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Toxicity of Fumigants -

Short Introduction

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Methyl bromide (Bromo-methane)

CH_3Br

- 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)

Effects of Methyl Bromide in Animals

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

NTP, 1992

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

Summary of Subchronic Inhalation Toxicity Studies with Methyl Bromide

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

Piccirillo & Piccirillo, Methyl Bromide in: Handbook of Pesticide Toxicology, 2010

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 gfailaure 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

Target Organs in Methyl Bromide Intoxication

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

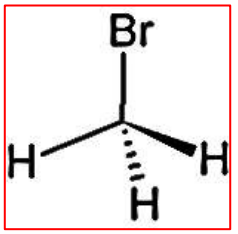
Kidney: oliguria, anuria

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

(Alavanja et al., Am J Epidemiol 2003)

Metabolism of Methyl Bromide and other Alkyl Halides

(Budnik, 2012)



CH_3-X (Cl, Br, I) → Br^-

Glutathione-S-transferase + GSH

-Cl < -Br < -I

Cytochrome P-450

S-Methylglutathione

CO_2 major metabolite

Alkylation of macromolecules

CH_3-S-CH_2-CH(NH_2)-COOH

S-Methylcysteine

HCHO **Formaldehyde** → HCOOH **Formic acid** → **Urinary excretion**

CH_3-SH

Methanethiol

C_1-Pool → CO_2 → **Exhalation**

Toxicity?

Incorporation

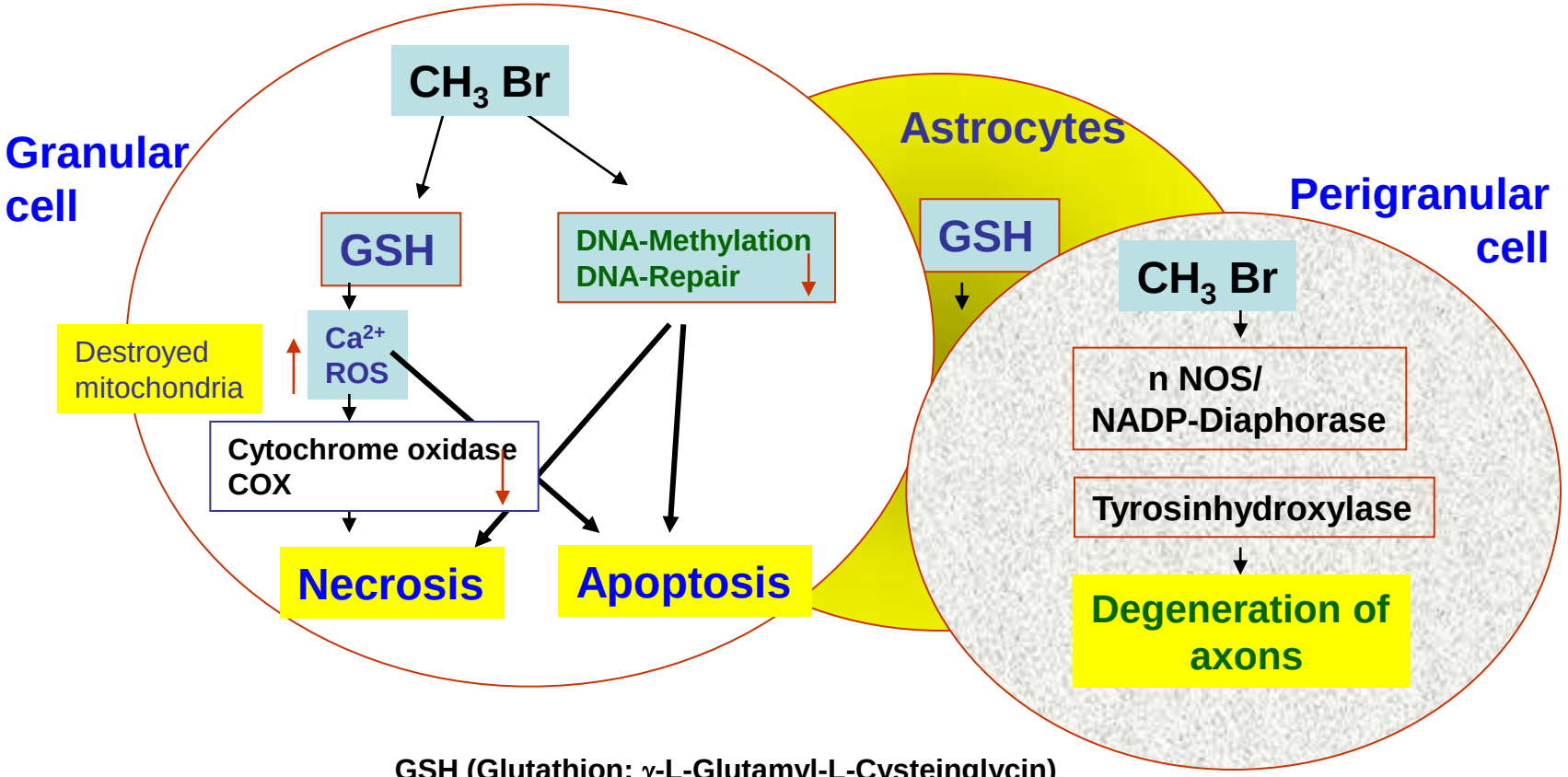
Transformation of methyl glutathione into toxic metabolites! (methanethiol and formaldehyde)

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

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



GSH (Glutathion; γ-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

de Souza, A. J Neurol Sci 2013; 335:36-41

Methyl Bromide Intoxication
- Case Report (2) -

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

Figures:

de Souza, A. J Neurol Sci 2013; 335:36-41

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

Sulfuryl fluoride – an Alternative to Methyl bromide?

SO_2F_2

Toxic effects are (partly) mediated by fluorine

Wen-Tien Tsai

Environmental and Health Risks of Sulfuryl Fluoride, a Fumigant Replacement for Methyl Bromide

J Environm Sci Hlth (Part C) 2010;28:125-145

Probable Decomposition Products of SO_2F_2

(electrical discharge, hydrolysis, combustion)

Compound	CAS No.	Molecular Formula
Bispentafluorosulfur oxide	42310-84-9	S_2OF_{10}
Fluorine	7782-41-4	F_2
Hydrogen fluoride	7664-39-3	HF
Hydrogen sulfide	7783-06-4	H_2S
Nitrogen trifluoride	7783-54-2	NF_3
Oxygen difluoride	7783-41-7	F_2O
Sulfur dioxide	7446-09-5	SO_2
Sulfur fluoramide fluorine	81625-84-5	$(SF_5)_2NF$
Sulfur fluoride fluorosulfate	81439-35-2	$S_2O_3F_6$
Sulfur fluoride peroxide	12395-41-4	$S_2O_2F_{10}$
Sulfur hexafluoride	2551-62-4	SF_6
Sulfur pentafluoride	5714-22-7	S_2F_{10}
Sulfur tetrafluoride	7783-60-0	SF_4
Sulfur tetrafluoride oxide	13709-54-1	SOF_4
Thionyl fluoride	7783-42-8	SOF_2
Trifluoromethyl sulfur pentafluoride	373-80-8	SF_5CF_3

Occupational exposure Limits of SO_2F_2 and its Probable Decomposition Products Containing Fluorine and / or Sulfur

SO_2F_2 and Its Decomposition Products	TLV[a]	PEL[b]	MAK[c]
Sulfuryl fluoride (SO_2F_2)	5 ppm	5 ppm	8.7 ppm
Bispentafluorosulfur oxide (S_2OF_{10}; as F)[f]	2.5 mg m^{-3}	2.5 mg m^{-3}	—
Fluorides (as F)	2.5 mg m^{-3}	2.5 mg m^{-3}	2.5 mg m^{-3}
Fluorine (F_2)	1 ppm	0.1 ppm	0.1 ppm
Hydrogen fluoride (HF)	3 ppm (Ceiling)	3 ppm	3 ppm
Hydrogen sulfide (H_2S)	5 ppm	10 ppm	10 ppm
Nitrogen trifluoride (NF_3)	10 ppm	10 ppm	—
Oxygen difluoride (F_2O)	0.05 ppm (Ceiling)	0.05 ppm (Ceiling)	—
Sulfur dioxide (SO_2)	2 ppm	2 ppm	0.5 ppm
Sulfur hexafluoride (SF_6)	1000 ppm	1000 ppm	1000 ppm
Sulfur pentafluoride (S_2F_{10})	0.01 ppm (Ceiling)	0.01 ppm (Ceiling)	0.025 ppm
Sulfur tetrafluoride (SF_4)	0.1 ppm (Ceiling)	0.1 ppm (Ceiling)	—
Thionyl fluoride (SOF_2; as F)[f]	2.5 mg m^{-3}	2.5 mg m^{-3}	—

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

Species	ppm	Duration	Effects
Mice	30	13 weeks	NOAEC
Rat	30	13 weeks	NOAEC
Rabbit	30	13 weeks	NOAEC
Dog	100	13 weeks	NOAEC

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)
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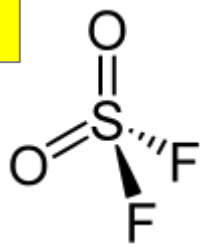
Sulfuryl fluoride – an Alternative to Methyl bromide?

SO_2F_2



Report of a fatal case from San Diego, California

Female, 37 years old (depression, methamphetamin 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 (hypocalciemia, hypomagnesiemia, hyperkaliema)
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