The Socrates Award Lecture
Chemical and Biological Warfare Agents

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“The decisive battles of any war are not won by the physical destruction of the enemy but by psychic imponderabilities which induce them in a decisive moment to lose the will to fight and to feel defeated.”
– Fritz Haber

Chemical Warfare (CW) Agent Categories

- Lung irritants
- Vesicants
- Blood (systemic)
- Nerve
- Harassing
  - Riot Control
- Psychoincapacitants
- Herbicides
- Olfactory agents

Example
- Phosgene
- Mustard, Lewisite
- Cyanide
- Sarin
- Tear gas
- BZ
- Agent Orange
- Skunk: Skatole (!)

Cl₂ + H₂O → HCl + HOCl

Ypres, Chlorine Gas attack, April 1915

Bleach, Ammonia and Terrorism

- Chloramines (NH₂Cl, NHCl₂) are generally more toxic than chlorine gas.
- Under some conditions, chlorine gas can be produced from civilian products.

World War I

- The following CW agents were responsible for most casualties in World War I:
  - Chlorine (Cl₂) High mortality
  - Phosgene High mortality
  - Mustard High morbidity
### Comparative Toxicities

<table>
<thead>
<tr>
<th>CW agent</th>
<th>Toxicity, inhalation (LC150) mg x min/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen cyanide*</td>
<td>2,500-5,000</td>
</tr>
<tr>
<td>Sarin (GB)</td>
<td>100</td>
</tr>
<tr>
<td>Sulfur mustard (HD)</td>
<td>1,500</td>
</tr>
<tr>
<td>VX</td>
<td>10</td>
</tr>
</tbody>
</table>

*oddball

### Physical Properties

At least as important as toxicity in chemical warfare.

<table>
<thead>
<tr>
<th>CW agent</th>
<th>Volatility, mg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen cyanide</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Sarin (GB)</td>
<td>22,000</td>
</tr>
<tr>
<td>Sulfur mustard (HD)</td>
<td>900</td>
</tr>
<tr>
<td>VX</td>
<td>10</td>
</tr>
</tbody>
</table>

### Hydrogen Cyanide

Blood agent

NaCN or KCN + H₂SO₄ = Bad news

About 10-20% of adults have a hereditary inability to detect the characteristic odor.

### Hydrogen Sulfide (H₂S)*

*Or, the case that wasn’t…

### The Ku Klux Klowns…

Wise County, Texas
Flammable Gas Tanks

Hydrogen Sulfide: Highly Toxic

\[ \text{H}_2\text{S} = \text{Blood agent, similar toxicodynamics to cyanide poisoning} \]

**TLV-TWA**
- Hydrocyanic acid: 10 ppm (11 mg/m\(^3\))
- Hydrogen sulfide: 10 ppm (14 mg/m\(^3\))

Compare:
- Methyl isocyanate: 0.02 ppm (0.047 mg/m\(^3\))

Vessicants

- **Mustard** (sulfur, nitrogen)
  - "King of CW agents" until nerve gas agents appeared in 1937.
- **Lewsite**
  - Extremely nasty.
  - Not used much (yet).

Blister Agents (Vesicants)

- Sulfur mustard
- Nitrogen mustard

Sulfur Mustard: Vesicant

- Lewisite

• No evidence that the Wise County conspirators ever intended to release toxic gas.
**Sulfonium Ion Formation**

![Diagram of Sulfonium Ion Formation](image)

**Base Reaction**

![Diagram of Base Reaction](image)

**Sulfur mustard**

Sulfonium ion + Guanine

**Guanine**

Sulfur mustard + Guanine

**Cross linking of DNA (G-G)**

**Mustard Toxicity: Two views?**

- **Choose your poison:**
  - DNA alkylation
  - DNA breaks
  - Transcription and protein synthesis inhibition
  - Glycolysis stops, loss of ATP
  - Autolysis
  - Poly (ADP-ribose) polymerase activated
  - Phospholipases and nucleases disinhibited
  - Glutathione reactions
  - Denaturing of thiol proteins
  - Loss of calcium
  - Lipid peroxidation, membrane damage
  - Cell death

- **or:**

**Mustard: Burns**

Mustard burns begin with redness and itching.
Pseudo-membrane formation - probably worst outcome.

Eye injury is serious, but not necessarily permanent . . .

Long Term Ocular Sequelae
- Exposure to 100 mg x min/m3 of sulfur mustard vapor causes acute blindness for 24-48 hours.
- Permanent blindness usually occurred about 14 years after acute corneal injury by mustard.

Mustard Toxicity Summary
“Single exposures, even if severe, as in military service, are not associated with statistically verifiable increases in mortality from tuberculosis and cancer; but repeated small exposures, such as occur in industrial operations, do increase cancer deaths significantly.”

National Research Council
Possible Long-Term Effects of Short-Term Exposure to Chemical Agents
Volume 2, 1984, p128.
Principles of Environmental Toxicology

**Lewisite**

![Lewisite molecule](image)

Toxicity data limited to mostly animal studies.

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**Lewisite: Toxicity Mechanisms**

- Reactions with sulphydryl groups of enzymes
- Inhibits pyruvate dehydrogenase complex
- Loss of calcium
- Lipid peroxidation, membrane damage
- Glutathione reactions
- Denaturing of thiol proteins
- Glycolysis inhibited
- ATP loss, cell death
- Cell death

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**Mustard/Lewisite Mixture Spray Tank**

500 kg, approx. 168 kg fill

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**Mustard Munition**

1,500 kg Aerial Munition
Mustard/Lewisite 636 kg fill

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**Nerve Agents**

- Soman (GD): A bad actor, even among other nerve agents
- GF (cyclosarin): Not far behind

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**Nerve Agents**

![Nerve agent molecular structure](image)
**Principles of Environmental Toxicology**

**V-Agents (VX, V-gas, etc.)**

\[
\begin{align*}
&CH_3-CH_2-O-\overset{\text{P}}{S}-CH_2-CH_2-N \quad CH_3 \\
&CH_3 \\
&CH_3-CH_2-O-\overset{\text{P}}{S}-CH_2-CH_2-N \quad CH_3
\end{align*}
\]

Soviet V-gas

**Inhibition of Acetylcholinesterase**

**Nerve agent (sarin)**

\[
\begin{align*}
&\text{Leaving group} \\
&CH_3 \\
&CH_3 \\
&\text{O} \\
&\text{(Serine)} \\
&\text{Acetylcholinesterase (AChE)}
\end{align*}
\]

**AChE Inhibition, cont’d**

\[
\begin{align*}
&\text{Phosphorylated enzyme} \\
&\text{O} \\
&\text{(Serine)} \\
&\text{Acetylcholinesterase (AChE)}
\end{align*}
\]

**Soman: Notoriously “age prone”**

\[
\begin{align*}
&\text{Aged enzyme} \\
&\text{O} \\
&\text{(Serine)} \\
&\text{Acetylcholinesterase (AChE)}
\end{align*}
\]

**Nerve Agent Intoxication**

<table>
<thead>
<tr>
<th>Neuromuscular</th>
<th>Autonomic</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twitching</td>
<td>Reduced Vision</td>
<td>Headache</td>
</tr>
<tr>
<td>Weakness</td>
<td>Small pupil size</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Drooling</td>
<td>Coma</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Sweating</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Sturred speech</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Respiratory depression</td>
</tr>
</tbody>
</table>

**V-gaz**

V-gaz was thickened further by the Soviets, with methyl methacrylate polymer...

SCUD-type warhead, 555 kg thickened VX (VR-55) fill.
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Making Demil: More Complicated

\[
\text{CH}_3 + \text{CH}_3 - \text{O} + \text{CH}_2 - \text{CH}_3 - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{CH}_2 - \text{CH}_3 - \text{CH}_3 + \text{CH}_2 - \text{H}_2 \text{O}
\]

Soviet V-gas

\[
\text{K} - \text{O} - \text{CH}_2 - \text{CH}_3 - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{CH}_2 - \text{H}_2 \text{O} - \text{CH}_2 - \text{CH}_3 - \text{CH}_3
\]

Potassium isobutyrate

\[
\text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O}
\]

Isobutyl alcohol

\[
\text{N}-\text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{N}-\text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O}
\]

N-methyl pyrrolidone

\[
\text{K} - \text{O} - \text{CH}_2 - \text{CH}_3 - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{CH}_2 - \text{H}_2 \text{O} - \text{CH}_2 - \text{CH}_3 - \text{CH}_3
\]

75% +

\[
\text{N}-\text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O} \rightarrow \text{N}-\text{CH}_3 - \text{CH}_2 - \text{N} - \text{CH}_3 + \text{H}_2 \text{O}
\]

25% +

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US Chemical Field Doctrine (c. 1950s)

“...The coverage of a target to a dosage of 100 mg-min/m³ (the LC₅₀) has not been considered, since the total casualties resulting therefrom can be largely in excess of that required to achieve the desired effect on target. Logistically, it is more desirable to achieve this effect on target with the minimum expenditures. Therefore, coverages of targets to a dosage of only 50 mg-min/m³ (the IC₅₀) have been calculated.”

Dept. of the Army, Air Force

“Capabilities and Employment of Toxic Chemicals”

October 13, 1958, p.36.

Principles of Environmental Toxicology

1958: 105 mm Sarin Howitzer Shell

Target Area Coverage Calculation Table

<table>
<thead>
<tr>
<th>Fractional factor</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>0.30</th>
<th>0.35</th>
<th>0.40</th>
<th>0.45</th>
<th>0.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contribution</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.16</td>
<td>0.24</td>
<td>0.32</td>
<td>0.40</td>
<td>0.48</td>
<td>0.56</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Expected</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.16</td>
<td>0.24</td>
<td>0.32</td>
<td>0.40</td>
<td>0.48</td>
<td>0.56</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Highest</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.16</td>
<td>0.24</td>
<td>0.32</td>
<td>0.40</td>
<td>0.48</td>
<td>0.56</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Lowest</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.16</td>
<td>0.24</td>
<td>0.32</td>
<td>0.40</td>
<td>0.48</td>
<td>0.56</td>
<td>0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Average</td>
<td>0.02</td>
<td>0.04</td>
<td>0.08</td>
<td>0.16</td>
<td>0.24</td>
<td>0.32</td>
<td>0.40</td>
<td>0.48</td>
<td>0.56</td>
<td>0.64</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Honest John Warhead w/ Sarin Bomblets

US MLRS

| US M55 Rocket (GB, VX) | Multiple Launch Rocket System |

Chinese MLRS

Chinese multiple launch rocket system (122mm), or a variant of the BM21.

Video still photograph, 1979 Sino-Vietnamese war.
### Binary Shells

Left: Chinese depiction of a binary (nerve) shell. Below: the US M687 binary (GB) howitzer shell.

### Mixing Munition


### Psychoincapacitants

- **3-Quinuclidinyl benzilate**
  - Incapacitating dose ~0.5 mg
  - Anticholinergic
  - (think: Jimson’s Weed)
  - Note CNS activity

- **Atropine**
- **Sernyl**

*Not shown in the image.*
Hemlock has come a long way…

“Next to LSD these compounds probably possess the greatest significance as possible psychochemical warfare agents. They are comparatively easily prepared and their effective doses are small. If cyclohexyl or cyclopentyl radicals replace the phenyl groups in the basic formula, the psychoactivity is heightened.”

Siegfried Franke, 1967

Psychoactive Substances

These are psychoactive substances if

$R_1 = \text{CH}_3 \text{C}_2\text{H}_5$  $R_2 = \text{C}_6\text{H}_5$

$R_3 = \text{C}_6\text{H}_5 \text{C}_6\text{H}_{11} \text{C}_5\text{H}_9$

Antidotes and Prophylaxis

Chinese decon kit with atropine injector and carbamate prophylaxis

Nerve Poisoning Treatment

Close up on Chinese gravity injectors for nerve poisoning treatment (oxime)

Biological Warfare

“Public health in reverse…”

Toxicological Comparison?

<table>
<thead>
<tr>
<th>BW agent</th>
<th>Inhaled lethal dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum A</td>
<td>4.8</td>
</tr>
<tr>
<td>SEB</td>
<td>0.025</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>0.008</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>0.00001</td>
</tr>
<tr>
<td>Coxiella burnetti</td>
<td>0.000002</td>
</tr>
</tbody>
</table>
**Principles of Environmental Toxicology**

### Tularensis

<table>
<thead>
<tr>
<th>Miles</th>
<th>Animals</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>6,000</td>
<td>599</td>
</tr>
<tr>
<td>3</td>
<td>10,000</td>
<td>600</td>
</tr>
<tr>
<td>5</td>
<td>200,000</td>
<td>5,000</td>
</tr>
</tbody>
</table>

**Table 1:** Lethal dose of animals exposed to aerosol of Francisella tularensis.

### Aerosol Field Trial, 1950

- **A-B Toxin Mechanisms**
  - e.g., ricin, botulinum, diphtheria toxin, etc.

### Smallpox

**Scientific Evidence vs. Political/Legal**

- **Fool me once…**

Case study for the eternal pessimist:

1979 Sverdlovsk anthrax release.

### Hemorrhagic Meningitis

April 1979, Sverdlovsk
### Anthrax

“...[The] weight of spores released as aerosol could have been as little as a few milligrams or as much as nearly a gram.”—Meselson et al, *Science*, 1994.

“... the claim that the amount of anthrax released was so great that it exceeded any possible peaceful purpose is not supported by this information. ... we cannot be sure that the Compound 19 facility in particular was in violation of the [BWC] treaty.” Jeanne Guillemin, *Anthrax: The Investigation of a Deadly Outbreak*, (1999).

### Anthrax Lethality

![Graph of anthrax lethality](image)

**Fig. 1.** Response of the cynomolgus monkey to aerosols of Bacillus anthracis.

### Anthrax: Cumulative Dose

![Graph of cumulative dose](image)

**Fig. 5.** Calculated cumulative dose of Bacillus anthracis at time of death.

### Tularemia and the Siege of Stalingrad

Ken Alibek bases his allegation on the

- Hundreds of thousands of tularemia infections that quickly arose at the beginning of the siege at Stalingrad.
- Collaborative statements of an elderly lieutenant colonel in the Soviet Red Army.
- Significantly high (70%) pulmonary involvement among those infected with tularemia.

### Tularemia Outbreak

14,000 cases of tularemia reported in Rostov, January 1942.

July 23, 1942, Panzer divisions (13th and 22nd), and SS *Wiking* Division enter Rostov.
Exposure

[The] generalized pulmonary form of tularemia was the prevalent type among the infected troops on Don-River (95.2%). This was caused by tularemia’s means of spread (primarily respiratory). Inhalation of dust when using the infected hay as bedding was the decisive infection-causing factor.


The Siege of Stalingrad

Other sources of infection

- Mosquitoes
- Contaminated food and water
- Ticks

Lanzhou FMD Research Institute Results

- Nucleic acid sequencing found 97-98% homology with PRC laboratory FMDV type O Hong Kong isolates.
- Lanzhou FMD Institute not willing to release virus stock for further testing.

Taiwan’s 1997 Foot & Mouth Outbreak

Epidemiological field work conducted by Institute for Military Medicine, Beijing Military Region
Without cooperation…

there will not be a definitive answer.