 form N-ethyldiethanolamine (EDEA), N-methyldiethanolamine (MDEA) and

Table 2
Toxic industrial alkylating agents.

Compounds	Mode of action	Treatment	References
Paint thinner	Causes oxidative DNA damage; generally causes damage in brain, kidney, liver, lung etc.; oxidative stress caused by creating an imbalance between ROS and RNS; Toluene present in the compound, causes the alkylation of DNA.	Budesonide and nitric oxide are administered against the respiratory distress	[47]
Ammonia	Chemical burns and oedema on the exposed tissues; respiratory tract obstruction, bronchial obstruction by debris, RBCs etc.; severe lesions can be formed on the skin, liver, heart; Histological changes have been shown to form crypts, squamous metaplasia, dysplasia of nasal epithelium etc.	No antidote; administration of humidified oxygen and bronchodilators; copious irrigation of the contaminated regions; dilution with milk if ingested	[48]
Nickel sulfate	Nickel causes crosslinking of amino acids to DNA, can alter gene mutation and induces formation of ROS; suppresses NK cells and reduces the production of cytokines	Diethyldithiocarbamate, triethylenetetraminedihydrochloride, sodium calcium tetraacetic acid are a few effective chelating agents. Disulfiram can also be used, however, there is potential risk of accumulation of nickel in the brain	[49,50]
Bleach	Highly corrosive on the contaminated region; reacts with the tissues, causing protein denaturation which in turn leads to cell death; the compound can also damage the airway leading to asphyxiation, damage the epithelial lining, damage the broncheoalveolar lining. The fumes can also cause cancer, liver damage etc.	No specific antidote; copious irrigation of the contaminated region; milk or water consumed to dilute the substance, physiological saline used in case of ocular exposure	[51,105]
Metal cleaners	Some cleaners contain very strong acids which tend to corrode the skin or the contaminated region; decrease in blood pressure, obstruction of airway; can also lead to collapse of heart and lungs; induce seizures, necrosis or burns on the contaminated region	No particular antidote exists. However, irrigation of the contaminated region is advised. Gastric lavage can be used to eliminate the contaminant if ingested, intravenous drip line can be used if required	[52,53]

Table 3
Chemical simulants for different blister agents.

Blister Agent	Chemical Simulants	Molecular Formula	Boiling Point	Melting Point	Phase	Structure
Sulfur mustard	a)Methyl salicylate; b)1,3-dichloropropane; c)2-chloroethyl-ethyl sulfide	a) $C_8H_8O_3$ b) $C_3H_6Cl_2$ c) C_4H_9ClS	220 °C	−9 °C	Liquid; Vapour	a)  b) c)
Nitrogen Mustard	a)Di (propylene glycol) monomethyl ether b)bis(2-chloroethyl)amine	a) $C_7H_{16}O_3$ b)$C_4H_9Cl_2N$	a) 184 °C b) 85 °C	a) −50 °C b)-212-214 °C	Liquid; Vapour	a:  b: 
Lewisites	Arsenic trichloride	$AsCl_3$	130.2 °C	−16.2 °C	Liquid; Vapour	
Phosgene oxime	N-(dichloromethylidene)hydroxylamine	CHCl2NO	185.1 °C	39 °C	Solid; liquid	

triethanolamine (TEA) respectively [67]. Hydrolysis of this mustard agent involves a base-catalysed component along with an external chloride ion. The mustards also alkylate the nucleophiles thiourea and 4-(4-nitrobenzyl) pyridine (NBP) and due to the kinetic behaviour, indicating a direct S_N2 pathway, an aziridinium ion intermediate is also involved [68]. The steps involved in the hydrolysis reaction of nitrogen mustard are depicted in Fig. 8 [as inspired by the studies conducted by Ref. [68].

Lewisite is also sparingly soluble in water. Lewisite hydrolyses at a very complex and high rate, which also involves several reversible reactions. Post-hydrolysis, the products, that is, a weak acid, a water–soluble germinal diol, a benzene soluble oxide and a relatively insoluble polymer exist in equilibrium. Lewisites, like other arsenous chlorides, are hydrolysed by water, forming hydrochloric acid and chlorovinylarsenous oxide, as shown in Supplementary Fig. 7. The concentration of H^+ ions (pH) plays an important role in hydrolysis. At higher pH, the hydroxyl ions cleave *trans*-lewisite oxide, thus, yielding acetylene and inorganic arsenite. However, with the increase in pH the reaction tends to slow down. Moreover, temperature plays a crucial role as well [69]. The temperature must be increased for cis-lewisite oxide to react with sodium hydroxide to yield vinyl chloride, acetylene, and inorganic arsenite. However, the trans-lewisite is decomposed by alkalis to yield acetylene. Due to the labile chlorine atoms, the trivalent arsenic, carbon groups and multiple bonds, lewisite tends to be highly reactive. Therefore, it undergoes nucleophilic substitution by water, hydrogen sulfide, mercaptan etc. Lewisite also undergoes reactions due to the trivalent arsenic, the carbon-arsenic bonds and its specific structure. In an aqueous and water-alcohol medium, lewisites and hydrogen sulphide react freely to form a slightly soluble 2-chlorovinylarsine sulfide. Heating lewisites tends to yield arsenic trichloride, tris-(2-chlorovinyl) arsine, and bis-(2-chlorovinyl) chloroarsine. The interaction of chlorine with anhydrous lewisite results in the breaking of the carbon-arsenic bond and yielding arsenic trichloride along with dichloroethylene. In aqueous solution, lewisites, and their oxides, in the presence of oxidants such as iodine, chloramines, hydrogen peroxide, hypochlorous acid etc. are easily oxidized to 2-chlorovinylarsonic acid.

Phosgene oximes hydrolyse in the presence of an alkali to form hydrogen chloride and hydrolamines very rapidly. The compound is non-persistent in the environment. Phosgene oxime has a half-life of ~80 days at unspecified pH and temperature. The anion in phosgene oxime protects the compound from its volatilization. As phosgene oxime is non-combustible, it can be decomposed upon heating. However, such a process produces corrosive and toxic fumes. Phosgene oxime is solid at temperatures below 95 °C and exists as white crystalline solid. However, the solid has a very high vapour pressure which can induce toxicity. Phosgene oximes are electrophilic in nature and hence are susceptible to nucleophiles. Thus, the compound can undergo base hydrolysis wherein, when phosgene oxime is reacted with sodium hydroxide, it decomposes into carbon dioxide, hydroxylamine, sodium chloride, and water, as shown in Supplementary Fig. 8 [as inspired by Ref. [26]. When phosgene oxime reacts with hydrazine, the compound turns into hydrogen cyanide and nitrogen [70].

7.2. Oxidation

The selective oxidation of sulfur mustard is an effective decontamination strategy. This is achieved by the oxidation of sulfur mustard to sulfoxide, which is a water-soluble mono-oxidized product and non-toxic. Selective oxidation is important as doubly-oxidized sulfone produces HDO_2 which is also a vesicant [71]. Oxidation of the vesicant with ozone has also proven to be effective. Although this is an effective strategy, care should be taken so as to avoid the formation of over-oxidized product sulfone. Chloramides also tend to be a viable decontaminating compound against sulfur mustard. It has also been found that hexamethylenetetramine, a nucleophilic compound, acts as a protection against sulfur mustard. Ozone treatment is also an effective treatment for nitrogen mustard decontamination. Moreover, sulfhydryl containing nucleophiles have also been found to be effective in preventing metabolic injury induced by nitrogen mustard. Sodium hydroxide has also been found to be an effective decontamination agent. Sodium hypochlorite, a bleaching agent, is one of the most effective decontamination compounds employed. It has shown to remove almost

Table 4
Marketed formulations for the decontamination of blister agents.

Decontamination formulation	Brand	Spectrum covered	State	Product mechanism of action	Adverse Effects	Composition	References
EasyDECON DF200	Sandia National laboratory	Blister agents; mildewstat, antiviral, antifungal, antibacterial	Liquid, fog or foam	Surfactants suspends the contaminant into the micelle which further react with H_2O_2, which disrupts the molecular bonds	Irritation and inflammation on the site of exposure (Eye, skin etc.); gastrointestinal discomfort; respiratory distress	Hydrogen Peroxide; Surfactant; Benzyl-C12-C16 alkyl dimethyl chlorides; Diacetin	[55];
DMSA (Dimercaptosuccinic acid)	Urals Polytechnic Institute	Lewisites, heavy metal poisoning, arsenic poisoning	Liquid, solid	A chelating agent which attenuates the wound size, reduces the impairment of the skin barrier and reverses neutrophil infiltration	Fainting; fever; Nausea, rash with flat lesions; diarrhoea; liver problems,; low blood neutrophil levels; allergic reactions	Dimercaptosuccinic acid	[57]
BAL (British Anti-Lewisite); 2,3-dimercaptopropanol	Oxford University	Lewisite	Viscous oily liquid	A dimercaprol based chelating agent which competes with the thiol residues by binding with the metal ion and is then excreted. However, the compound is toxic inducing fever, vomiting etc. it can also mobilize and relocate lead into the brain leading to neurotoxic effects	Nausea; vomiting; redness and swelling in case of ocular exposure; fever; numbness if ingested; possible tachycardia, hypertension, nephrotoxicity	Dimercarpol	[59] [59],
RSDL(Reactive skin decontamination lotion)	Defence Research and Development, Canada	Mustard agents	Liquid	Follows S_N2 mechanism for the degradation of the contaminant. Reduced the perinuclear vacuoles and inflammation in the epidermis and dermis	Systemic toxicity; Transient comatose state; irritation and inflammation on ocular exposure	2,3-butanedionemonoxime,	[60,61]
SERPACWA (Skin Exposure Reduction Paste against Chemical Warfare Agents)	U.S. Army	Mustard Agents, Nerve agents, Toxins	Liquid	Forms a layer on the surface blocking the penetration and contamination of the surface	No adverse effects reported	Polytetrafluoroethylene; perfluoroalkylpolyether	[62]
DDgel (Dermal decontamination gel)		Mustard agents, Nerve agents	Liquid	Uses Kollidron SR a formulation which universally binds to the chemicals and fuller's earth to absorb and remove the chemical contaminants.	No adverse effects reported	Lutrol, Fuller's earth; Kollidron SR (polyvinyl acetate and povidone) bentonite; water; ethanol	[63]
PDK (Personal Decontamination kit) 1, PDK-2, PDK (CC2), RDP	DRDE, Defence Research and Development organisation	Blister agents, nerve agents, radiological contaminants	Solid	Fuller's earth works by absorbing the liquid droplets of the chemical warfare agent for effective decontamination. The CC2 oxidises the contaminant and the surfactant soaked napkin is used to wipe off the liquid and solid matter	None	Polythene laminated aluminium pouch; Fuller's Earth; N,N′-dichloro-bis (2,4,6) trichlorophenylurea; Surfactant soaked napkins	[1]

all contaminants completely with high efficacy. However, the compound has a property to degrade over time and thus lose its efficacy. Moreover, harmful fumes which are a by-product of sodium hypochlorite oxidation, also act as a potential threat to the responders. Hydrogen peroxide also has a high decontamination efficacy against sulfur mustard. The removal of sulfur mustard by hydrogen peroxide (3%) decreases the residue below the limit of detection within 30 min of application. However, a catalyst is required to aid in the reaction; bi-carbonate ion tends to dramatically increase the oxidation of sulfur mustard, by generating peroxycarbonate. Moreover, with the increase in the reaction time, the concentration decreased furthermore [75]. Hydrogen peroxide is a highly effective decontamination compound against nitrogen mustard as well. The nitrogen mustard residues were reduced below the level of decontamination within 30 min after treatment with 3% hydrogen peroxide. Moreover, an increase in reaction time can prove to be even more effective. Hydrogen peroxide is usually used along with catalysts, such as bi-carbonate ions to aid in oxidation of the contaminant. Active metabolites like hydrogen peroxide were found to be extremely efficient against lewisites also. The amount of lewisite is decreased considerably within 1 h of treatment with 3% hydrogen peroxide solution [55]. Generally, the oxidation rate increases in highly acidic and neutral solutions, and it is at the lowest as the pH value approaches 5. In the alkaline solutions the reaction rate decreases with increase in pH of the solution [72].

7.3. Dehydrohalogenation

The β-elimination of chlorine atoms under the influence of a strong

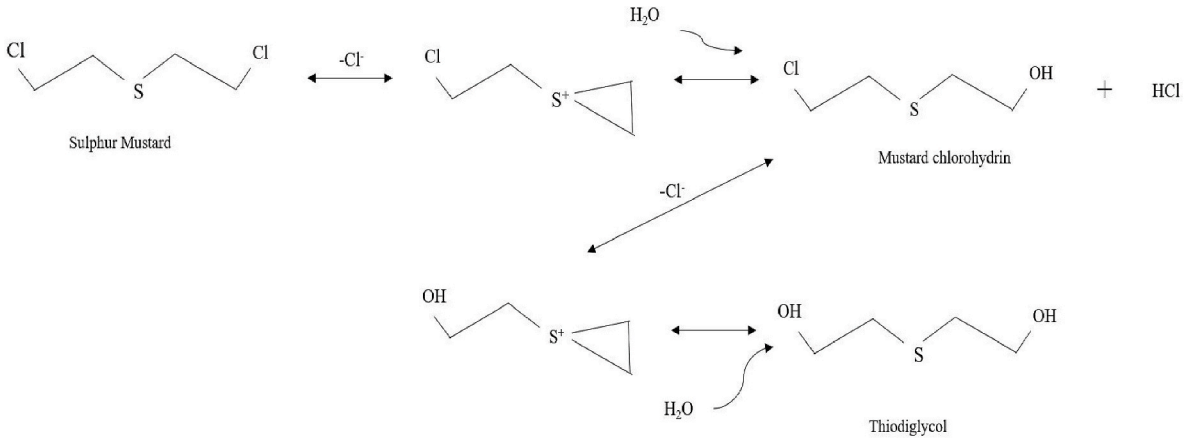


Fig. 7. Hydrolysis reaction of sulfur mustard.

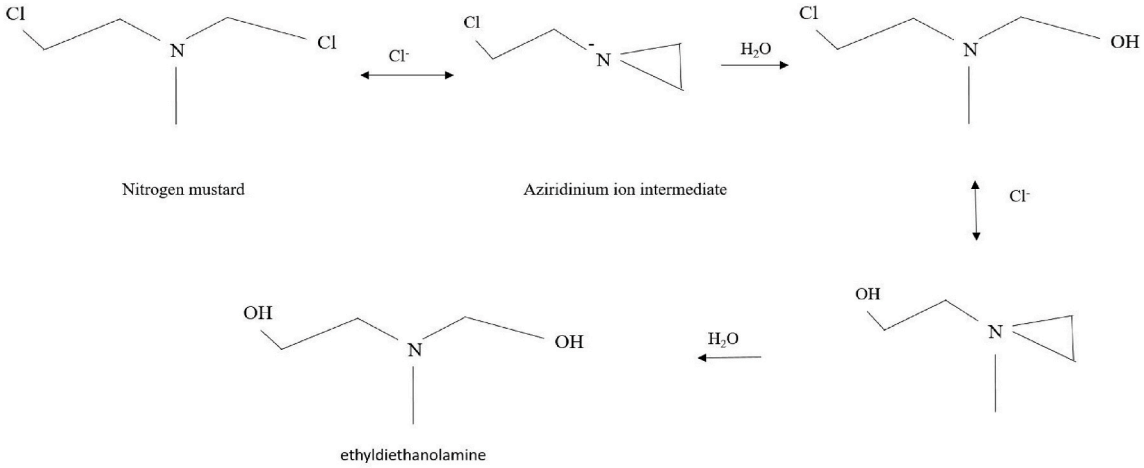


Fig. 8. Hydrolysis reaction of nitrogen mustards.

base coverts sulfur mustard into divinylsulfide (DVS) in the presence of HCl. This technique is generally performed using potassium hydroxide resulting in the hydrolysis and dehydrochlorination of sulfur mustard. This strategy is used in DS2 (decontamination solution 2) which contains diethylenetriamine, monomethyl ether, and sodium hydroxide to decontaminate the skin surfaces of the first responders and medical personals[71]. A destructive sorbent based on nanocrystalline and nanodispersive $TiO_2$was developed. Herein, it has been found that Ti(IV) acts as a Lewis acid and promotes the cleavage of the labile Cl–Cl bond leading to the dehydrohalogeation of the mustard agent [73].

7.4. Mechanism of action of decontamination via other materials

7.4.1. Titanium oxide and other composites

Methods like photocatalytic oxidation have proven to be highly effective means of decontamination [74]. UV irradiation tends to polymerize sulfur mustards and other blister agents. Catalysts like Pt/TiO_2 can efficiently accelerate the photolytic oxidation of the contaminants within 10 min. Increase in relative humidity tends to accelerate the photolytic oxidation process [75]. It has also been found that a Zn^{2+}, Ge^{4+} or Fe–Cu co-doped titanium dioxide nanoparticles exhibited excellent photocatalytic reduction of the CWAs [76,77].

Nano-TiO_2 also acts as an effective decontamination agent for inanimate surfaces. The molecules in sulfur mustard are oxidized by disrupting the carbon and sulfur bonds of the compound, thus degrading it [24]. Interestingly, it has also been observed that nano $ZnTiO_3$, when used as a formulation on a skin contaminated with 2-chloroethyl ethyl sulphide (2-CEES), caused disruption of the epidermis and dermis, and no further formation of bullae. Further, the study also showed that the alveolar sacs and bronchial damages were not found post decontamination. The study also revealed that there was no further damage to the DNA and the contaminated cells after decontaminating with $ZnTiO_3$. [78].Although an efficient strategy, the means of performing photolytic degradation requires greater investment and refined technology.

Sodium perborate-tetrahydrate can be used as an alternative of hydrogen peroxide along with WO_3 (tungsten oxide) catalysts. WO_3 catalysts show remarkable decontamination efficacy.

7.5. Mechanism for the removal of blister agents via metal–organic frameworks

Due to the risks of dehydrohalogenation and hydrolysis by-products of blister agents such as sulfur mustard, partial oxidation of the compounds is considered. However, the process should be controlled using a selective oxidant because of the possibility of over-oxidation. This is because over-oxidation can lead to the formation of a sulfone product which is nearly as toxic as sulfur mustard itself. Therefore, metal organic frameworks are considered. The sulfur mustard is captured in metal organic frameworks (MOFs) that are hydrophobic in nature. Linker methyl groups, e.g. {Zn4O (3, 5- dimethyl-4-carboxypyrazolato) 3 (Zn-DMCP)} are projected into its pores, which induce hydrophilicity in the MOFs. A study revealed that UiO-66 systems integrated onto air-permeable silk fibroin fibres provided a proof of the concept of self-detoxifying textile/MOF composite protective fabric. The fabric was

successfully able to hydrolyse 2-CEES [79].

Another study reported a benzimidazole-containing covalent organic framework, for example, BABE-TFPy COF (1-(4, 7-bis (4-aminophenyl)-1*H*-benzoimidazole-2-yl) ethan-1-ol-1, 3, 6, 8-tetrakis (4-formylphenyl) pyrene), used for detection of mustard compounds. This is accomplished as a result of the crystallinity, high porosity, excellent chemical stability and abundantly accessible benzimidazole sites and the COF coated quartz crystal microbalance (QCM) sensor. It was observed from a temperature-varying micro gravimetric experiment that there was an enthalpy change. This enthalpy change strongly suggests a dual-hydrogen bonding formed between the BABE-TFPy COF and the 2-CEES molecule resulting in the recognition of 2-CEES [80].

7.6. Alternative techniques for decontamination of blister agents

Pyrolysis (thermal treatment, without oxygen) can be considered a viable technique for the decontamination of blister agents. Due to the decontamination strategy being generally temperature dependent, at lower temperatures, it has been found that the decontamination reaction rates have a relatively lower efficiency. However, care should be maintained as blister agents are flammable. Another technique utilized can be plasma-based destruction. In this process, the agents are subjected to temperatures of around 3000–15000K, generated by a plasma arc. Such a high temperature breaks down the chemicals into atoms. Use of molten metal systems (typically with Fe or Ni heated baths); neutralisation (e.g. using potassium peroxymonosulfate), treatment with chlorine dioxides, ionisation radiations, UV electrochemical oxidation, etc. are a few effective techniques that can be employed for effective decontamination.

The characteristics and the composition of the contaminated material/surface have a tremendous effect on decontamination. The structural characteristics, that is, porosity of the material, reactivity with the decontaminant, etc. are major factors which need to be considered for developing decontamination formulations for inanimate surfaces. Similarly, in the case of animate surfaces, toxicology of the decontamination solution on the host, biocompatibility, biodegradability, chemical interactions with the contaminant and its by-products inside the exposed host play a vital role in developing decontamination formulations.

8. Possible pharmacological targets

There are no effective treatment strategies against blister agents as of yet. This is usually because of strict regulations and high toxic effects of the blister agents. However, chemical simulants of these blister agents are used to determine possible therapeutic agents against these compounds.

Various strategies and formulations have been developed to be used on the exposed individual. With the eye being one of the most susceptible targets for exposure by a blister agent, proper washing of the contaminated site is recommended. Cyclopenolate along with an eye ointment can be used as an effective strategy. Skin being another primary and direct target needs to be decontaminated as soon as possible after contamination. Activated carbon and fuller earth are highly effective at adsorbing the contaminant present on skin. Exposure site should be washed with potassium permanganate. Calamine, promethazine containing lotions or sterile petroleum jelly should be applied on the exposed areas to reduce the severity of the toxicity. Morphine sulphate can be administered if severe pain ensues. Endotracheal intubation has been suggested as one of the main steps in exposed individuals experiencing respiratory distress. Cricothyroidotomy can be performed if there is an obstruction in the airway due to vesicant formation. Supplemental oxygen can also be administered. Aspiration of bronchoalveolar lavage or charcoal hemoperfusion is an effective strategy to diminish the toxic effects of the contaminant. N-acetyl cysteine inhalation has been observed to be effective [81,82].

Studies have reported that glutathione detoxification provided protection against cytotoxicity against 2-CEES [83]. In this study, it was found that CDDO-Me (methyl-2-cyano-3, 12-dioxooleana-1, 9-dien-28-oate) induced the expression of nuclear localisation nuclear factor erythroid 2- related factor 2 (Nrf2). This caused an elevation in the expression of Glutamata-Cysteine Ligase modifier (GCLM) gene, which in turn increased the GSH. The increased GSH activity caused a reduction in cytotoxicity effects of 2-CEES.

Another effective strategy can be the post-treatment of 2-CEES exposed individuals with metalloporphyrin catalytic antioxidant AEOL 10150 [84]. AEOL 10150 was found to reduce inflammation and oxidative stress. Moreover, AEOL 10150 was analysed to be an effective treatment solution for lung injuries due to 2-CEES. Studies have also been conducted on the lung injuries caused by 2-CEES exposure to determine effective treatment strategies, wherein, it was found that the animal models lacking p55 receptor for TNFα (TNFR1−/−) had better protection against the toxic effects [32]. The increase in Cu Zn-superoxide dismutase was also delayed or absent. Hence, it was concluded that the loss of receptor TNFR1−/− could blunt the toxicological responses of 2-CEES.

Silibinin, a natural flavanone, has been found to attenuate the effects of 2-CEES induced skin-injuries, and oxidative stress. The therapeutic agent was found to cause a reduction in DNA damage, cell necrosis and apoptosis. The compound was found to reverse the increase in the skin bi-fold thickness, activation of transcription factors NF-κB and AP-1. Also, optimising the dose could provide an effective solution against the skin injuries caused by vesicants [85].

A study was performed to determine the protective effect of iodine against sulfur mustard. The iodine application was found to cause immediate reduction in the inflammation, necrosis, and epidermal hyperplasia. Along with iodine, COX-2 (cyclooxygenase-2) levels were evaluated. COX-2 levels were found to aid in regeneration of the epidermis [86,87].

Usually, agents or compounds used to treat the contamination with the mustard agents are considered potential remedies against the effects of halogenated oximes. Anti-histamines, anti-inflammatory, and immunosuppressant drugs prove to be useful in reducing the inflammatory responses of contamination. Systemic analgesics are preferred over topical aesthetics, to reduce the severity. Although there are no specified drugs or solutions against these vesicating agents, antioxidants, protease inhibitors, PARP inhibitors, angiogenesis inhibitors, calcium modulators, anti-inflammatory agents, and flavanones, have been found to provide significant comfort against the toxic effects. Adexone, steroid and non-steroidal anti-inflammatory drugs, voltaren™ can dramatically reduce the effects of skin injury in the exposed individuals [88]. Along with these drugs, dimercaprol, octylhomovanillamide and indomethacin were also found to be highly effective in preventing damage due to sulfur mustard exposure [89].

Although no specific antidotes have been synthesized against nitrogen mustard, bacteriostatic agents such as 1% silver sulfadiazine can be used as a measure against secondary microbial infections and burns. Mild analgesics, antihistamines and diazepam can be administered to alleviate pain and irritation.

9. *In-vitro* and *in-vivo* action of the decontaminating agents

DDgel (Dermal Decontamination gel) is a formulation developed as a topical decontaminating agent against CWAs. *In-vitro* studies on human skin cells have shown that DDgel had a higher decontamination efficacy over RSDL (Reactive Skin Decontamination Lotion) solution. The formulation was able to successfully remove the chemical contaminant from the surface as well as the contaminants that had penetrated the epithelium. This is due to the mechanism of action of the DDgel formulation wherein, it binds and absorbs chemical from the skin to remove the contaminants. Moreover, the risk of cross-contamination was found to be significantly lower. The DDgel was also found to cut

the risk of skin delipidation, irritation and membrane fluidization due to the lack of detergents as its ingredients. The DDgel however, uses polyvinyl acetate and povidone that have a universal binding ability against chemicals which aids in the removal of the contaminants [63].

SERPACWA (Skin Exposure Reduction Paste Against Chemical Warfare Agents) is used as a MOPP (Mission Oriented Protective Posture) gear to delay or reduce the exposure of CWA on skin surface. An *in-vivo* analysis showed no penetration of mustard agents through a 0.15 mm layer of SERPACWA. *In-vivo* studies on rabbits showed that the toxic effects, lesions on the skin of the model organism were much less severe when pre-treated 4-h prior with SERPACWA with respect to the control group. The dermal irritation was also found to be blocked for 24–48 h of contamination [62] [*'Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA)'*,n.d.] [104].

RSDL (Reactive Skin Decontamination Lotion) was developed as a decontamination solution against CWAs. In an *in-vivo* study, SKH-1 hairless mice were contaminated with sulfur mustard. Post-contamination, RSDL was applied onto the contaminated skin surface with a sponge. It was observed that erythema had significantly decreased from the first hour itself. Although the formulation did not lead to a decrease in the perinuclear vacuoles, it increasingly reduced the epidermis separation and necrosis of the basal cells in the mouse. It was concluded that RSDL used in high ratio was successful in the complete removal of the toxicant from the contaminated organism [90,91].

British-Anti Lewisite (BAL), basically a dimercarpol based formulation, is a chelating agent effectively used as an antidote against Arsenic poisoning (especially lewisites). This chelating compound competes with the thiol groups in proteins to bind with Arsenic and other heavy metals. However, studies have also suggested that this compound can have extreme side effects [92]. *In-vivo* studies conducted on SKH-1 mice models have shown British-Anti Lewisite to have significant effect on protecting against the cutaneous damage caused by lewisites. It was also observed that apart from reduction in necrosis of the cells and skin damage, the compound was also able to reverse the neutrophil infiltration caused by lewisite contamination [93].

DMSA (2, 3-dimercaptosuccinic acid) and its derivatives, are also used as successful decontamination formulations against various chemical warfare agent. Monoisoamyl DMSA (MiADMSA), a derivative was found to be successful against lewisites due to the lipophilic nature of the compound. The chelating agent is able to successfully chelate the arsenic poisoning extracellularly and intracellularly. Apart from chelation, the compound was also found to cause a substantial reduction in the oxidative stress caused by the CWAs in the human keratinocyte cells [94]. An *in-vivo* study conducted on guinea pigs showed that MiADMSA formulation was able to decrease the arsenic load on the brain significantly. Moreover, the formulation was also able to effectively aid in the recovery of the alterations to the acetylcholinesterase and other neurotransmitters. The results also indicated a significant decrease in the ROS levels in the contaminated cells.

Sodium hypochlorite particularly follows a S_N2 mechanism, for the degradation of the blister agent. Moreover, it removes the peri-nuclear vacuoles and reduces inflammation in the epidermis [95,96]. Hydrogen peroxide on the other hand, causes a micelle formation and thus disrupts the molecular bonds of the contaminant [111]. However, there is a possibility of the blister agent to enter the victim's body and result in deleterious toxic effects. In such scenarios, it is important to administer antidotes to alleviate these toxic effects. Interestingly, there is no specific antidote against these CWAs. Although, there do exist alternatives such as anti-oxidants, anti-inflammatory modulators, PARP inhibitors, etc. that can be used to provide a counter against the toxic effects. Through extensive research, it has also been proposed that melatonin can be used as an effective strategy to counteract the DNA damage caused by blister agents. This particular strategy targets the hydrogen-atom transfer (HAT) mechanism, quenching the mustard agent and resulting in a lesser toxic by-product, that is, thiirane [97]. Melatonin-based therapy, thus, leads to the reduction in the formation of ROS. This is achieved by the nucleophilic substitution of the radical melatonin, resulting in the release of ethylene and chlorine atom, forming N-methylaziridine. As a result of the genotoxic stress caused by DNA fragmentation, PARPs are activated. PARP being a caspase-3 substrate, it further leads to the cell undergoing apoptosis. However, if PARP inhibitors are administered post-ingestion of the CWAs, the extent of cytotoxicity and the chances of the cell death can be minimised [110]. Interestingly, as exposure to mustard agents causes stress in the endoplasmic reticulum, it causes disruption of the Ca^{2+} homeostasis maintained inside the cell. This results in the cell undergoing apoptosis. Calcium ion modulators can be administered to avoid the disruption of the cell calcium homeostasis.

Diclofenac, is a class of non-steroidal drug which particularly inhibits the cyclooxygenase (COX1 and COX2) levels apart from being anti-inflammatory and antipyretic [109].Dimercarpol, a dithiol, was developed as an antidote against heavy metal toxicity. Dimercarpol is a lipophilic chelating agent which acts by forming a stable ring structure consisting of sulfhydryl and metal groups [108]. This leads to the neutralisation of the toxicity of lewisite based CWAs. Octylhomovanillamide and heptylvanillamide have been found to be extremely effective against the topical effects of sulfur mustard exposure. It was observed that these compounds reduce oedema in skin and heptylvanillamide particularly was shown to reduce the mRNA levels of GM-CSF, IL-6, Ilβ in the model organism [98,99].

An *in-vitro* study was conducted on male porcine skin contaminated with sulfur mustard. The contaminated skin was then treated with Woundstat, a haemostatic agent which showed a decrease in the penetration of the contaminant applied on the skin. The frequency of oedema was low. Moreover, Woundstat also caused a significant decline in lesions and thus reduced the amount of the contaminant present in internal organs, for example, liver, along with the improvement of blood flow and prevention of deleterious effects on the contaminated victim [100]. Another *in-vivo* study comparing the efficacy of various haemostatic agents such as Woundstat, QuickClot were evaluated for their decontamination efficacy against sulfur mustard. Through *in-vitro* studies conducted on male and female pig skins, it was found that Woundstat showed the best efficacy and was relatively as effective as Fuller's earth [101].

10. Disposal strategies

The Chemical Weapons Convention (CWC) deemed it necessary to not only dispose of the blister agents, but also their by-products as a result of hydrolysis. Moreover, the by-products need to also be rendered safe for discharge into open environments.

One of the most efficient means of disposal is biodegrading the agents. Hence, landfills are created and the blister agents are disposed off into these landfills. But in these landfills, sulfur mustard reacts with microbial proteins and is thus highly toxic to the microbes. Also the by-products of the alkaline hydrolysis are toxic.

For disposal of lewisite-sulfur mustard mixtures, a treatment strategy was developed. The compound undergoes hydrolysis first followed by electrolysis and electrocoagulation yielding formate, acetate, arsenous, and various other arsenic acids. The arsenic precipitates as a result of electrocoagulation and the remaining organic acids are mineralized in fluidised bed reactors as a carbon source [107]. The thousands of tons of leftover arsenic has a multitude of purposes, that is, in microelectronics, optics, solar power facilities etc.

Another strategy used is the JACADS (Johnston Atoll Chemical Disposal System) disposal technology. This involves the disassembly of chemical agent-filled munitions and the use of incinerators. The munitions are disassembled and the chemical agents are drained out of the munitions. After that the agents are incinerated in specific furnaces, designed for agent destruction.

However, there are situations wherein, the munitions are leaky and the facilities are compromised. In such a scenario, explosive detonation

technology is used which destroys agents and is energetic, reducing them to water, carbon dioxide and mineral salts.

11. Destruction

Many methods have been used for the destruction of the stockpiled agents. These agents have been stored in containers, or as munitions (such as artillery projectiles, rockets etc.). There can be explosives, fuses, propellant, etc. so as to trigger a reaction. Usually an accident or an intentional sabotage can trigger a chain of reactions or an explosion which can leak the chemical agent enough to contaminate a large area of air, land, and water supplies, along with the living beings inhabiting the area. Therefore, careful and methodical approaches are followed, such as complete and effective neutralisation of the chemical agent, as performed by Russia, using monoethylamine water solutions. Use of sand, hydrogen peroxide, water etc., aids in the rapid hydrolysis and degradation of blister agents. Incineration can also be performed, however, blister agents are known to be flammable, and hence, care must be taken. Dumping the chemical agent and their degraded waste into the sea and land mines have been practiced but the residues tend to contaminate the geographical area, thus affecting the living organisms. However, in the case of rockets, conventional disposal techniques aren't effective. This is because even a slight trigger can lead to deleterious outcomes. Moreover, the lack of stability of nitrocellulose (used in M55 rockets) poses a threat, as their decay is an exothermic process, further increased by rise in temperature and is autocatalytic. Therefore, primarily, the rockets are doped with a stabilizer, 2-nitrodiphenylamine, to react with the acid nitrate before catalysing further decay. Therefore, when the decay reaches a threshold level, the rockets are methodically disintegrated and disposed off. Finally, oxidizing agents like sodium hypochlorite solution (used to clean rooms, containers), calcium hypochlorite slurries (effective decontamination of water sources), super tropical bleach, Dutch powder etc. can be effectively utilized for the effective decommissioning of the CWAs.

12. Conclusion

From this review, it is concluded that there is not much awareness about the extremity of the after-effects of contamination via blister agents. Due to limited information, there are still no specific and effective antidotes against the toxic effect of the vesicants. A few decontamination strategies are available; however, the strategies are generic. The toxicity level and time of action is different for all the blister agents. Hence, a few minutes are enough for compounds like phosgene oximes to enter the host and start causing toxicological effects. Due to the symptoms of almost all blister agents being similar, it is quite difficult to judge proper diagnostic measures against different blister agents. Although the majority of toxic effects remain the same throughout the class of the agents, there still exists some difference due to the compounds being different. Therefore, better means of detection and decontamination strategies must be developed. Specific Antidotes must be developed against these blister agents as an unprecedented attack may cause catastrophic results.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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