

Toxicology of Methyl Chloride

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What is methyl chloride?

- ▶ Common names chloromethane/monochloromethane
- ▶ Clear, colorless extremely flammable organic solvent
- ▶ Non-irritating ether smelling odor that is faintly sweet to the taste
- ▶ Moderately soluble in water and decomposes via the following chemical pathway:



Chemical and Physical Properties

Empirical Formula	CH ₃ Cl
Molecular Weight	50.46
Melting Point	-97.6 °C
Boiling Point	-23.7 °C
Vapor Pressure	3,670 mm Hg at 20 °C
Solubility (H ₂ O)	6,263 - 7,400 mg/L at 20 °C
Log K _{OW}	0.91
Blood-air PC	2.12 - 2.49 (10 ppm)
Odor Threshold	100 ppm
Conversion Factor (25 °C)	1 ppm (v/v) = 2.064 mg/m ³

Where is methyl chloride found in the environment?

- ▶ Ubiquitous in the environment
- ▶ Primary natural sources include the ocean, microbial fermentation and biomass fires
- ▶ Non-anthropogenic sources contribute between 90 and 99% of the total release into the environment
- ▶ Anthropogenic sources are primarily produced and consumed industrially and are generally not released to the environment

How might one be exposed to methyl chloride?

- ▶ Applied as a methylating agent in the production of silicones, butyl rubber, TML, methyl cellulose, plastics, agrichemicals, dyes, perfumes, resins, and pharmaceuticals
- ▶ Utilized as a blowing agent for some polystyrene (e.g., Styrofoam[®]) and polyurethane foams
- ▶ Improper disposal of vinyl chloride waste
- ▶ Cigarette smoke, aerosol propellants, and chlorinated swimming pools

Toxicokinetics - Absorption

- ▶ Almost exclusively absorbed through inhalation
- ▶ Minor routes include dermal absorption (moderate) and ingestion (low)
- ▶ CH_3Cl is readily absorbed by the lungs and rapidly attains steady-state concentrations in expired air and the blood within 1-2 hr of continuous exposure
- ▶ Blood:air partition coefficient (PC): 2.1-2.5 (10 ppm)
- ▶ Two groups of individuals can be identified based on their rate of CH_3Cl metabolism: “slow metabolizers” and “rapid metabolizers”

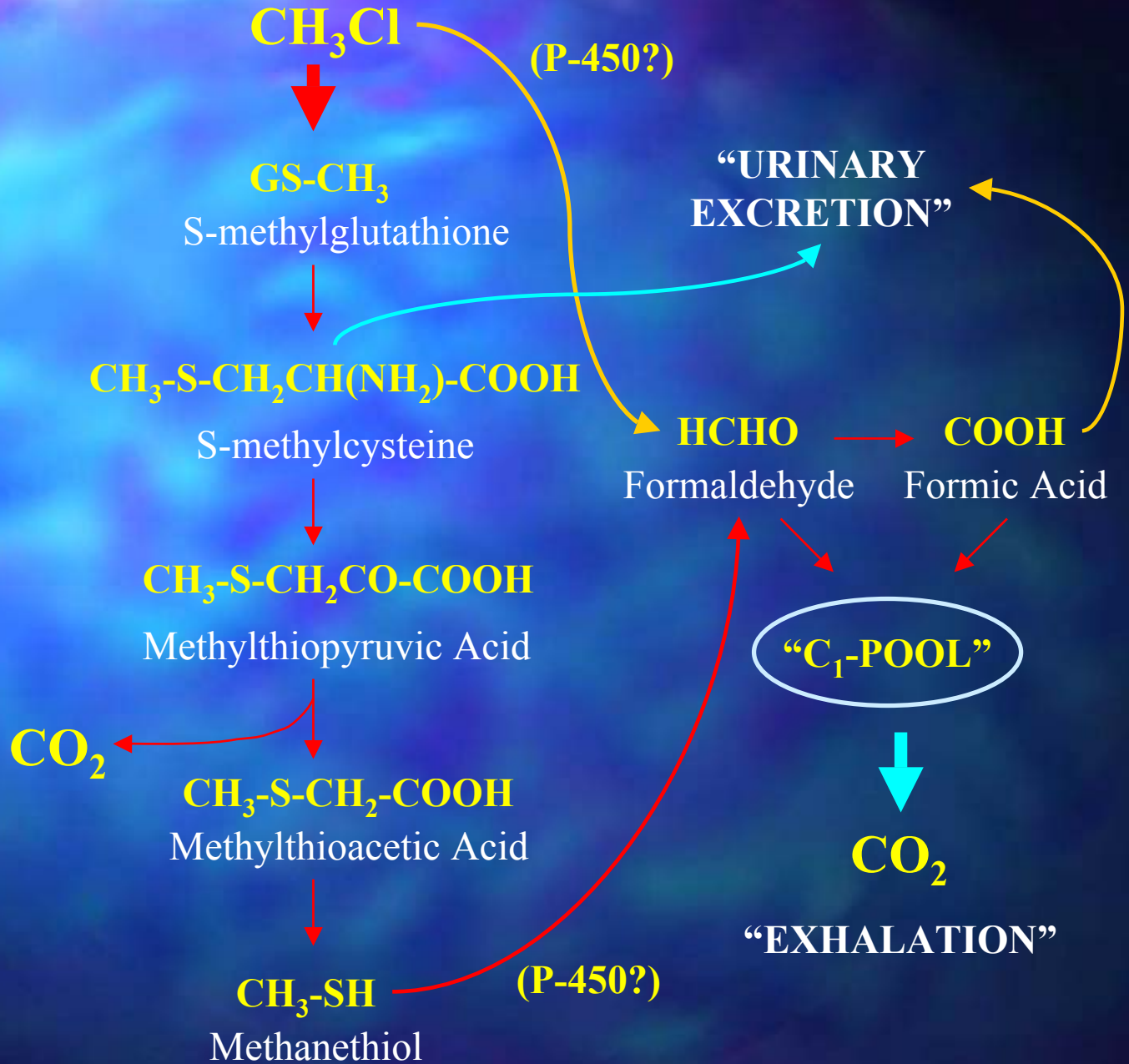
Toxicokinetics - Distribution

- ▶ CH_3Cl distributes rapidly to the liver, kidneys, (CNS), spleen, testes, and brain
- ▶ ^{14}C -labeled CH_3Cl studies indicate that although ~80% of CH_3Cl is acid-soluble the remainder is distributed among cellular macromolecules (e.g., DNA, RNA, protein, and lipid)
- ▶ However, accurate determinations are limited by the high volatility and rapid metabolism of CH_3Cl

Toxicokinetics - Metabolism

- ▶ Principle Phase: conjugation with glutathione (GSH)
- ▶ Secondary Phase: P-450 (CYP2E1) oxidation of GSH-CH₃Cl conjugation intermediates resulting in the formation of formaldehyde (HCHO)
- ▶ Alternate step (minor): direct dehalogenation of CH₃Cl to HCHO via a cytochrome P-450-mediated oxidation pathway
- ▶ HCHO enters the “One-Carbon Pool” where it becomes available for macromolecule synthesis (e.g., DNA, RNA, protein, & lipid) or expired as CO₂

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Toxicokinetics - Excretion

- ▶ Exhalation: Carbon dioxide (>45%)
- ▶ Urinary Excretion in the form of various sulfur-containing compounds (suggested biomarkers of exposure)
 - ▶ S-methylcysteine
 - ▶ N-acetyl-S-methylcysteine
- ▶ Elevated urinary S-methylcysteine levels were observed in 4 of 6 chemical workers exposed to 30-90 ppm CH_3Cl over the course of a 7-day work week (van Doorn et al., 1980)

Signs & Symptoms of CH₃Cl Exposure

- ▶ Principally acts as a depressant of the CNS
- ▶ Symptoms of CH₃Cl exposure indicative of CNS toxicity include:
 - ▶ headache
 - ▶ dizziness
 - ▶ double vision
 - ▶ fatigue
 - ▶ personality changes
 - ▶ ataxia
 - ▶ death
 - ▶ confusion
 - ▶ uncoordinated movements
 - ▶ nausea
 - ▶ vomiting
 - ▶ convulsions
 - ▶ coma

Secondary Toxicological Effects

- ▶ Heart, gastrointestinal tract, liver, kidneys, & lungs
- ▶ Signs of CH₃Cl exposure indicative of CNS toxicity:
 - ▶ Tachycardia
 - ▶ Low blood pressure
 - ▶ Cirrhosis (liver)
 - ▶ Blood urea N₂
 - ▶ Proteinuria
 - ▶ Increased pulse rate
 - ▶ EKG abnormalities
 - ▶ Albuminuria
 - ▶ Increased creatinine

What makes methyl chloride toxic?

- ▶ Direct methylation of cellular macromolecules
- ▶ Increase in inflammatory messengers (e.g., $\cdot\text{OH}$, OONO^- , $\cdot\text{NO}$ and other ROI)
- ▶ Depletion in tissue GSH levels significantly effects tissues capacity to protect itself against the oxidative effects of free radicals and other ROS
- ▶ P-450 metabolism may directly produce high levels of formaldehyde (HCHO): genotoxic agent

Reducing the Risk of Exposure

- ▶ Stay clear of contaminated areas and work places known for using methyl chloride
- ▶ Familiarize yourself with the essential safety equipment, and proper disposal protocols for products containing methyl chloride
- ▶ Limit exposure of breathing smoke from burning vinyl chloride and silicone rubber products
- ▶ Test water sources for CH_3Cl contamination

Medical Treatment & First Aid Measures

- ▶ Inhalation - remove to fresh air immediately and administer artificial respiration as required
- ▶ Contact (skin) - remove contaminated clothing and administer appropriate first aid measures in case of frostbite
- ▶ Contact (eyes) - flush eyes immediately for at least 15 minutes
- ▶ Ingestion - do not induce vomiting

“CONSULT A PHYSICIAN IMMEDIATELY”

Regulated Exposure Limits

- ▶ OSHA Permissible Exposure Limit (PEL) of 100 ppm TWA; 200 ppm ceiling for 5-min maximum peak of 300 ppm for any 3-hr period
- ▶ ACGIH TLV-TWA 50 ppm
STEL 100 ppm
- ▶ IARC Group 3 (possible human carcinogen)