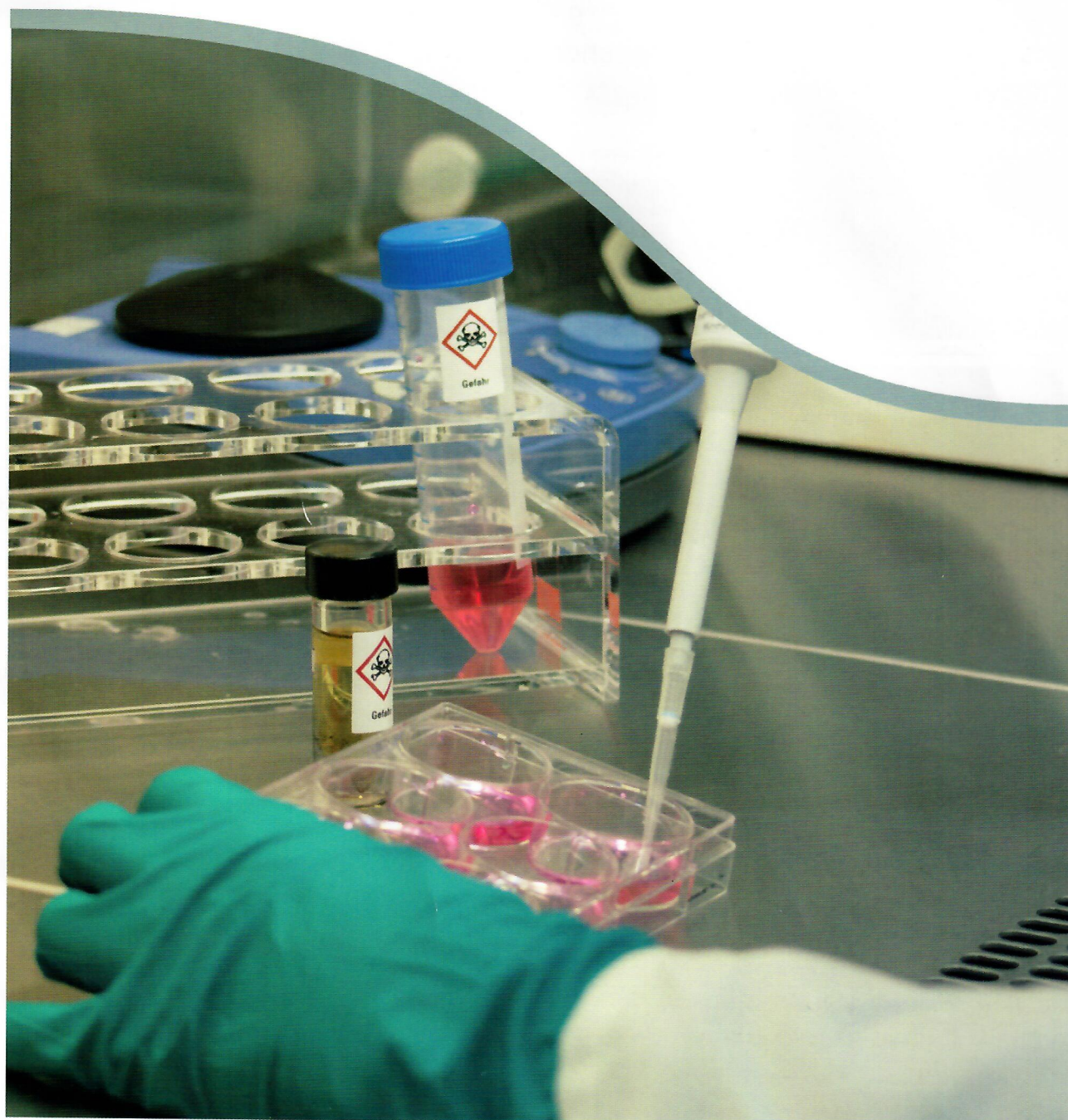


Wehrmedizinische Monatsschrift

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Bundeswehr Institute of Pharmacology and Toxicology

16th Medical Chemical Defense Conference

*100 years after the first use of sulfur mustard -
re-emerging threats of chemical warfare agents
and current state of medical research*

April 05 - 06, 2017, Munich





Bundeswehr Institute of Pharmacology and Toxicology

16th Medical Chemical Defense Conference

**Dear congress participants, dear readers of the
Wehrmedizinische Monatsschrift,**

when we started to prepare the 16th Medical Chemical Defense Conference which was held from April 05 - 06, 2017 in Munich, we did not have a presentiment that this cruel nerve gas attack against the civilian population would happen in Syria just one day prior to our meeting. This incidence demonstrated again that – despite of international agreements and established control mechanisms – chemical weapons are still available for armed forces, terrorists and even criminals and that they are willing to use them in a contemptuous manner. This underlines the importance of international cooperation among physicians, biologists, chemists, pharmacists, veterinarians and also engineers to develop analytics, drugs, technology and procedures in order to protect our troops and the civilian population against chemical weapons. An international conference like our meeting in Munich will help to pave the way towards better protection and treatment, which is unfortunately only available for some chemical warfare agents.

We selected a painting from John Singer Sargent with the title “Gassed” as cover picture of this year’s conference booklet and this supplement. The painting depicts the aftermath of a mustard gas attack during World War I, with a line of wounded soldiers walking towards a dressing station. Sargent was commissioned by the British War Memorials Committee to document the war and visited the Western Front in July 1918 spending time with the Guards Division near Arras, and then with the American Expeditionary Forces near Ypres. The painting was finished in March 1919 and voted picture of the year by the Royal Academy of Arts in 1919. It is now held by the Imperial War Museum in London. There could not be a better painting to introduce our this year’s conference that has the topic:

***100 years after the first use of sulfur mustard
re-emerging threats of chemical warfare agents
and current state of medical research***

The first deployment of sulfur mustard took place on July 12, 1917 in Ypres, Belgium, almost exactly 100 years ago. More than 50,000 tons of chemical warfare agents (CWA) including chlorine, phosgene, and mustard gas were de-

ployed by both sides during World War I. Official figures estimate about 1.3 million casualties directly caused by chemical warfare agents during the course of the war. Based on that, chemical warfare was abandoned by the Geneva Protocol in 1925 and later on by the Chemical Weapon Convention (CWC), with 192 member states as of April 2017. However, as we have all recognized, times have newly changed.

The use of nerve and blister agents in Syria, as mentioned above, and Iraq demonstrates that chemical warfare has changed its face: from large-scale battlefield deployment towards malicious terror or asymmetric incidents. The threat arising from CWA is as great as never before. Although some well-established therapies against CWA poisoning do exist, lacking antidotes or specific therapeutics for sulfur mustard injuries and also some nerve agents, e.g. soman, present us with major medical challenges. These facts underline the ultimate need of cutting-edge scientific research in order to face the reappearing threats of chemical warfare agents.

More than 200 experts from 29 different countries – Hawaii to Japan or Brazil to Norway – participated in this year’s congress. We had 27 conference lectures from renowned speakers, addressing a plethora of different topics. These included sessions with historical aspects of chemical warfare starting in World War I, the current use of CWA in Syria and Iraq, but also top-class scientific presentations reporting about up-to-date fields of basic research with special focus on the molecular toxicology of sulfur mustard, toxic lung injury induced by pulmonary acting noxious compounds, as well as analytical methods and experimental tools.

The congress management was significantly different than in the past. The newly introduced electronic registration process made registration and package booking more convenient, and detailed information regarding conference and social program was provided in advance. However, to achieve continuous improvement we thank all participants for their suggestions and criticism which will help us “to make it better”. As result of the evaluation, we will extend the next meeting in 2019 to two full days to



Tabea Zubel (Konstanz, Germany)



Bernhard Stenger (Munich, Germany)



Tamara Zorbaz (Zagreb, Croatia)

(Bilder: Julia Herbert, München)

allow more time for poster presentations and in-depth discussion.

Another novelty was the introduction of a scientific award for the best poster presented by a PhD student. The response to that was overwhelming: from the more than 50 submitted poster abstracts – as much contributions as never before – 20 abstracts submitted by PhD students were considered for the poster award. An international scientific committee of 6 scientists with outstanding reputation had selected a short-list of three excellent abstracts in advance. The three candidates presented their work in a short talk. The audience evaluated the oral presentations and its score accounted for 50% of the overall result. The other 50% resulted from an interview of each presenter by a local international scientific committee. All nominees convinced with excellent presentations and posters, that made the decision most difficult. At the end, jury and audience agreed in their ratings and decided as follows:

1st place: Tabea Zubel (Konstanz, Germany)

Development of a mass spectrometric platform for the quantitation of mustard-induced nucleic acid damage

2nd place: Bernhard Stenger (Munich, Germany)

Effect of N-acetylcysteine and glutathione on alkylating agents-induced TRPA1-channel activation

3rd place: Tamara Zorbaz (Zagreb, Croatia)

New uncharged potent reactivators of AChE and BChE inhibited by nerve agents

I hope that the participants are persuading the conference as the same success as I do. It was a great honor for me to host the 16th Medical Chemical Defense Conference and I say a cordial “Thank you” to my staff, especially to Major Dr. Tanja Popp and Lieutenant Colonel Dr. Dirk Steinritz, for their excellent support and professional work prior, during and after our meeting.

You will find the Abstracts of the conference lectures in the print version of this issue of the *Wehrmedizinische Monatsschrift*. The poster abstracts will be available in the internet version (downloadable from www.wehrmed.de and www.sanitaetsdienst-bundeswehr.de).

With best wishes

Colonel Prof. Dr. Horst Thiermann
Director of the Bundeswehr Institute
of Pharmacology and Toxicology,
Munich, Germany



Poster Award: 3rd Place

Tamara Zorbaz (Zagreb, Croatia):

New uncharged potent reactivators of AChE and BChE inhibited by nerve agents

NERVE AGENT INTOXICATION

Inhibition of central nervous system AChE

Respiratory center depression

Seizures

Long-term neurological impairments

CURRENT PROBLEMS IN THE FIELD

Death

Available therapy is not effective enough

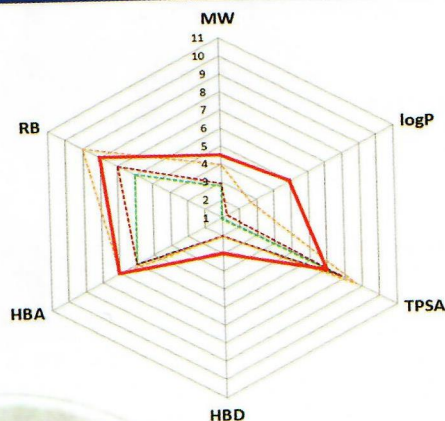
Standard oximes do not cross the BBB sufficiently

Standard oximes are not efficient enough for every nerve agent

Newly synthesized uncharged oximes have been evaluated by:

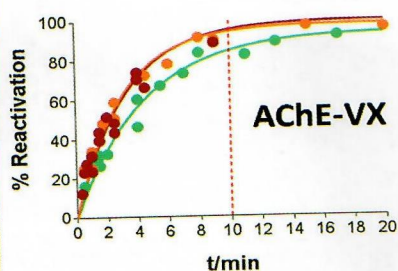
In silico methods

Physico-chemical properties are within the recommended range for a successful CNS drug



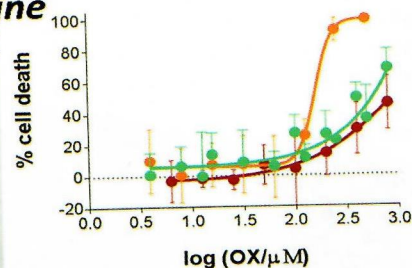
In vitro methods

Micromolar affinity for AChE/BChE ($K_i = 2-170 \mu\text{M}$)



Reactivation efficacy of nerve agent-inhibited AChE is as follows:
VX > sarin > cyclosarin > tabun

Human neuroblastoma SH-SY5Y cell line



Up to 100 μM concentration there is no significant cytotoxic effect ($\text{IC}_{50} > 600-800 \mu\text{M}$)

IN VIVO ...

New uncharged oximes have been evaluated by *in silico* and *in vitro* methods. They show promising *in vitro* reactivation potential of acetylcholinesterase (AChE; EC 3.1.1.7) inhibited by different nerve agents. Good permeability of novel oximes through the blood-brain barrier (BBB) is expected due to favourable physicochemical properties. Novel reactivators are not cytotoxic for the possible target cells (i.e. human neuroblastoma cell line SH-SY5Y) at both the active and *in vivo* achievable concentrations. Further experiments with novel oximes will include *in vivo* evaluation of their therapeutic potential.