Toxicity of Fumigants -
Short Introduction

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Methyl bromide (Bromo-methane)

- Highly volatile, odourless alkyl halide (addition of chloropicrin as a sensory warning agent)
- Methylating agent (e.g. pharmaceutical industry)
- Biological byproduct (phytoplankton, biomass burning)
- Used since 1932 as an insecticide
- Fumigant in farming (during and after harvest)
- Desinfectent for wood, furniture, warehouses etc. (freight containers)
- Toxic at low exposure levels (MAK: 1 ppm, BLW: 12 mg Br/l Plasma)
- High potency as ozone-depleting compound
- Use of methyl bromide is banned (2005 / 2015), but critical use exemptions are possible (where no adequate alternative is available)

\[ \text{CH}_3\text{Br} \]
### Effects of Methyl Bromide in Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>ppm</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>10</td>
<td>no effect</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>no effect (NOAEC)*</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>exposure terminated after 20 weeks (high mortality), but toxic effects persisted, e.g. body weight↓, activity↓, neurotoxicity males &gt; females, e.g. hind leg paralysis, tachypnea etc. Autopsy: degenerative changes in cerebellum etc. no carcinogenic effect</td>
</tr>
</tbody>
</table>

* NOAEC in rats: 30 ppm (13 weeks)  
NOAEC in dogs: 20 ppm (6 weeks)  

NTP, 1992
## Summary of Subchronic Inhalation Toxicity Studies with Methyl Bromide

<table>
<thead>
<tr>
<th>Study</th>
<th>Species (strain)</th>
<th>Exposure (h/days/weeks)</th>
<th>Overall NOEL</th>
<th>Neurotoxicity NOEL (effect)</th>
<th>Neurotoxicity LOEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subchronic neurotoxicity (Norris et al., 1993)</td>
<td>Rat (SD)</td>
<td>6/5/13</td>
<td>30 ppm</td>
<td>30 ppm</td>
<td>70 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (NTP, 1992)</td>
<td>Rat (SPF Wistar)</td>
<td>6/5/3; 6/7/1</td>
<td>18 ppm</td>
<td>18 ppm</td>
<td>51 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (Kato et al., 1986)</td>
<td>Rat (SD)</td>
<td>4/5/6</td>
<td>&lt;150 ppm</td>
<td>200 ppm (dec. body weight)</td>
<td>300 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (Haber et al., 1985) (NTP, 1992)</td>
<td>Rat (F344/N)</td>
<td>6/5/13</td>
<td>30 ppm</td>
<td>60 ppm (dec. body weight)</td>
<td>120 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (Japanese Ministry of Labour, 1992)</td>
<td>Rat (F344/DuCrj)</td>
<td>6/5/13</td>
<td>7.5 ppm</td>
<td>117 ppm (clinical pathology)</td>
<td>293 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (Wilmer et al., 1983)</td>
<td>Rat (Wistar)</td>
<td>6/5/13</td>
<td>6.4 ppm</td>
<td>42 ppm (liver pathology)</td>
<td>No neurotoxicity</td>
</tr>
<tr>
<td>Subchronic toxicity (NTP, 1992)</td>
<td>Mouse (B6C3F1)</td>
<td>6/5/13</td>
<td>20 ppm</td>
<td>80 ppm (hematology)</td>
<td>120 ppm</td>
</tr>
<tr>
<td>Subchronic toxicity (Japanese Ministry, 1992)</td>
<td>Mouse (Crj:BDF1)</td>
<td>6/5/13</td>
<td>30 ppm</td>
<td>60 ppm (body weight, hematology, urinalysis)</td>
<td>No neurotoxicity</td>
</tr>
</tbody>
</table>
Toxicity of Methyl Bromide

**Acute Exposure**
Symptoms depend on level of exposure and individual susceptibility (latency period of 2 - 48 h)

- **Skin irritation**
  (blistering, burns, contact dermatitis etc., is common when the gas is trapped in masks, gloves, boots etc.)

- **Eye** (corneal burns, irritation)

- **Inflammation of the bronchi and lung, pulmonary edema**
  (flu like symptoms, chest pain, shortness of breath)

- **Central nervous system**
  Three phases can be distinguished:
  1. disturbed vision, diplopia, headache, vertigo, vomiting, delirium, syncope
  2. Cerebral irritation (seizures, myoclonus, respiratory failure etc.)
  3. Recovery phase if the patient survives

- **Other** (e.g. renal tubular damage, liver injury)

Recovery after acute intoxication is slow and neurological and psychiatric sequelae are frequent
Toxicity of Methyl Bromide

Chronic Exposure

• **Neurological symptoms**
  mental confusion, lethargy, loss of initiative, depressed libido, personality changes, apathy, amnesia, aphasia, blurred vision, dysarthria, polyneuropathy and muscle weakness

• **Renal dysfunction**
  oliguria or anuria, associated with proteinuria and hematuria, may develop in serious cases; dialysis may be required
Central (and peripheral) nervous system: headache, dizziness, nausea etc.

**Lung:** reduction of lung function, chest pain, shortness of breath, inflammation of the lung

**Liver:** degenerative changes

**Kidney:** oliguria, anuria

**Prostate (†):** Methyl bromide is associated with increased risk for prostate cancer

*Target Organs in Methyl Bromide Intoxication* (Alavanja et al., Am J Epidemiol 2003)
Transformation of methyl glutathione into toxic metabolites! (methanethiol and formaldehyde)

Hemoglobin adduct formation
DNA-adduct formation
Formation of oxidatively damaged DNA (8-OHdG secretion)
Epigenetic changes (methylation status, chromosomal aberrations)
Cell - apoptosis - necrosis
Granular cell

Perigranular cell

Mechanism of Methyl Bromide-induced Neurotoxicity

Neuronal loss in dorsal root ganglia and axonal degeneration in nerve roots and proximal nerve segments have been shown

Diminished energy metabolism and increased apoptosis/necrosis rates in granular cells

CH$_3$ Br

GSH

DNA-Methylation
DNA-Repair

Ca$^{2+}$

ROS

Cytochrome oxidase

COX

Necrosis

Apoptosis

GSH (Glutathion; $\gamma$-L-Glutamyl-L-Cysteinglycin)

Source: Prof. Budnik
Methyl Bromide Intoxication - Case Report (1) -

Patient: male, 30 years old

Emergency department:
patient is drowsy and irritable, disorientated to time and place

Four days ago:
blurred vision

One day ago:
difficulty in walking and swaying since 24 hrs
slurred speach, weakness lower limbs, inability to get up from the supine position, weakness progressed involving both upper limbs

Medical history:
he worked at a chemical factory, packaging methyl bromide
safety precautions were inadaequate
(masks, boots or gloves were not used routinely)

Next day:
bifacial weakness, paraparesis worsening
Methyl Bromide Intoxication - Case Report (2) -

CT brain: normal
Lumbar puncture: normal
Blood counts: normal
Biochemistry: normal
Art. blood gas: normal

Day 4 MRI:
Figure A / B characteristic symmetric findings (brainstem, cerebellum)

Day 15 MRI:
Figure D significant resolution, but midbrain lesions persisted (arrow)

Treatment: supportive care, physiotherapy

Day 10: level of consciousness starts to improve
Day 15: patient is alert, mild ataxia, impaired joint position sense both lower limbs

Figures:

de Souza, A. J Neurol Sci 2013; 335:36-41
Sulfuryl fluoride – an Alternative to Methyl bromide?

Toxic effects are (partly) mediated by fluorine

Probable Decomposition Products of $\text{SO}_2\text{F}_2$

(electrical discharge, hydrolysis, combustion)

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS No.</th>
<th>Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bispentafluorosulfur oxide</td>
<td>42310-84-9</td>
<td>$\text{S}<em>2\text{OF}</em>{10}$</td>
</tr>
<tr>
<td>Fluorine</td>
<td>7782-41-4</td>
<td>$\text{F}_2$</td>
</tr>
<tr>
<td>Hydrogen fluoride</td>
<td>7664-39-3</td>
<td>$\text{HF}$</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>7783-06-4</td>
<td>$\text{H}_2\text{S}$</td>
</tr>
<tr>
<td>Nitrogen trifluoride</td>
<td>7783-54-2</td>
<td>$\text{NF}_3$</td>
</tr>
<tr>
<td>Oxygen difluoride</td>
<td>7783-41-7</td>
<td>$\text{F}_2\text{O}$</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>7446-09-5</td>
<td>$\text{SO}_2$</td>
</tr>
<tr>
<td>Sulfur fluoramide</td>
<td>81625-84-5</td>
<td>($\text{SF}_5$)$_2\text{NF}$</td>
</tr>
<tr>
<td>Fluorine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfur fluoride</td>
<td>81439-35-2</td>
<td>$\text{S}_2\text{O}_3\text{F}_6$</td>
</tr>
<tr>
<td>Sulfur fluoride peroxide</td>
<td>12395-41-4</td>
<td>$\text{S}_2\text{O}<em>2\text{F}</em>{10}$</td>
</tr>
<tr>
<td>Sulfur hexafluoride</td>
<td>2551-62-4</td>
<td>$\text{SF}_6$</td>
</tr>
<tr>
<td>Sulfur pentafluoride</td>
<td>5714-22-7</td>
<td>$\text{S}<em>2\text{F}</em>{10}$</td>
</tr>
<tr>
<td>Sulfur tetrafluoride</td>
<td>7783-60-0</td>
<td>$\text{SF}_4$</td>
</tr>
<tr>
<td>Sulfur tetrafluoride oxide</td>
<td>13709-54-1</td>
<td>$\text{SOF}_4$</td>
</tr>
<tr>
<td>Thionyl fluoride</td>
<td>7783-42-8</td>
<td>$\text{SOF}_2$</td>
</tr>
<tr>
<td>Trifluoromethyl sulfur</td>
<td>373-80-8</td>
<td>$\text{SF}_5\text{CF}_3$</td>
</tr>
</tbody>
</table>
## Occupational exposure Limits of SO$_2$F$_2$ and its Probable Decomposition Products Containing Fluorine and / or Sulfur

<table>
<thead>
<tr>
<th>SO$_2$F$_2$ and Its Decomposition Products</th>
<th>TLV$^a$</th>
<th>PEL$^b$</th>
<th>MAK$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfuryl fluoride (SO$_2$F$_2$)</td>
<td>5 ppm</td>
<td>5 ppm</td>
<td>8.7 ppm</td>
</tr>
<tr>
<td>Bispentafluorosulfur oxide (S$<em>2$OF$</em>{10}$; as F)$^f$</td>
<td>2.5 mg m$^{-3}$</td>
<td>2.5 mg m$^{-3}$</td>
<td>—</td>
</tr>
<tr>
<td>Fluorides (as F)</td>
<td>2.5 mg m$^{-3}$</td>
<td>2.5 mg m$^{-3}$</td>
<td>2.5 mg m$^{-3}$</td>
</tr>
<tr>
<td>Fluorine (F$_2$)</td>
<td>1 ppm</td>
<td>0.1 ppm</td>
<td>0.1 ppm</td>
</tr>
<tr>
<td>Hydrogen fluoride (HF)</td>
<td>3 ppm (Ceiling)</td>
<td>3 ppm</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Hydrogen sulfide (H$_2$S)</td>
<td>5 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
</tr>
<tr>
<td>Nitrogen trifluoride (NF$_3$)</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>—</td>
</tr>
<tr>
<td>Oxygen difluoride (F$_2$O)</td>
<td>0.05 ppm (Ceiling)</td>
<td>0.05 ppm (Ceiling)</td>
<td>—</td>
</tr>
<tr>
<td>Sulfur dioxide (SO$_2$)</td>
<td>2 ppm</td>
<td>2 ppm</td>
<td>0.5 ppm</td>
</tr>
<tr>
<td>Sulfur hexafluoride (SF$_6$)</td>
<td>1000 ppm</td>
<td>1000 ppm</td>
<td>1000 ppm</td>
</tr>
<tr>
<td>Sulfur pentafluoride (S$<em>2$F$</em>{10}$)</td>
<td>0.01 ppm (Ceiling)</td>
<td>0.01 ppm (Ceiling)</td>
<td>0.025 ppm</td>
</tr>
<tr>
<td>Sulfur tetrafluoride (SF$_4$)</td>
<td>0.1 ppm (Ceiling)</td>
<td>0.1 ppm (Ceiling)</td>
<td>—</td>
</tr>
<tr>
<td>Thionyl fluoride (SOF$_2$; as F)$^f$</td>
<td>2.5 mg m$^{-3}$</td>
<td>2.5 mg m$^{-3}$</td>
<td>—</td>
</tr>
</tbody>
</table>

TLV = Threshold limit value (ACGIH, US)  
PEL = Permissible exposure limit (OSHA, US)  
MAK = Maximum allowable concentration (DFG, German)

Wen-Tien Tsai  
J Environm Sci Hlth (Part C)  
2010;28:125-145
Effects of Sulfuryl Fluoride in Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>ppm</th>
<th>Duration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>30</td>
<td>13 weeks</td>
<td>NOAEC</td>
</tr>
<tr>
<td>Rat</td>
<td>30</td>
<td>13 weeks</td>
<td>NOAEC</td>
</tr>
<tr>
<td>Rabbit</td>
<td>30</td>
<td>13 weeks</td>
<td>NOAEC</td>
</tr>
<tr>
<td>Dog</td>
<td>100</td>
<td>13 weeks</td>
<td>NOAEC</td>
</tr>
</tbody>
</table>

Higher Concentrations (100, 300 ppm): body weight decreased, mottled teeth, neuro-, nephro- and hepatotoxicity; lung and nasal tissues were injured.

Acute Exposure: lethal at approx 400 to 1100 ppm

Wen-Tien Tsai
J Environm Sci Hlth (Part C)
2010;28:125-145
Sulfuryl fluoride – an Alternative to Methyl bromide?

Report of a fatal case from San Diego, California

Female, 37 years old (depression, methamphetamine user)

acute intoxication after exposure to sulfuryl fluoride / chloropicrin (she was under a tarpaulin used to enclose an apartment complex)

Typical symptoms of such an intoxication: electrolyte abnormalities (hypocalcemia, hypomagnesiemia, hyperkaliemia) delayed dysrhythmias, torsades de points, dead three hours after arrival at ED

Fluoride concentration: 24 mg/l

Treatment with calcium gluconate, magnesium, phenobarbital

Schneir, A. et al. 2008;46:850
Summary and Conclusion

Pesticides used for container fumigation exhibit pronounced toxicity at low concentrations (e.g. methyl bromide, sulfuryl fluoride).

Replacement of one chemical by the other will shift the problems, but not solve them.

Preventive measures should include stricter controls and non-chemical solutions, such as heat inactivation.
Thank you for your attention