TOXICOLOGY OF C_1 - C_3 CHLORINATED HYDRO-CARBONS

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INTRODUCTION

Chlorinated C_1-C_3 hydrocarbons are mostly used as solvents and some, e.g. viny chloride and vinylidene chloride, in the production of plastics (PVC). Methyl chloride has been used as a refrigerant. Fluorine-containing chlorinated hydro carbons are still utilized as refrigerants and as propellants, e.g. in spray cans. Some of the C_3 compounds, e.g. allylic chlorides, are used as chemical agents and as pesticides.

Chlorinated compounds have been known for a long time. 1,2-Dichloroethane, for instance, was synthesized as early as 1795 by Dutch chemists and was therefore called "Dutch Oil". Chloroform was first synthesized in 1839/1840 and in 1847 used as inhalation narcotic by Simpson. Due to their chemical and physical properties i.e. high lipid solubility, high volatility and suitable boiling points and due to their cheapness the technical use of these compounds has increased enormously since about 1930 (1).

General Toxicology

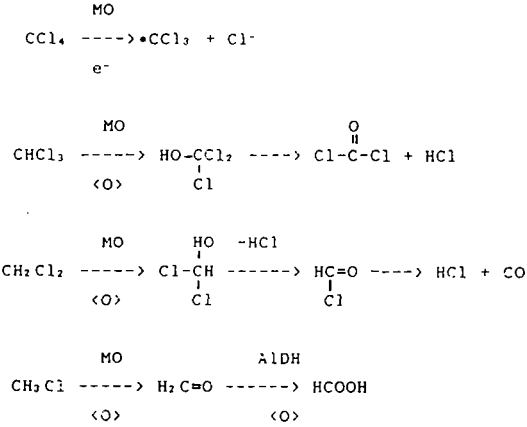
The acute toxicity of chlorinated hydrocarbons is characterized by narcotic effects. The high lipid solubility of these compounds leads to a rapid passage of the blood-brain barrier. After absorption of high doses signs of narcosis appear quickly. Death during this early stage of intoxication occurs by paralysis of the respiratory center. There is a pronounced effect on the heart particularly on the "stimulation conduction system" with typical sensitization against catecholamines which leads to arrhythmia and ventricular fibrillation. For these reasons the administration of catecholamines is contraindicated in cases of intoxication with chlorinated hydrocarbons. Lower doses can lead to fatigue cephalalgia and, in particular after chronic action, to uncharacteristic psycho-neurotic disorders. These effects can be caused by the substances themselves or by their metabolites.

Some of the chlorinated compounds cause typical lesions of the parenchyma especially that of the liver but also the kidney.
The metabolites are mainly responsible for the latter effect and for the carcinogenic activity of some chlorinated hydrocarbons.

Metabolism and specific toxic effects of chlorinated hydrocarbons:

1. C_1-compounds

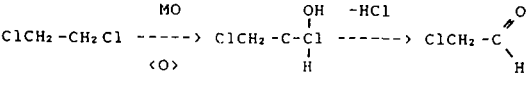
The C_1-compounds are bioactivated by monooxygenases (MO) according to the following scheme:



Tetrachloromethane is activated via "reductive metabolism". One of the C-Cl bonds is cleaved homolytically and an electron is transferred to the chlorine atom. The resulting trichloromethyl radical is responsible for the toxic effects of terachloromethane. It can produce further radicals and "reactive oxygen species" and it induces lipid peroxidation. CCl_4 causes centrolobular adiposis hepatica, cirrhosis and necroses of the liver. Damage of the kidney parenchyma can lead to anuria.
Chloroform is also subject to reductive metabolism. In the oxidative metabolism of $HCCl_3$ the highly reactive and toxic phosgene is formed.
In the metabolism of methylene chloride, carbon monoxide is formed. Higher level exposure to CH_2Cl_2 can therefore lead to CO-hemoglobin formation.
Methyl chloride is metabolized via formaldehyde to formic acid. It can *produce degenerative damage in the central nervous system.*

2. C_2-compounds

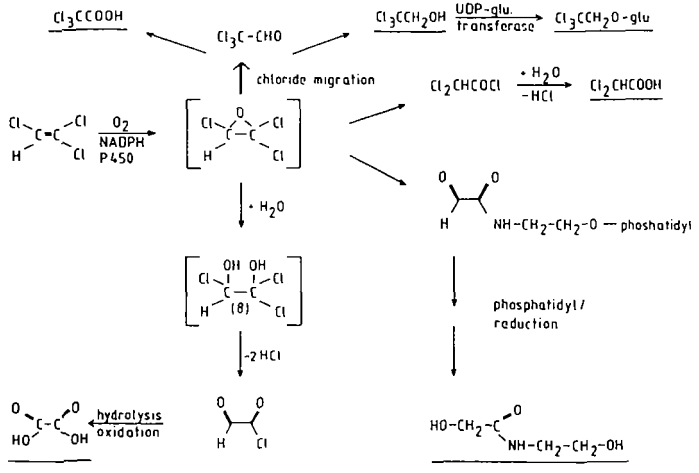
Saturated vicinal halogenated compounds can be activated by two different bioactivation mechansims.



enzyme

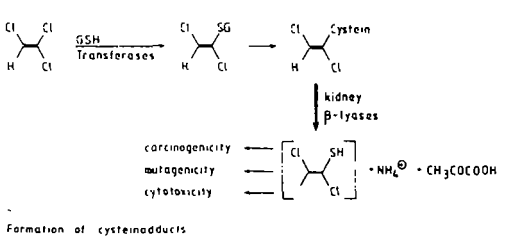
b) $ClCH_2-CH_2Cl + GSH \xrightarrow{\text{enzyme}} ClCH_2-CH_2SG + HCl$

Pathway a) yields chloroacetaldehyde which can be responsible for toxic and genotoxic effects. Vicinal halogenated hydrocarbons can form glutathione monoconjugates. They are of the mustard gas type and are extremely reactive. The high toxicity and the carcinogenic effects of the vicinal halogenated hydrocarbons probably depend on this bioactivation mechansim.
The metabolism of trichloroethylene is presented as an example of the biotransformation of chlorinated ethylenes. The underlined compounds have been found as metabolites in urine.



In the case of trichloroethylene or tetrachloroethylene there is, in addition, another possible activation mechanism which is probably responsible for the carcinogenic effects of these compounds in the kidney.

Metabolic pathways of trichloroethylene



Formation of cysteinadducts

The cysteine adduct is cleaved by β-lyases in the kidney, the unstable SH-adduct (in brackets) and its degeneration or rearrangement compounds are presumably the species responsible for the cytotoxic, mutagenic and carcinogenic effects.

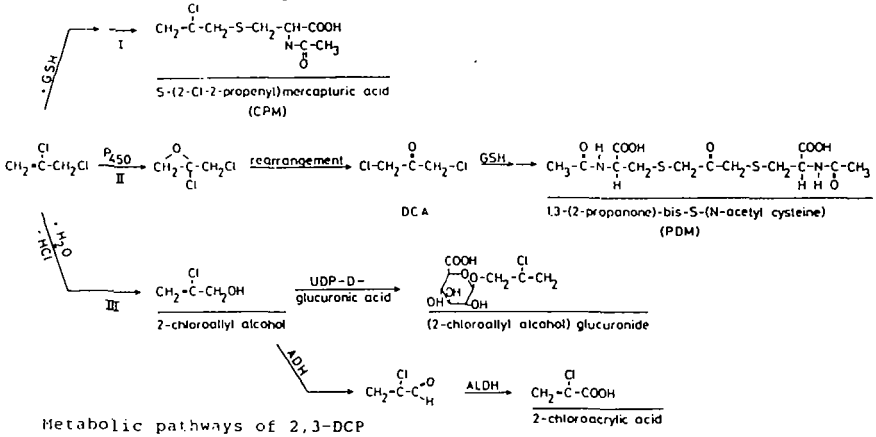
Carcinogenicity of the C1- and C2-compounds

All chlorinated C_1- and C_2-hydrocarbons are carcinogenic or suspected of being carcinogenic, except 1,1,1-trichloroethane (methylchloroform).

3. C_3-compounds

Of the C_3-chlorinated hydrocarbons only 1,2-dichloropropane has importance as solvent, especially in Italy. Metabolism and toxicology of the saturated compounds are similar to that of the saturated C_2-compounds.

Of the unsaturated C_3-substances, allylic chlorides are of particular interest. Allylic compounds with suitable leaving groups are directly mutagenic (without metabolic activation) and genotoxic and they form adducts with DNA-components; some of them are carcinogenic. As an example, the metabolic scheme of 2,3-dichloro-1-propene is presented. Besides having direct genotoxic activities, allylic compounds can also be bioactivated to further mutagenic and carcinogenic metabolic intermediates.



Metabolic pathways of 2,3-DCP

Chlorinated C_3-compounds containing oxygen require special consideration because some of them belong to the group of strongest known mutagens and carcinogens. *Epichlorohydrin* $CH_2\text{-}\overset{O}{\overset{\diagdown\diagup}{}}\text{CH-CH}_2\text{-Cl}$ *is used as reagent in the formation of epoxide plastics and is mutagenic, genotoxic and carcinogenic.* 1,3-dichloropropan-2-ol was found in instant soups and certain soup spices. It is mutagenic and carcinogenic. 1,3-dichloropropan-2-one (1,3-dichloroacetone) is a metabolite of 1,2-dichloropropene. It was found in drinking and bathing water and in waste water from chlorine bleached paper pulp. It is a strong mutagen and carcinogen. 2-chloroacrolein $CH_2\text{-HCl-CHO}$ is also found in water, is carcinogenic and one of the strongest mutagens in S.typhimurium TA100.

The bis-(1-chloroalkyl)ethers are extremely powerful carcinogens.