

Overview of Solvents

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A Solvent is any substance, usually a liquid, that dissolves another substance. This results in a solution. They are either water based (aqueous) or hydrocarbon based (organic). Most used in industry are organic. They are used in degreasing, cleaning, thinning and extraction. There are over 30,000 industrial solvents. Their main use is as chemical intermediates. Important features of solvents include (a) solubility: Dermal absorption, anesthetic quality, and general industrial efficiency depend on degree of lipid solubility. A few are amphipathic (soluble in both water and oil.) (b) flammability: Some are highly explosive whereas others, such as halogenated hydrocarbons are used to extinguish fires. The National Fire Prevention Association rates flammability from 0-non flammable to 4-explosive. Measurements of flash point and ignition temperature will help determine this property. (c) volatility: Since inhalation is the most common way to become ill from a solvent, its volatility is important in determining exposure. Its vapor pressure and evaporation rate are the key areas to observe. An aprotic solvent is one that has strong ionic power and can dissolve both ionic or inorganic as well as organic materials. Solvents like water and alcohol are protic because they contain hydrogen attached either to oxygen or nitrogen, and are acidic in nature. Aprotic solvents leave the anionic portions unencumbered and are highly reactive for a chemical reaction, whereas protic solvents solvate anions strongly. Thus protic solvents lower the reactivity of compounds.

Functional families of solvents include:

alcohols, amines, amides, carboxylic acids, esters, glycols, halogens, and ketones.

PHARMACOLOGY

Pulmonary: Lipid soluble vapors cross the alveolar-capillary membrane. % retained for most organic solvents is 40 to 80 % at rest. Labor increases the retention 2-3x.

Percutaneous: Determined by not just fat solubility but also water solubility and volatility. The most dangerous solvent for skin absorption would have a low volatility rate, be both lipid and water soluble.

DISTRIBUTION

Tend to go to lipid rich tissue. This includes nervous system and liver. Also in organs with large blood flow such as heart and skeletal muscle.

METABOLISM

A number are metabolized by alcohol and aldehyde dehydrogenase (trichlorethylene). Competition for these enzymes with alcohol consumption accounts for alcohol intolerance or degreaser's flush. Also taking Antabuse will cause reactions to occur with solvent exposure. Chronic alcohol use previously may induce more enzyme and result in lower solvent blood levels. Other solvents produce toxic metabolites which interfere with clearing mechanisms.

EXCRETION

Either through exhalation of unchanged solvent through respiratory exchange or through urinary output of metabolites. The parent half life is from minutes to several days. Bioaccumulation is usually not a problem clinically.

MONITORING

For certain compounds, biological monitoring is more accurate than environmental monitoring. At times short exposure to high dose is more important and environmental monitoring, done expeditiously, is best in those cases. Some solvents with low skin penetration or poor pulmonary vapor exposure (low volatility) should rely more on environmental monitoring. The ACGIH recommends BEIs for: n-hexane

Select nonhalogenated solvents in common use include the following:

Carbon disulfide Nitromethane

Dioxane Pyridine

Dimethylformamide Turpentine

Stoddard solvent Butyl mercaptan

Isophorone Dimethyl sulfoxide

1-Nitropropane 2-Nitropropane

Naphtha-coal tar Naphtha-petroleum

CARBON DISULFIDE CAS 75-15-0 S-C-S

(CS, carbon disulphide, carbone sulfide, dithiocarbonic anhydride)

PEL -TWA = 4 ppm or 12 mg/m³; STEL 12 ppm(OSHA)

After a brief trial in medicine, it was first used commercially, in 1851 as a phosphorus solvent in the manufacturing of matches. Then the use spread to refining of paraffin and petroleum, and the extraction of plant and animal oils. With the discovery of the "cold" vulcanization process and the viscose rayon industry its use became more widespread. To soften rubber so that thin sheets are possible, strips of rubber are dipped into a mixture of carbon disulfide and sulfur monochloride. This was known as "cold" vulcanization. This process was abandoned after severe toxic effects were documented. In the U.S., today, it is used as a :
Chemical intermediate for rayon, cellophane, carbon tetrachloride, xanthogenates, soil disinfectants, herbicides, carbonyl sulfide, adhesives and other compounds. Also in the manufacturing of electronic vacuum tubes, a solvent for phosphorus, selenium, bromide, iodide, fats and resins. As a fumigant for commodities, an agent in metal treatment and plating, corrosion inhibitor, polymerization inhibitor for vinyl chloride, agent in the removal of metals from waste water, veterinary antihelminthic, instant color photography, and regenerator for transition metal sulfide catalysts.

TOXICITY:

CS is efficiently absorbed by ingestion, skin or inhalation. In animals a steady plasma state is reached in 15 minutes and RBC in 2 hours with 90% bound to RBCs. It reacts with amines and thiols directly and forms dithiocarbamate metabolites which inactivate metalloenzymes by chelation. Neurotoxicity is of the filamentous dying back type similar to n-hexane. Secondly metabolites produced through P-450 and mixed oxidase reactions directly interfere with hepatic pathways..

Lipid metabolism is interfered with, which may have an effect of cardiovascular function. 8-20% of CS is eliminated unchanged in breath. 0.5% in urine. 50-90% is metabolized in the body. 1/2 life is 1 hour in blood. Urine metabolites include, inorganic sulfates, thiourea, 2- mercapto-2-thiazolin abd 2-thiothiazolidine-4-carboxylic acid. The latter metabolite is the marker of choice and replaces the older iodine-azide method. Antabuse is partially metabolized to carbon disulfide and is potentially neurotoxic accordingly.

CS dermal effects can cause pain or full thickness burns. CS is one of the strongest skin irritants known. Skin exposure alone can lead to vomiting, dizziness, cardiac arrhythmias and coma.

Ocular - immediate painful conjunctivitis.

Ingestion - 15 ml have been fatal. Acutely a major overdose leads to coma, convulsions spasmodic tremor, cyanosis, cardiovascular collapse, and pulmonary failure.

Inhalation of large amounts has been fatal. 500 ppm has been determined life threatening. At 200 ppm with an outdoor spill, Headaches, nausea,, burning of eyes, throat, lips or skin, dizziness, SOB, vomiting were reported.

Chronic effects-On CNS effects- many additional theories of action. Affective personality state. suicidal ideation., severe insomnia, bad dreams, impotence, atypical parkinsonism, cerebellar signs, hearing loss, sensory changes. 80% had cogwheel rigidity, 48% had resting tremors, 52% had intention tremor, peripheral nerve sensory changes in 62%. Even levels of 20 ppm over years may cause a peripheral neuropathy. Optic neuritis is found with this poison.. Delayed choroidal filling is an important clue to the diagnosis. Central scotoma, and posterior pole pigmentation are sometimes seen.

Increased cardiovascular risk with more arteriosclerosis and probably direct toxic effect of the product. Liver effects are limited, Scant renal effect evidence, Questionable spermatogenesis evidence. Has some endocrine effects including reducing thyroid and is not classified as a carcinogen.

NIROMETHANE:(nitrocarb) CH_3NO_2

TWA-TLV = 100 ppm

Used as solvent in the electronics industry and as a rocket fuel. Also used in the manufacturing of chloropicrin, a fumigant and race car fuel.

Can be a skin irritant, and a hepatotoxin. In animals convulsions and coma can occur. Irritates skin and mucous membranes.

DIOXANE: (Diethylene dioxide, diethylene ether) $\text{C}_4\text{H}_8\text{O}_2$

IDLH 299 ppm PEL 100 ppm (skin) OSHA; NIOSH 1ppm for 30 minutes.; ACGIH TLV 25 ppm

Solvent for resins and oils. Very flammable and form explosive mixtures with air. Mucous membrane irritant. Pleasant odor with an air threshold of 170 ppm. At 0.1 to 3% vapor concentration the odor and irritation can warn you but chronic exposure at these levels can lead to CNS depression, pulmonary edema and death. Renal and Hepatic injury can occur with this agent. An animal carcinogen. Workers around high levels experience headache, nausea, vomiting, pulmonary irritation, drowsiness and hepatic and renal damage. Other features are: it is a defatting

agent, has poor warning properties of the warning threshold, can cause corneal damage.

PYRIDINE (azine, azabenzene) C₅H₅N

PEL 5 ppm IDLH 3600 ppm

Used in the synthesis of organic compounds and agricultural chemicals.

Manufacturing of rubber, paints, dyes, pharmaceuticals, and explosives.

Inflammable liquid. Very unpleasant odor at 1 ppm, olfactory fatigue can occur.

Acute ingestion - Hepatic and renal damage. Usual problems are Skin sensitization, CNS depression, dizziness headaches, mucous membrane irritability, confusion, syncope, coma and renal and hepatic toxicity.

DIMETHYLFORMAMIDE (CH₃)₂NCHO PEL 10PPM TWA IDLH is 3500ppm.

A colorless liquid solvent. Exposure are dermal and inhalational. hepatotoxin. can become systemically toxic via dermal absorption. Manufacturing polyurethane products and in the pharmaceutical industry. Biopsied samples in workers show hepatocellular injury. Anorexia, nausea, disulfiram-type reactions with ethanol, abdominal pain. Alanine aminotransferase to aspartate aminotransferase ratio is elevated and greater than 1. Resolution of findings in 16 months.

NITROPROPANE (1-NITROPROPANE) CH₃CH₂CH₂NO₂ TLV 25ppm 2-

Nitropropane is more toxic and has a TLV of 10ppm.

A liquid solvent used for propellants, organic cellulose, and other organic materials such as esters, resins, dyes, fats and waxes. 2-Nitropropane is a hepatotoxin. Both are irritants to the lungs, nose and eyes. Fulminant liver failure has been reported with 2-Nitropropane. 2-nitropropane has been used since the 1940s as a solvent. Also as a rocket propellant. Exposures may occur in highway maintenance, shipbuilding, plastic production and construction industry. A resin sealer to water pipes in a confined space has caused poisoning. Autopsy showed massive hepatocellular necrosis. 9 other deaths from coating applications in poorly ventilated areas. Absorbed through skin or lungs.

NAPHTHA PEL 500ppm(Petroleum naphtha) 100ppm (Coal tar naphtha)

Coal tar naphtha is a light yellow solvent that boils between 110 to 190 degrees C.

CNS depressant and respiratory irritant. Coal tar naphtha is a mixture of aromatic hydrocarbons including toluene, xylene, cumene and benzene.

Petroleum distillate derived naphtha contains aliphatic hydrocarbons and also contains benzene.

Coal tar derived naphtha, due to its aromatic hydrocarbon content, is more toxic to CNS, renal, hepatic and, due to the greater benzene amounts, bone marrow.

Dermatitis can result.

DIMETHYL SULFOXIDE No PEL or TLV.

May carry toxic compounds through the skin. Causes cataracts in some animal models but not in man. Used in interstitial cystitis. A highly polar universal solvent.

By itself, is generally not toxic.

ISOPHORONE Pel 4ppm TWA same Water limits(EPA) 5.2ml/L

Used as a solvent for metal cans, vinyl chloride-acetate based coating system, metal paints, nitrocellulose finish, inks used in plastics and polystyrene formulations. Mainly in vinyl coatings and inks. Also in agricultural products. Patients at higher risk work in screen printing, coating manufacturing and certain adhesive formulators. C₉H₁₄O is also known as isoacetophorone and isoforon. A clear liquid with a boiling point of 215 degrees C. Half life in air of 5 hours but can last for days in water.

Respiratory and skin irritation common in printing plants due to the product. No liver, kidney or blood effects from product. 10 ppm for 10 minutes tolerated satisfactorily but 25 ppm produced irritation of eyes and upper respiratory complaints. Nervous system effects from 5 to 8 ppm. Not below 5 ppm. Mainly fatigue and malaise, headaches, loss of concentration.

In animal studies it is a animal carcinogen with renal tubular adenomas in male but not female rats. No specific neuropathology noted.

BUTYL MERCAPTAN also known as thiobutyl alcohol

Colorless flammable liquid. TLV 0.5ppm OSHA PEL is 10 ppm. Very bad odor. It is a mucous membrane irritant. Odor threshold is 0.01ppm.

STODDARD SOLVENT White spirits or mineral spirits. PEL 100ppm

A colorless fluid used in paint thinners and degreasing operations. It is 15% aromatic compounds and 85% paraffins and naphthenic hydrocarbons. It is a CNS depressant and a skin, eyes, and respiratory tract irritant. Odor threshold is 0.9ppm. Does not produce adequate warning via odor.

ISOBUTYL MERCAPTAN C₄H₁₀S Recognition odor of 0.00097ppm.

Skunk like odor. Highly reactive with oxidizing materials and moderately flammable. It is an irritant with moderate toxicity with inhalation or ingestion.

OSHA PEL and TWA of 10ppm. Emits toxic odors when heated to decomposition or when reactive with acids.

TURPENTINE C₁₀H₁₆ PEL 100ppm with IDLH of 1900ppm. Derived from Pinus pinacea tree as an oleoresin. Used as an insecticide and a general flammable solvent. Inhalation, ingestion or skin absorption. Mucous membrane irritant at 75ppm. CNS depressant. Consist of 9% camphene, 83% a-pinene, 2% b-pinene, 7% other terpenes. A skin irritant.

Some halogenated solvents are discussed below:

TRICHLOROETHYLENE

CAS: 79-01-6

1987 TLV = 50 ppm, 200 ppm STEL (ACGIH); OSHA PEL 100 ppm, 8 hour TWA; 200 ppm acceptable ceiling; 300 ppm maximal ceiling (5 minutes in 2 hours); NIOSH 25 ppm TWA.

Noninflammable, mobile liquid

Uses. Degreasing solvent; dry cleaning and extraction: chemical intermediate; medical(limited)

Exposure: inhalation

Toxicology. A central nervous system depressant. carcinogenic in animals.

At levels of 500 ppm in volunteers- CNS signs of dizziness, light headedness, lethargy, impairment in visual motor response tests. At 300 ppm or less, acutely, no alteration in performance. With mean levels of 200 to 300 ppm however (more chronic exposure), prenarctic symptoms occurred such as a feeling of inebriation and visual disturbances. Mild liver dysfunction can also result . Hearing deficits can occur at toxic levels over a prolonged time frame.

At 100-200 ppm (chronic) workers reported fatigue, vertigo, dizziness, headaches, memory loss, and impaired ability to concentrate. Also paresthesias, muscular pains and gastrointestinal disturbances occur at around 100 ppm. Intolerance to alcohol with a facial and neck flush occur. Mildly irritating to the skin. due to defatting.

Direct eye contact produces injury to the cornea. With a mixture of solvents, Seppalainen et al.(1980) found abnormally slow nerve conduction studies which increased stastically significantly ($p<0.05$) in the high exposure group. The relatively slow nerve conductriion persisted 3 to 9 years after they were bi konger exposed to the solvents. Trichlorethylene was one of the solvents. In fact EMG abnormalities such as fibrillations and loss of motor unir\ts increased in this group. EEG abnormalities in solvent exposed groups show stastically signigificant differences. With jet fuel mixtures the workers (n=30, Mean 17 years) showed lower amplitude, less obsevable rhythmic activity and higher alpha peak frequencies.)

Breath analysis for TCE is a more accurate index than measurement of metabolites in urine (trichloroethanol and trichloroacetic acid.

Intragastric administration of 2.4 g/kg, five times a week for 78 weeks resulted in murine hepatocellular carcinomas (a form of liver cancer) in 31 of 48 mice. AT 1.2 g/kg 26 of 50 male mice (52%) were affected with 5 % of controls affected. An increase of renal adenocarcinomas was also found in male rats.

No teratogenic effects on rodent assays but some mild fetotoxic effects were seen at 1800 ppm. Even 300 ppm showed fetotoxic effects in mice but not rats. No conclusive evidence of fetotoxicity in humans. An increased incidence of menstrual disorders and in males, decreased libido, has been reported. Chronic neurologic encephalopathy may occur especially Type 1, 2a and 2b ISW (Bardode and Vyskocil, Grandjean, Lilis)(see SOLVENTS).This solvent has caused a generally reversible cranial and peripheral neuropathy associated with sensory loss and motor weakness in the trigeminal nerve and to a lesser extent in the facial and optic cranial nerves. Volunteers exposed for two 4 hor periods at average concentrations of 110 ppm showed statistically significant decreases in performance ability on tests of perception, reaction time, memory, and manual dexterity campared to their performance before exposure.(Salvini) In male and female Mongolian gerbils, 3 months of inhalation to 60 ppm followed by 4- months of recovery produced increases increases in brain protein activity levels associated with brain damage.(Haglid)

1,1,2-TRICHLORETHANE

CAS: 79-00-5

1987 TLV 10 ppm (45 mg/m³) 8 hour TWA OSHA PEL (skin)

Colorless liquid

Uses: Chemical intermediate, solvent

Exposure: Inhalation, skin absorption

In animals it is a CNS depressant. It also causes liver and kidney damage. No cases of human intoxication or systemic effects have been reported. Lethal concentration for rats was 2000 ppm. 500 ppm was fatal to half the rats. Application of 0.5 ml to the skin of guinea pigs was lethal to all animals within 3 days. It is not highly irritating to the skin or eyes, but may injure the skin by defatting. There is limited evidence of carcinogenicity in animals at this time.

1,1,1-TRICHLORETHANE (Methylchloroform)

CAS: 71-55-6

TLV =350 ppm (1910 mg/m³) ceiling-15 minutes (NIOSH) and 350 ppm 8 hour TWA 1988(OSHA); 450 ppm STEL(ACGIH)

Solvent and cleaning agent

Inhalation, moderate skin absorption

A central nervous depressant

A number of human fatalities in closed spaces due to sudden deaths from sensitization of the myocardium to epinephrine. Based on animal studies, human effects can be expected as 20,000 ppm for 60 minutes will create coma and perhaps death.; 10,000 ppm for 30 minutes - marked incoordination.; 2000 ppm for 5 minutes - dysequilibrium. 900 to 1000 ppm for 20 minutes - lightheadedness, incoordination, and impaired equilibrium. At 350 ppm impairment of psychomotor task performance. (not consistently.)

At around 200 ppm matched pairs of exposed textile workers showed no evidence of cardiovascular, hepatic or renal injury over a six year study.

No clear oncogenic potential.IARC

Odor threshold ranges from 16 to 400 ppm

REFERENCE:

- 1. NIOSH Organic Solvent Neurotoxicity; Current Intelligence Bulletin 48 March 31 1987**
- 2. WHO Nordic Council of Ministers (1985). Organic solvents and the central nervous system, EH5. Copenhagen, Denmark: 1-35**
- 3. Baker EL, Smith T, Landrigan P (1985). The neurotoxicity of industrial solvents: a review of the literature. Am J. Ind Med 8: 207-217**
- 4. Haglid K., Briving C, Hansson HA, Rosengren L (1981). Trichlorethylene: long-lasting changes in the brain after rehabilitation. Neurotoxicology 2:659-673.**
- 5. Grandjean E, Munchinger R, Turrian v, Haas P, Knoepfel H, Rosenmund H (1955) Investigations into the effects of exposure to trichlorethylene in mechanical engineering. Br J Ind Med 12:131-142**

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