



Review

A critical review of liquid, low toxicity chemical warfare agent simulants: Enhancing accuracy, safety, and methodological approaches for sampling

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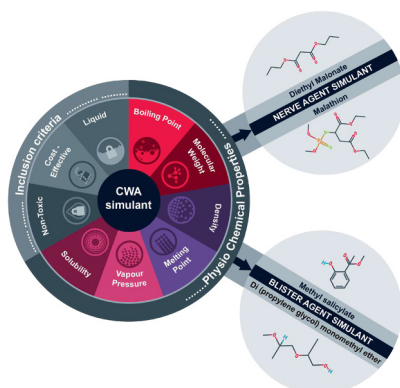
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HIGHLIGHTS

- Enabling hazard-free detection study of chemical warfare agents using simulants.
- Focus on nerve and blister agents, covering G- and V-series/Novichok, and mustard agents.
- Key selection criteria and limitations of simulants affecting detection accuracy.
- Recommendation toward standardised sampling protocols for CBRN emergencies.

GRAPHICAL ABSTRACT



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ABSTRACT

The use of simulants is a crucial aspect of studying the behaviour and effects of chemical warfare agents (CWAs) and toxic industrial chemicals (TICs) without the inherent dangers associated with handling and utilising the actual hazardous substances. This review assesses the selection and application of simulants for different classes of CWAs, including nerve agents such as soman, V agents and blister agents such as sulphur and nitrogen mustards. Several simulants were examined, including diethyl malonate, malathion, methyl salicylate, and di (propylene glycol) monomethyl ether, to ascertain their structural and physicochemical properties, yet present minimal toxicity risks. A key insight from this review is the importance of aligning simulant physicochemical properties, such as hydrophobicity, volatility and solubility to those of CWAs. This ensures data relevancy in sampling accuracy and method validation. Our findings demonstrate the efficacy of utilising multiple simulants to model complex interactions within different environmental and forensic matrices, thereby enhancing the precision and reliability of detection and verification procedures. By concentrating on liquid-based simulants and excluding gaseous and solid agents, this review offers a focused assessment of existing sampling methodologies for liquid CWAs in field conditions. It concludes by proposing a unified approach to sampling standards that mitigates the risk with the objective of enhancing the practicality and reliability of detection methods while

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ensuring personnel safety. Furthermore, this review provides crucial insights for developing robust, field-deployable CWA sampling strategies that strike a balance between accuracy, accessibility and low toxicity.

1. Introduction

Despite international treaties, such as the Chemical Weapons Convention (CWC), the use of prohibited chemicals remains a significant threat to national and international security, as evidenced by recent conflicts and domestic incidents, including the Salisbury poisoning [11, 49]. According to the Global Public Policy Institute, more than 330 chemical weapon attacks occurred in the years between 2012 and 2020 [20]. Effective sampling and chemical analysis of relevant materials is crucial as it provides definitive evidence regarding the presence or absence of hazardous agents, as highlighted in numerous studies [3,51, 58]. Validated and standardised methods for CWAs and their degradation products for all environmental matrices, as well as the identification of priority contaminants for method development have been identified as high priorities for the Environmental Protection Agency [82]. It is, therefore, imperative to identify and recover hazardous chemicals effectively, as well as remediate to reduce the risk of exposure to civilians and military personnel.

The review focuses on liquid-based, non-toxic simulants, excluding gaseous and solid simulants, providing a targeted assessment that supports the development of robust, field-deployable sampling strategies for liquid CWAs. Specific objectives are therefore (i) to give an overview of CWAs and the challenges in analysing and sampling of these, (ii) to assess and evaluate liquid, low-toxicity simulants based on similar physiochemical properties with CWAs and (iii) to provide suggestions for suitable simulants to develop controlled sampling experiments for CBRN scenarios by minimising exposure risks to personnel. By addressing these objectives, this review seeks to enhance the understanding and application of low toxicity, liquid simulants in CBRN response activities.

2. Chemical warfare agents

CWAs are highly toxic synthetic chemicals that are classified according to their physiological effect and are categorised into nerve, choking, blood and blistering agents [30,50]. Unlike explosives, whose destructive effects are limited and driven by sheer force, CWAs incapacitate or kill through toxicological mechanisms. Of the thousands of dangerous compounds, only a small number meet the criteria to be classified as CWAs, including high toxicity, fast action and persistence [1]. These compounds, their precursors and respective salts are all listed in the three schedules of the CWC. Schedule 1 includes the well-known nerve agent's sarin (GB), soman (GD) and tabun (GA), as well as the toxin ricin [50]. Riot control agents are not included in these Schedules, although their use in warfare is prohibited under Article One of the Chemical Weapons Convention (CWC) [36].

Given their high persistence and lethality across these four classes, nerve and blister agents are regarded as potent analytes that should be sampled from the environment for forensic examinations of CWA-related incidents [26]. Many analytical tools for sample preparation and chromatographic separation of these target compounds, have been developed. GC, HPLC-UV and capillary electrophoresis have uses in screening, while GC-MS as well as HPLC-MS have good sensitivity and retrospectivity for the determination of non-polar and less polar organic

biomarkers of CWAs. GC-MS is primarily used in conjunction with derivatisation procedures for polar compounds [64]. Testing a range of physiochemically divergent simulants will ensure that the methods employed are suitable for use in incidents involving a range of chemical agents. The exclusion criteria for the simulants used in this study are their state at room temperature. The emphasis was placed on liquids as opposed to gases or solids, and fuming liquids and acutely toxic compounds are also excluded. Although this review presents an overview of all four classes of CWAs and touches on simulants for all, the focus lies on nerve and blister agents as both blood and choking agents are gases and therefore outside the remit of this review.

2.1. Blood agents and their simulants

Blood agents are gases that contain cyanide or arsenic and interfere with the normal utilisation of oxygen by body tissues, thereby impairing bodily functions. These agents inflict cellular damage by severing the electron transport process in the mitochondrial inner membranes. The two principal blood agents are hydrogen cyanide (Fig. 1) and cyanogen chloride (CNCl) [68]. Hydrogen cyanide was used by Iraq against Iran during the Iran/Iraq conflict from 1983 to 1988. However, the effectiveness of blood agents as conventional warfare agents is limited by their high volatility; yet their potential as a terrorist tool in enclosed areas is evident [18,70]. Symptoms of cyanide poisoning include apnoea, respiratory distress, convulsions, nausea, cardiac arrest and, ultimately, death. Treatment must be administered quickly to be effective [68].

Literature and data on simulants for blood agents is scarce. The only identified study addressing this topic is by Bigiani et al. [5], which explores the use of acetonitrile (ACN) as a simulant for hydrogen cyanide. In their study, they evaluated the gas-sensing performances of nano-composite systems based on $\text{Mn}_3\text{O}_4\text{-Ag}$ and $\text{Mn}_3\text{O}_4\text{-Ag}$ in DPGME for detecting ACN as a hydrogen cyanide simulant [5]. As hydrogen cyanide is a gas, ACN must also be used in gaseous form to be representative of its toxic counterpart. At room temperature ACN is present in liquid form and usually readily available in many laboratories as it is a common solvent. Fig. 1 shows the chemical structures of both hydrogen cyanide and ACN, clearly demonstrating that both are nitriles. ACN however, has a methyl group in place of the proton, which significantly reduces its toxicity. This is because the toxic, cyanide ion (CN^-) is not released through simple deprotonation as with hydrogen cyanide or dehalogenation as with cyanogen chloride [77].

Table 1 presents a comparison of the physicochemical properties of hydrogen cyanide and ACN. ACN has a slightly higher molecular weight, yet both are highly soluble, with hydrogen cyanide being completely miscible. Additionally, ACN has a higher density than hydrogen cyanide and a significantly higher boiling point, lower melting point and is a gas, while ACN is a liquid at room temperature. Furthermore, hydrogen cyanide is more toxic and poses greater environmental and health risks. Hydrogen cyanide has a much higher vapour pressure, indicating higher volatility. Both are highly water soluble, with hydrogen cyanide being completely miscible.

2.2. Choking agents and their simulants

Choking agents, sometimes also referred to as asphyxiates, include a range of gases and aerosols that act as irritants, corrosive agents and/or highly reactive substances. During World War I, the use of chlorine gas at Ypres, was the first major, successful chemical attack of the war [70]. Those with high water solubility tend to damage the upper airways first, while those with low water solubility damage the lower airways and

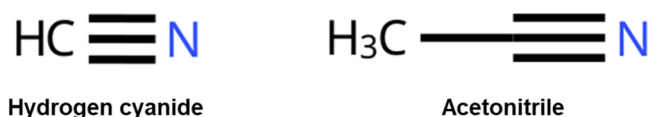
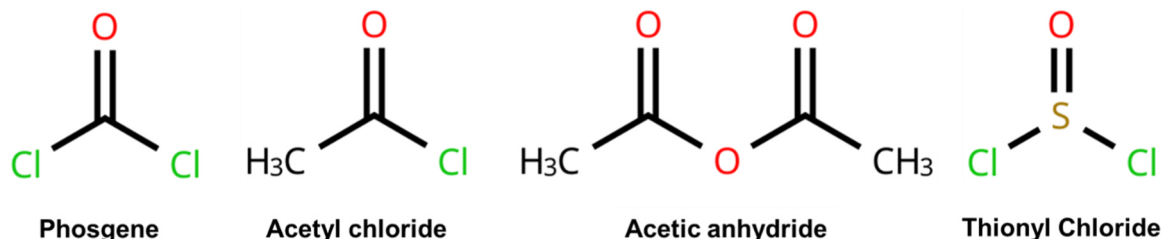


Fig. 1. Chemical structure of hydrogen cyanide and its simulant acetonitrile.

Table 1

Physicochemical properties of hydrogen cyanide and ACN retrieved from PubChem.

Physicochemical Properties	Hydrogen cyanide	Acetonitrile
Molecular weight	27.025 g/mol	41.05 g/mol
Solubility	Miscible	Greater than or equal to 100 mg/mL at 22.5 °C
Density	0.6875 g/mL at 20 °C	0.787 g/mL at 20 °C
Boiling Point	25.55 °C at 760 mm Hg	81.6 °C at 760 mm Hg
Melting Point	−13.28 °C	−44 °C
Toxicity	Flammable, Acutely toxic, Environmental hazard, Health hazard	Flammable, Irritant
State at room temperature	Gas	Liquid
Vapour pressure	742.0 mm Hg	88.8 mm Hg
Water solubility	Miscible	> 800 g/L at 25 °C

**Fig. 2.** Chemical structure of phosgene and its simulants acetyl chloride, acetic anhydride and thionyl chloride.**Table 2**

Physicochemical properties of phosgene and one of its simulants (retrieved from PubChem).

Physicochemical properties	Phosgene	Acetyl chloride
Molecular weight	98.91 g/mol	78.50 g/mol
Solubility	Slightly in water, freely in benzene/toluene /glacial acetic acid and most liquid hydrocarbons	Decomposed violently by water or alcohol
Density	1.3719 g/mL at 25 °C	1.1051 g/mL at 20 °C
Boiling point	8.2 °C at 760 mm Hg	51 °C
Melting point	−118 °C	−112.7 °C
Toxicity	Corrosive, Acutely toxic, Health hazard, Compressed gas	Flammable, Corrosive, Irritant
State at room temperature	Colourless gas or very low-boiling, volatile liquid	Colourless, fuming liquid
Vapour pressure	1420 mm Hg at 25 °C	287.0 mm Hg
Water solubility	Slight	Violent reaction

alveoli [68]. An example of such an agent is phosgene. Upon contact with water, it decomposes into carbon dioxide and hydrochloric acid, causing corrosive damage to the internal organs. In contact with biomolecules, it attaches to amino- and thiol groups, resulting in cytotoxic damage [24].

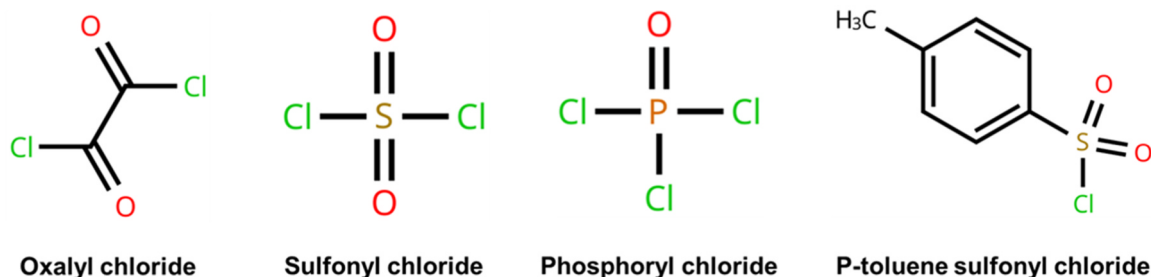
Simulants for choking agents are more widely researched and readily

available. Some, low toxicity simulants are listed in this review. Due to the structural similarity of acetyl chloride with phosgene, it was identified as the most similar simulant. Acetyl chloride (AC) differs in its chemical structure only by one chloride, which is replaced by a methyl group (Fig. 2). The development of fluorescent probe detection technology has allowed quicker, less limiting practical application for the detection of phosgene [69]. However, in water, it has a violent decomposition reaction and therefore must be handled with utmost care [38]. Other physicochemical properties are compared in Table 2. Phosgene is denser, more volatile and highly toxic, existing as a gas or volatile liquid, whereas acetyl chloride is a fuming liquid that reacts violently with water, with lower volatility but significant corrosive and flammable risks.

The chemical structure of acetic anhydride (AA), another simulant for phosgene, differs in structure from others as it contains two ketones and an ester rather than the chlorides present in phosgene. However, it is acutely toxic, which may render it unsuitable in sampling trials [39].

Thionyl chloride (TC) is composed of a central sulphur atom bonded to two chlorides and a ketone (Fig. 2; [69]). It, too, is a fuming liquid, with acute toxicity.

Other examples of simulants include oxalyl chloride (OC), sulfonyl chloride (SC), phosphoryl chloride (POC), p-toluene sulfonyl chloride (TosCl) (Fig. 3), diethyl chlorophosphite (DCP), hydrochloric acid (HCl) and chloroacetyl chloride (CAC) (Fig. 4) to name but a few [69]. Their detailed physicochemical properties are outside the scope of this paper, which focuses on the sampling of liquid simulants with low toxicity.

**Fig. 3.** Chemical structure of oxalyl chloride, sulfonyl chloride, phosphoryl chloride, p-toluene sulfonyl chloride.

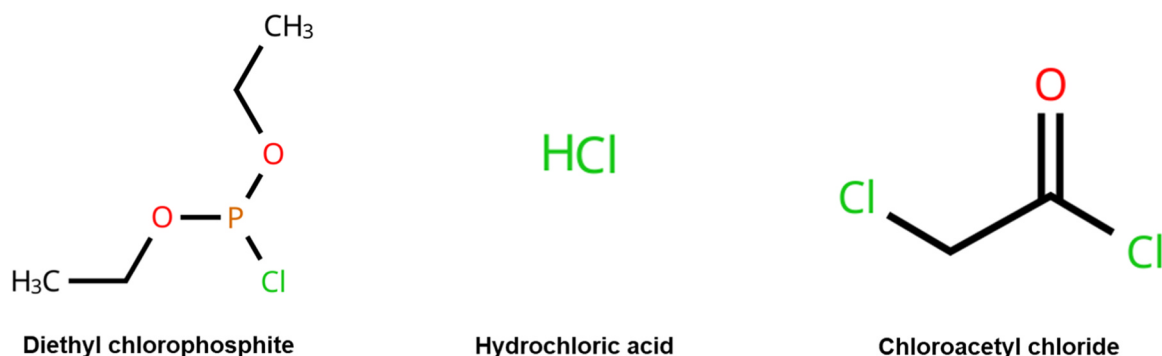


Fig. 4. Chemical structures of diethyl chlorophosphite, hydrochloric acid and chloroacetyl chloride.

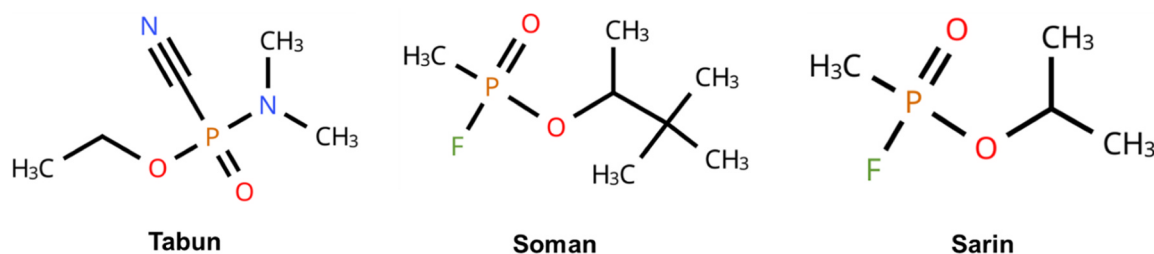


Fig. 5. Chemical structures of G-agents tabun, soman and sarin.

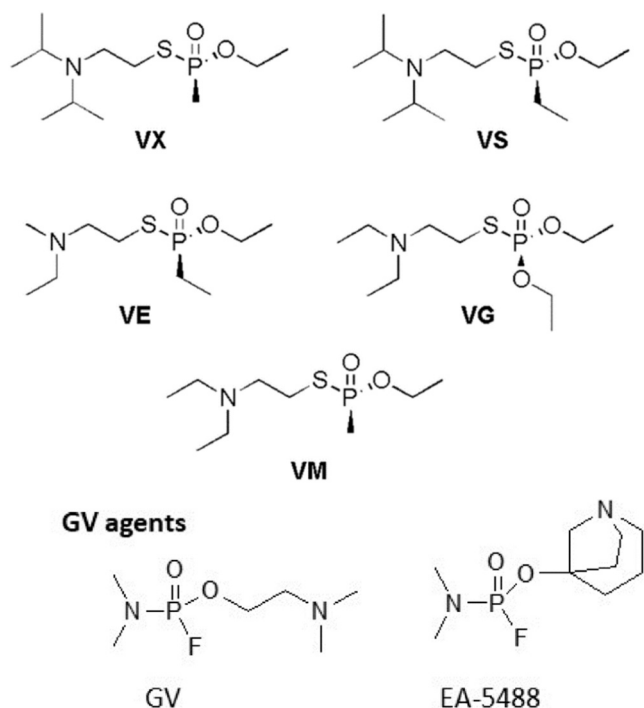


Fig. 6. Chemical structures of V-agents after Al-Faiyz et al. [2] and GV-agents after Pampalakīs & Kostoudi [56].

2.3. Nerve agents

Considered to be the deadliest CWAs organophosphorus nerve agents can be divided into four series: the G-, the V-, the GV-, and the Novichok agents [61]. Their mechanism of action inhibits acetylcholinesterase, the enzyme that breaks down acetylcholinesterase, thus leading to overstimulation of the nervous system [75].

Carbamates, which contain quaternary nitrogen salts and are solids,

constitute another class of nerve agents [43,52]. Carbamate nerve agents (CMNAs) are a type of lethal cholinesterase inhibitor. In a 2022 paper Palermo et al. claim that carbamates are substantially distinct from organophosphorus nerve agents, both in terms of their chemical composition and their toxicological effects (2022). No analogous scheduled compounds have been identified for carbamates [55].

The G-series agents were developed by German (G-) scientists Gerhard Schrader and Richard Khun in the 1930s and 1940s (Fig. 5). As volatile compounds, the primary entry for G-agents is inhalation. However, they can also penetrate the dermis [62]. The LD₅₀ for tabun is 1000 mg/person, whereas 1700 mg/person is the limit for sarin and only 350 mg/person for soman [86].

The LD₅₀ for VX was found to be much lower at 0.1 mg/kg, thus corresponding to 7.5 mg/75 kg person [44]. The V-series agents constitute a group that exhibits higher toxicity than the G-agents. These agents are readily absorbed through the skin, are oily liquids with low volatility and therefore primarily present a percutaneous hazard. This series of agents was developed by the British in the 1950s and 1960s during their research into insecticides. Therefore, some V-agents exhibit clear similarities with insecticides. GV-agents are more complex compounds with properties that are in-between the G- and the V-agents (Fig. 6).

The Novichok agents, also known as A-series agents, were developed in Russia under the Foliat program between the 1970s and 90 s [16]. These are binary nerve agents, and their chemical structure remains a subject of controversy. It is thought that the most probable structure is that of a phosphorofluoridate derivative of substituted acetamide or guanidine, and these were subsequently included in the CWC list of banned substances (Fig. 7).

All organophosphorus compounds (G, V and Novichok's) share common chemical structures, a phosphoryl group, two lipophilic groups, and a leaving group [84,87].

Following the synthesis of sarin by the Aum Shinrikyo cult in 1994 and its release in the Tokyo Subway in 1995, public awareness of these agents increased [70]. The same nerve agent was later used in Syria during the civil war, and more recently, Novichok agents were implicated in attempted assassinations in the United Kingdom. The most

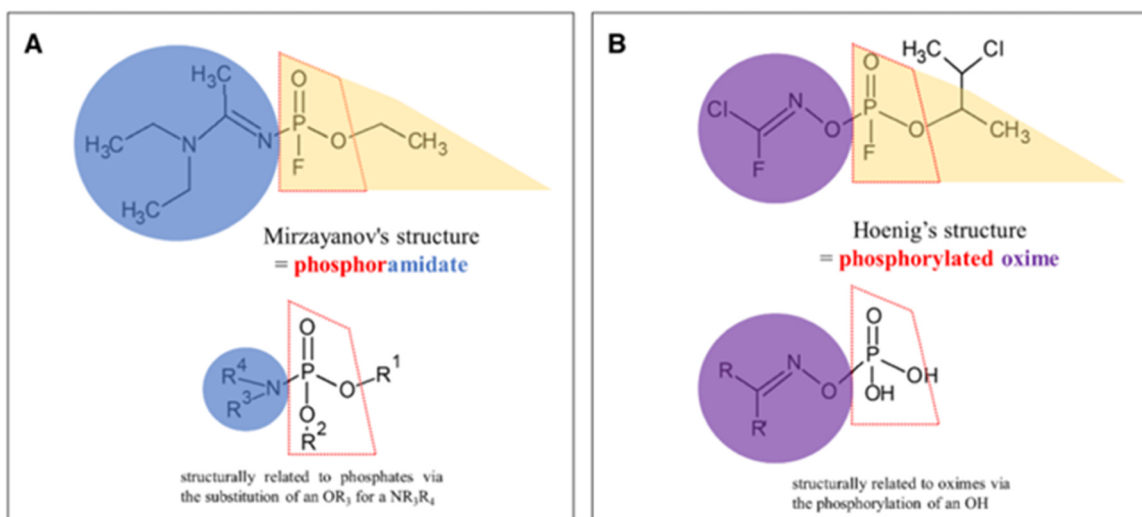


Fig. 7. Proposed chemical structures of Novichok agents after A) Mirzayanov and B) Hoenig from Noga & Jurowski [43].

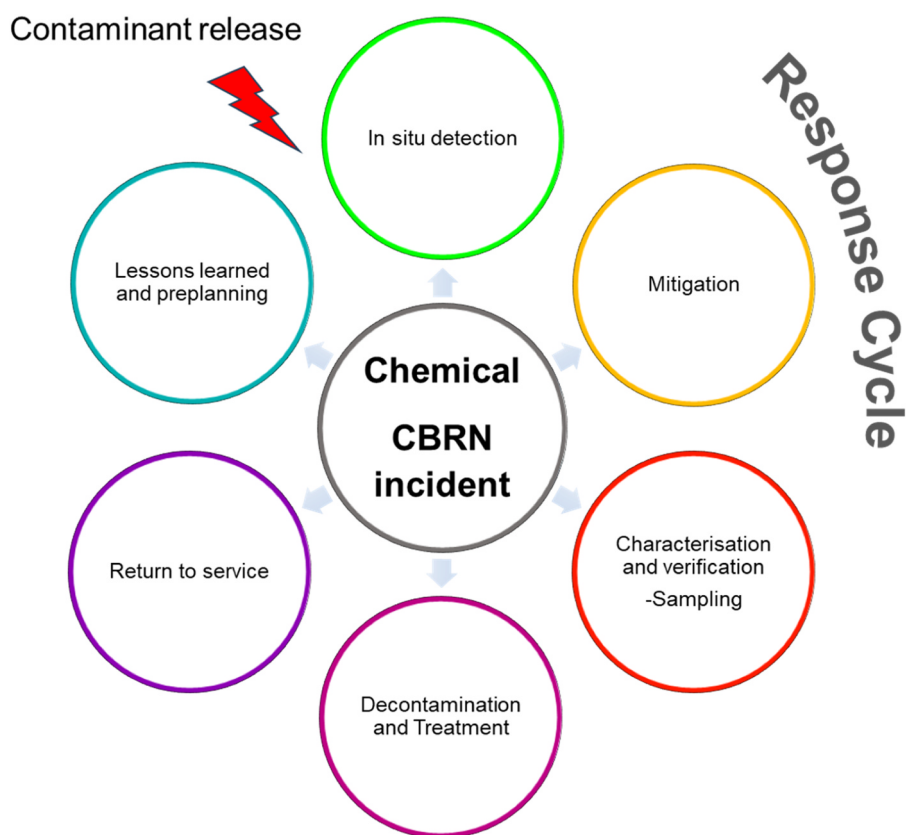


Fig. 8. Response cycle following a chemical CBRN Incident.

recent openly reported case involving a Novichok agent was the attempted assassination of Alexei Navalny during a domestic flight in Russia in 2020 [56].

2.4. Blister agents

In contrast to the highly toxic nerve agents, which cause death with minimal exposure, the severity of the injury inflicted by blister agents can range from incapacitation through burns to blindness and, in high exposure cases, may result in death [53,70]. The greatest number of chemical casualties during World War I, though fewer than 5 % of these

casualties died, was produced by Mustard-type agents [70]. Blister agents are classified into three groups: yperites, lewisites and urticants [27,60]. Yperites are composed of sulphur and nitrogen mustards, which are classified in Schedule One of the CWC. In contrast to what the commonly used name 'mustard gas' suggests, blister agents are not gaseous but rather mostly weaponised as sprays. They only cause death by asphyxiation when inhaled at high concentrations. However, a lethal dose of liquid mustard gas on the skin, is only 4–5 g [80]. Nitrogen and sulphur mustards are highly electrophilic compounds, causing blistering through adhesion between layers of the skin. They are carcinogenic and cytotoxic as they alkylate DNA [59]. Sulphur mustard was the first

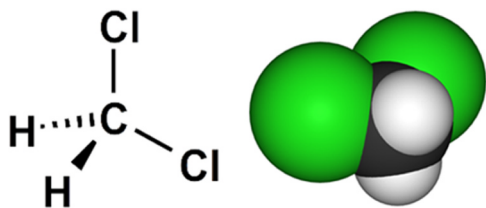


Fig. 9. Chemical structure of dichloromethane (DCM), the recommended extraction solvent by the OPCW.

vesicant chemical weapon ever used, with its first widespread use documented during World War I. Following several sporadic military attacks, sulphur mustard was again used on a large scale during the Iran-Iraq war [64,65]. Because of its simple structure and easy synthesis, sulphur mustard is the most likely CWA to be used in a terrorist event [85]. While there is a body of literature on simulants for lewisites, such as arsenic trichloride (AsCl_3), this paper focuses on simulants for sulphur and nitrogen mustards [34].

3. Challenges in sampling and analysing CWAs

With the release of any hazardous chemical including CWAs or toxic industrial chemicals (TICs), response must be quick and efficient. The overarching objective of immediate incident response is to facilitate the rapid detection of hazardous agents, followed by detailed identification and monitoring (DIM) over time and over large areas [13]. Following initial intelligence sampling and preliminary in situ detection employing DIM equipment, the collection of samples is rendered more complicated by the need to limit exposure time whilst conducting accurate, representative and cost-effective sampling (Fig. 8). Hill & Martin [22] suggest a mobile verification laboratory, in an airplane, with full capabilities to quantify and detect CWAs and their degradation products in all type of samples, to cut out sample transportation. Though it may seem plausible, this has not yet come into effect.

The uneven distribution of contaminants in the environment presents a challenge to obtaining consistent results from samples collected with traditional sampling methods [54,79]. Ideally, a sample should accurately represent the distribution and composition of contaminants; however, heterogeneity can introduce significant errors [79]. Grab sampling, a simple and low-cost method, is the least representative due to its inability to address heterogeneous contamination [37]. Despite its continued status as the preferred approach for water collection according to NATO's Sampling and Identification of Biological, Chemical, and Radiological Agents (SIBGRA) guidance [41], its inherent limitations highlight the need for alternative strategies. One such strategy is composite sampling, which combines multiple samples into a single bulk sample, enhances representativeness but may reduce detection sensitivity, particularly for liquid samples [17,57]. Standard filtration methods have been shown to mitigate this limitation [17]. Multi-increment sampling (MIS) involves the systematic collection of samples over a grid to produce a pooled sample and provides the most comprehensive assessment of contamination [79]. Additionally, capturing spatial heterogeneity is possible when conducted in three dimensions.

Besides environmental matrices, surfaces are a matrix of interest, especially in urban settings [81]. However, direct extraction from surfaces is not always feasible, nor is it a desirable process. An alternative and desirable method to recover the contamination without damaging the surface is indirect sampling through wipe or swab sampling. Wipe sampling of CWAs and their degradation products is an inherently complex problem [81]. Although there is some literature on wipe sampling for CWAs, there is no established technique for wipe sampling of specific target analytes [6]. Conventional wipes and swabs present challenges due to the morphological characteristics of surface

variations. For example, not all surfaces are smooth, and a cotton swab or wipe may become stuck on uneven surfaces. Although, the use of solvents, allows the transfer of contamination from the surface to the wipe for better wiping efficacy, it has some limitations. It limits the preservation time prior to analysis of the contaminant, and may damage the surface, introducing contamination into the sample. Consequently, some assert that the most effective use of wipes for sampling CWA-contaminated surfaces is with dry, non-particulate wipes [26].

Little has been reported on commercial wipes impregnated with appropriate solvents for sampling contaminated surfaces [26]. A study by Willison [81] identified the optimal wipe materials and conditions for recovering nitrogen mustard degradation products from surfaces. An unexpected finding was that cotton gauze, commonly used for other wiping applications, had elevated concentrations of native analytes and/or background interferences, most likely from the manufacturing process, thus limiting its use for wipe sampling of nitrogen mustard degradation products. Using a wipe already known to contain a targeted analyte could lead to quality assurance issues and possible false positives. Filter paper wipes were deemed a better choice because they did not require pretreatment or have any interferences [81]. This study was limited to one specific agent and its degradation products, therefore further studies investigating other CWAs are needed to determine the optimal conditions for wipe sampling. The OPCW Scientific Advisory Board has recommended that wipes and swabs be analysed within one month of sample collection and that, whenever possible, extracts should be stored rather than the wipes themselves due to likely storage instability. Furthermore, extracts should be prepared in dichloromethane (DCM) and stored in the dark at 4°C with Teflon-lined caps [76] (Fig. 9). DCM (CAS number 75–09–2) is a polar, aprotic solvent. As such, it has a significant dipole moment but cannot form hydrogen bonds. DCM can dissolve both polar and non-polar compounds, making it highly versatile. Of note, however, is its toxicity and carcinogenicity, as well as its potential to affect the central nervous system [28].

Recently, researchers have been exploring novel wipe sampling methodologies that utilise adsorbents. Activated carbon is well established as a sorbent material for hazardous substances [14,23,42,45,47,74,78]. Despite its use in protective clothing, little research has been conducted on its use as a sampling tool. A study by Imran et al. [26] investigated the use of a triple-layered composite wipe for sampling nerve and blistering agent simulants on porous and non-porous surfaces. The combined performance of the solvent extraction efficiency and wiping efficacy of the composite wipe determined the methodology's efficiency. A contact time of one minute was sufficient to adsorb approximately 95 % of the analyte on a non-porous surface such as glass. However, a longer contact time was required to achieve higher wiping efficacy on porous surfaces, such as rubber, wood, painted metal, and concrete. With a contact time of four minutes, the ACF-based composite wipe was able to adsorb analytes from porous surfaces with efficiencies ranging from 68 % to 82 % [26]. Novel research is also exploring the use of metal-organic frameworks (MOF) and functionalised reactive polymers, with some promising results in facilitating the removal and degradation of nerve agents [11,71]. Although degradation of nerve agents is outside of the scope of this paper, the research in the area is worth mentioning.

The North Atlantic Treaty Organization (NATO) places special emphasis on the importance of accuracy in sampling and recommends the implementation of standard operating procedures (SOPs), rules of procedure (ROPs) and quality control (QC) measures, such as field blanks [41]. Despite these guidelines, the selection of the sampling method remains a critical determinant of reliability.

3.1. Selection of simulants

Simulants are widely used in research to enable safe study and testing by replicating the behaviour of chemical warfare agents (CWAs) while minimising hazards such as toxicity. Selecting appropriate

Table 3

Physicochemical properties of interest for suitability selection in sampling studies.

Physicochemical property	Reason for interest
Solubility	Ability to be soluble in solvents
Viscosity	The flow characteristics of the simulant should resemble those of the CWA, especially for liquid-phase agents
Molecular weight	Molecules larger than 500 Da are unlikely to penetrate through skin
Log K_{ow}	Hydrophilicity/lipophilicity is a key parameter in tissue penetration and partitioning into water key for sampling in liquids and sorption studies
State at room temperature	Ability to separate liquid and solid simulants and reject any gaseous chemicals
Vapour pressure	An indicator of persistence and possible inhalational risk
Water solubility	To indicate the likelihood of dissolution in water
Toxicity	Danger to the scientist when conducting sampling studies
Density	Comparable dispersion and deposition
Boiling and melting points	Determining the phase of the substance under certain environmental conditions

simulants requires careful consideration to ensure relevance and accuracy. Earlier in this review, simulants for blood and choking agents were discussed, with a primary focus on liquid simulants. A more comprehensive selection is explored in Sections 3.1.1 to 3.1.4.

Some selections focus on chemical structure similarity to mimic specific reactions. Whilst maintaining structural similarity is desirable specific functional groups equate to high toxicity. This method may be employed when looking at protection and decontamination studies, for example to investigate the hydrolysis or oxidation of CWAs [60,71]. However, for the purposes of optimising sampling strategies for CBRN incidents, another approach is more useful. By focusing on matching physicochemical properties, such as viscosity, solubility and volatility the simulants' physical form and behaviour can be compared to their toxic counterparts [30,33]. While both approaches can be combined to some extent, it is important to select simulants suitable to the specific application. Gaining an understanding of the physicochemical properties of potential chemical alternatives is crucial during the simulant assessment process. First, the inherent hazards of a chemical, such as its ability to disrupt biological processes, its physical dangers and its environmental

fate, including degradation and persistence, are determined by its intrinsic physicochemical properties and its interaction with various systems. In the case of organic and inorganic chemicals, these properties are determined by molecular structure. Second, physicochemical properties help to exclude chemicals likely to present specific physical or toxicological hazards. Such important information can be obtained relatively quickly and inexpensively from databases such as PubChem, making it feasible to collect it in the early stages of the alternatives simulant process [10]. The key physicochemical properties for the selection of suitable simulants in this study include solubility, viscosity, toxicity and density to name a few (Table 3).

Proper selection of simulants requires a thorough understanding of the target agents, with particular attention to the properties that are most relevant to the intended application. It is essential to recognise that findings from simulant studies may not fully translate to live agents or may only be partially applicable, due to differences in their chemical properties [71]. Therefore, simulants cannot replicate all properties of CWAs. The matching of relevant properties from the CWAs to the simulant is complex, and to combat this complexity, the use of many varied simulants allowing for a broader assessment of different properties is common [25,29,4]. Many CWAs exhibit specific chemical reactivity that is challenging to replicate in simulants. This is particularly true in the context of detection and decontamination studies where matching reactivity in simulants is important [61]. In some cases, reactive additives are employed to enhance the properties of the simulants, facilitating more accurate representation of the CWAs in question. The reactive additives may also be added to polymers for example to facilitate the degradation of CWAs and their simulants [19,31,66,7]. Generally, simulants cannot be generic and must be chosen to approximate specific behaviours relevant to a specific study.

During this literature review, two papers of particular significance were identified. The objective of the papers by James et al. [29] and Lavoie et al. [33] was to identify the optimal simulant match for the CWA in question. Fig. 10 and Table 4 summarise their results. James et al. [29] selected 40 chemicals of low dermal toxicity covering a wide range of compounds. While this paper only discusses liquid simulants, James et al. differentiated between solid and liquid simulants. The key physicochemical properties for liquid simulants are shown in Fig. 10 as a scatter plot in which the Log K_{ow} , a measure of hydrophobicity, is plotted

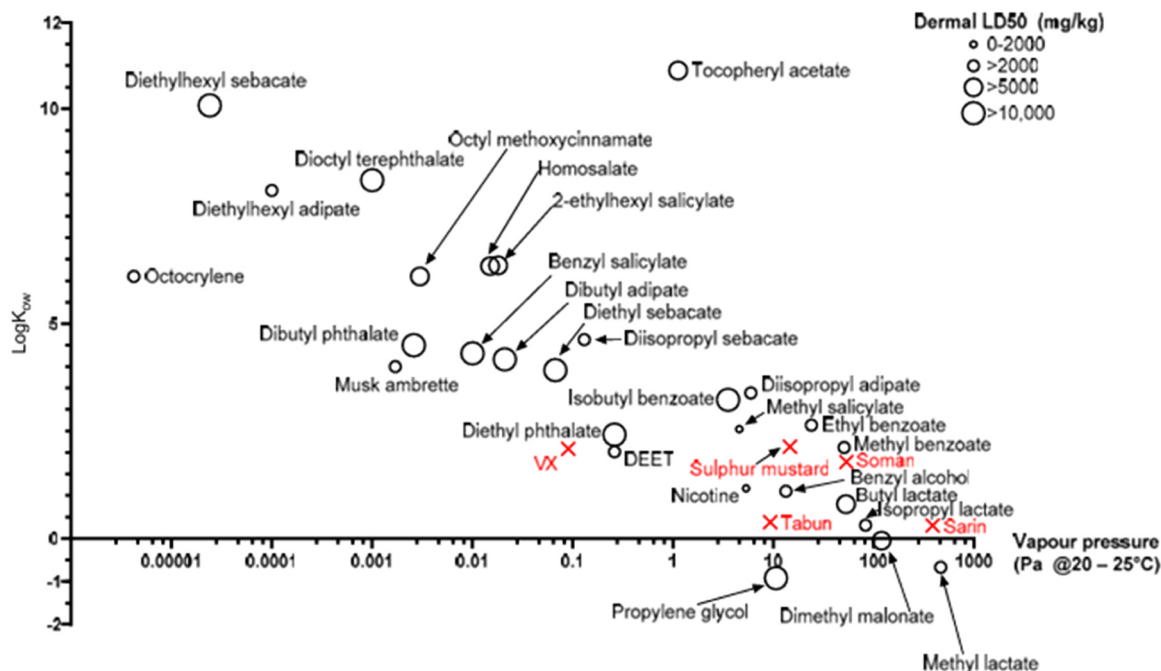
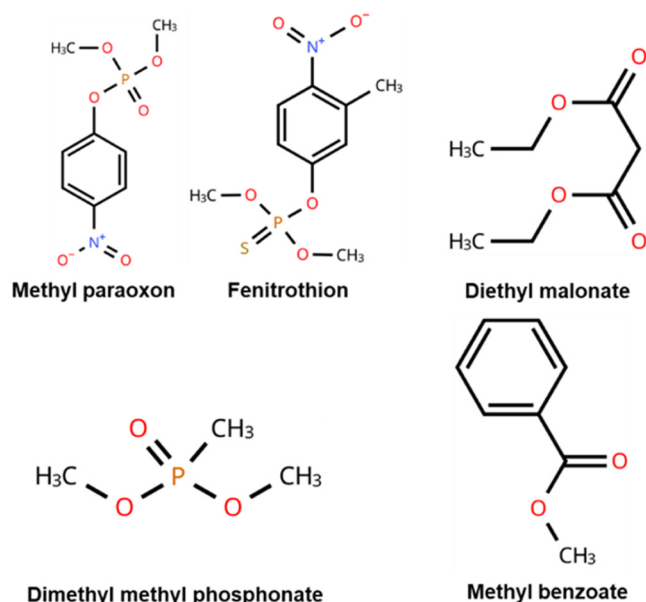


Table 4

CWA simulants listed in decreasing order of similarity based on [33].

CWA simulants based on	Tanimoto coefficient ≥ 0.6	Euclidean distance ≤ 0.25
Sarin (GB)	Di-isopropyl fluorophosphate, Di-isopropyl methyl phosphonate, Dimethyl methyl phosphonate, Trimethyl phosphate	Dimethyl methyl phosphonate, Di-isopropyl methyl phosphonate, Diethyl ester phosphonic acid, 1-Butanethiol, Diethyl ethyl phosphonate
Soman (GD)	Di-isopropyl fluorophosphate, Di-isopropyl methyl phosphonate, Dimethyl methyl phosphonate, Trimethyl phosphate	Di-isopropyl methyl phosphonate, Diethyl ethyl phosphonate
Tabun (GA)	None	Diethyl ester phosphonic acid, Diethyl ethyl phosphonate
Mustard gas (HD)	2-Chloroethylethylsulfide	2-Chloroethylethylsulfide
VX	Amiton, Malathion, Bis(2-ethyl-1-hexyl)2-ethyl-1-hexylphosphonate	Amiton
Lewisite	None	Lewisite oxide

**Fig. 11.** Chemical structure of methyl paraoxon, fenitrothion, diethyl malonate, dimethyl methyl phosphonate and methyl benzoate.

against vapour pressure, a measure of persistence and possible inhalational risk. Methyl benzoate, for example, is deemed to be a close match to soman, whereas ethyl benzoate is deemed to be a close match to sulphur mustard, even though the simulants are only structurally slightly different from one another (Fig. 10).

Lavoie et al. [33] published a similar paper a decade earlier. The authors used the Tanimoto coefficient and the Euclidean distance to assess the simulant similarity. The Tanimoto coefficient is a measure of the degree of similarity between two molecules, with a value of 1 indicating complete structural identity and a value of 0 indicating a high degree of dissimilarity. The Euclidean distance is a measure of dissimilarity, with 0 representing a perfectly similar molecule. The most similar simulants based on these measurements are listed in Table 4. While di-isopropyl fluorophosphate (DFP) was identified as the most suitable simulant for sarin (GB) and soman (GD) based on the Tanimoto

Table 5

Physicochemical properties of simulants fenitrothion and dimethyl methyl phosphonate retrieved from PubChem.

Physicochemical Properties	Fenitrothion	Dimethyl methyl phosphonate
Molecular weight	277.24 g/mol	124.08 g/mol
Solubility	Low solubility in aliphatic hydrocarbons; soluble in most organic solvents	Miscible in alcohol, ether, benzene, acetone, carbon tetrachloride; insoluble in heavy mineral oil
Density	1.3227 g/mL at 25 °C	1.1507 g/mL at 20 °C
Boiling Point	118 °C	181 °C
Melting Point	0.3 °C	< 50 °C
Toxicity	Irritant, Environmental hazard	Flammable, Corrosive, Irritant, Health Hazard
State at room temperature	Yellow liquid	Clear colourless liquid with a pleasant odour
Vapour pressure	0.000054 mm Hg at 20 °C	0.962 mm Hg at 25 °C
Water solubility	Hardly at 38.0 mg/L at 25 °C	Miscible in water

coefficient, this chemical is highly toxic, rendering it unsuitable for use in human decontamination or exposure trials. The same is true for 2-chloroethylethylsulfide (CEES), also known as half mustard. While Lavoie et al. [33] provides an effective method for categorising the similarity of simulants, it also highlights the limitations of their approach when selecting simulants with low toxicity, which is a key requirement mentioned in this review.

In general, simulants must exhibit stability and persistence across a range of conditions allowing for sampling from a range of matrices. For example, low vapour pressure indicates low volatility, contributing to environmental stability and persistence. Similarly, melting and boiling points indicate the environmental behaviours and state of a compound at room temperature. Other critical factors include water solubility, relative toxicity and degradation rates. Hydrolysis, a process whereby chemical bonds in the agents are broken down by reaction with water, reduces the toxicity of the CWAs by converting them into less harmful byproducts [48].

3.1.1. Simulants for G-agents

The identification of suitable simulants for G-agents was split into general simulants simulating any G-Series compound and specific simulants mimicking soman. Out of five different simulants identified for G-agents, two of these, diethyl malonate and methyl benzoate, are considered close simulants for soman, while the remaining three, methyl paraoxon, fenitrothion and dimethyl methyl phosphonate, are regarded as simulants for G-agents in general (Fig. 11).

In comparison to methyl benzoate and diethyl malonate, dimethyl methyl phosphonate (DMMP), methyl paraoxon and fenitrothion are all structurally more similar with G-series nerve agents. Mainly as these simulants all possess a central phosphorous atom, with a terminal oxide and three singly bonded substituents. However, the absence of a good leaving group, avoids the nucleophilic attack of the natural enzyme in the human body by the central phosphorus [87]. Therefore, these simulants are less toxic than the nerve agents themselves. While not all compounds with phosphoryl groups are highly toxic, many, particularly those that mimic nerve agents, can pose significant health risks due to their chemical structure and effects on the nervous system. For example, methyl paraoxon, the active metabolite of the insecticide parathion, is acutely toxic [83]. Other simulants that are frequently used are fenitrothion and dimethyl methyl phosphonate (DMMP) (Fig. 11) [26,73]. Both are classed as irritants only (Table 5). Sullivan et al. used DMMP in their study as a simulant for organophosphorus compounds with high molecular weight, in the assessment of adsorption and desorption from activated carbon fabrics (ACF) (2004). Imran et al. also used DMMP in their 2020 study of sampling contaminated surfaces with a newly

Table 6

Physical properties of soman and its simulants diethyl malonate and methyl paraoxon retrieved from PubChem and [46].

Physicochemical Properties	Soman	Diethyl malonate	Methyl benzoate
Molecular weight	182.17 g/mol	160.17 g/mol	136.15 g/mol
Solubility	Miscible in both polar and non-polar solvents	Miscible with ethanol, ether; very soluble in acetone/benzene, soluble in chloroform	Readily in organic solvents such as ethanol, diethyl ether, chloroform
Density	1.0222 g/mL at 25 °C	1.0551 g/mL at 20 °C	1.0837 g/mL at 25 °C
Boiling Point	198 °C	200 °C	199 °C
Melting Point	−42 °C	−50 °C	−12.35 °C
Toxicity	Acutely toxic, Corrosive, Combustible	Irritant	Irritant
State at room temperature	Colourless liquid, odourless to fruity	Colourless liquid with a sweet ester odour	Colourless liquid
Vapour pressure	0.41 mm Hg at 25 °C	0.19 mm Hg at 25 °C	0.38 mm Hg at 25 °C
Water solubility	Slightly at 21 g/L	Slightly at 20 g/L at 20 °C	Very slightly at 2.1 g/L at 20 °C

developed triple layered composite wipe. Additionally, using heat of adsorption as a measure of comparison, DMMP was found to be an excellent simulant to mimic the adsorption of sarin in MOF structures as well [1]. DMMP is a commonly chosen simulant when the primary objective is to mimic nerve agents' chemical structure [67].

Though fenitrothion, a broad-spectrum organophosphate insecticide, has low mammalian toxicity, it is not approved for use in EU countries as a contact insecticide [21]. Fenitrothion's structure contains a phosphorothioate group, thus sharing some structural similarity to soman's phosphoryl group, making it useful as a simulant for developing new treatment methods for CWAs [84]. To limit the effects of the chemical on the acetylcholinesterase, thus destroying the phosphoryl group, cleaving both or one of the lipophilic groups of the central phosphorus atoms is necessary. The structural similarities between the

chemical structures of fenitrothion and other OP molecules suggest that they may follow similar decomposition pathways [84]. Despite its similarities to nerve agents in structure, fenitrothion does not have the same acute toxicity, making it suitable for use in controlled, non-hazardous research environments.

Important to note here is that there are many other simulants, not discussed here, which may be better matches for chemical similarity, however, have some major drawbacks such as acute toxicity. Examples include diethylcyanophosphate (DECP) and diethylchlorophosphate (DCP) [15,8]. Finally, the physicochemical properties of fenitrothion and DMMP differ significantly from those of soman with marked disparities in terms of persistence, water solubility, boiling and melting points. For example, Soman has the highest boiling point (198 °C), while fenitrothion has the lowest (118 °C), and DMMP's is 181 °C. In terms of density, fenitrothion has the highest, followed by DMMP and soman. Soman is highly toxic and is highly volatile, while fenitrothion has the highest molecular weight. In comparison, DMMP is less toxic, has a lower molecular weight and is more soluble in water than soman (Table 5).

Diethyl malonate and methyl benzoate on the other hand, differ significantly in their chemical composition from G-series nerve agents. Diethyl malonate was identified as a suitable simulant for soman on the grounds that it has low toxicity in terms of exposure post-volatilisation and mimics the behaviour of soman[30,4]. Diethyl malonate is an irritant only. With two ester and two ethoxy groups (-OCH₂CH₃) diethyl malonate may not be structurally like G-series nerve agents, but its physiochemical properties are comparable. Methyl benzoate, on the other hand, was selected based on its Log K_{OW} and vapour pressure alone [29].

It is an organic compound characterised by its phenyl ring as well as ester functional group (Fig. 11). It, too, exhibits very similar physicochemical properties to soman, as shown by their boiling points at around 198–200 °C. However, there is a significant difference between their melting points and water solubility. Soman has the highest molecular weight, while methyl benzoate has the lowest. All three compounds are readily soluble in organic solvents. Methyl benzoate has the highest density, whereas soman has the lowest. Diethyl malonate has the lowest melting point, while methyl benzoate has the highest. Soman is acutely toxic and hazardous, whereas diethyl malonate and methyl benzoate are

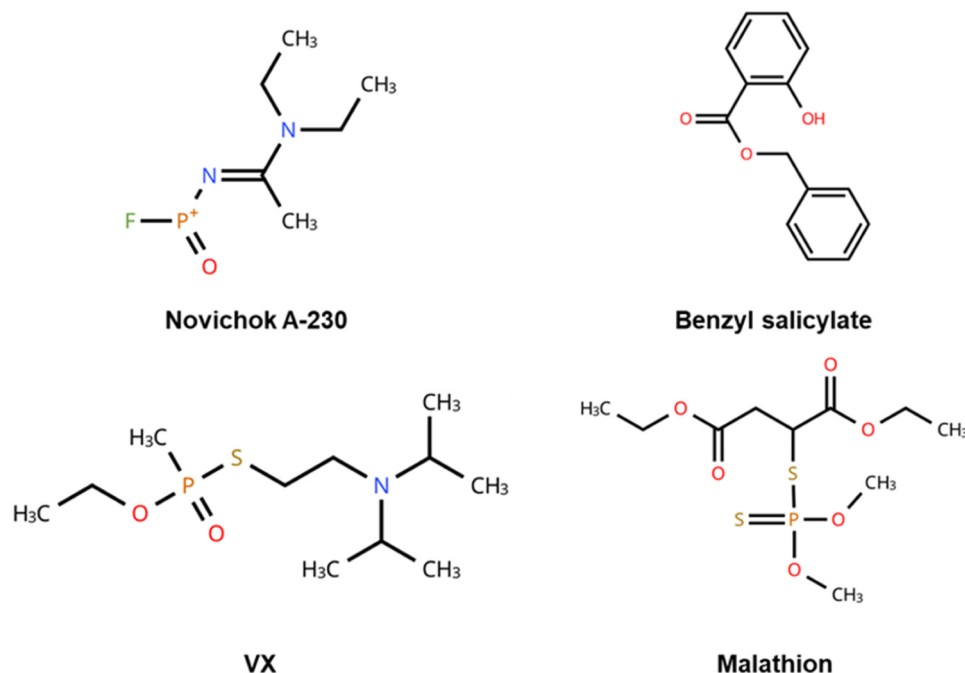


Fig. 12. Chemical structure of Novichok A-230, benzyl salicylate, VX and malathion.

Table 7

Physicochemical properties of Novichok A-23, VX and its simulants benzyl salicylate and malathion retrieved from PubChem and [43,56].

Physio-chemical Properties	Novichok A-230	Benzyl salicylate	VX	Malathion
Molecular weight	179.15 g/mol	228.24 g/mol	267.37 g/mol	330.4 g/mol
Solubility	Soluble in organic solvents	Slightly soluble	Soluble in organic solvents	Miscible with many organic solvents
Density	1.27 g/mL	1.175 g/mL at 20 °C	1.0083 g/mL at 25°C	1.2076 g/mL at 20 °C
Boiling Point	300°C	320°C	298°C	156–157°C
Melting Point	–30°C	24°C	–10°C	3.85°C
Toxicity	Acute toxicity	Irritant, Environmental hazard	Acute toxicity	Irritant, Environmental hazard
Appearance	Colourless to light yellow liquid	Colourless, thick liquid	Clear, colourless to amber-coloured liquid	Yellow to dark-brown liquid
Vapour pressure	0.1 mm Hg at 25°C	7.8×10^{-5} mm Hg at 25°C	0.000878 mm Hg at 25 °C	0.00004 mm Hg at 25 °C
Water solubility	Low solubility	8.8 mg/L at 20°C	Moderately soluble	143 mg/L at 20°C

Table 8

Physicochemical properties of simulants 2-chloroethyl methyl sulphide, 2-chloroethyl phenyl sulphide and Chloroethyl ethyl sulphide retrieved from PubChem.

Physicochemical Properties	2-chloroethyl methyl sulphide	2-chloroethyl phenyl sulphide	Chloroethyl ethyl sulphide
Molecular weight	110.61 g/mol	172.68 g/mol	124.63 g/mol
Solubility	Soluble in non-polar, or slightly polar organic solvents	Soluble in organic solvents	Soluble in organic solvents
Density	1.10 g/mL at 20°C	1.18 g/mL at 20°C	1.0663 at 20°C/4°C
Boiling Point	144°C	250°C	156°C
Melting Point	–102°C	–40°C	–100°C
Toxicity	Flammable, Corrosive, Acutely toxic, Irritant, Health hazard	Corrosive, Acutely toxic, Irritant, Health hazard	Flammable, Corrosive, Acutely toxic, Health hazard
Appearance	Yellow liquid with a stench	Liquid	Colourless liquid with a mild sulphide odour
Vapour pressure	7.8 mm Hg at 20°C	0.02 mm Hg at 25°C	3.4 mm Hg at 25°C
Water solubility	Slightly soluble	Poorly soluble	Slightly soluble

only mild irritants. Soman has the highest vapour pressure, making it the most volatile, with diethyl malonate being the least volatile. Soman and diethyl malonate are slightly soluble in water, while methyl benzoate is only very slightly soluble (Table 6).

Emphasised must be here that these types of simulants cannot be used to make inferences about specific detection or decontamination methods of G-series nerve agents that require the phosphonyl group or presence of the phosphorous atom, as they do not possess these.

3.1.2. Simulants for V- and Novichok agents

The authors selected Novichok A-230 and VX as examples of the V- and Novichok agent classes respectively, and they are visualised in Fig. 12. Both VX and Novichok A-230 contain a phosphoryl group, just

like the G-series agents. However, they additionally possess one tertiary amine. While the physicochemical properties of the V- and Novichok agents are not readily available on the Internet in databases such as PubChem, it can be generally stated that the V-series agents are generally colourless to amber colour, oily liquids with low vapour pressure [54,56].

Benzyl salicylate is a relatively simple chemical compound that is commonly used in the cosmetics industry. It is a derivative of salicylic acid and contains one ester, two phenyl rings and a hydroxyl group (Fig. 12). As such, it has an aromatic character and can absorb UV radiation. It has a sweet smell and is classified as an irritant only, thus rendering it suitable for use in human decontamination trials [29,72,9].

The central phosphorus atom is a distinctive feature of organophosphates. Malathion, along with VX and Novichok A-230, have this in common and are, therefore, part of the phosphonodithioates group. Malathion is an organophosphorus insecticide, with a central phosphorus atom attached to a thiophosphate group, and two ester groups extending outward, with one sulphur group at each end [40]. It is an acetylcholinesterase inhibitor, a property it shares with the V- and Novichok agents [56,61]. Malathion has however a much lower order of toxicity after dermal exposure and is commonly used to treat head lice and scabies [30].

The highest boiling point is observed for benzyl salicylate at 320°C, followed closely by Novichok A-230 at 300°C and VX at 298°C. Malathion exhibits a significantly lower boiling point at 156–157°C. Furthermore, Novichok A-230 has the lowest melting point, retaining its liquid state at low temperatures. Malathion has a melting point of 3.85°C, while VX melts at –10°C and benzyl salicylate at 24°C. VX and Novichok A-230 are highly toxic, whereas both simulants are classed as irritants and environmental hazards only. It can be concluded that these substances may be unsuitable for uncontrolled, outdoor environmental sampling studies. Novichok A-230 has the highest vapour pressure at 0.1 mm Hg, indicating greater volatility compared to benzyl salicylate (7.8×10^{-5} mm Hg), VX (0.000878 mm Hg), and malathion (0.00004 mm Hg). Novichok A-230 is highly toxic, dense and is volatile. Benzyl salicylate is less toxic and has higher boiling and melting points but is only slightly soluble in water. VX is acutely toxic with moderate

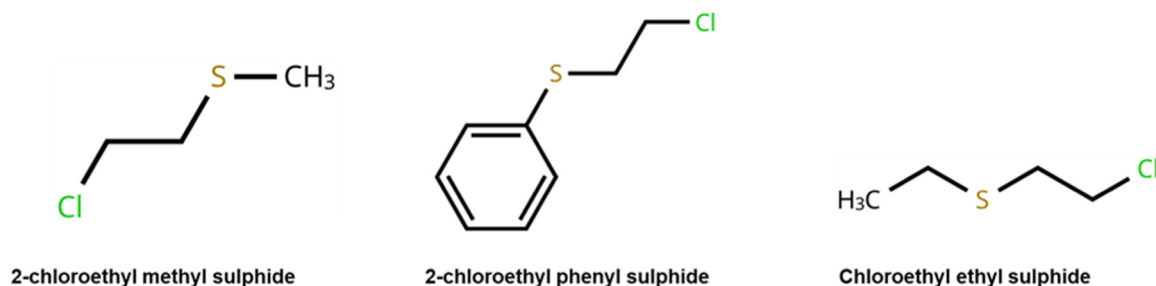


Fig. 13. Chemical structures of simulants 2-chloroethyl methyl sulphide, 2-chloroethyl phenyl sulphide, chloroethyl ethyl sulphide.

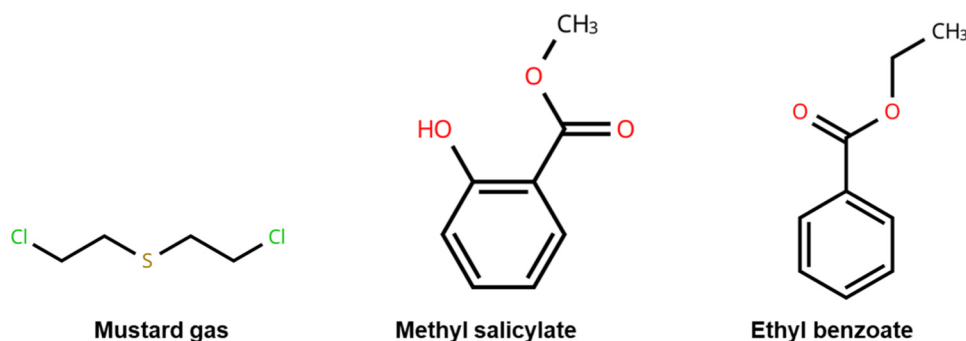


Fig. 14. Chemical structures of mustard gas and its simulants methyl salicylate, ethyl benzoate.

Table 9

Physicochemical properties of mustard gas, methyl salicylate and ethyl benzoate retrieved from PubChem.

Physicochemical Properties	Mustard gas	Methyl salicylate	Ethyl benzoate
Molecular weight	159.08 g/mol	152.15 g/mol	150.17 g/mol
Solubility	Highly soluble in organic solvents	Highly soluble in organic solvents	Soluble in organic solvents
Density	1.2741 g/mL at 20°C/4°C (liquid) 1.338 g/mL at 13°C (solid)	1.174 g/mL at 25°C	1.043–1.050 g/mL
Boiling Point	215–217°C	220–224°C	75.50°C
Melting Point	13–14°C	–8.6°C	–34°C
Toxicity	Acutely toxic	Irritant	Irritant
Appearance	Oily yellow-brown liquid with garlic taste and mustard odour	Colourless yellowish or reddish liquid with odour of wintergreen	Colourless refractive liquid with an aromatic odour
Vapour pressure	0.11 mm Hg at 25°C	0.03 mm Hg at 25°C	0.26 mm Hg at 25°C
Water solubility	609 mg/L at 25°C	Slightly soluble	0.72 mg/mL at 25°C

solubility, while malathion, despite being the heaviest, is more miscible in organic solvents and has the highest water solubility (Table 7).

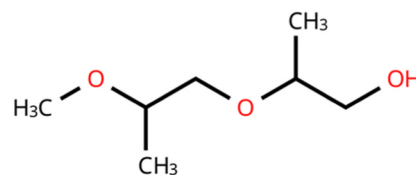
3.1.3. Simulants for sulphur mustard

Half mustards are common simulants used when structural similarity is required for specific detection or decontamination studies for examples. In earlier studies, 2-chloroethyl methyl sulphide (CEMS) and 2-chloroethyl phenyl sulphide (CEPS), were used to simulate sulphur mustards in soil. The relatively low vapour pressure and high boiling point of CEPS indicate that it does not easily evaporate but remains in liquid form under standard conditions (Table 8). In a study trialling the removal of sulphur mustards from water using a carbon filter,

chloroethyl ethyl sulphide (CEES), also known as half-mustard was used (Fig. 13). Sulphur mustard's chemical structure is characterised by its two chloroethyl groups attached to the central sulphur. All three discussed simulants share this structural similarity of a central sulphur atom bonded to a chloroethyl group ($-\text{CH}_2\text{CH}_2\text{Cl}$). However, the substitution of one chloroethyl group with a methyl group, a phenyl ring and an ethyl group, decreases the toxicity of the simulants. As a result, numerous studies have been conducted using half-mustards, which are less toxic and can be safely handled in a standard chemical fume hood, without requiring glove boxes or specialized facilities.[35]. Nevertheless, these simulants are all acutely toxic and therefore come with significant health risks.

CEES was also employed in a study investigating the removal of CWAs with active carbon fibres (ACF) [32].

One of the most common simulants for sulphur mustard is methyl salicylate (MeS). MeS exhibits comparable persistence, volatility and water solubility to sulphur mustard and is the least harmful simulant identified (Fig. 14; Table 9)[30,63]. Like CEES, MeS can be used in sorption studies [4]. Imran et al. [26] used MeS to simulate mustard gas on furnishings for their sorption study using ACF. MeS does not share the same functional groups as mustard gas but is characterised by a methyl ester group and a phenyl ring with a hydroxyl group attached at position two. Therefore, it is mostly used in studies requiring low toxicity and



Di (propylene glycol) monomethyl ether

Fig. 16. Chemical structure of di (propylene glycol) monomethyl ether (DPGME).

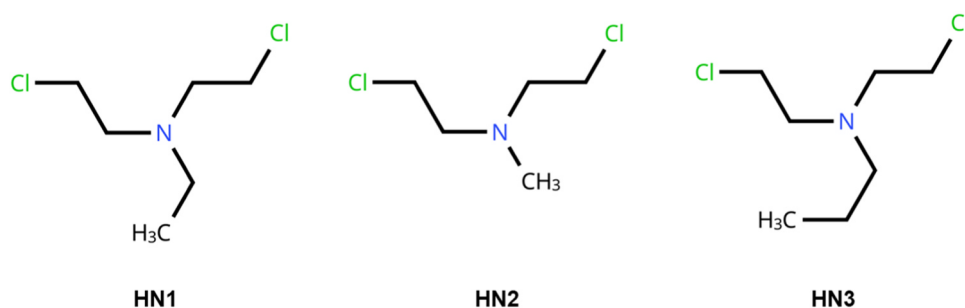


Fig. 15. Chemical structures of nitrogen mustards HN1, HN2, HN3.

Table 10
Physicochemical properties of HN2 and di (propylene glycol) monomethyl ether retrieved from PubChem.

Physicochemical Properties	HN2	Di (propylene glycol) monomethyl ether
Molecular weight	156.05 g/mol	148.20 g/mol
Solubility	Highly soluble in organic solvents	Miscible
Density	1.118 at 25 °C/4 °C	0.95
Boiling Point	87 °C	190 °C
Melting Point	108–110 °C	–80 °C
Toxicity	Corrosive Acute Toxic Health Hazard	Irritant
Appearance	Colourless to yellow, oily liquids	Colourless liquid with a weak odour
Vapour pressure	0.17 mm Hg at 25 °C	0.3 mm Hg at 25 °C
Water solubility	Hydrolyse in water quickly	Very good

comparable physiochemical rather than structural features.

James et al. [29] published a subsequent paper that contradicted their earlier findings, which had identified MeS as the best simulant for sulphur mustard. Instead, they propose the slightly more volatile ethyl benzoate as a more suitable alternative due to its greater similarity in volatility (Table 9). Ethyl benzoate differs from MeS structurally by only a small variation, as it lacks the hydroxyl group attached to the second position of the phenyl ring. This research suggests that using several simulants for one CWA may in fact be a better strategy than relying on a single one [29].

Mustard gas has the highest density at 1.2741 g/mL in its liquid form and 1.338 g/mL in its solid state. Methyl salicylate has a density of 1.174 g/mL, whereas ethyl benzoate is the least dense, with a density ranging from 1.043 to 1.050 g/mL. Methyl salicylate has the highest boiling point (220–224 °C), closely followed by mustard gas (215–217 °C). Ethyl benzoate has a significantly lower boiling point at 75.50 °C. Furthermore, methyl salicylate exhibits a melting point (–8.6 °C) that is similar to that of mustard gas (13–14 °C). Ethyl benzoate has the lowest melting point at –34 °C. As stated by James et al. [29], ethyl benzoate has a higher vapour pressure at 0.26 mm Hg, followed by mustard gas (0.11 mm Hg) and methyl salicylate with the lowest vapour pressure at 0.03 mm Hg. Both simulants also exhibit notable differences in their water solubility relative to mustard gas (Table 9).

3.1.4. *Simulants for nitrogen mustards*

The vesicants HN1, HN2, and HN3 were selected as representative examples of nitrogen mustards (Fig. 15). These compounds are related to mustard gas (Fig. 14) but contain nitrogen atoms in place of sulphur atoms (Fig. 15). Like sulphur mustard, nitrogen mustards chemical structures are characterised by their two chloroethyl groups attached to the central nitrogen. Nitrogen mustards are known for their blistering effects and their capacity to alkylate DNA, which renders them as potential CWAs. However, they also have applications in chemotherapy [12,65]. Both sulphur and nitrogen mustard compounds are reactive alkylating agents that can covalently bind to nucleophilic groups. These groups include amine, carboxyl, sulfhydryl, and imidazole moieties found in DNA, RNA, and proteins [65]. The structures of the vesicants HN1, HN2 and HN3 can be seen in Fig. 15.

Generally, nitrogen mustards can be simulated by half mustards like CEMS or CEEPS. A simulant, which does not mimic these functional groups is di (propylene glycol) monomethyl ether (DPGME) (Fig. 16). As it does not contain the chlorine or nitrogen atoms, its use for specific detection or decontamination based on chemical reactions, is limited. However, it is a good simulant for mimicking physiochemical properties without the inherent toxicity risks making it useful for sampling studies or human decontamination trials [5]. DPGME is characterised by its central ether linkage and the methyl ether and hydroxyl group (–OH) at the end.

Table 11
Summary of physicochemical properties of CWAs (grey columns) and their selected simulants (white columns).

Physicochemical properties	Soman	Diethyl malonate	VX	Malathion	Mustard gas	Methyl salicylate	HN2	Di (propylene glycol) monomethyl ether
Molecular weight	182.17 g/mol	160.17 g/mol	267.37 g/mol	330.4 g/mol	159.08 g/mol	152.15 g/mol	156.05 g/mol	148.20 g/mol
Solubility	Miscible in both polar and non-polar solvents	Miscible with ethanol, ether; very soluble in acetone/benzene	Soluble in organic solvents	Miscible with many organic solvents	Highly soluble in organic solvents	Highly soluble in organic solvents	Highly soluble in organic solvents	Miscible
Density	1.0222 g/mL at 25 °C	1.0551 g/mL at 20 °C	1.0083 g/mL at 25 °C	1.2076 g/mL at 20 °C	1.2741 g/mL at 20 °C/4 °C (liquid) 1.338 g/mL at 13 °C (solid)	1.17 g/mL at 25 °C	1.118 at 25 °C/4 °C	0.95
Boiling Point	198 °C	200 °C	298 °C	156–157 °C	215–217 °C	220–224 °C	87 °C	190 °C
Melting Point	–42 °C	–50 °C	–10 °C	3.85 °C	13–14 °C	–8.6 °C	108–110 °C	–80 °C
Toxicity	Acutely toxic Corrosive Combustible	Irritant	Acute toxicity	Irritant Environmental Hazard	Acute toxic	Irritant	Corrosive Acute Toxic Health Hazard	Irritant
State at room temperature	Colourless liquid, odourless to fruity	Colourless liquid with a sweet ester odour	Colourless to amber-coloured liquid	Yellow to dark-brown liquid	Oily yellow-brown liquid with garlic taste and mustard odour	Colourless yellowish or reddish liquid with odour of wintergreen	Colourless to yellow, oily liquids	Colourless liquid with a weak odour
Vapour pressure	0.41 mm Hg at 25 °C	0.19 mm Hg at 25 °C	0.000878 mm Hg	0.00004 mm Hg	0.11 mm Hg at 25 °C	0.03 mm Hg	0.17 mm Hg at 25 °C	0.3 mm Hg
Water solubility	Slightly at 21 g/L	Slightly at 20 g/L at 20 °C	Moderately soluble	143 mg/L at 20 °C	609 mg/L at 25 °C	Slightly soluble	Hydrolyse in water quickly	Very good

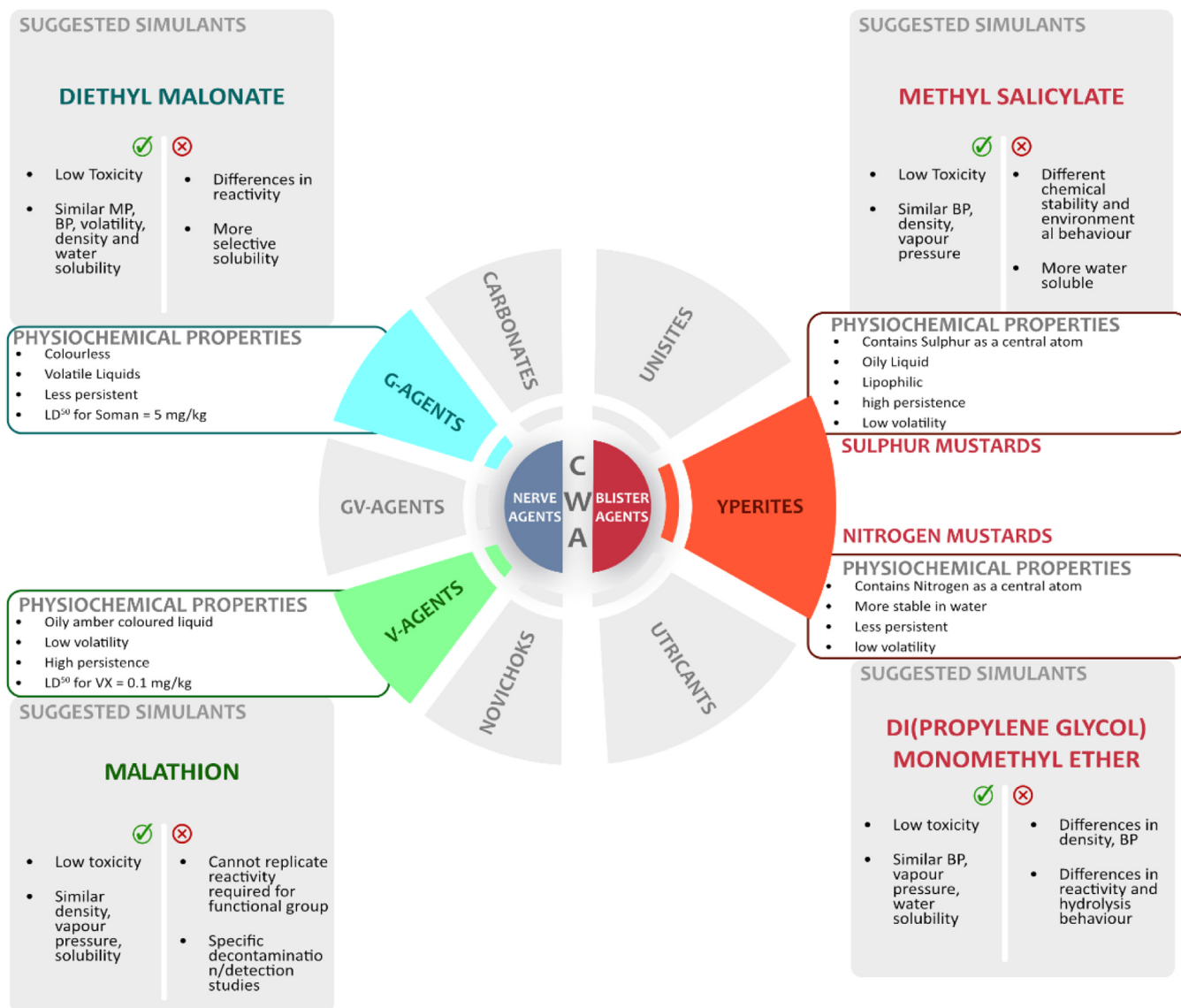


Fig. 17. Comparison of suggested simulants with their toxic counterparts.

The physicochemical properties of HN2 and DPGME are presented in Table 10. Their molecular weights are relatively similar, as are their solubilities. However, there are significant differences in their boiling points and melting points, indicating that phase changes will occur more readily for HN2 than its simulant. DPGME has a vapour pressure of 0.3 mm Hg, making it more volatile and more likely to evaporate into the gas phase than its toxic counterpart, which has a vapour pressure of 0.17 mm Hg.

3.2. Mitigating the risks

To mitigate the risk associated with conducting the sampling experiments, only well-researched liquid simulants of low toxicity were considered in the final selection for this review. It is therefore essential that the simulant can be used in high concentrations (above the LD₅₀) to simulate actual chemical incidents. Furthermore, the focus of this research lies with liquids rather than solids and gases. This approach allows the exclusion of blood and choking agents from the research, thereby shifting the focus to non-toxic simulants of nerve and blister agents only.

Four liquid simulants of low toxicity were identified for possible use in sampling trials. Two of the selected simulants mimic the class of nerve

agents, with the remaining two mimicking blistering agents. Diethyl malonate was selected as a simulant for the G-Agent soman. Soman has been used in armed conflicts, including the Iran/ Iraq conflict and thus has real-life applications [70,75]. Moreover, diethyl malonate is an irritant and not acutely toxic. Malathion was selected to simulate V /Novichok agents. It is a relatively inexpensive option that is readily available, has similar physicochemical properties and is an irritant only. Furthermore, it possesses some structural and reactive similarity with the CWA. Methyl salicylate, a simulant for sulphur mustard, is well-researched and has been selected based on its lack of toxicity and similarity in all physicochemical properties, with a possible exception of its vapour pressure. Di (propylene glycol) monomethyl ether was chosen as a simulant for nitrogen mustards (Table 11). All these simulants are commercially available from Sigma Aldrich at low cost.

These simulants may be used in controlled environments to study properties and effects similar to those of CWAs, thereby facilitating safe research and training for sampling. One must also point out that how simulants compare to CWAs in field applications, is in fact not identical and more research in this area is needed. Therefore, to mitigate the shortcomings of one simulant, recent studies have recommended the use of multiple simulants for a single CWA to gain a more comprehensive understanding of chemical interactions in different matrices. The focus

of this study is on validating sampling protocols for a range of different groups of CWAs rather than a single specific CWA, thus utilising simulants for different CWAs will allow for a more comprehensive assessment of sampling methods for forensic investigations, environmental sampling and the development of effective sampling plans for CWAs (Fig. 17).

4. Conclusion

This review emphasises the critical role of well-chosen simulants in advancing safe and effective sampling methodologies for CWAs, particularly for nerve and blister agents. Simulants must exhibit similar physicochemical properties as the CWAs they represent, including hydrophobicity, volatility and solubility, to ensure accurate and reliable sampling studies without excessive exposure due to toxicity. The selection of low-toxicity simulants such as diethyl malonate, malathion, methyl salicylate and di (propylene glycol) monomethyl ether allows researchers to simulate real-life scenarios with minimised risk, thereby supporting both environmental and forensic sampling efforts. It has been demonstrated that using a combination of simulants may facilitate a more comprehensive representation of CWAs, capturing a range of interactions across environmental matrices such as soil and water. The focus of the review on low toxicity, liquid simulants address a pressing need for controlled experiments that reflect real CWA scenarios, a gap that has not yet been filled by traditional sampling methods.

In conclusion, this review provides a foundational reference for low toxicity, liquid simulants for future sampling studies and field applications. The aim is to enhance the precision and safety of CWA sampling in both controlled and real-world environments and to contribute to the development of standardised, field-deployable sampling protocols that balance accuracy, safety and ease of use. However, it is crucial to emphasise the dissimilarities between simulants and CWAs, as these can impact the transferability of simulant studies to events relating to CWAs. This challenge can be addressed by employing a range of different simulants to mimic a broad spectrum of properties.

Environmental implications

Chemical warfare agents (CWAs) are not only toxic to humans, but also animals and the environment. They degrade slowly under ambient conditions. Research is therefore often conducted using simulants. Though there is little impact on the environment, due to the small amounts of simulant used, the selection and use of low-toxicity simulants for CWAs, minimises risks during research and sampling further. The findings emphasise the importance of choosing simulants with similar physicochemical properties to CWAs, ensuring effective and realistic field simulations. These advancements can lead to better preparedness for CWA related incidents, protecting both ecosystems and human populations from the harmful effects of toxic CWAs.

CRedit authorship contribution statement

Coulon Frederic: Writing – review & editing, Supervision. **Webb Sally:** Writing – original draft, Methodology, Investigation, Formal analysis. **Temple Tracey Jayne:** Writing – review & editing, Supervision.

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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Data availability

No data was used for the research described in the article.

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