



# Workshop on Chemical Warfare Agents: Toxicity, Emergency Response and Medical Countermeasures

26 - 27 September 2016 , Paris, France

Dr Zrinka Kovarik, member of the SAB  
Institute for Medical Research and Occupational Health, Zagreb, Croatia





# Workshop on Chemical Warfare Agents: Toxicity, Emergency Response and Medical Countermeasures

26 - 27 September 2016 , Paris, France

**Topic 1. Chemical weapon toxicity and mechanisms of action**

**Topic 2. Emergency response to a chemical terrorist attack**

**Topic 3. Medical countermeasures and decontamination against CWA**



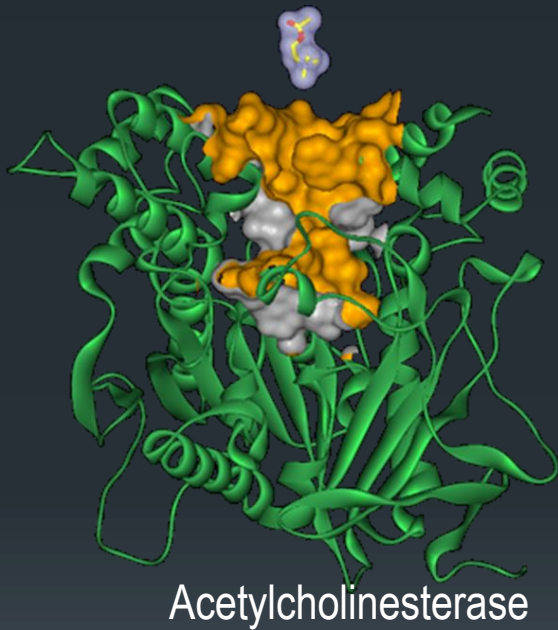
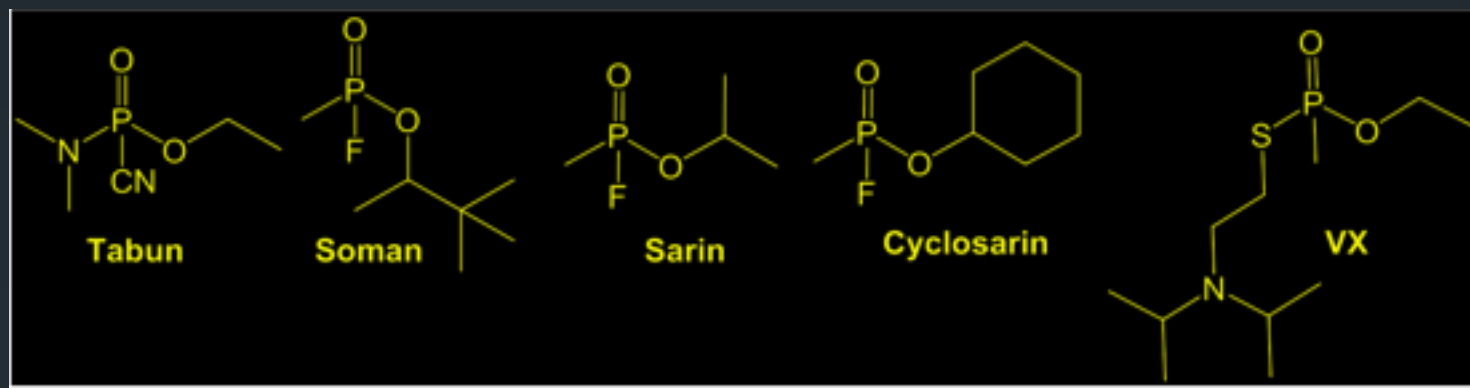


OPCW

## **Topic 1. Chemical weapon toxicity and mechanisms of action**

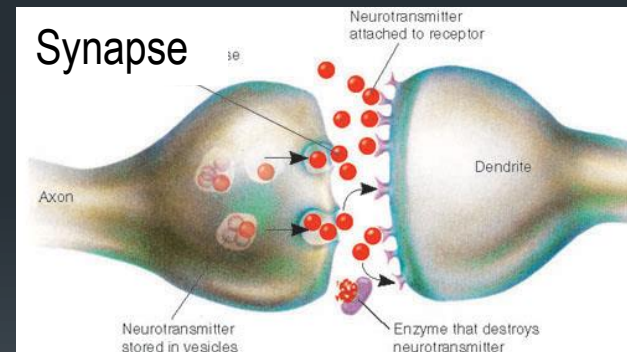
- (a) Toxicity of nerve agents
- (b) Toxicity of vesicants
- (c) Long-term health effects of nerve agents and vesicants
- (d) Human toxicological values of chemical warfare agent

# Toxicity of NA



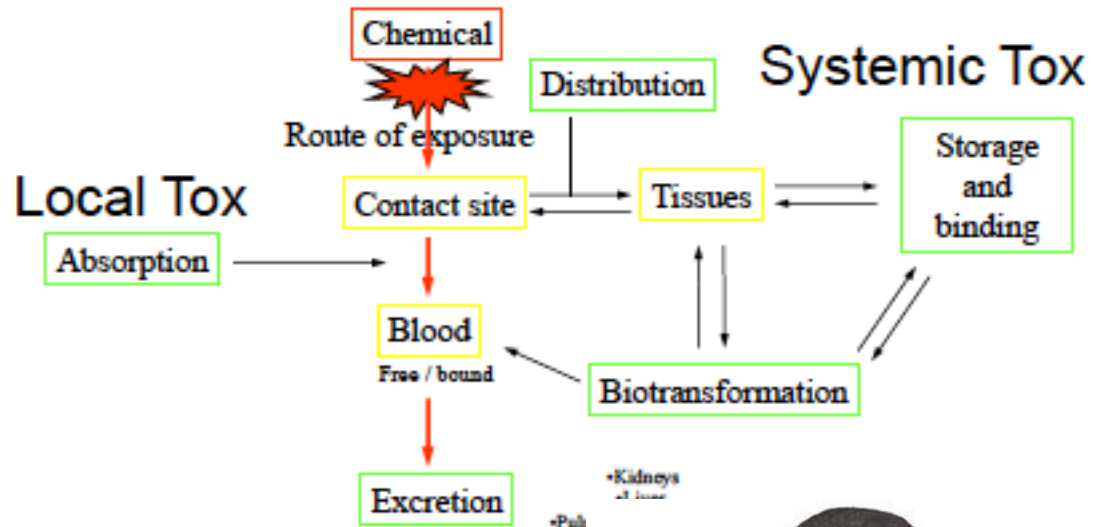
The inhibition leads to an accumulation of acetylcholine in the synaptic cleft and prolonged stimulation of muscarinic and nicotinic receptors. This stimulation triggers toxicity symptoms such as widespread hypersecretions, bronchoconstriction, miosis, cardiovascular changes and convulsive seizures.

Their main mechanism of toxicity is inhibition of acetylcholinesterase - enzyme that degrades the neurotransmitter acetylcholine.



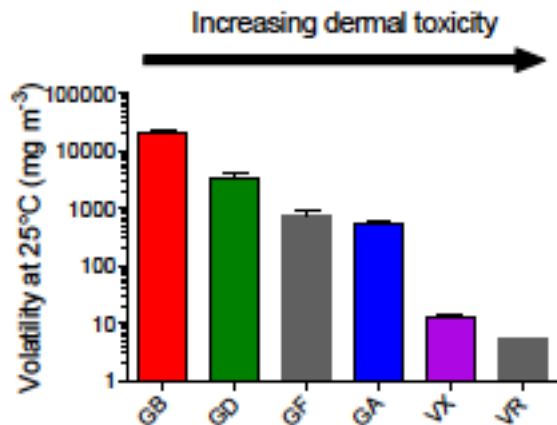
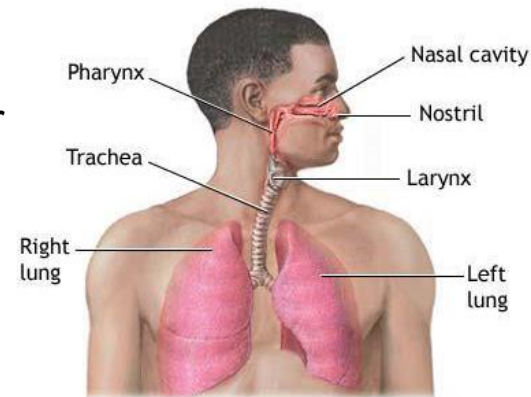
Respiratory effects can arise from a combination of peripheral changes (e.g. bronchoconstriction and airway over-secretion, diaphragm paralysis) or central effects (alteration of the respiratory drive) and can lead to death.

The toxicity mechanism of NA depends on the route of exposure and toxicokinetics of the agent



NAs (like sarin, tabun) can be dispersed in the form of liquid aerosols or vapours that will penetrate unprotected respiratory tract or mucosa.

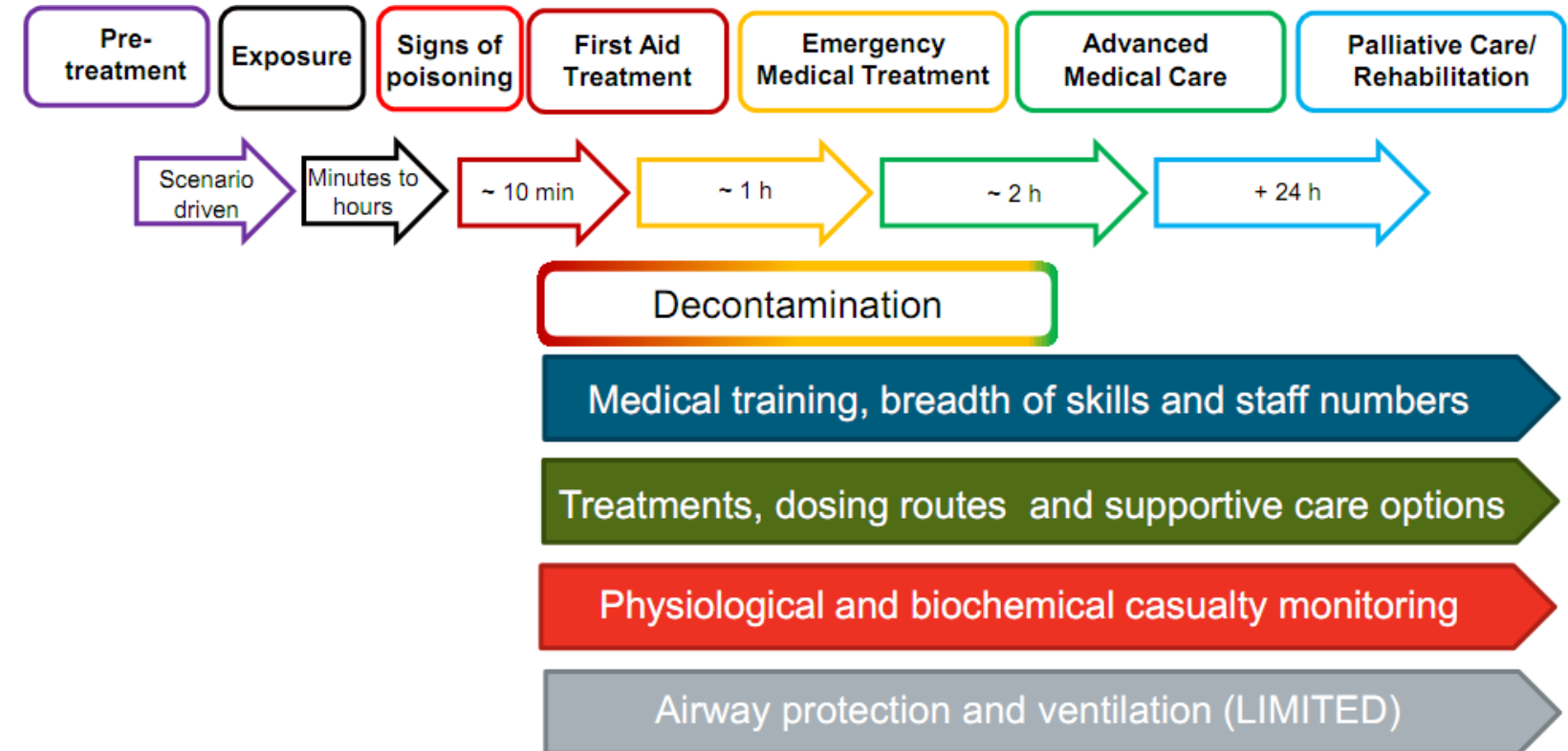
Inhalation is the fastest way into blood and tissue distribution.



Low volatility, persistent NAs, like VX, can readily penetrate the skin. This route of poisoning is particularly difficult to treat because it results in a slower onset of poisoning and an extended exposure to the toxic agent.

# Countermeasures of NA poisoning

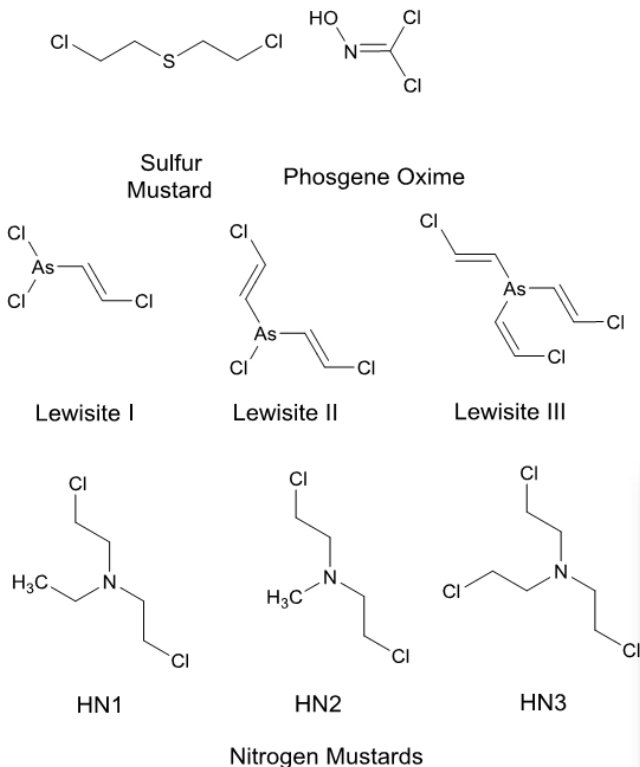
- should be treated as a continuum: there is a need to recognise appropriate measures across the timelines of exposure and treatment.
- Controlling contamination is critical in casualty care.



# Acute toxicity mechanisms of vesicants

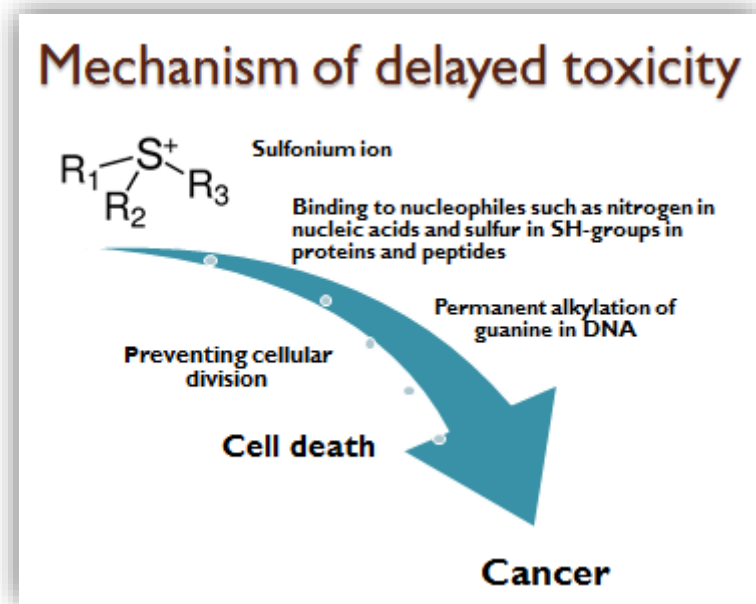
## Vesicants

- Sulfur Mustard
- Nitrogen mustards
- Lewisite
- Phosgene oxime



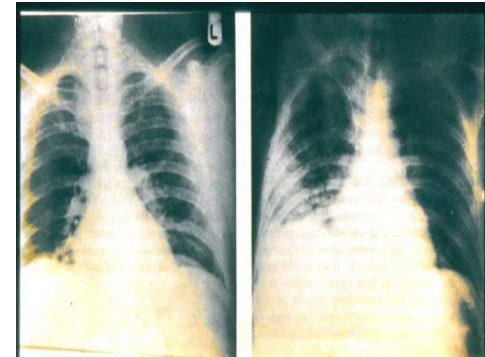
The massive inflammatory reaction that characterises poisoning by vesicants in general, and SM in particular, is followed by destruction of the affected tissue and further inflammation during the healing process.

➤ There is a continuing need to identify early biochemical events to better understand the mechanisms that lead to vesicant injury. In this regard OMICS technologies and *in vitro* assays have shown great promise.



## Organs usually affected after SM exposure

- Respiratory system
- Reproductive system
- Nervous system
- Skin
- Eye
- Blood
- Gastrointestinal
- Immune system





# Long-term health effect of nerve agents and vesicants

Late complications:

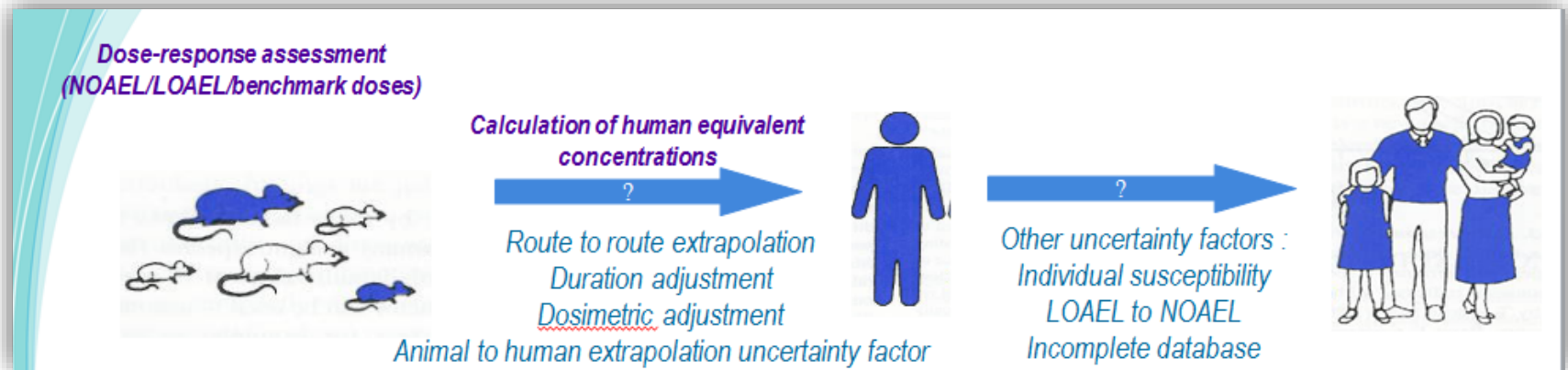
- **respiratory tract** (78%) - dispnea, hemoptysis, pulmonary fibrosis, lung carcinoma, pneumonia, bronchial and tracheal stenosis, emphysema, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, etc.
- **nervous system** (45%) – PTSD, chronic depression, loss of libido, anxiety...
- **skin** (41%) – dry skin, burning sensation, pruritus, atrophy, hypo- and hyperpigmentation, scarring...
- **eyes** (36%) - burning sensation, itching, blurred vision, vision loss, retina ulcer, corneal thinning and opacity, keratitis, uveitis, conjunctivitis...

**Reproductive system** - Inhibition of spermatogenesis, sexual dysfunction...

**Genotoxicity** - sister chromatid exchanges in the peripheral lymphocytes, varieties in enzymes involved in epigenetic changes

**Carcinogenicity** - lungs, larynx

# Human toxicological values of CWA: current knowledge and prospects



- ✓ Actionable information requires that both *in vitro* and *in vivo* toxicological data be extrapolated to humans for assessing timely health impacts.
- ✓ While reference values for making decisions are available, given the complexity of toxicity mechanisms, risk assessments have high degrees of uncertainties.
- ✓ The best suited emergency response strategies will be situation dependent.

## **Topic 2. Emergency response to a chemical terrorist attack**

The concept of emergency response to a chemical incident

Biological markers of exposure to chemical warfare agents

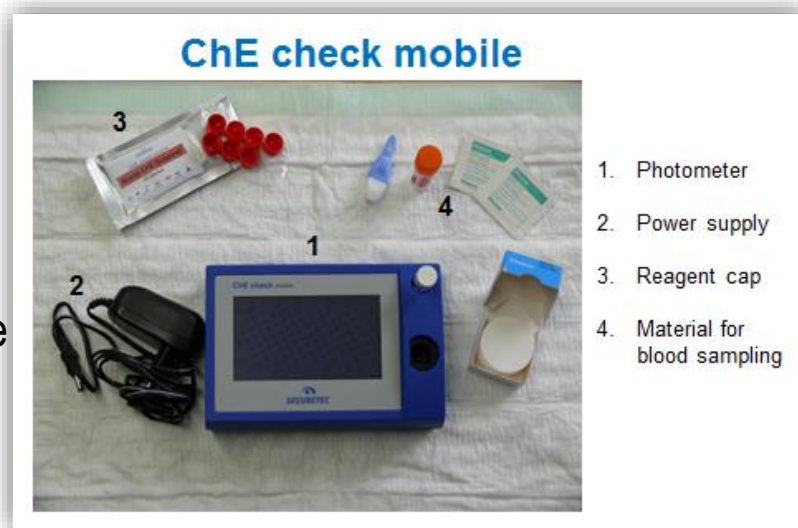
Clinical detection of nerve agent exposure

Clinical detection of vesicants exposure

Field detection of chemical warfare agents

# Biological markers of exposure to chemical warfare agents

- ✓ On-site laboratory analysis is important for confirmation of clinical diagnosis and as an early indicator in case of low-level exposure or delayed onset of signs. At present, on-site assays are available for determination of cholinesterase activity in whole blood, a key parameter for detecting exposure to NAs and OP pesticides, and for skin detection of SM.



- ✓ Unequivocal proof of exposure to CWAs can be achieved by analysis of biomedical samples which requires sophisticated, laborious and expensive off-site methods.
- ✓ Biosensors represent the first point of detection and are valuable for point-of-care diagnostic tests.
- ✓ There is a need to understand if there are markers suited for industrial chemicals (e.g. chlorine).
- ✓ There may also be opportunities for the use of biomarkers present in vegetation.
- ✓ Biomarkers of NAs fall into two main groups, free metabolites and adducts to proteins. It was noted that metabolites identifying exposure to chemical agents may also be found in hair and nail clippings.

# Field detection of chemical warfare agents

Handheld detector integrated Raman and FTIR technology



Gemini

Detector intended to quickly identify unknown liquid and solid CAs



FirstDefender RMX



TruDefender

HazMatID

HazMatID Elite

JSLSCAD

IMS detectors are the most commonly deployed military chemical monitoring detectors.



Raid-M-100



Sabre 4000



APD 2000



ChemPro100

Understanding the limitations and the ability to recognise false positive and negative signals is required to use these devices most effectively.

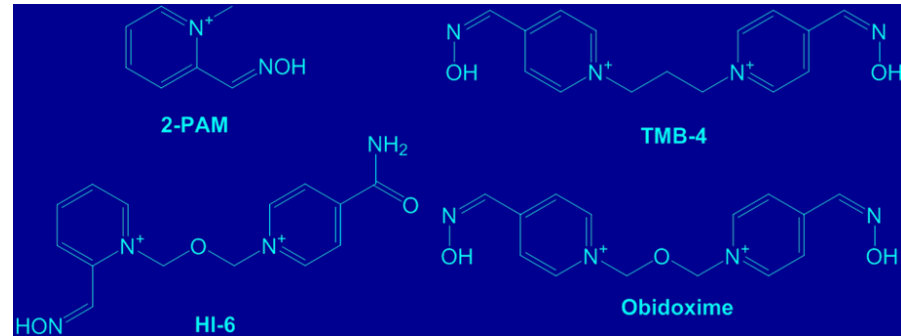
For optimal safety, a combination of detectors can be used to maximise the chances of detecting agents during operations in the field, or in some cases to assist the taking of samples for subsequent analysis by OCPW designated laboratories.

### **Topic 3. Medical countermeasures and decontamination against CWA**

- (a) Existing and future countermeasures against nerve agents and vesicants
- (b) Current and emerging strategies for organophosphate decontamination

## Existing and future countermeasures against nerve agents and vesicants

- ✓ Response time for treatment is critical and should be characterised and understood for the choice of countermeasures. AChE activity monitoring can be of critical importance to recognise exposure, before signs and symptoms of poisoning intensify.
- ✓ Oximes are not universally effective against AChE inhibited by different CWAs – more work is required to identify the most suitable oximes.
- ✓ Dosage must also be optimised for specific oximes due to the possibility of undesired side effects if they are administered in high dose.



- ✓ Countermeasures for lewisite (BAL and DMPS) chelate and remove arsenic from the site of injury, reducing the vesicant effect. More hydrophilic chelating agents are preferable to prevent BBB.
- ✓ There are many manuals on how to respond to chemical incidents, but there is little standardisation or response procedures for a general civilian population. A compilation of information categorised by whom it applies best to, could usefully serve as a reference collection.

# Current and emerging strategies for CWs decontamination

- ✓ Validated and emerging strategies for CW decontamination include chemical, physical, and biological methods, with special attention to the use of decontaminating enzymes.
- ✓ Decontamination of people, equipment and the environment involves many types of materials and material properties. Best practices for use of decontamination solutions in contact with different surfaces and materials are important to understand.



## Various targets to decontaminate



Efficient toward GSV nerve agents  
-no oral toxicity  
-no dermal toxicity  
-no environmental impact





# Outcomes

- a) **Developments across the fields should be regularly monitored and efforts made to bring experts working in both civilian and governmental organisations together to share best practices.**
- b) **New approaches to address old and continuing problems must also be considered.** For example, sulfur mustard was first used as a weapon of war almost 100 years ago, yet to this day the precise mechanism by which it produces blisters is not understood. Only when it is, will it be possible to rationally design drugs that could be used to reduce or prevent blistering.
- c) **Treatment of exposure to toxic chemicals requires medical countermeasures and decontamination procedures** (for victims of exposure, infrastructure and the environment).
- d) On-site and point-of-care detection methods to identify exposure and trigger response to chemical agent exposure represent a first line of defence. **Given the time-critical nature of treatment, a thorough review and evaluation of existing tools would be valuable for verification and investigative purposes.**
- e) There are many overlapping methods and technical dimensions in response to chemical agents and biological toxins, an example of the **convergence of chemistry and biology**. Efforts should be made to build networks that bridge communities of medical and emergency responders to share best practices and experience. These networks could be used to help maintain strong links between the SAB and the BTWC community.



ORGANISATION FOR THE PROHIBITION OF CHEMICAL WEAPONS

**Thank you for your attention!**