Development of Novel Means for Decontamination of Skin Contaminated by Nerve Agents and Industrial Chemicals

[Vývoj nových prostředků pro dekontaminaci kůže zasažené nervově paralytickými látkami a průmyslovými chemikáliemi]

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25-11-2010

Content

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2. Decontamination projects
3. Development of novel decontamination means
4. Coopeation with companies and products

Possible Terroristic Misuse x War Conflict

Matsumoto (Japan)

Osaka (Japan)

Tokyo (Japan)

World War I

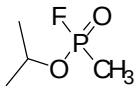
Iraq-Iran War

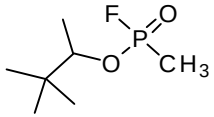
Tokyo Sarin Subway Attack

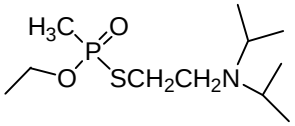
Saddam Hussein bombing of the Iraqi Kurdish town of Halabja

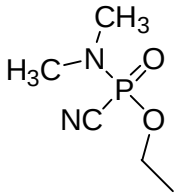
Nerve Agents and Pesticides

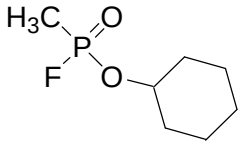
NERVE AGENTS:

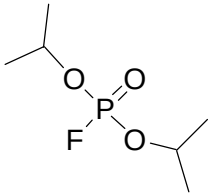

Sarin

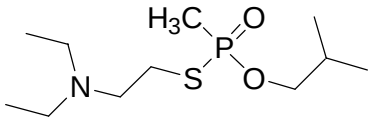

Soman

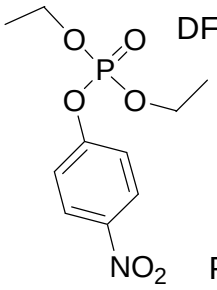

VX


Tabun


Cyclosarin

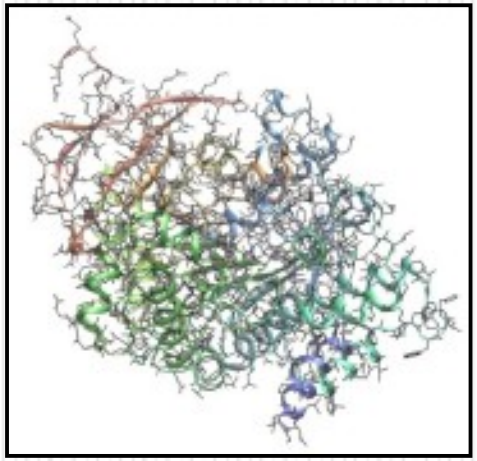

DFP


Russian VX


Paraoxon

AChE inhibition:

Enzyme Sarin Inhibited Enzyme



Acetylcholinesterase
AChE
EC 3.1.1.7

⇒CHOLINERGIC CRISIS
⇒DEATH

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Decontamination - General

BEFORE INTOXICATION →

Prophylaxis (= Pretreatment)
-Pyridostigmine, Physostigmine
-Transant (HI-6)
-PANPAL, etc.

Nerve Agent

AFTER INTOXICATION →

Decontamination
-reactive or non-reactive
-personal or mass

Treatment
-anticholinergic drugs
-acetylcholinesterase reactivators
-anticonvulsants

Decontamination - General

Personal decontamination

-personal decontamination mean

-well-trained person (soldier)

-immediate application of decontamination mean (minutes after exposure)

Mass decontamination

-collective decontamination

-not prepared people (panic expected)

-first possible application – 1 hour after exposure

Decontamination - General

REACTIVE

IPP-11 (Russia)

Alldecont (Germany)

RSDL (Canada)

SORPTION

IPP-95 (Poland)

M291 (USA)

IPB-80 (Czech Republic)

Decontamination Projects

SUBSTANCE - Development of New Skin Decontamination and Desinfection Agent Based on Micelar Systems (MoD, Czech Republic)

=> Personal decontamination

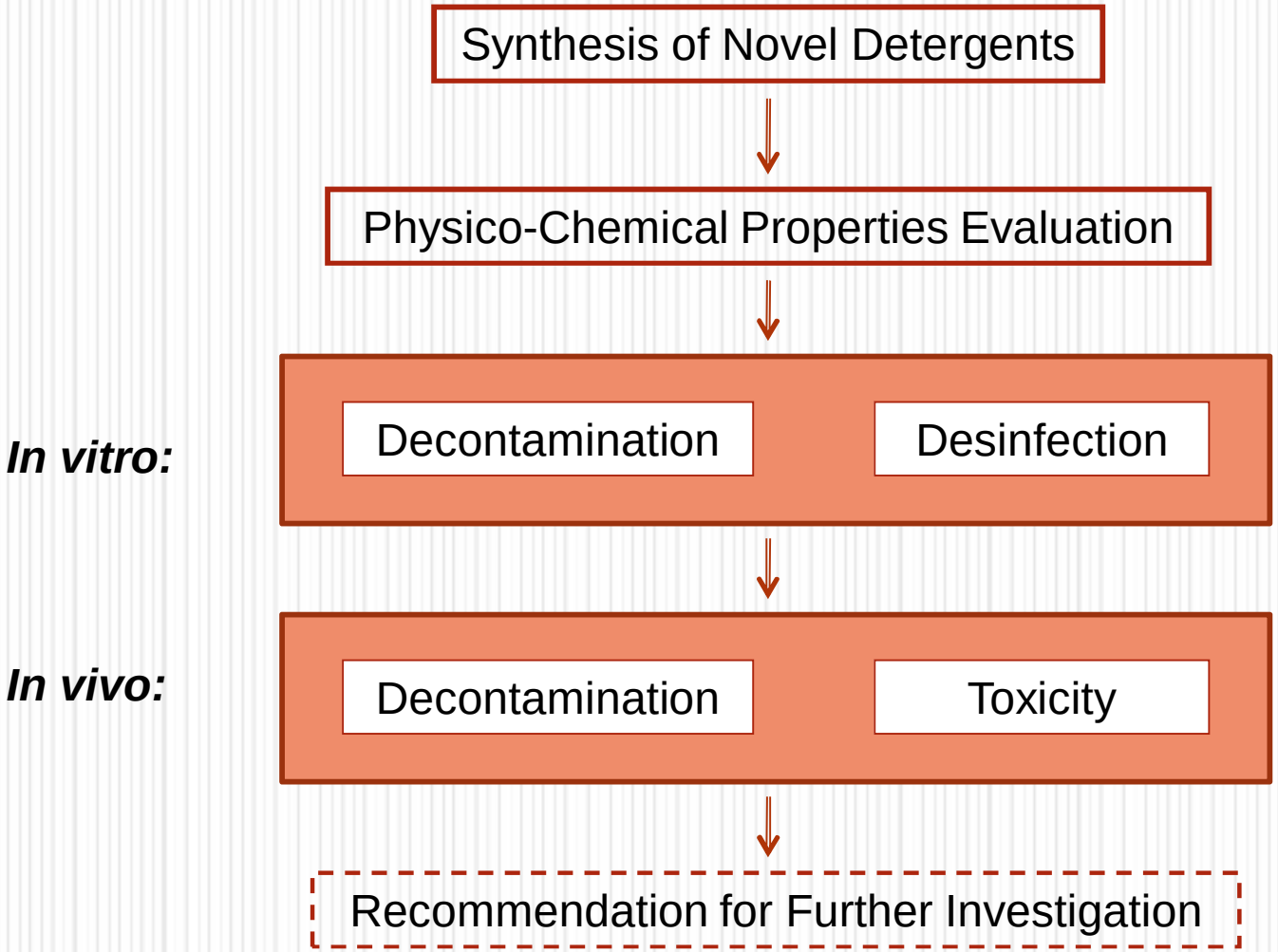
SUBSTANCE

ORCHIDS - Evaluation and Optimisation of Emergency Mass Casualty Decontamination (European Commission)

ORCHIDS

=> Mass decontamination

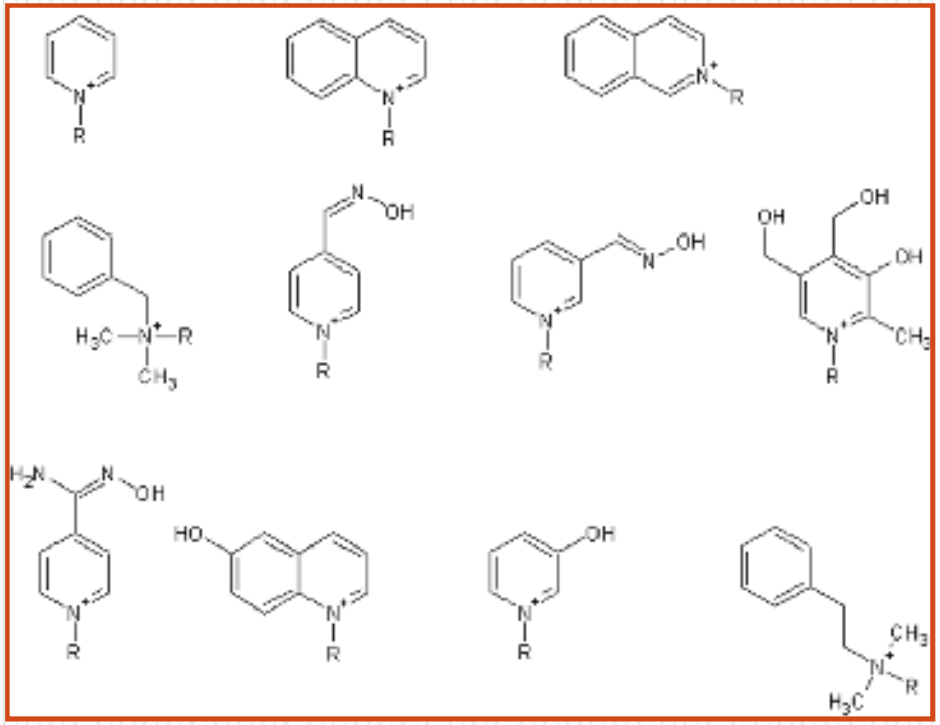
Development of Novel Decontamination Means



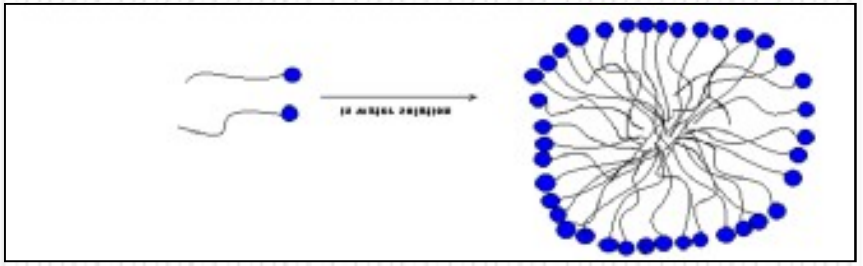
Synthesis of Novel Detergents

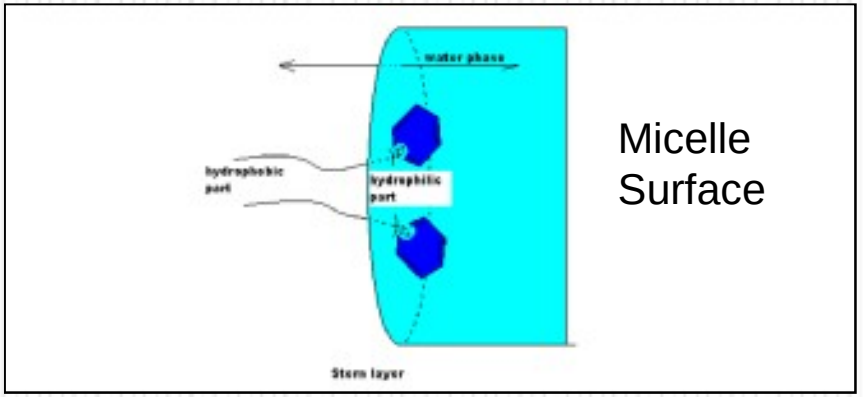
SUBSTANCE

Chemical Structures:



Micelle Creation:





Micelle Surface

- **enhanced hydrolysis of nerve agents** in micellar environment
-thanks to the presence of quaternary nitrogen – also **desinfection activity**
=> many decontamination means based on micellar origin

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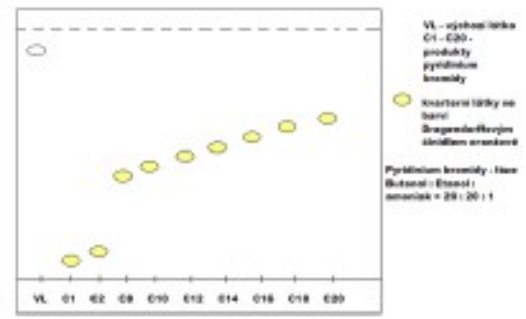
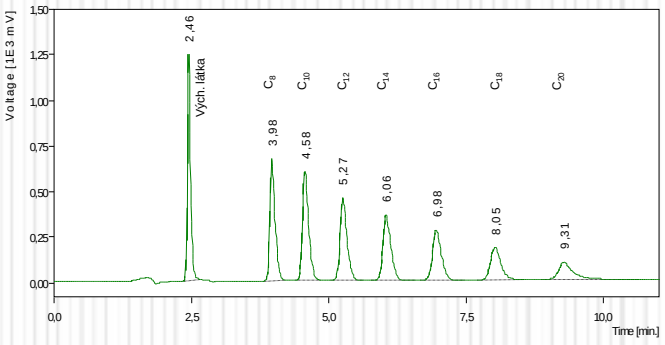
Physico-Chemical Properties

SUBSTANCE

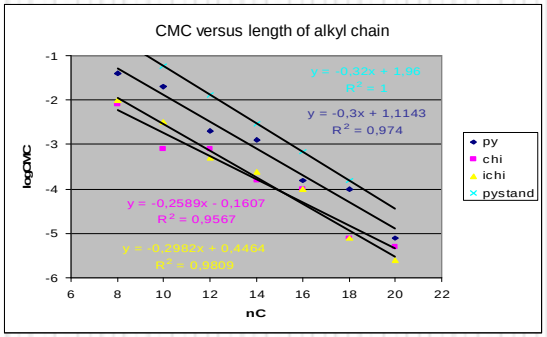
TLC:



HPLC:



CMC:



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In vitro Decontamination

SUBSTANCE

- **Model substrates:**

  nerve agents,
  p-nitrophenyl acetate, p-nitrophenyl benzoate, p-nitrophenyldiphenyl phosphate, p-nitrophenyl p-toluene sulfonate, fenitrothion,…

- ***Detergents:***

  newly synthesized detergents (with and without functional groups),
  cetyltriphenylphosphonium bromide, cetyldimethylethanol ammonium bromide; cetyldimethylethyl ammonium bromide; cetyltributylphosphonium bromide; cetyltrimethylammonium bromide,…

- **Nuclephiles:**

  pralidoxime, α-benzoinoxime; acetaldoxime, butane 2,3-dione monoxime,…

In vitro Decontamination

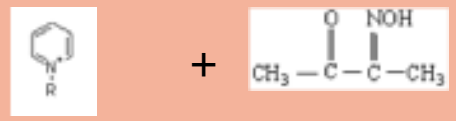
SUBSTANCE

Three different types of systems:

1.

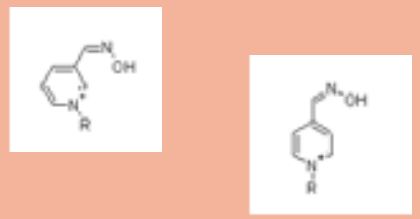
Non-functionalized Detergents

2.



Non-functionalized Detergents + Nucleophile

3.



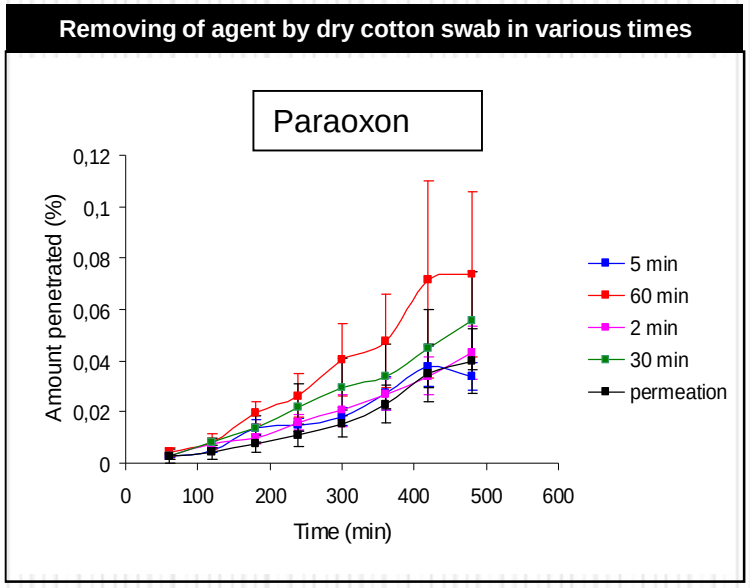
Detergent and Nucleophile in one Molecule

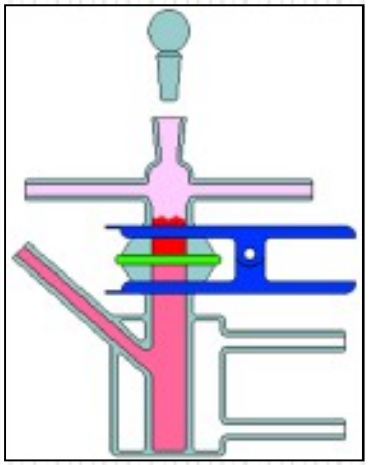
• TIWARI S., GHOSH KK., MAREK J., KUCA K.: Cationic micellar catalyzed hydrolysis of pestocide fenitrothion using α- nucleophiles. ***Letters in Drug Design and Discovery***, 2009, 7(3) 194-199.
• TIWARI S., GHOSH KK., MAREK J., KUCA K.: Functionalized surfactant mediated reactions of carboxylate, phosphate and sulphonate esters. ***Journal of Physical Organic Chemistry***, 2009, 23(6) 519-525.
• TIWARI, S; GHOSH, KK; MAREK, J; KUCA, K.: Comparative study of nucleophilic efficacy of pralidoxime towards phosphorus, sulfur and thiophosphorus based esters, ***React Kinet Catal Lett***, 2009, 98(1) 91-97
• TIWARI, S., KOLAY, S., GHOSH, K., KUCA, K., MAREK, J. Kinetic study of the reactions of p-nitrophenyl acetate and p-nitrophenyl benzoate with oximate nucleophiles. **International Journal of Chemical Kinetics**, 2009, 41(1) 57-64.
• TIWARI S., GHOSH KK., MAREK J., KUCA K.: Spectrophotometric determination of the acidity constants of some oxime based α-nucleophiles. ***J. Chem. Eng. Data***, 2010, 55(3), 1153–1157.

In vitro Decontamination – Skin Penetration Studies

- Franz-type diffusion cells
- Pig dermatomed dorsal skin (500 μm)
- Enzymatic assessment – modified Ellman´s method

Removing of agent by dry cotton swab in various times





In vitro Desinfection

SUBSTANCE

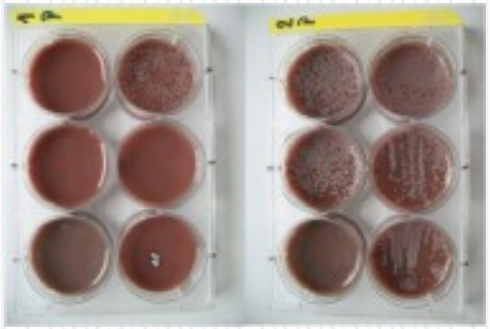
Faculty of Pharmacy, Charles Univesity in Prague (Czech Republic):

1. *Staphylococcus aureus* CCM 4516/08 (SA)
2. *Staphylococcus aureus* H 5996/08 (MRSA)*
3. *Staphylococcus epidermidis* H 6966/08 (SE)
4. *Enterococcus* sp. J 14365/08 (EF)
5. *Escherichia coli* CCM4517 (EC)
6. *Klebsiella pneumoniae* D 11750/08 (KP)
7. *Klebsiella pneumoniae* J 14368/08 (KP-E)**
8. *Pseudomonas aeruginosa* CCM 1961 (PA)

1. *Candida albicans* ATCC 44859 (CA)
2. *Candida tropicalis* 156 (CT)
3. *Candida krusei* E28 (CK)
4. *Candida glabrata* 20/I (CG)
5. *Trichosporon asahii* 1188 (TA)
6. *Aspergillus fumigatus* 231 (AF)
7. *Absidia corymbifera* 272 (AC)
8. T*richophyton mentagrophytes* 445 (TM)

Faculty of Veterinary Medicine, Brno (Czech Republic):

1 . Bacillus Anthracis (Antrax spores)



Centre of Biological Defence, Techonin (Czech Republic):

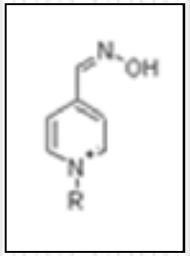
1. Escherichia Coli
2. *Bacillus Subtilis*

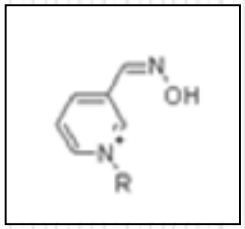
Goteborg University, The Sahlgrenska Academy (Sweden):

1. Staphylococcus Epidermidis
2. *Escherichia Coli*

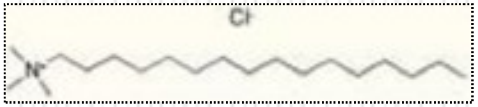
Decontamination and Desinfection

SUBSTANCE



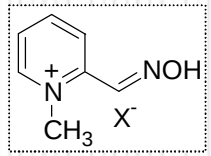


The Most Active Compounds



Detergent

+



Acetylcholinesterase Reactivator

- **<u>Quaternary</u>** compounds
- Alkyl chain – **<u>C12</u>**, **<u>C14</u>** and C16
- Oxime group **=> <u>oximate anion</u> – hydrolysis** of nerve agents

In vitro - Skin Penetration of Detergents

- infinite dose
- diffusion cells
- UV spectrofotometry
- 5% water solutions and concentrates

Detergent	Abs (nm)	permeation after 24 h	
		5% solution	concentrate
Althosan MB 50%	263	not detectable	6.134 µg.cm^{-1}
Sodium Alkylbenzensulphonate 80%	261	not detectable	-
Triton X	277	not detectable	not detectable

NO SKIN PENETRATION

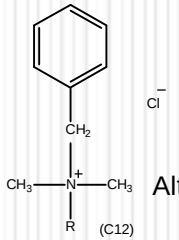
ORCHIDS

SUBSTANCE

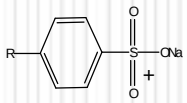
* each concentration on 12 cells

In vivo - Acute Toxicity of Novel Detergents

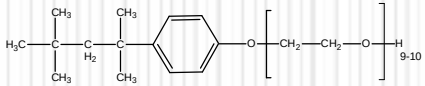
SUBSTANCE ORCHIDS



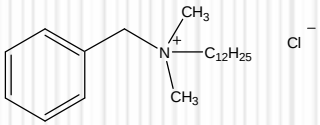
Althosan MB 50%



Sodium Alkylbenzensulphonate 80%



Triton X



Benzyldimethyldodecyl Ammonium Chloride

N-Dodecyl Pyridinium Bromide

Detergent	LD_{50} (24 h; $mg.kg^{-1}$)	
	p.o	*i.m.*
Althosan MB 50%	< 1000	< 1000
Sodium Alkylbenzensulphonate 80%	> 2000	> 2000
Triton X	> 1000	< 1000
Benzyldimethyldodecyl Ammonium Chloride	> 500	< 100
N-Dodecyl Pyridinium Bromide	> 200	< 100

* laboratory white male mouse, estimated values

LOW TOXICITY

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Acute Toxicity of Decon Means

Decon mean	LD_{50} (24 h; $ml.kg^{-1}$)	
	p.o	i.m.
FLORAFREE©	> 6	> 6
NEODEKONT©	> 6	> 6
DERMOGEL©	> 6	> 6
ARGOS©	> 6	5.0 (3.6 – 6.6)

NON TOXIC

* Wistar rats, max. *p.o.* and *i.m.* dose = 6 $ml.kg^{-1}$

Argos© (F)
Sodium Alkylethersulfate, Cocamide DEA, Sodium Alkylbenzensulphonate,…

FloraFree© (GB)
Aqua, Pottasium Tallate, Pottasium Cocoate, Trideceth-5, Cocamide DEA, Dimethyl Oxazolidine, Isopropyl alcohol, Sodium borate, Tetrasodium EDTA, Triclosan, CL 19140, CL 42090

Dermogel© (ESP)
Aqua, Sodium Laureth Sulphate, Lauryl Sulphate TEA, Glycerin, Cocamide DEA, Cocamidopropyl Betaine, Citric Acid, Sodium Chloride, Lanolin Ethoxylate, Parfume, 2-Bromo-2-nitropropano-1,3-diol, 2,4-Dichlorobenzyl Alcohol

Neodekont© (CZ)
Aqua, Silica, Bentonite, Pentasodium Triphosphate, TEA-Dodecylbenzene Sulfonate, Cocamidopropyl Betain, Cocamice MEA, Cocamide DEA, Citric Acid, Pentasodium Pentanate, Sucrose Cocoate, Parfum, Benzyl Alcohol, Methylchloroisothiazoline, Methylisothiazoline, CL 42090

In vivo Skin Decontamination

Nerve Agent Toxicity:

- ***In vivo* studies**: LD_{50} [$mg.kg^{-1}$] of selected nerve agents and pesticides
- **Administration:** i.m., i.p., p.o., s.c., p.c.
- Tested **species:** mouse, rat, guinea pig


1) fixation


2) shaving


3) replacing into digestor


4) agent application (*p.c.*)


5) agent exposure


6) treatment


7) releasing


8) monitoring

In vivo Skin Decontamination

- Wistar male rats
- Paraoxon (p.c., 24 h) LD_{50} = 4.373 (1.588 – 8.843) $mg.kg^{-1}$
- VX (p.c., 24 h) LD_{50} = 0.0849 (0.079 - 0.100) $mg.kg^{-1}$
- 5% water solutions (**Florafree, Neodekont, Dermogel, Argos**)
- treatment after 2 min

PARAOXON Decon mean	LD_{50} after decontamination (mg.kg-1)	ID
FLORAFREE©	5.91	1.35
NEODEKONT©	7.07	1.62
DERMOGEL©	10.86	2.48
ARGOS©	10.00	2.29

VX Decon mean	LD_{50} after decontamination (mg.kg-1)	ID
FLORAFREE©	1.00	11.7
NEODEKONT©	3.25	38.2
DERMOGEL©	3.90	45.9
ARGOS©	> 5.00	> 58.8

In vivo Skin Decontamination

- **RSDL versus Desprach**
- RSDL = polyethyleneglycols, 2,3-butandionemonoxime (DAM), Dekon 139
- Soman, VX agent and sulphur mustard
- Rats, p.c. administration

Decon Mean	LD_{50} soman (mg/kg)	ID
-	20,58 (16,91 - 25,03)	----
DESPRACH	88,28 (55,76 - 278,14)	4,29
RSDL	55,42 (39,29 - 94,63)	2,69

Decon Mean	LD_{50} VX agent (mg/kg)	ID
-	0,105 (0,075 - 0,147)	----
DESPRACH	8,05 (4,39 - 10,81)	76,7
RSDL	< 6,0	< 57,1

Decon Mean	LD_{50} sulf mus (mg/kg)	ID
-	17,16 (13,01 - 22,64)	----
DESPRACH	404,56 (299,94 – 467,77)	23,6
RSDL	478,64 (391,16 – 1226,53)	27,9

In vivo Skin Decontamination

- **Glove filled by sorbent DESPRACH**
- Company CHEMCOMEX Praha, a.s.
- Better handling (soldier-friendly)
- Decontamination depends on amount of sorbent inside the glove

Recommendation for Further Investigation

Basic Research Results

Companies

Novel Products

Market

Searchng for the Appropriate Company
Discussions
Participation on Developmental Projects

Further Investigation
Whole Decon Mean Design
Product Development

Products

NEODEKONT

- liquid soap
- decontamination of **radionuclides** on **skin** and **all common surfaces**
- **no skin irritation**

Active substances:

chelating agents, surfactants, soluble polymer sorbent

Current Users:

- NPP Temelin, NRI Rez Prague, nuclear medicine departments

Products

HVĚZDA (trans. STAR)

- bi-component mixture
- decontamination of warfare agents **G, V, H,** biological agens – e.g. spores of *B. anthracis (**antrax**)*
- suitable for **skin** and **common surfaces**

Active substances:

Quaternary ammonium salts (as surfactant),

hydrogen peroxide

Users:

- Fire Rescue Service of CR, Army of CR, NATO NRF 3

(2004), civil use – broad spectrum disinfection

- **Staff:**

Prof. Jiri Cabal

Prof. Jiri Kassa

Dr. Ladislav Novotny

Dr. Miroslav Pohanka

Dr. Kamil Musilek

Dr. Daniel Jun

Dr. Jana Karasova

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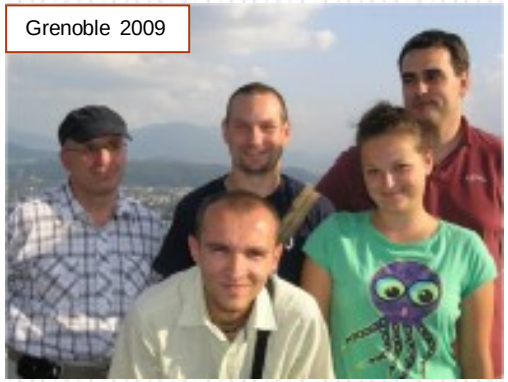
Jan Marek

Jan Misik

Ruzena Pavlikova


Grenoble 2009

- **Laboratory Assistants:**

Martina Hrabinova

Jana Uhlirova

Eva Vodakova

- **Decon Co-operation:**

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Dr. Josse – CRSSA, France

Prof. Ghosh - Pt. Ravishankar Shukla University, India


Hradec Kralove 2009

- **Projects:**

ORCHIDS (EU) [http://www.orchidsproject.eu/]

SUBSTANCE (MoD CZ)

- **Companies:**

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Thank you very much for your Attention.