OPEN

Exposure to organophosphorus compounds: best practice in managing timely, effective emergency responses

Frédéric Dorandeu, Christopher Singer, Steven Chatfield, Robert P. Chilcott and Jonathan Hall

Increasing indications, reports and studies demonstrate that threats from the deliberate use of chemical weapons remain high and are evolving. One of the deadliest classes of chemical weapons are the organophosphorus nerve agents. It is now clear that both state and non-state actors have the ability to deploy and use these types of weapons against individuals and the wider civilian population posing a real and significant threat. The objective of this article is to provide an overview of the issues impacting on a timely critical response to the accidental or deliberate release of Organophosphorus Nerve Agents in order to enhance the understanding of their effects and provide guidance on how first responders might better treat themselves or victims of exposure through a discussion of available evidence and best practices for rapid skin decontamination. The article also examines use of the current nomenclature of 'wet' and 'dry' to describe different forms of decontamination. One of the key conclusions of this article is that adequate preparedness is essential to ensuring that responders are trained to understand the threat posed by Organophosphorus Nerve Agents as well as how to approach a contaminated environment. A key aspect to achieving this will be to ensure that generic medical countermeasures are forward-deployed and available, preferably within minutes of a contamination and that first responders know how to use them. *European Journal of Emergency Medicine* 30: 402–407 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

European Journal of Emergency Medicine 2023, **30**:402–407

Keywords: CBRN, decontamination, emergency responders, medical countermeasures, nerve agents, organophosphorus compounds

Correspondence to Jonathan Hall, PGDip Exec Leadership, Resilience Advisors Network, Dartmouth TQ6 9HA, UK
Tel: +44 (0)1905 700123; e-mail: jon.hall@resilienceadvisors.eu

Received 15 December 2022 **Accepted** 6 June 2023.

Background: The need for special consideration of organophosphorus nerve agent

In its June 2022 Chemical, Biological, Radiological, Nuclear (CBRN) defence policy, the North Atlantic Treaty Organisation (NATO) identifies that non-state actors 'believe that a Weapons of Mass Destruction or deliberate use of CBRN materials has the potential to sow panic and strain national response capabilities' [1]. It concludes that the risk of use or proliferation by non-state actors is likely to continue to grow. The same document identifies that NATO faces a 'widening spectrum of chemical threats, ranging from traditionally understood chemicals to Novichoks and pharmaceutical based agents (PBAs) that challenge detection, response and protection'.

We have seen Venomous agent X (VX) used by state and non-state actors (for instance in the 2017 assassination of Kim Jong-Nam) and Sarin used extensively in the Syria conflict between 2013 and 2019. Use is not confined to the G and V series agents, with fourth-generation agents (the Novichoks) being encountered in 2018 (Salisbury and Amesbury, UK) and 2020 (Siberia).

From those examples, fourth-generation agents appear well suited for targeted use against individuals, being hard to detect, extremely potent and highly persistent (hence the importance of skin decontamination). The method of deployment has seen techniques that ensure skin absorption which then necessitates decontamination in addition to medical interventions to save life. Additionally, the Salisbury incident, where an Organophosphorus Nerve Agent was used, showed that responders may be affected even while wearing basic personal protective equipment (PPE), further demonstrating the need for specific guidance covering the management and examination of scenes and the handling and treatment of casualties. Given the extreme toxicity and physicochemical properties of Organophosphorus Nerve Agent, the suitability of current standard PPE (e.g. nitrile gloves) is a significant issue as is the fact that response times to decontaminate and treat victims who have received gross levels of exposure are likely to exceed the window of opportunity to provide effective decontamination and treatment.

What are organophosphorus nerve agents and how do they work?

Organophosphorus Nerve Agents are irreversible inhibitors of both central and peripheral cholinesterase's (ChE), enzymes that degrade the neurotransmitter acetylcholine (ACh) after its release in the synaptic cleft [2]. Poisoning

results from ACh accumulation and subsequent uncontrolled activation of cholinergic synapses. ACh interacts with two main types of receptors: muscarinic (M) and nicotinic (N). Stimulation of M-type receptors will typically induce increased secretions, smooth muscle contraction and a bradycardic effect on the heart muscle. Nicotinic effects include contraction of skeletal muscles. Stimulation of the respiratory muscles will first induce contraction then paralysis. Nicotinic effects in ganglionic synapses also explain some of the organophosphorus symptomatology such as increased heart rate. Central Nervous System effects include seizures, which may lead to long-term neurological sequelae. Death is usually caused by mixed central and peripheral respiratory distress.

When vapours are used, such as with the more volatile 'G agent' (a range of organophosphate nerve agents including; tabun, sarin, soman and cyclosarin), the first contact will be with the eyes (inducing miosis), nose and upper respiratory tract secretions. If the organophosphorus penetrate the bloodstream (high dose of vaporised agent, liquid agent penetrating the skin), then other signs and symptoms may occur such as transient mydriasis. After skin contact, systemic absorption may be slow and so the onset of effects may be considerably delayed.

Given this differential, it is worth reviewing the basic structure and function of human skin and hair and how Organophosphorus Nerve Agents affect them.

The barrier function of skin is predominantly due to the outermost '*stratum corneum*' [3]. This thin (10–20 μm) layer is essentially a mixture of lipids and proteins and may be coated with a thin film of oil (sebum). This biochemical composition provides a formidable barrier to hydrophilic (water soluble) substances. However, chemicals which are lipophilic (fat soluble) may preferentially partition into the *stratum corneum*. The rate and extent to which lipophilic chemicals (such as Organophosphorus Nerve Agent) partition into the skin is a factor which will affect decontamination performance: extensive partitioning will reduce the amount of chemical available on the skin surface which, in turn, will reduce the efficacy of decontamination [4]. Furthermore, partitioning of a chemical into the skin may create a 'reservoir' of several mg of chemical per cm^2 of skin. In the case of certain Organophosphorus Nerve Agents, this may represent a supra-lethal dose which, being protected within the lipid-rich environment of the *stratum corneum*, is not readily amenable to conventional forms of decontamination.

Depending on the physicochemical properties of the contaminant, it may either remain within the *stratum corneum* (where it will gradually be lost to the environment through evaporation or the natural process of desquamation) or diffuse into the lower layers of the skin with subsequent systemic absorption. This is often a slow process and explains why percutaneous exposure to low-volatility nerve agents such as VX and Novichoks can take some time before signs and symptoms of toxicity become evident. At least 15 factors influence the ability of compounds to penetrate the skin [5]. One important parameter is also the surface tension or how the droplet of agent will behave on the surface of the skin [6]. Organophosphorus could either quickly spread on the surface or stay as a droplet for a long time. This has an impact on the amount of agent that can be displaced from the skin surface.

This basic introduction to the structure of skin explains why water, as a method of decontamination, is a potentially dangerous practice: wetting skin contaminated with Organophosphorus Nerve Agent can encourage partitioning of the contaminant into the *stratum corneum* rather than dissolution into the water although washing with water can still have a beneficial effect with some agents. Contemporary (evidence-based) guidance recommends avoiding any form of water-based decontamination [7]. The enhanced skin absorption of lipophilic chemicals in the presence of water is driven by simple thermodynamics and is known as the 'rinse-in' or 'wash-in' effect [4]. The efficacy of soap and water for decontamination is thus still a matter of debate [8]. It also depends heavily on the water solubility of the Organophosphorus Nerve Agent, as different agents have very different degrees of solubility.

Human hair is very similar to skin in that the outer layers are also highly lipophilic. It has been demonstrated that this can allow both extremely rapid and extensive partitioning of chemicals, resulting in all conventional forms of decontamination being completely ineffective within minutes of exposure [9]. For this reason, removal (clipping or cutting) of heavily contaminated hair may be the only safe option for casualties, although further research is required [10]. This guidance may well be relevant for animals in the event of contamination but is beyond the scope of this article.

How to recognise organophosphorus compound poisoning and Initial responses to chemical incidents

The organophosphorus toxidrome needs to be understood by responders in order to recognise organophosphorus poisoning and to differentiate it from opioid poisoning which induces similar signs and symptoms except for increased secretions [11].

Given the relative infrequency of incidents involving deliberate, large-scale release of organophosphorus chemicals on civilian populations, a bespoke response focussed on Organophosphorus Nerve Agents is not a realistic option. As a result, civilian and military responders tend to utilise a generic, 'all hazards' emergency response that can promote survivability of Organophosphorus Nerve Agent exposure prior to the

deployment of specialist Hazardous Materials (HazMat) or CBRN resources.

The primary aim when mounting an initial response to casualties contaminated with Organophosphorus Nerve Agents is damage limitation through potentially life-saving procedures of evacuation, disrobing and emergency decontamination [10]. Actions after the initial response are commonly undertaken by specialist resources that are unlikely to be readily available during the earliest stages of a CBRN incident.

While basic, the three procedures in the initial response will undoubtedly improve clinical outcomes for exposed individuals when compared to the historical approach of standing off to await deployment of specialist resources. The rationale for evacuation is self-evident, while the need to remove clothing should be considered on a case-by-case basis. It should be noted that more advanced decontamination is not an automatic follow-on to the initial response, and the actual need for decontamination must be taken into consideration at an early stage.

Historically, decontamination has largely been based on cleansing with water. However, work over the last two decades has provided a large body of scientific evidence upon which more effective decontamination strategies and protocols have been developed. Aside from social, religious and privacy issues, water decontamination carries a risk of hypothermia and has deleterious effects on trauma patients with acute haemorrhage, which could occur with a chemically loaded improvised explosive device.

There are variations within and between countries regarding how disrobe and decontamination are performed. However, no country appears to have a CBRN-specific rapid response that operates independently of a standard Hazardous Material response for mass casualty incidents (with the possible exception of pre-deployment in response to intelligence or planned, large-scale public events). Where available, CBRN-specific resources are an addition to a HazMat response that form part of the secondary response, for example, the strategic stockpiling of specific antidotes and medical equipment (such as multiple patient oxygen delivery systems or intraosseous kits for rapid delivery of antidotes).

Types and levels of decontamination: emergency decontamination – wet or dry

It is important to understand that the aims of initial and specialist decontamination are different, although disrobe is a critical prerequisite for both and always a sound procedure. When performed as part of the initial response, removing chemical contaminants from the body can be considered 'emergency decontamination' and akin to first aid, with the aim to prevent further penetration of the agent and mitigate the lethal effects, achieving the best result in the fastest time possible with limited or no resources.

Emergency decontamination is critical to the well-being of contaminated casualties since decontamination effectiveness decreases rapidly with time [10]. Responders should be aware that emergency decontamination is a potentially life-saving intervention that must be performed as soon as possible. In contrast, specialist decontamination would ensure that all casualties are as clean as practically possible before leaving the warm zone of an incident. Its primary purpose is to prevent the spread of secondary contamination to equipment and the potential intoxication of care providers.

Current practice often suggests that one of two approaches can be taken: 'dry' or 'wet'. The risks associated with both 'wet' and 'dry' decontamination are clearly evidenced within this article. However, there is an additional limitation imposed by this overly-simple nomenclature in that other forms of decontamination do not fall readily into either category, while their utilisation arguably has the potential to offset the risks associated with both aqueous (wet, water-based) and non-aqueous (dry) decontamination. There is a potential 'third way' to decontaminate, involving the non-specialist use of proprietary products, subject to their immediate availability.

Dry decontamination has traditionally referred to the use of adsorbent or absorbent material, such as fuller's earth, article towels, incontinence pads or wound dressings. For the reasons outlined above, it is considered that the understanding of the responder community may be better served by this being described as 'non-aqueous' so as not to preclude consideration of further options.

Wet decontamination traditionally refers to the application of water, which clearly requires access to a source of water. Again, it is considered that the understanding of the responder community may be better served by this being described as 'aqueous' so as not to exclude alternative products.

Alternative products such as Reactive Skin Decontamination Lotion are also available for use on skin for select chemical warfare agents such as Organophosphorus Nerve Agent and related compounds. These are not aqueous, neither are they dry; which is why a shift in nomenclature ('aqueous' vs. 'non-aqueous') is to be encouraged.

Decisions on which form of decontamination is appropriate depends on the contaminant. The default option is non-aqueous decontamination [7,10]. However, if the contaminant is clearly caustic or in powder form, water should be the decontaminant of choice. It is also paramount to keep in mind that Organophosphorus Nerve Agents will not be neturalised by non-aqueous decontamination systems. For extremely toxic compounds in powder form (e.g. VX embedded in an inert

powder used for decontamination), dry decontamination may disseminate particles and potentially pose a risk to casualties and responders. It is also important to keep in mind that Organophosphorus Nerve Agent nerve agents will not be neutralised by aqueous or non-aqueous decontamination systems (such as adsorbents) unless neutralising agents are included in the formulation of the product.

Types and levels of decontamination: specialist decontamination

Specialist decontamination is also referred to as 'technical decontamination', 'thorough decontamination', 'secondary decontamination', 'clinical decontamination' or 'medical decontamination'. Specialist decontamination requires transportable units which usually combine approaches (complete disrobing, aqueous and non-aqueous decontamination). These resources may take some time to become operational, reinforcing the criticality of performing initial phase emergency decontamination. They require significant numbers of personnel and cannot quickly decontaminate large numbers of casualties, especially non-ambulant individuals. The units also risk accumulation of toxic vapours, which can be mitigated by emergency decontamination and initial disrobing before entering the decontamination chain [10]. Owing to the relatively slow process, triage may be necessary to manage a large number of casualties. Decontaminating environments are a significant consideration for both incident recovery and immediate management of patients in clinical settings, and presents their own challenges that are outwith the scope of this article.

Current organophosphorus response – the first point of care

The very first point of care in any incident is likely to be provided by emergency responders at the scene. Levels of medical training, equipment and life-saving interventional skills will vary among first responders, so we must assume that the very first on scene may possess only basic knowledge, equipment and skills. Guidance for this cohort is essential in order to allow them to:

(1) Identify the potential for a CBRN-related incident using for instance the step 1-2-3 PLUS approach [12]
(2) Maximise the safety of the public by containing further contamination, for example, by limiting egress of ambulatory casualties from the incident scene and by cordoning the area.
(3) Provide basic immediate care to victims – the casualties should be instructed to evacuate to a place of safety away from the source of danger, to disrobe and conduct emergency decontamination.

In identified or suspected cases of Organophosphorus Nerve Agent poisoning, the first point of medical care will need to:

(1) Don PPE that is appropriate for an Organophosphorus Nerve Agent incident.
(2) Conduct triage and decontaminate.
(3) Stabilise the patient (airway, breathing using high flow oxygen or ventilate if needed, control haemorrhage, set up IV access).
(4) Take samples for substance identification, deploy medical counter measures, re-assess [13].

Given the mechanism of action and effects of organophosphorus, there is a globally established antidote protocol based on the rapid administration of a 'triple therapy' of antimuscarinic (e.g. atropine sulphate), oxime (reactivating the inhibited Cholinesterase Enzymes) and anticonvulsant drugs to quickly abate the seizures that some agents will rapidly induce. This triple therapy can either be delivered separately or in combination with autoinjectors such as the French Ineurope [14].

A standard and widely available antimuscarinic drug is atropine sulphate, which provides a generic antidote to all organophosphorus by reducing the effect of excess ACh (resulting from inhibition of acetylcholinesterase; AChE). The main clinical effect of antimuscarinic drugs is to reverse bradycardia, bronchospasm and bronchorrhea. They have no effects on the nicotinic symptoms that can only be alleviated through reactivation of the enzyme AChE.

Oximes are a class of drugs that may reverse organophosphorus-induced AChE inhibition which primarily occurs through formation of a phosphylated complex at the active site of the enzyme [15]. This complex may subsequently undergo spontaneous reactions (e.g. dealkylation of the Organophosphorus Nerve Agent) in a process known as ageing [16], resulting in a more stable complex that will render oxime therapy futile.

Owing to the absence of a reactivator efficient on all the agents, many countries have historically adopted the approach of fielding a single drug as a generic countermeasure despite known limitations.

Anticonvulsants (e.g. benzodiazepine like diazepam or midazolam) can minimise seizure-related neuropathology (associated with seizures and status epilepticus) in the Central Nervous System following organophosphorus exposure. The ability to induce seizures depends on the agent and the route of penetration. The longer the seizures the higher the probability of brain damage, hence the choice made by some countries like France to add an anticonvulsant in the same autoinjector whereas others choose to have separate autoinjectors.

While administration of atropine, oxime and a benzodiazepine is generally accepted as a standard therapy for Organophosphorus Nerve Agent intoxication, the availability of each drug and its form may be a limiting factor outside a hospital environment or prior to mobilisation

of national stockpiles. Therefore, there is considerable variation within and between countries in terms of which drugs may be rapidly available at the scene of an incident, as well as the point at which antidotes should be administered (i.e. hot, warm and cold incident zones), as well as the routes of administration (oral, intramuscular, intravenous or intraosseous). For example, the UK has specialist teams (Hazardous Area Response Teams and Special Operations Response Teams) that can administer antidotes within the hot and warm zones of an incident. In other countries, evacuation of casualties from the hot to the warm zone is required prior to triage and treatment of casualties. The absence of advanced medical treatment within a CBRN hot zone is a widely acknowledged problem described as a 'therapeutic vacuum' [17].

Other considerations

It is conceivable that explosives may be used to disseminate CBRN material. Under such a scenario, traumatic injuries may occur simultaneously to chemical exposure, resulting in contaminated wounds. In the case of extremely toxic compounds such as Organophosphorus Nerve Agents, trauma casualties may be at high risk of death. The issue of wound contamination and decontamination is thus very theoretical [18,19].

Historically, weak bleach (hypochlorite) solutions (ca. 0.5%) have been advocated for use. However, this practice is not supported as the tolerable concentration of bleach is generally insufficient for the timely neutralisation of chemical contaminants and may itself result in toxicity. Current evidence suggests that powder-based, absorptive haemostatic products are effective skin and wound decontamination products for chemical warfare agents [18,19], although the specialist nature of such products would likely preclude their availability at the scene of a civilian CBRN incident. Some recent studies have shown that products like Woundstat might be interesting, but the protocol used is not directly applicable to field situations except when wound contamination takes place while managing a casualty and when action can be taken immediately.

Scalp hair may be disproportionately contaminated following overhead delivery of a liquid contaminant. While hair provides a substantial degree of protection for underlying scalp skin, lipophilic contaminants can rapidly partition into it, rendering decontamination ineffective within minutes of exposure and so current US guidance [10] recommends hair removal if

(1) contamination is known to have occurred;
(2) the contaminant is known to be toxic; and
(3) residual contamination has been confirmed.

This guidance may well be relevant for animals in the event of contamination but is beyond the scope of this article.

Limitations and conclusion

The article does not speak in detail about the medical management of those contaminated by organophosphorus nor does it address mass or public casualty issues. It relates primarily to actions by first responders at the scene of an incident.

Rather, the article provides a consolidated source of information for front-line emergency responders so that they are better prepared to respond to and manage incidents involving contamination with organophosphorus (Organophosphorus Nerve Agent Pesticide). It addresses the compounded effect of critical factors: environment, equipment, agent/biochemical effects, recognition of toxidrome, panic and stress, and why guidelines and protection for front-line responders need to be simple and clear. In this respect, mnemonics are useful [20].

It introduces a question regarding the appropriateness of current nomenclature for decontamination and whether this might be inhibiting consideration of alternative processes while highlighting the need to ensure that adequate stockpiles of medical countermeasures are available for rapid deployment when required.

Acknowledgements

The article has been produced by the Resilience Advisors Network with a financial contribution from Emergent BioSolutions. Expert contributions have been collated from independent authors.

Disclaimers: The article is an independent review of current knowledge and thinking by the authors. There has been no editorial contribution from either organising or financing organisations.

Conflicts of interest

There are no conflicts of interest.

References

1 NATO. NATO's Chemical, Biological, Radiological and Nuclear (CBRN) Defence Policy 2022. https://www.nato.int/cps/en/natohq/official_texts_197768.htm. [Accessed 1 May 2023]
2 Reymond C, Jaffre N, Taudon N, Menneteau M, Chaussard H, Denis J, *et al.* Superior efficacy of HI-6 dimethanesulfonate over pralidoxime methylsulfate against Russian VX poisoning in cynomolgus monkeys (Macaca fascicularis). *Toxicology* 2018; **410**:96–105.
3 Brain KR and Chilcott RP. Physicochemical factors influencing skin absorption. In: Chilcott RP and Price S, editor. *Principles and practice of skin toxicology*. Chapter 6 ed. John Wiley & Sons; 2008.
4 Chilcott RP. Dermal aspects of chemical warfare agents. In: Marrs TC, Maynard RL, Sidell FR, editor. *Chemical warfare agents*. Second ed. John Wiley & Sons; 2007.
5 Li BS, Cary JH, Maibach HI. Should we instruct patients to rub topical agents into skin? The evidence. *J Dermatolog Treat* 2019; **30**:328–332.
6 Gorzkowska-Sobas A. Chemical warfare agents and their interactions with solid surfaces. Norwegian Defence Research Establishment (FFI), 2013 Contract No.: FFI-rapport 2013/00574. https://www.ffi.no/en/publications-archive/chemical-warfare-agents-and-their-interactions-with-solid-surfaces. [Accessed 1 June 2023]
7 Chilcott RP, Larner J, Matar H. UK's initial operational response and specialist operational response to CBRN and HazMat incidents: a primer on decontamination protocols for healthcare professionals. *Emerg Med J* 2019; **36**:117–123.

8 Kashetsky N, Law RM, Maibach HI. Efficacy of water skin decontamination in vivo in humans: A systematic review. *J Appl Toxicol* 2022; **42**:346–359.
9 Matar H, Pinhal A, Amer N, Barrett M, Thomas E, Hughes P, *et al*. Decontamination and management of contaminated hair following a CBRN incident. *Toxicol Sci* 2019; **171**:269–279.
10 Chilcott RP, Larner J, Matar H, editors. Primary response incident scene management: PRISM guidance, volumes 1-3, second edition, office of the assistant secretary for preparedness and response, biomedical advanced research and development authority. 2018. https://www.medicalcountermeasures.gov/barda/cbrn/prism/. [Accessed 2 January 2023].
11 Eddleston M, Chowdhury FR. Organophosphorus poisoning: the wet opioid toxidrome. *Lancet* 2021; **397**:175–177.
12 Home Office (July 2015) initial operational response to a CBRN incident. https://www.jesip.org.uk/uploads/media/pdf/CBRN%20JOPs/IOR_Guidance_V2_July_2015.pdf. [Accessed 1 June 2023].
13 Gent N, Milton R, editors. *CBRN incidents: clinical management & health protection*. 2nd ed. Public Health England; 2018.
14 Rousseau JM, Besse Bardot I, Franck L, Libert N, Lallement G, Clair P. [Interest of Ineurope syringe for nerve agent intoxication]. *Ann Fr Anesth Reanim* 2009; **28**:482–488.
15 Masson P, Nachon F. Cholinesterase reactivators and bioscavengers for pre- and post-exposure treatments of organophosphorus poisoning. *J Neurochem* 2017; **142**:26–40.
16 Masson P, Nachon F, Lockridge O. Structural approach to the aging of phosphylated cholinesterases. *Chem Biol Interact* 2010; **187**:157–162.
17 Bourassa S, Paquette-Raynard E, Noebert D, Dauphin M, Akinola PS, Marseilles J, *et al*. Gaps in prehospital care for patients exposed to a chemical attack - a systematic review. *Prehosp Disaster Med* 2022; **37**:1–10.
18 Dalton C, Hall C, Lydon H, Jenner J, Chipman JK, Graham JS, *et al*. The percutaneous absorption of soman in a damaged skin porcine model and the evaluation of WoundStat as a topical decontaminant. *Cutan Ocul Toxicol* 2018; **37**:172–179.
19 Lydon H, Hall C, Matar H, Dalton C, Chipman JK, Graham JS, *et al*. The percutaneous toxicokinetics of VX in a damaged skin porcine model and the evaluation of WoundStat as a topical decontaminant. *J Appl Toxicol* 2018; **38**:318–328.
20 Giaume L, Daniel Y, Calamai F, Derkenne C, Kedzierewicz R, Demeny A, *et al*. 'I AM THOR/DUST DAHO': mnemonic devices used by the Paris Fire Brigade to teach initial measures in undertaking a CBRN event. *Crit Care* 2021; **25**:116.