Mitra Mudd LLC

Residual Solvents

Overview

What are residual solvents?

What levels are acceptable?

Classification of residual solvents

Health concerns

What are residual solvents?

Residual solvents are chemicals used in processing and manufacturing of goods and pharmaceuticals that remains in the final product.

What levels are acceptable?

The amount of residual solvent found in the final product is a direct indicator of product quality and processing methods.

Although well-established, processing procedures with defined quality metrics have the ability to remove most if not all solvents, sometimes a minuet amount remains in the final product.

Permitted daily exposure (PDE) is defined in the present guideline as a pharmaceutically acceptable intake.

We can think of this as a “maximum safe daily limit”.

Classification of residual solvents

The solvents in this guideline are evaluated for their possible risk to human health and placed into one of three classes as follows:

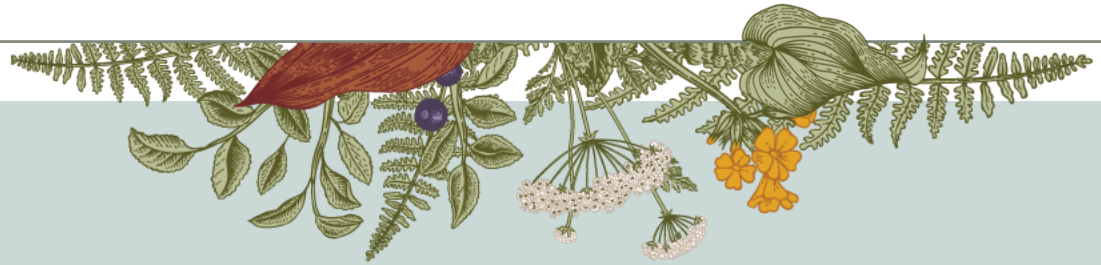
Class 1

Class 2

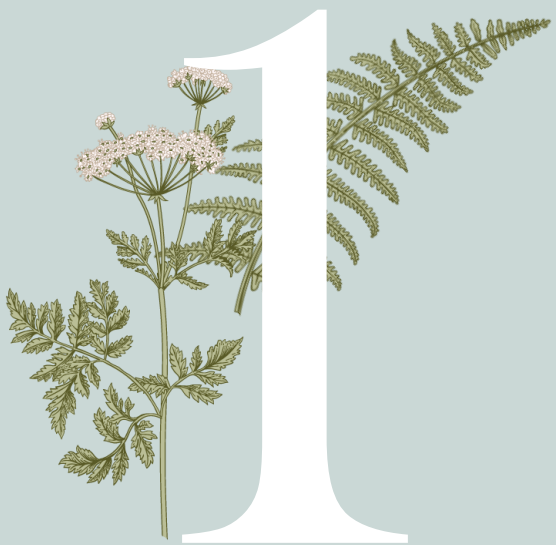
Class 3

Class 1 solvents: Solvents to be avoided

Strongly suspected and known human carcinogens, environmental hazards



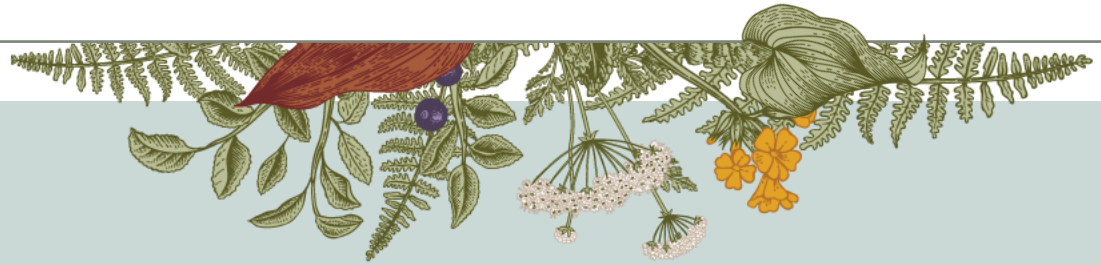
Solvents in Class 1 should not be used in the manufacture process due to their unacceptable toxicity & environmental effects.



Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental Hazard

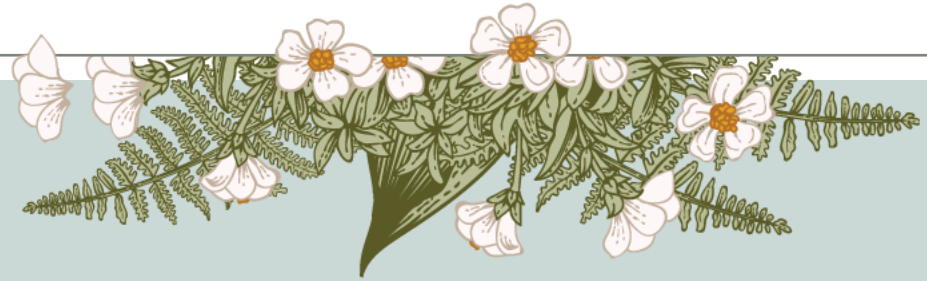
Class 2 solvents: Solvents to be limited

Non-genotoxic carcinogens & irreversible toxicity such as neurotoxicity or teratogenicity



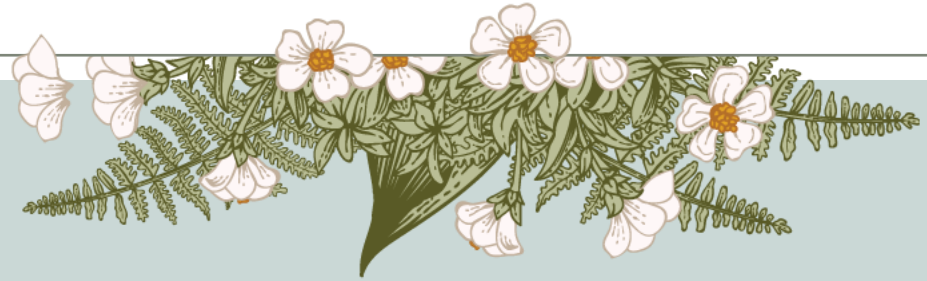
Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chloroform	3.6	360
Hexane	2.9	290
Methanol	30	3000
Methylene Chloride (DCM)	6	600
Toluene	8.9	890
Xylenes	21.7	2170
Tricholoethylene	0.8	80

Health Concerns



- Acetonitrile: Long-term exposure results in cyanide poisoning.
- Chloroform: Likely to be a carcinogenic to humans at high dose level.
- Hexane: Nerve damage and effects on learning and memory have also been found in animals ingesting n-hexane.
- Methanol: Blindness and death! (often found in “lab grade” & “reagent grade ethanol)
- Methylene Chloride (DCM): Nausea, vomiting, gastrointestinal ulceration and bleeding. Increase risk of developing cancer

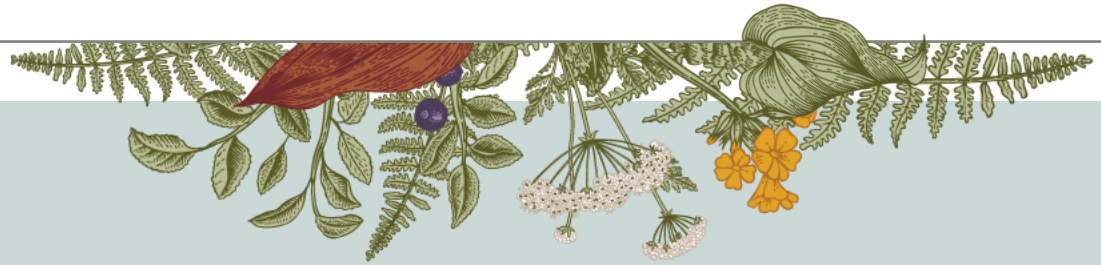
Health Concerns



- Toluene: Apoptotic neurodegeneration in the cerebellum and hippocampus.
- Xylenes: Effects of mild CNS depression include headache, lightheadedness, dizziness, confusion, nausea, impaired gait, and blurred vision
- Tricholoethylene: Kidney cancer and possibly liver cancer and non-Hodgkin lymphoma. CNS effects including headache, dizziness, lack of coordination, stupor, and coma.

Class 3 solvents: Solvents with low toxic potential

Low toxic potential to man

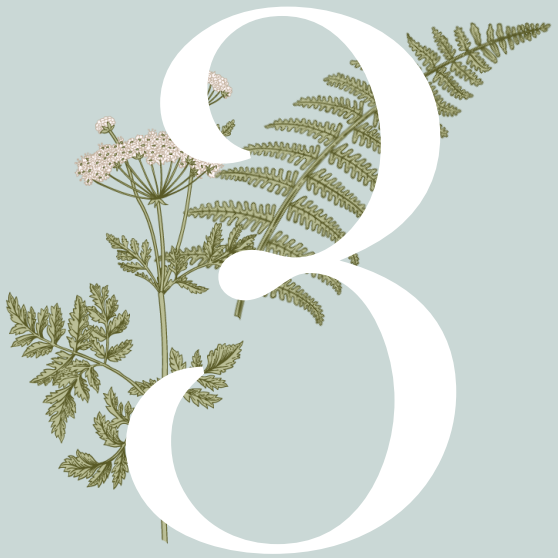


Concentration limit (ppm)

5000

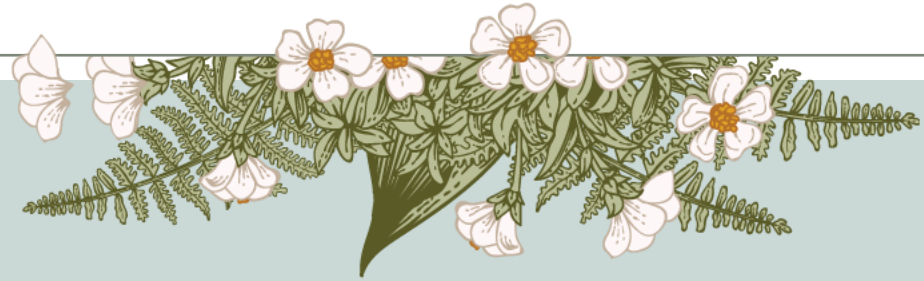
or

50 mg/day



Solvents	
Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
Butanol	Methyl acetate
Butyl acetate	pentane
Ethanol	Pentanol
Ethyl acetate	Propyl acetate
Ethyl ether	Formic Acid
Ethyl formate	

Health concerns



- Solvents classified as Class 3 are not known as a human health hazard at levels normally accepted in pharmaceuticals.
- Long-term data and studies on the toxicity or carcinogenicity for many of the solvents in Class 3 are not available. However, the data we currently have indicates that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Thank you

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