Trends in Analytical Chemistry 168 (2023) 117282

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

A review of sensing technologies for nerve agents, through the use of agent mimics in the gas phase: Future needs

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ARTICLE INFO

Keywords:
Chemical warfare agents
Gas phase
Field deployment
Sarin
Dimethyl methylphosphonate
Sensors

ABSTRACT

Portable gas sensing has become an important technology in preventive and protective measures for users working with the disposal of nerve agents. The use of powerful benchtop instruments is not adequate for those situations where a single individual or a group needs to be informed of the presence of toxic substances and need to implement protection measures. Portable sensors are the right technology that can be used as an early warning system in military operations and for public health. The aim of the work presented in this review is to present a detailed summary of the current sensing technology available within the scientific literature for the detection of nerve agent simulants in the gas phase, focussing on the recognised sarin surrogate: dimethyl methylphonate (DMMP). The use of real chemical warfare agents for testing is highly restricted to government agencies and much of the work is kept secret. The use of simulants for the development of sensing technology has been widely established for nerve agents to reduce the potential risk to personnel and to offer a realistic, simple molecule to try and test the technology. The present review compiles a comparison of different sensors and their respective sensing mechanisms based on different chemical, spectroscopic, or electrochemical and biological properties. These sensing technologies are then compared to the U.S environmental protection agencies standard for concentration of Sarin at 15 ppb (known lethal dose). Surface acoustic wave, quartz crystal microbalance, semiconductor, chemicapacitor and colorimetric sensors have proven to show potential with desirable properties for fast response times and high sensitivity. However, only some work developed using semiconductor detectors present a reliable system able to detect DMMP with low limit of detection (0.05 ppb), fast response time (0.02 min) and good recovery times (0.5 min) and adequate portability that makes them suitable to be integrated in drone systems, wearables, and low-weight devices.

1. Introduction

Considered to be the deadliest group of chemical weapons available, nerve agents are organophosphorus compounds (OPCs) that affect the receptors of the central nervous system (CNS) [1]. After the first world war, Germany was heavily reliant on other countries to source its food. As a result, scientists were working on different ways to increase internal food production within Germany. In 1936, Dr Gerhard Schrader at IG Farbenindustrie (Germany) synthesised an organophosphorus insecticide but it was deemed unfit for commercial use as it had an unselective potency [2,3].

These findings were sent to the Nazi government, who insisted Dr Schrader weaponised the organophosphorus insecticide to create tabun, the first nerve agent [4]. Dr Schrader would later go on to synthesize sarin in 1937 which was more toxic than tabun [2,3]. This was not the first time the effects of organophosphorus compounds were discovered, Lange and Krueger experienced the toxic effects first-hand in 1932 but decided not to pursue further [5,6]. Further discoveries came after the Nazi's enlisted Dr Richard Kuhn in 1943 to research the key mechanism behind the potency of tabun and sarin. Eventually Kuhn and his team determined it was acetylcholinesterase (AChE) inhibition; with this discovery Kuhn synthesised soman in 1944, although it was never mass-produced. Tabun, sarin and soman were classed as the "G-Agents" a sub-group of nerve agents, presented in Fig. 1 [2,3,7,8].

In 1952, Dr Ranajit Ghosh was working on a replacement for dichlorodiphenyltrichloroethane (DDT) by using organophosphate esters of various 2-aminoethanethiols [4,9]. The substitute was extremely toxic to mammals and was not ideal for commercial use. These finding were sent to the laboratories at Porton Down and later forwarded to the US government for weaponization [1,3]. Through the UK-US

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https://doi.org/10.1016/j.trac.2023.117282
Received 29 July 2023; Received in revised form 12 September 2023; Accepted 12 September 2023
Available online 19 September 2023

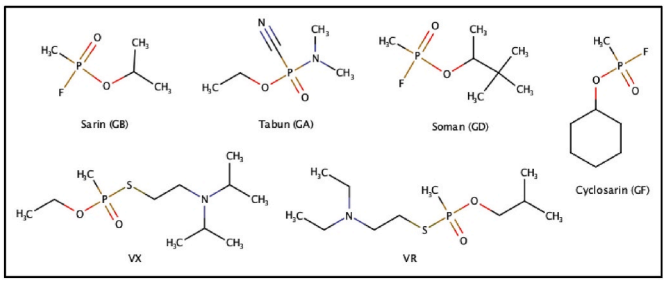

Fig. 1. Structures of the G-agents: Sarin, soman, tabun and cyclosarin and the V-agents: Vx and Vr.

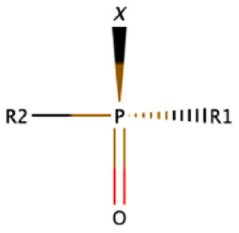

Fig. 2. Generic structure for an organophosphorus compound; two alkyl substituents (R1 & R2) and a leaving group (X).

partnership VX was created, a third-generation chemical warfare agent that was more toxic than sarin and persisted longer in the environment. The V-agents were expanded upon by Russia and China (Fig. 1.), who had been working independent from the allies, to synthesize their own V-agents [4,10].

The chemical warfare convention was introduced in 1993 by the Organisation for the Prohibition of Chemical Weapons (OPCW), in a show of support towards the complete disarmament of chemical warfare agents; 130 countries signed the convention [11]. An additional 35 countries joined the convention, before it came into force in 1997 [12,13]. Similar to the Geneva Protocol of 1925, the chemical weapons convention (CWC) prohibited the use of chemical warfare agents (CWAs) but also prohibited their development, production and stockpiling. Furthermore, any current stockpiles had to be declared and destroyed [14].

The OPCW defines a chemical weapon as 'a chemical used to cause intentional death or harm through its toxic properties'. The definition also includes the use of munitions and devices to transport and disperse the toxic chemical, plus the equipment used in direct conjunction [11]. Not all toxic chemicals are classed as chemical weapons due to their heavy use within industry; these agents are placed into schedules and regulated by the CWC [10]. As of the 30th June 2022 there are currently 193 member states, and up to 99% of the world's declared chemical weapons stockpiles have been destroyed [13,15].

It has been widely accepted within the scientific community that there is an "unofficial" fourth generation of nerve agents called novichoks (The A agents). The existence of novichoks were first reported in 1992 by Dr Vil Mirzayanov after publishing an article accusing the USSR of breaking the CWC [3,16]. There has been much speculation around the structure of the Novichoks, but it is believed to have an organophosphorus group, a fluorine bond and phosgene oxime which increases the toxicity [17,18]. The most recent reports of Novichok have been around the attempted assassinations of Sergei Skripal and his daughter Yulia Skripal in 2018 [2,19,20]. It is unknown which countries are in possession of the Novichok agents but it is now recognised by the OCPW as a potential threat [2,6,18].

Even with the chemical warfare convention and the oversight of the OCPW, the use of nerve agents remains a viable option for terrorist organisations. As a result, countries must continue to carryout scientific research on CWAs to produce better protective equipment. However, under the CWC there are only small quantities of the real agent available for scientific research. Furthermore, these samples are kept in a handful of scientific institutes and require specialist training to handle the agent. As a result, it is common practice for a company or institute to use a mimic of a chemical warfare agent which reduces the risk associated.

For nerve agents, OPCs are normally used as mimics containing an oxygen atom bound to a phosphorus atom (phosphoryl bond), two alkyl substituents (R1 & R2) and a leaving group (X) as shown in Fig. 2. To reduce the toxicity for mammals, the oxygen atom can be substituted with a sulfur atom to create a thiophosphoryl bond [21,22]. The broad range of configurations available for residues and leaving groups makes it difficult to produce a classification system for a variable quantity of derivatives [12]. Some examples include phosphates, phosphonate, phosphorofluoridate and phosphorthioamidate but all OPCs are derivatives of phosphoric, phosphonic or phosphinic acids [21]. Recognised mimics for nerve agents are dimethyl methylphosphonate (DMMP), diethyl ethylphosphonate (DEEP), diisopropyl methyl phosphonate (DIMP) [23] and diethylchlorophosphate (DCP) [24]; DMMP is the most common (Fig. 3).

In the last five years, there have been several reviews published on different types of semiconducting materials which are applied in the determination of gas and volatile organic compounds (VOCs) based nerve agents. In 2022 Ramanavičius et al., published a review on gas sensors that focused on the use of titanium oxide. The overall conclusion was that composite materials could doped with titanium oxide and be utilised for more advanced applications [25]. Previously Ramanavičius et al. published a review in 2020 on the design of sensors using titanium oxide [26]. Alternatively, reviews have been completed that look at a wide range of metal oxides and how they can be used as chemoresistive sensors for CWAs [27,28]. Apart from semiconducting materials and metal oxides there has been reviews completed on biosensors that could be used for CWAs [29], but these have their own drawbacks which are discussed in 5.9. Generally, the scientific literature contains reviews on metal oxides and semiconductors, this review intends to bring together the different types of sensors available for the detection of nerve agents through the use of nerve agent mimics. Identify strengths and weakness associated with each sensor and determine the most effective sensing mechanism.

2. Toxicity

Naturally, the body uses a neurotransmitter called acetylcholine (ACh) to activate nicotinic and muscarinic receptors which are directly responsible for cholinergic transmission within the CNS. To ensure the synapses and the neuromuscular junction is not overexcited due to a build-up of ACh, the body uses an enzyme called acetyl cholinesterase (AChE) to hydrolyse ACh into choline and acetate [30,31]. However, a

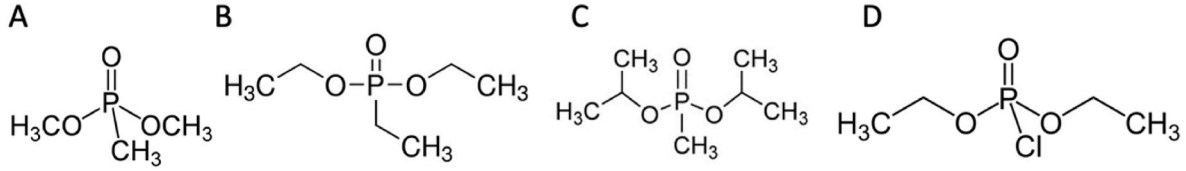

Fig. 3. The structure of dimethyl methylphosphonate (A), diethyl ethylphosphonate (B), diisopropyl methyl phosphonate (C) and diethylchlorophosphate (D).

Table 1
The acute exposure guideline for Sarin, Soman, Tabun and Vx detailing the concentrations required to cause a particular effect within 10 min of exposure.

	Sarin [33] (ppb)	Soman [34] (ppb)	Tabun [35] (ppb)	Vx [36] (ppb)
Non-disabling but will discomfort	1.2	0.46	1	0.052
Irreversible damage and long-term effects	15	5.7	13	0.65
Fatal to humans	64	49	110	2.7

nerve agent can irreversibly inhibit AChE and cause a build-up of Ach to occur within the synapse. As a result, the respiratory muscles are paralysed, and the victim dies of respiratory paralysis; this can be instantaneous if the concentration is high enough [10].

For agents absorbed into the body by inhalation, the median lethal concentration and time (LCt50) is used to measure toxicity. Furthermore, nerve agents can be absorbed through the skin and the lethal toxicity can be measured by median lethal dose (LD50). For example, the deadliest nerve agent only requires 10 mg to be absorbed through the skin to kill a 70 kg male, alternatively inhaling just 5 mg/min/m^3 also proves to be lethal [6]. Additional effects can be observed proportional to the concentration received: meiosis, eye pain, rhinorrhoea, vomiting, bronchorrhea, bronchoconstriction, bradycardia (the killer B's) and dyspnoea [30,32].

The centre for disease control and prevention (CDC) in the united states have determined the minimal risk levels (MRLs) for Sarin [33], Soman [34], Tabun [35] and Vx [36] after 10 min of exposure, this has been detailed in Table 1. It is important for early warning system to be able to detect **concentrations** of nerve agents below 0.65 ppb which is the concentration of Vx that causes irreversible damage. The **detection time** is also an important aspect and effective sensors need to be able to detect nerve agents within 10 min. Having effective sensors that produce fast responses at low concentrations surpass the need for effective treatments.

3. First response

Like most chemical warfare treatments, clothing or tissue exposed to nerve agents requires an initial decontamination step. This involves the removal of clothing (trapped vapours) and cleaning the skin with high volumes of water or sodium hypochlorite [32]. There are several antidotes available to treat nerve agent poisoning: atropine, diazepam, and pralidoxime chloride [37].

The main antidote is atropine as it is active against all nerve agents and works by reversing cholinergic overload at muscarinic receptors by competing with ACh. The initial dose is 2 mg with repeat administration occurring every 5–10 min [10]. However, atropine is unable to resolve seizures caused by nerve agent poisoning, there is some evidence to support the use of benzodiazepines for treatment of these patients. Therefore, diazepam is used to offset convulsions [30,31]. Pralidoxime (2-PAM or 2-pyridine aldoxime chloride) is included to treat the nicotinic effects, including muscle fasciculation followed by depolarisation paralysis and assists in the regeneration of AChE, re-establishing muscle polarisation [10].

On the battlefield, British and American personnel have access to MARK I kits that contain these three drugs preloaded into autoinjectors with the correct concentration to assist with quick battle first aid. Alternatively the MARK 1 can be substituted for the more recent Antidote Treatment Nerve Agent Autoinjector (ATNAA) [38]. A pre-treatment of reversible acetylcholinesterase inhibitor pyridostigmine can be administered to military personnel at risk of exposure to nerve agents, this limits the enzyme pool available to nerve agents [31]. Finally, even with these antidotes, patients will need to be constantly monitored and provided with supportive care [10].

The complexity of treatments and the very hazardous nature of the

Table 2
A summary of analytical methods used for the identification of chemical warfare agents and there derivatives taken from the 2022 SAM published by the EPA.

Author(s)	Technique	Title	Limit of detection (ppb)	Year	Ref
Lewis	GC-MS or HPLC-UV	TO-10 A: Determination of Pesticides and Polychlorinated Biphenyls in Ambient Air Using Low Volume Polyurethane Foam (PUF) Sampling Followed by Gas Chromatographic/ Multi-Detector Detection (GC/MD)	0.01–50 (dependant on analyte)	1999	[41]
McClenny et al.	GC-MS	TO-15: Determination of Volatile Organic Compounds (VOCs) in Air Collected in Specially-Prepared Canisters and Analyzed by Gas Chromatography/ Mass Spectrometry (GC/MS)	0.5	1999	[42]
Woolfenden et al.	GC-MS	TO-17: Determination of Volatile Organic Compounds in Ambient Air Using Active Sampling Onto Sorbent Tubes	2.86–275 (dependant on analyte)	1999	[43]
Campisano	GC-MS	EPA/600/R-16/ 115: Analytical Protocol for Cyclohexyl Sarin, Sarin, Soman and Sulfur Mustard Using Gas Chromatography/ Mass Spectrometry	5.7–11.4 (dependant on analyte)	2016	[44]
Campisano	GC-MS	EPA/600/R-12/ 653: Verification of Methods for Selected Chemical Warfare Agents (CWAs)	25	2013	[45]
Willison et al.	LC-MS-MS	EPA/600/R-15/ 097: Adaptation of the Conditions of U.S. EPA Method 538 for the Analysis of a Toxic Degradation Product of Nerve Agent VX (EA2192) in Water by Direct Aqueous Injection-Liquid Chromatography/ Tandem Mass Spectrometry	0.013	2016	[46]
Campisano	GC-MS	EPA/600/R-16/ 116: Analytical Protocol for VX Using Gas Chromatography/ Mass Spectrometry (GC/MS	11.4	2016	[47]

Table 3
A list of screen technologies identified by the EPA for detection of Sarin at 15 ppb.

Company	Name	Response Time (mins)	Physical effort	Consumable item(s)	Cost per Sample
Anachemia	C2	2	Minimal	Colour ticket	$9
Draeger	Civil Defence Kit	2	Hand strength needed for pump operation	Tubes (boxes of 10)	$11
MSA	Single CWA Kit	2	Hand strength needed for pump operation	Tubes (boxes of 10)	$8
Proengin	AP2C	0.17	Minimal	Hydrogen supplies; batteries. Scraper tips for liquid sampling (packs of 10).	$3
Truetch	M18A3 Ticket	3	Minimal	Colour tickets	$4

organophosphorus agents, even at ppb level, highlights the need for an early detection system, able to provide enough warning to allow personnel to protect themselves. This sensor system would avoid the use of the already mentioned first response measures.

4. Benchtop analytical methodologies for organophosphorus analysis

The Environmental Protection Agency (EPA) in the United States has established a Homeland Security Research Program (HSRP) that pulls together a list of analytical methods for chemical warfare agents. In partnership with other laboratories and agencies, these methods and techniques are regarded as the golden standard for analysis [39]. The HSRP forms a subset of the Selected Analytical Methods for Environmental Remediation and Recovery (SAM) produced by the EPA, to standardise the analytical methods used by a laboratory on samples taken from a contaminated scene [40]. Within the 2022 edition of the SAM, there are seven different analytical methods for the determination of nerve agents, these methods have been detailed in Table 2.

Based on the methods described in Table 2, the sample can be collected in a sorbent polyurethane foam cartridge [41,43], silica-coated stainless steel canister [42] or specialised wipes [44]. These samples are then sent to accredited laboratories that can perform the methods listed in the SAM, using either gas chromatography mass spectrometry (GC-MS) or liquid chromatography mass spectrometry (LC-MS). To quickly confirm the presence of a nerve agent at the scene, the methods listed in the SAM are not ideal due to the numerous steps involved from collection, transportation, preparation, analysis; the window for a result is extended.

Therefore it is important to have onsite screening methods available that produce fast responses, and its results can be easily interpreted by non-scientific personnel: military, police, medical, public [48]. This makes laboratory-based techniques like chromatographic and spectrophotometric methods, not ideal for early warning systems. There are trials being conducted which involve the use of mobile laboratories, parked just off site to the incident but once again, its practicality would be dependent on the circumstances and availability of a mobile laboratory [48]. As a result, there is an increasing interest into portable warning systems for in-situ analysis, with vast strides having already been made to increase their usability and reliability [49].

In 2007, the EPA produced a report on the different screening technologies being used in facilities that deal with CWAs; this contained commercial kits, test paper, handheld electronics, and colour-indicating tubes [50]. For each test, three samples were taken and subjected to concentrations deemed by the EPA to be hazardous to health (Table 1). The following factors were monitored, response time, false positives/false negatives, ease of use, cost and response indication [51]. Among the report was a list of sensors that could successfully detect sarin at 15 ppb, summarised in Table 3. However, the report determined each sensor reviewed had its own drawbacks for example the Draeger Civil Defence Kit and the MSA Single CWA Kit would produce false positives in the presence of hydrocarbon interferents. Furthermore, colour indicating tubes were simple to use in principle but turned out to be difficult and time consuming to collect the sample. Ultimately, a sensor advantage would be directly linked to the disadvantage associated with that sensor [50,51].

5. Gas sensing for organophosphorus compounds

Among the recognised methodologies, there are different types of sensing mechanisms that are currently being developed. This section details the different types of sensors that are being used to detect the sarin surrogate: DMMP. In the last 10 years there has been an increased interest in the production of portable sensors, in this review over 50% of the sensors explored were manufactured in 2015 or later. This could be attributed to the increase in advertisement for drones and wearable technology; both having military applications for chemical warfare [52,53]. Drones are now routinely used in military operations and there is the potential for a semiconductor to be installed for remote gas sensing [53]. While a colorimetric sensor could be installed into the uniform of a solider and change colour in the presence of a nerve agent [52]. The marking criteria from the EPA report detailed in section 4 has been used to review other types of sensor technologies used for CWAs.

5.1. Surface acoustic wave sensors

The surface acoustic wave (SAW) sensor was first introduced in 1979 by Wohltjen and Dessy [54]. The sensor involves the use of interdigital

Table 4
A comparison of surface acoustic wave sensors within the literature between 1993 and 2022.

Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
Grate et al.	Acid Polymer FPOL	20	2	0.27–0.47	DMMP	1993	[58]
Zimmermann et al.	AT-cut quartz/SiO2/polysiloxane polymer.	350	–	–	DMMP	2001	[59]
Joo et al.	PIB, PECH, PIP, PDMS, PBDA	5000	–	–	DMMP	2007	[60]
Wen et al.	ST-X quartz substrate o-phenylenediamine (o-PD)	100	20	20	DMMP	2007	[61]
Matatagui et al.	Quartz/Novolac	25	6	–	DMMP	2011	[62]
Matatagui et al.	Quartz/SiO_2	40	4	–	DMMP	2012	[63]
Pan et al.	SXFA	24	0.15	0.58	DMMP	2020	[64]
Pan et al.	25-(thioalkyl-alkoxy)-p-tertbutylcalix [4]arene	10	7.1 6.35	–	DIMP DMMP	2020	[65]
Grabka et al.	HBA polysiloxane (PMFOS)	13	13.3	–	DMMP	2021	[66]
Pan et al.	Viscoelastic fluoroalcoholpolysiloxane	1.21	1.67	0.83	DMMP	2022	[67]

Table 5
A comparison of quartz crystal microbalance sensors within the literature between 2004 and 2022.

Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
Pei et al.	ZnO-modified MnO_2 nanofibers	35	–	–	DMMP	2010	[71]
Öztürk et al.	PMeT	100	–	–	DMMP	2016	[72]
Alev et al.	Tungsten disulfide	5	370	–	DMMP	2022	[69]

transducers (IDTs) mounted to a piezoelectric substrate (quartz crystal), as well as the addition of a sensing layer to aid with selectivity [55]. An electrical signal is applied to the input IDT to create an acoustic wave due to interactions (periodic compression and rarefaction) with the piezoelectric material. Once the acoustic wave strikes the output IDT, the signal is converted back into an electrical signal. The propagation factors can be altered by different parameters for example, a change in mass [54]. As a result, the addition of a chemical to the sensing layer will alter the acoustic wave generated and the signal produced [56]. Depending on the type of SAW sensor used, the wave could be rayleigh, love or stoneley waves [54]. Fig. 1 from Go et al. [57] offers a good description of the mechanism of action and explanation on sensing principles.

Since 1993 there has been research into manufacturing different SAW sensors for the detection of CWAs, this has been detailed in Table 4. The majority of sensors listed do not meet the EPA Criteria as the limit of detection (LOD) is above the concentration deemed hazardous to health: Sarin 15 ppb [33]. However, there are a handful of sensors that can detect DMMP and DIMP below 15 ppb that were developed in 2020, 2021 and 2022. Amongst the three SAW sensors there is a sensor produced by Pan et al. that can detect as low as 1.21 ppb using a viscoelastic fluoroalcoholpolysiloxane coating, theoretically able to detect Sarin, Soman, Tabun and Vx [33–36]. Furthermore, this sensor is fast acting and can produce a response time in one hundred seconds while recovery takes around 50 s. However, it should be noted the manufacturing process can be inconsistent resulting in the surface morphology being drastically different.

5.2. Quartz crystal microbalance sensors

A quartz crystal microbalance (QCM) is made up of a resonating quartz plate (a piezoelectric material) coated in a sensing material. The plate is surrounded on each side with a metal electrode which applies the voltage. When the QCM is connected to an oscillating circuit it will display its own characteristic frequency [56]. Furthermore, the resonance frequency can be reduced if the mass of the plate is increased. This principle can be directly used for chemical sensing due to a chemical in the gaseous phase being directly adsorbed on to the sensing material and altering the mass; these changes can be detected up to parts per billion [49]. Fig. 1 from Alazani et al. [68] offers a good description of the mechanism of action and explanation on sensing principles.

Within the last 15 years there have been a handful of QCM sensors produced able to detect lethal concentration of G agents summarised in Table 5. The most recent sensor in 2022 by Alev et al. using a Tungsten disulfide coating has demonstrated a good LOD: 5 ppb [69]. At this concentration, the sensor can detect below concentrations of G-agents deemed by the EPA to cause Irreversible damage and long-term effects. However, the response time is ineffective taking up to 370 min for a response. The concentrations listed by the EPA in Table 1 is only for 10 min of exposure, an extended period subjected to a nerve agent would reduce the concentration needed to cause irreversible damage and death [33–36]. Furthermore, QCM based systems can suffer from non-specific binding altering the mass of the sensor and produce a high error rate. As a result, the delicate nature of the system would make QCM's unsuitable for portable systems [70].

5.3. Film Bulk Acoustic Resonator Sensors

For problems that require a higher frequency beyond 100 MHz, film bulk acoustic resonators (FBAR) can be used as a replacement for SAW and QCM sensors [73]. Fig. 1 from this paper offers a good description of the mechanism of action and explanation on sensing principles. As a result of the FBAR's higher resonate frequency around the GHz range, the device is extremely sensitive to changes in mass. The FBAR sensor is similar to the SAW and QCM sensors and works on the same principle, a mass change will cause the resonance frequency to change [74]. The main difference is the configuration of the sensor, the piezoelectric material (thickness can vary) is sandwiched between two electrodes; a sensing material is coated onto the top electrode. Underneath is an isolation layer that traps the acoustic wave within the piezoelectric material [75].

The majority of the research within this field has been conducted by Chen et al. who have produced two FBAR sensors for the detection of DMMP in the gas phase. The first FBAR was coated in Cu^{2+}/11-mercaptoundecanoic acid while the second sensor was coated in poly vinylidene fluoride [74,76]. Both sensors produce moderate response and recovery times but are not ideal for the detection of nerve agents as the LODs is 100 ppb [74] and 5000 ppb [76] respectively. The Cu^{2+}/11-mercaptoundecanoic acid bilayer could only be used to detect concentrations below fatal concentrations of Soman [34]. Similar to the problems observed with the QCM based systems, FBAR's can be affected by non-specific binding, causing an unwanted to change in mass. Without the addition of a counter measure to avoid this, the FBAR system would not be ideal in the field [77].

5.4. Cantilever sensors

A cantilever is a $\leq$1 μm thick silicon strip that is coated on the surface with receptor molecules. One half is fixed to a substrate while the other half is left suspended over a small area (like a diving board), this is where the sensing area is located [78,79]. Fig. 2 from Lang et al. [78] offers a good description and the associated text is also offering good basis to understand functioning. There are two different modes the cantilever can operate in: static (liquids) and dynamic (gas). Depending on the mode selected, the cantilever can detect changes in surface stress and mass respectively [80]. For dynamic mode to work, the cantilever requires a piezoelectric actuator to establish a resonance frequency. When a mass is adsorbed, the resonance frequency will decrease, this can be used for detection. Like most hand-held sensors, cantilevers are small, easy to use and provide fast response times [78].

Limited work has been conducted for cantilevers in response to nerve agents in the gas phase. There have been two studies, the first in 2006 by Zuo et al. using a SiO_2 + Cu^{2+}/11-MUA coating to detect DMMP at 20 ppb between 5 and 10 min [80]. The second in 2022 by Biapo et al. using TiO_2 nanorods but the limited of detection was not efficient for an early warning system being 105000 ppb [81]. Overall, both cantilevers have moderate response times when compared to other sensors discussed in this review. The main benefit of cantilevers is their ability to regenerate but a portable system could still be affected by non-specific binding making the measurement inaccurate. A secondary reference cantilever would have to be included into the system to protect it from interferences and vibrational changes [82]. Furthermore, the LOD for both sensors are above the accepted standard by the EPA.

Table 6
A comparison of semiconductor sensors within the literature from 2009 to 2017.

Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
Lee et al.	SnO_2 Mo5Sb1 Ni_2(I)	100	10	80–100	DMMP	2009	[84]
Tiwari et al.	PPy/CuPc/CTAB/$NaClO_4$	5000	0.08	No recovery	DMMP	2010	[85]
Lee et al.	SnO_2(C)600	20	–	No recovery	DMMP	2011	[86]
Yoo et al.	SWCNT-polyaniline	10000	0.09	0.02	DMMP	2015	[87]
Yoo et al.	nanoparticles + admixture of Al	100	0.03	1.6	DMMP	2015	[88]
Jun et al.	PPy-coated SnO_2	0.05	0.02	0.5	DMMP	2017	[89]

5.5. Semiconductor sensors

The basic principle of a semiconductor is the alteration of the resistive properties of the sensing material in the presence of the target analyte. Several materials have been used as a semiconductor within the scientific literature, largely metal oxides but others include modified carbon nanotubes, zeolite, graphene and conductive polymers [56]. These materials can then be deposited onto chips, making semiconductors: small, energy efficient, robust, and easy to manufacture. This makes semiconductors ideal candidates for portable systems or the use of multiple semiconductors with in a portable system can create an array for the detection of multiple chemicals [49]. Fig. 2 offers a good description and the associated text is also offering good basis to understand functioning. Saruhan et al. [83] offers a good explanation to understand basic functioning in their Fig. 2 and associated text.

There are currently several semiconductors available for the detection of nerve agents in the gas phase, these have been summarised in Table 6. The semiconductor produced by Jun et al. using a polypyrrole coated SnO_2 tube-in-tube structure is the only sensor that meets the EPA Criteria as the limit of detection (LOD) is below the concentration deemed hazardous to health: Sarin 15 ppb [33]. The majority of the remaining sensors could be used to detect lethal concentrations of the G-agents excluding sensors produced by Tiwari et al. and Yoo et al. (single walled carbon nanotubes). In general, the semiconductors listed in Table 6 have fast responses and four out of the six can be reused but are not very selective.

5.6. Chemicapacitor sensors

Instead of monitoring the changes in resistance, chemicapacitors detect change in the dielectric properties of a material [90]. In this case, the sensing material (polymer) acts as the dielectric, when the chemical is adsorbed the capacitance of the sensor will be altered due to a change in permittivity. The change in capacitance will aif in the determination of volatile substances as shown by Blue et al. [91]. Fig. 1 in this paper offers a good indication of the fundamentals of action for this type of sensors. There are two versions, one that involves interdigitated electrodes mounted onto an inert substrate to form two meshed combs [92]; the substrate polymer is then placed on top. The second option involves a parallel plate sensor where the polymer is placed on top of the substrate, with a layer of metal on the top and bottom [91]. The first option is easier to manufacture but requires the need to be heated for reliable sensitivity unlike the parallel plate [92]. Either version, chemicapacitors are small (the size of a c grade battery) and can be used within a portable system [93].

There has been particularly little research conducted for gas sensing of CWAs using chemicapacitors. However, in 2005 Snow et al. produced a chemicapacitor constructed from single-walled carbon nanotube electrodes coated in polycarbosilane, that can detect as low as 0.5 ppb [90]. Concentrations of G-agents at this level are considered by the EPA non-disabling but will cause discomfort [33–35]. Additionally, this sensor is theoretically able to detect concentrations of Vx lower than the concentrations that can cause permanent damage. Overall, having a sensor that can detect as low as 0.5 ppb will decrease the number of causalities with irreversible damage and long-term effects. Furthermore, the response time is moderate being 6 min and 10 s while the sensor has a fast recovery, only taking 4 s [90].

5.7. Field effect transistor

In a field effect transistor (FET), a sensing material (semiconductor channel) is used to connect a source electrode to a drain electrode. Between the two, there is a third electrode known as the 'gate' which regulates the conductivity of the channel [94]. Depending on whether the FET device is positive or negative, the conductance will vary. A decrease is due to a utilisation of electron carriers (positive), whilst an increase is because there has been a build-up of electron carriers (negative). The target analyte will react with the sensing material and alter the specific capacitance, enabling a detection [95]. The mechanism of action has been described in Figure 17.11 of the Fraden's book in sensor technologies [96].

Overall, FET devices are easy to miniaturize (good for portability), has low power consumption and does not require vast amounts of money to manufacture [94]. However, the FET devices currently available for sensing of CWAs in the gas phase summarised in Table 7 are not able to detect concentrations of DMMP at 15 ppb. As a result, the sensors do not meet the EPA requirements and would be deemed unsafe; the majority would be unable to detect lethal concentrations of sarin, soman and Vx being 64 ppb, 49 ppb and 2.7 ppb. The sensor produced by Wu et al., in 2022 using single walled carbon nanotubes would only be useful for the detection of fatal concentrations of Soman [34].

5.8. Colorimetric sensors

In the presence of a target analyte a colorimetric sensor will change colour, providing a visual response to the user [100]. The focus of colourimetry is to remove the need for other instrumentation within a sensor, for example a processing unit. As a result, manufacturing costs are reduced due to the smaller size and sensors are more robust as there are less components to break. Depending on the colorimetric sensor used, the result could be instantaneous [101].

Within the last six years, there has been an increase within the literature of colorimetric sensors being used for the detection of nerve agents in the gas phase, summarised in Table 8. Some studies have gone

Table 7
A comparison of field effect transistor sensors within the literature from 2010 to 2022.

Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
Kong et al.	SWCNT-HFIPP	50	–	–	DMMP	2010	[97]
Yang et al.	SiNW – CPBA	100	<1.67	5	DMMP	2020	[95]
Alzate-Carvajal et al.	Graphene	105	23	–	DMMP	2021	[98]
Wu et al.	HFIPPH – SWCNTs	26.93	5–10	0.92	DMMP	2022	[99]

Table 8
A comparison of colorimetric sensors within the literature from 2017 to 2020.

Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
Aich et al.	Triphenylamine–benzimidazole	2480	1	–	DCP	2017	[103]
Qin et al.	HOFO + PEG membrane	26	5	–	DCP	2019	[100]
Zheng et al.	TAZ-based conjugated polymer (P1)	0.7	Nearly instantaneous	–	DCP	2020	[101]
Oh et al.	Polydiacetylene (PDA)/upconversion nanocrystals (UCNs)	390000	<0.02	–	DMMP	2020	[104]

further to include the use of fluorescence to aid in detection, but this can be hindered by the surrounding environment, photobleaching and fluorescence quenching agents [100,102,103]. Colorimetric sensors have demonstrated to have fast response times but appear to be only one use. The sensors produced by Zheng et al. using a TAZ-based conjugated polymer have proved to be effective with high sensitivity and a nearly instantaneous response for DCP [101].

5.9. Biosensors

Biosensors use a biological component (enzymes, proteins, receptors, antibodies) as a specific recognition site to detect a target analyte. When the two meet, a binding event will occur which can be converted into an electrical signal by the transducer [105]. The signal will be proportional to the binding event and can be used to calculate the concentration of the analyte. However, the correct conditions must be observed for the sensor to be specific to the analyte, due to most of the components being temperature-dependant. Going beyond the ideal laboratory conditions could compromise the sensor, making it less robust and reliable compared to other sensors discussed [106].

There has been limited use of biosensors for the detection of nerve agents in the gas phase. The first biosensor was produced by Arduini et al., in 2007 by immobilizing butyrylcholinesterase [107] and the second by Tang et al., in 2016 creating a QCM biosensor hybrid [108]. The incorporation of biosensors into the design of other sensing technologies helps increase the selectivity of the sensing element [108]. However, neither of the two biosensors listed has a LOD below the EPA standard, Arduini et al. can detect Sarin at 100 ppb while Tang et al. can only detect DMMP at 1971 ppb. As a result, both sensors are impractical for early warning systems, even though Arduini et al. biosensor can produce a response in 30 s.

6. Discussion

Without considering the performance of the different sensors on limit of detection at ppb level, low response time and recovery time, there are other important considerations needed to be considered when studying their use in a portable system or in the field.

Overall, each type of sensor has a list of advantages and disadvantages, if a particular group of sensors share a similar mechanism, it is likely it will suffer with the same problems. For example, sensors that rely on a change in mass will always be affected by non-specific binding, making it an unsuitable candidate as a portable sensor [70,77]. As a result, this type of system must rely on the addition of a specific coating to make the sensing element specific or the introduction of a secondary sensing element to act as a reference [82]. In some cases, this could increase the size and complexity of the sensor, hence price. Moreover, systems like the quartz microbalance can be severely affected by vibrations, which almost immediately rules them out as part of any portable device subjected to movement or heavy use. Both surface acoustic wave (SAW) and Film Bulk Acoustic Resonator Sensors (FBARS) present similar problems in terms of resistance to vibrations and their performance as part of systems on mobile platforms would also be severely affected. This is in general a recurrent problem for those devices relying on piezoelectric systems. The systems may have practical use as sensing elements of fixed detection devices in areas presenting low risk of vibrations.

Furthermore, there are some sensors that can be affected by temperature, making them impractical for field work. For example, Biosensors, use enzymes that can denature due to increase in temperature, this could result in a false result [106], especially when operated in harsh environments. This effect can be reduced or ameliorated by adding a thermostatic layer to the device, but this would increase architecture complexity and power consumption in any portable system. These can be of use in those scenarios where power is not an issue or the external temperature is stable, for example inside buildings.

However, based on the results of this review the use of semiconductor or colourimetric sensors are ideal for mobile portable systems. They can withstand high temperatures and harsh environments while proving an easy way to detect the change, either through the change in resistance or a change in colour respectively [89,101]. There are advantages for semiconductor versus colorimetric sensor, as the former can offer lower limits of detection, being reusable and can be better at compound-selectivity than the later and easy to miniaturize. However, colourimetric sensors also have advantages in terms of simplicity as they may not require energy sources to operate, if based on change of colour of materials change, and can be family specific, which is some environments may be better than those sensors that are compound specific.

Together with the analytical parameters already discussed, the future of gas sensors for the detection of organophosphorus compounds in field applications, either on board of drones or as part of wearable systems imply a robust design. The expectation is that, as technology continues to advance, sensors will become smaller, with lower limits of detection and more cost-effective, enabling their widespread deployment in real-world scenarios. However, given the previous literature assessment there is still much more research needed in this field as only one published sensor [89] presents suitable qualities to qualify for field deployment. In the context of their use on board of drones, gas sensors integrated into their systems would allow for rapid and remote monitoring of large areas, especially in situations involving chemical attacks, spills, industrial accidents, or even potential terrorist threats. These will become a part of a network of sensors that will enable the detection of low concentrations of organophosphorus compounds, enhancing the early warning capabilities.

For these sensors to be integrated into protective gear they need to be small, rough, using little or no power and they need to provide continuous monitoring of the surrounding air for toxic substances with fast response rates and short recovery times.

In both scenarios, sensors need to be able to be integrated in a network and signals shared enabling real-time analysis. The information collected through these sensor networks could help in the understanding of the chemical dispersion of the chemical in the clouds and to predict their dispersion patterns with coupled with weather information.

The above reflection is only a mirror of the general needs for small but powerful sensors able to detect molecules in the mid-range molecular weight with higher selectivity and lower detection limits. Gas analysis for these are usually performed off-line using powerful (bulky) benchtop instruments. There is a general lack of these type of small detectors for the identification of molecules in the gas phase able to be

Table 9
A comparison of optimum sensors from different sensing technologies within the review.

Technology	Author(s)	Coating Material	Limit of detection (ppb)	Response Time (mins)	Recovery Time (Mins)	Analyte	Year	Ref
SAW	Pan et al.	Viscoelastic fluoroalcoholpolysiloxane	1.21	1.67	–	DMMP	2022	[67]
QCM	Alev et al.	Tungsten disulfide	5	370	–	DMMP	2022	[69]
Semiconductor	Jun et al.	PPy-coated SnO_2	0.05	0.02	0.5	DMMP	2017	[89]
Chemicapacitor	Snow et al.	SWCNT coated polycarbosilane	0.5	6.17	0.07	DMMP	2005	[90]
Colorimetric	Zheng et al.	TAZ-based conjugated polymer (P1)	0.7	Nearly instantaneous	–	DCP	2020	[101]

fitted in mobile platforms (i.e. drones) and wearables. Whereas there is a good range for small molecules, this is not the case for those presenting a higher level of complexity.

7. Conclusions

Laboratory based instruments are well established and prove to be effective at detecting nerve agents and associated simulants. Chromatography and mass spectrometry systems (GC-MS and LC-MS) are highly sensitive and able to detect very small concentrations of the target analyte. Modern laboratory-based instruments are becoming more acceptable and being installed in mobile laboratories for in-situ analysis. However, a trained operator is required to interpret the data and this process can be time consuming. Early warning system require detection to be within 10 min based on EPA minimal risk levels. Despite the advantages laboratory instruments provide, alternative sensing technologies remain an appropriate choice for first response.

Hand-held sensors are normally cheap, small and require less energy than laboratory-based instruments. This review has discussed a variety of hand-held sensors with different sensing mechanisms available for the detection of nerve agents. Furthermore, sensors do not require physical samples for detection and in theory can provide a rapid response. There are multiple factors used for comparison of sensors, in particular the limit of detection (LOD) and how it compares to minimal risk level of each of the nerve agents. If the LOD is above the MRL the sensor is impractical and not effective for early response. The optimum sensor for each sensing technology that meet EPA requirements discussed in this review has been compiled in Table 9.

There are 5 optimum sensors that meet the EPA standard for the detection of sarin at 15 ppb [33,50]. However, there is only one sensor that can detect OPs at concentrations that would only cause discomfort to humans, this being the semiconductor by Jun et al. On paper this sensor proves to be effective at detecting DMMP in a short amount time with the ability to be used again shortly after use due to its recovery time. Although this sensor has good results and provides a benchmark for other sensor development, the data published is only theoretical and lack real-world scenarios.

Future work should be focused on gaining data on real world scenarios and having sensors that are selective for the analyte of interest. This could be potentially achieving by using a molecular imprinted polymer (MIP) as the sensing material. A MIP is a synthetic analogue that mimic the "lock and key" mechanism found in biological enzymes or antibody–antigen complexes [109,110] without the disadvantages of biosensors.

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.

Data availability

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

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