

A blue-tinted microscopic image of neural tissue, showing a complex network of neurons and their processes. The image is used as a background for the slide.

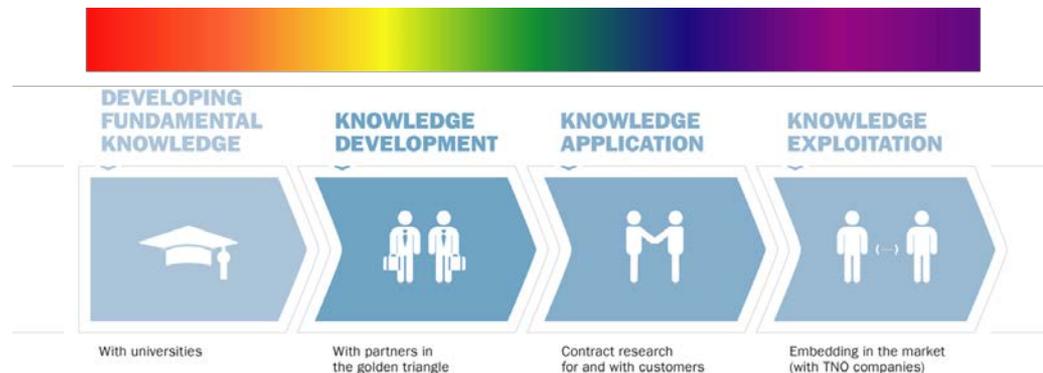
# › SCOPOLAMINE EFFICACY IN A NERVE AGENT GUINEA PIG MODEL FOR CIVIL SCENARIOS

AMN TNO CBRN Protection -CHEM1003 | Dr. Marloes Joosen

**TNO** innovation  
for life

# TNO, THE NETHERLANDS

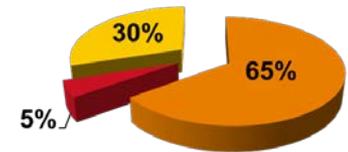
- › Special legal entity (TNO law, 1932) - Not-for-profit
- › Applied science, focused on smart solutions to complex multidisciplinary issues
- › Working across 9 research domains with ~3000 people
  - › By Law, the Dutch MoD has outsourced all research activities to TNO DSS in a strategic relationship



## CUSTOMER BASE

- › The only facility in The Netherlands that is allowed to produce chemical warfare agents for defensive purposes.
- › Designated laboratory for the OPCW
- › Over 50 years of experience in chemical and biological protection
  - › Primarily in the Defence area
  - › For and with Dutch and foreign governments
  - › Application of knowledge for other customers

- Ministry of Defence
- National government ('other')
- Other customers



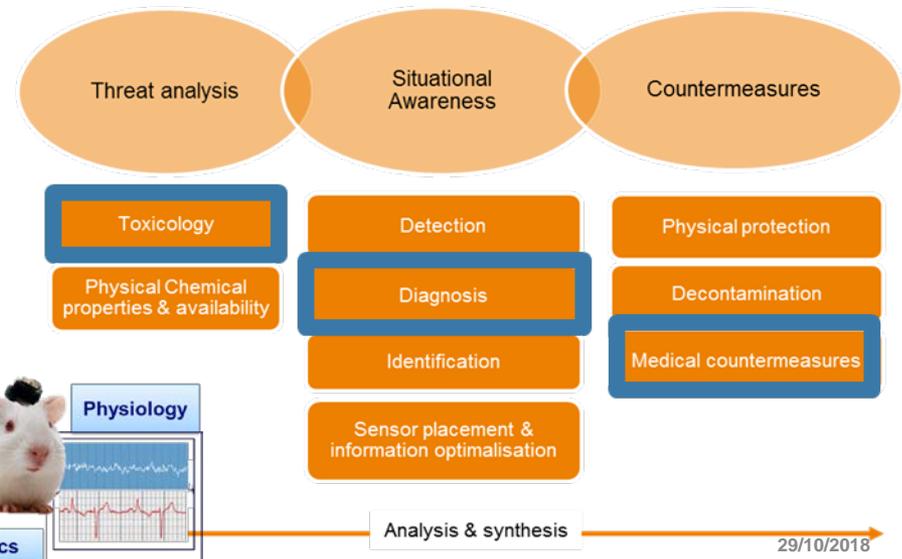
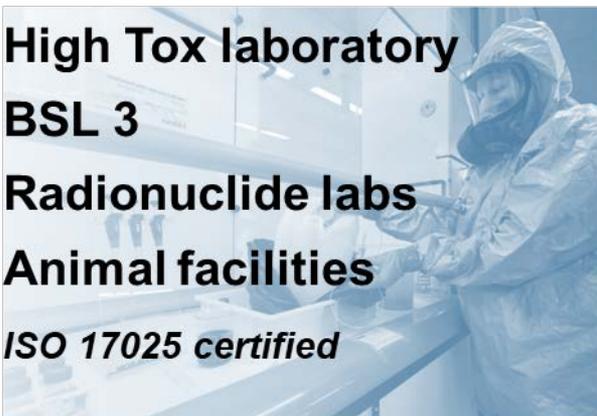
**High Tox laboratory**

**BSL 3**

**Radionuclide labs**

**Animal facilities**

*ISO 17025 certified*

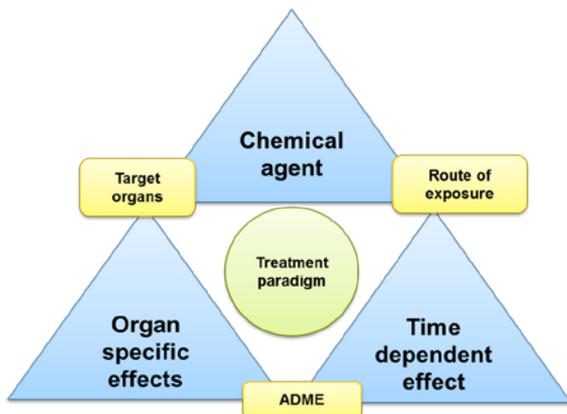


**FACILITIES**

βScopolamine efficacy in a nerve agent guinea pig model for civil scenarios

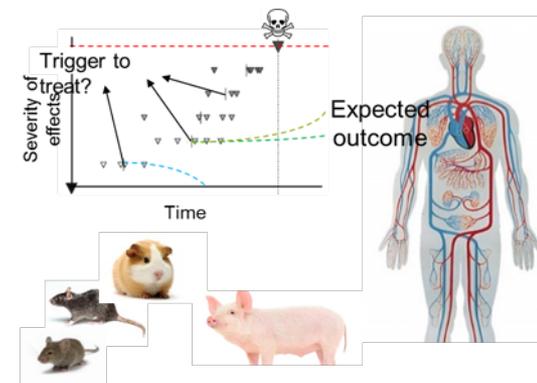
29/10/2018

- › Animal models are required in case human efficacy studies are not ethical or clinical trials are not feasible
- › Development of appropriate translational models for chemical exposure
  - › To enable appropriate evaluation of Medical countermeasures
    - › Designated chemicals (doses)
    - › Variety of exposed subjects (gender, age, level of protection)
    - › Time and type of intervention
    - › Defined end-points



## ***Combination of factors crucial for choices in animal model development***

***Experience from military applications used for civil applications in BARDA Animal Model Development Network***





- › Develop a Guinea pig model for a civil nerve agent exposure scenario to evaluate the efficacy of intranasal scopolamine to increase survival
  - › **Critical aspects**
    - › Delayed Standard of care for nerve agents leading to 50% 24 h survival
      - › Historical testing mainly for military scenarios in which treatment is administered @ 1 minute
      - › A lot is known, but...
    - › Probit slope for nerve agents is **steep** – complicating delayed treatment
    - › Development of signs is **variable** – fixed treatment time may increase variability
    - › Dose **extrapolation** of Standard of care and scopolamine
    - › Is survival rate @24 h the optimal **readout** –add information with minimal additional effort

***How did we approach these challenges?***

1

**Animal model development -Sarin**  
Delayed Standard of care  
Construct LD50 curve



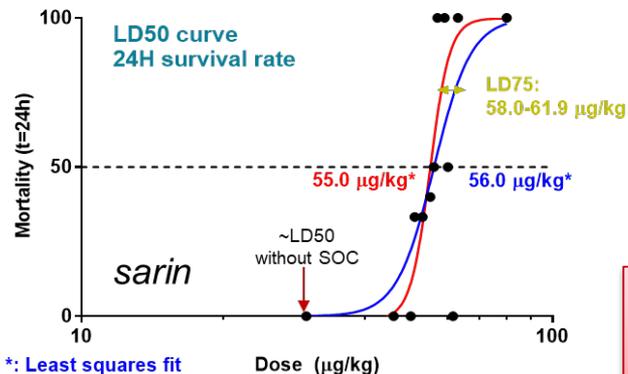
Male guinea pigs equipped with temp sensor  
24 h video monitoring

Modified Up/ down method s.c sarin  
~25 animals required

**During development: modifications in close consultation with BARDA team:**

- Number of autoinjector equivalents – lowered to 1
- Treatment time – from fixed time after dosing to “fixed” clinical state

**Model dose determined at 50% 24 h survival**

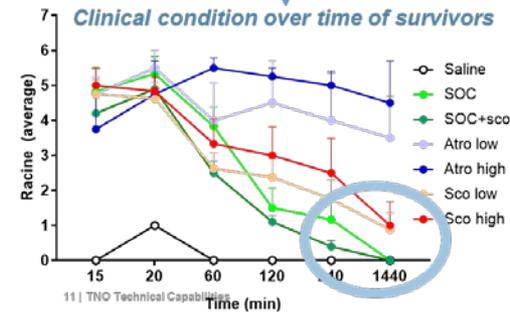
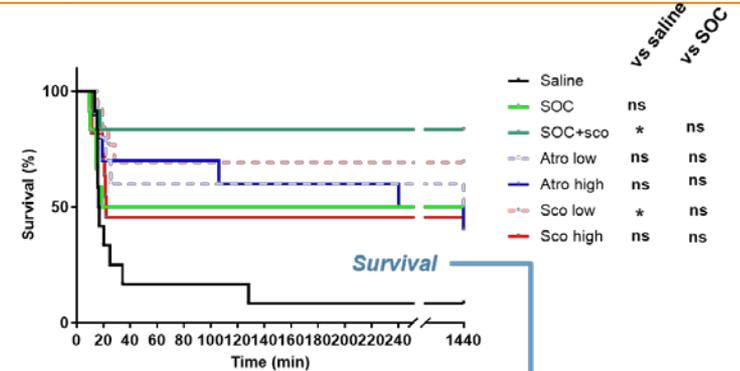


\*: Least squares fit  
\*: Robust fit

SOC intramuscular:  
0.13 mg/kg atropine  
8.7 mg/kg 2-PAM  
0.7 mg/kg midazolam

2

**Evaluate scopolamine efficacy**  
- On top of Standard of Care  
- As stand alone treatment



Indications for benefit of scopolamine –  
yet model at slightly too low statistical  
power to show significance

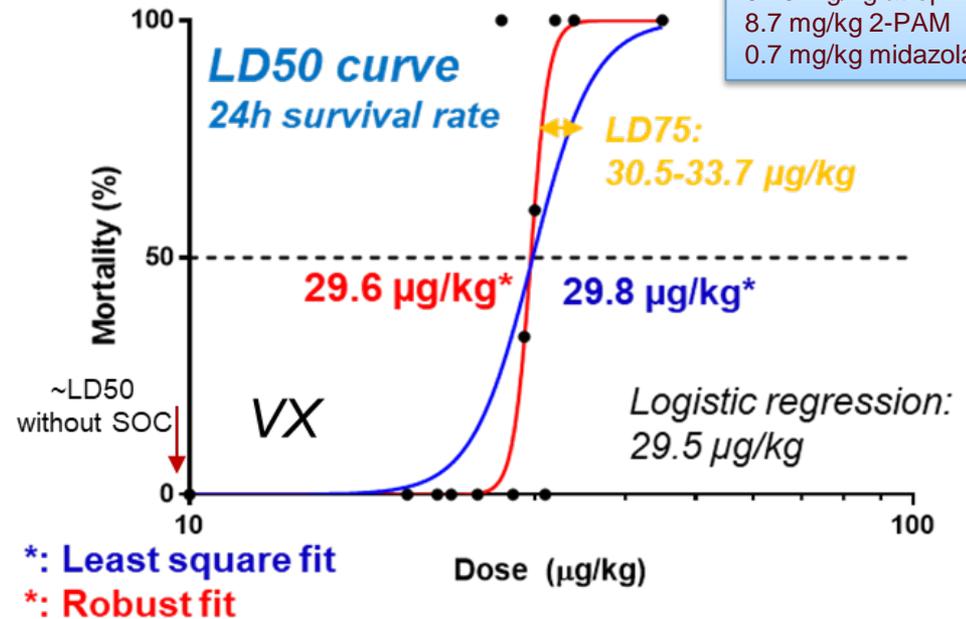
# CHANGED TO VX MODEL

Following sarin experiments agreed:

**Use same approach with VX**

*More persistent agent, less brain penetration*

- One autoinjector equivalent
- Delayed treatment at “fixed” clinical state severe resp. distress



- › Model dose determined at ~35% 24 h survival (31 µg/kg s.c.)
- › In contrast to sarin challenged animals, at 24 hours animals had not always recovered completely using 1 SOC equivalent
  - › **Model yielding more “room for improvement”**  
**in other words – increased statistical power**

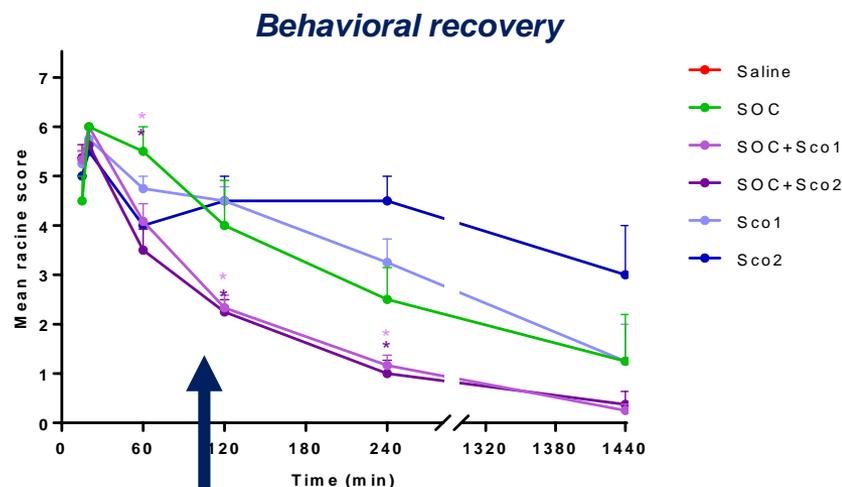
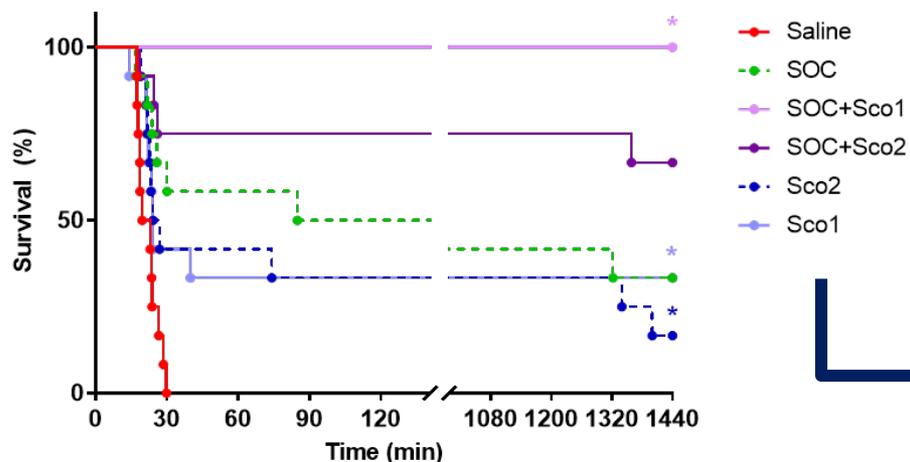
# EFFECTS OF SCOPOLAMINE IN VX MODEL

## › Changes agreed with BARDA team:

- › Use 30-35% 24 hour survival as VX target effect
- › Lower scopolamine doses from 2 and 5 mg/kg to 1 and 2 mg/kg

### Scopolamine efficacy in VX model:

- Statistically significant improvements in 24 hour survival
- Both as a stand alone and adjunct to SOC

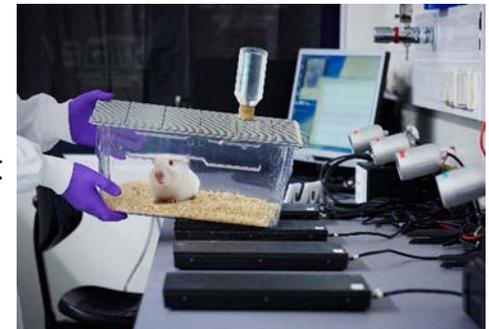


### Surviving animals show improved recovery

- As adjunct: clinically “healthy” animals @24 h
- Stand alone: as good as SOC



- › **Animal models developed in close consultation with BARDA team**
  - › Guinea pig model for sc sarin and VX, based on similar methods
  - › *Lessons learned*
    - › Agent choice important
    - › Definition of treatment time – transfer of standardized scoring
      - › Earlier treatment generally reaches higher efficacy
    - › Allow for sufficient power in experiment – minimize number of animals
      - › Definition and selection of control group to compare to (30 vs 50% survival)
      - › Analysis of 24 hour readout could allow for evaluation at earlier time points
  
- › **Beneficial effect of scopolamine as adjunct- and stand alone treatment in nerve agent exposure**
  - › Statistical significance is reached in the adjusted VX model
  - › Finalizing experiments and evaluating optimal possibilities within project
    - › Dosing and admin routes



› THANK YOU FOR YOUR ATTENTION

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