RISK ASSESSMENT FOR GENOTOXICITY, MUTAGENICITY AND CARCINOGENICITY OF SHORT CHAIN CHLORINATED HYDROCARBONS

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Introduction

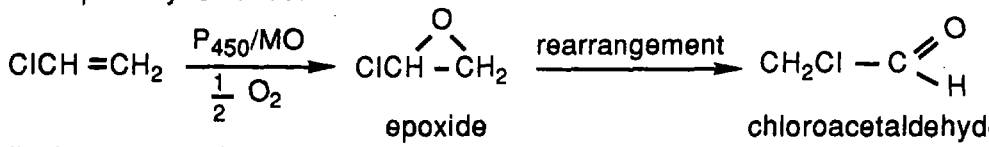
1,2-Dichloroethane was synthesized already as early as 1795 by Dutch chemists. Chloroform was used since 1847 as inhalation narcotic. Since about 1920-1930 volatile chlorinated hydrocarbons are used technically, in particular as solvents, but also for production of plastics, pesticides and other important chemicals. These compounds were long considered as non-hazardous compounds for human health. At high doses signs of narcosis appear quickly and death can occur by paralysis of the respiratory center. These substances, in general, are central nervous system depressants but there is a pronounced effect on the heart, with typical sensitization to catecholamines leading to arrhythmia and ventricular fibrillation. Lower doses can entail fatigue, cephalalgia and uncharacteristic psycho-neurotic disorders.
In the last twenty years, short chain chloroaliphatics have gained increased interest as environmental and occupational toxins, in particular as genotoxins. The genotoxic effects depend, in general, not on the compounds per se but on their metabolites and metabolic intermediates. In this paper we focus on mutagenicity and carcinogenicity since these are presently the most risk factors to human health.

Metabolic activation

In general, three different metabolic pathways are involved in the formation of reactive genotoxic intermediates of these compounds.

1. Oxidations by cytochrome P_{450} dependent monooxygenase (MO)
   Formaldehyde and phosgene can be formed with chloromethanes and chloroacetaldehydes, chloroacetyl chlorides and epoxides with C_2-chlorohydrocarbons (chloroethanes, chloroethenes).

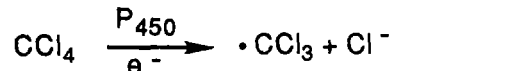
Example vinyl chloride:



epoxide chloroacetaldehyde

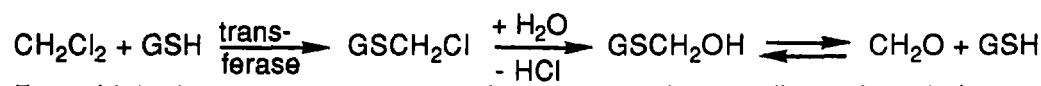
Both the epoxide and chloroacetaldehyde are conceivable genotoxic intermediates forming etheno-adducts with DNA.

2. Reduction by the cytochrome P_{450} dependent MO system.
   Radicals are formed, in particular with polychlorinated compounds.
   Example: carbon tetrachloride:



trichloromethyl radical

3. Cytosolic glutathione (GSH)-transferases induced GSH-conjugation.
   A wide spectrum of different reactive intermediates some of which are even unknown to date are formed following GSH-conjugation.
   Example methylene chloride:



Formaldehyde is considered to be the genotoxic intermediate of methylene chloride.

4. In the metabolism of allylic chlorides also alcohol dehydrogenase can be of importance.

Mutagenicity and carcinogenicity

In table 1 the mutagenic and carcinogenic properties as well as the categorisation of the US TLV-list and the German MAK-list of some representative chlorohydrocarbons are shown. Clear epidemiological evidence for carcinogenicity in humans was only found for vinyl chloride (A1 in the TLV-list and the MAK-list). Although for some compounds sufficient evidence for carcinogenicity in animal experiments at very high doses were found, only 1,2-dichloroethane was categorized under III A2 in the German MAK-list (III A2 "carcinogenic in animal experimentation only; namely under conditions which are comparable to those for possible exposure of a human being at the work place"). 1,1,1-Trichloroethane and hexachloroethane are the only volatile chlorinated hydrocarbons of technical importance which are not yet categorized

under III in the MAK-list. Hexachloroethane is, however, presently in process and the classification can change in the near future. All other compounds (table 1) are classified as suspected carcinogens (IIIB, German MAK-list).

Table I Mutagenicity, Carcinogenicity, TLVs of the US TLV-list, MAK values of the German MAK-list and categorisation of some chlorinated hydrocarbons

Substance	1) Mutagenicity in S.typhimurium	1) Carcinogenicity in animals	TLV ppm		MAK ppm	
Methyl chloride	+	in	50	---	50	III B
Dichloromethane	+	s	50	A 2	100	III B
Chloroform	-	s	10	A 2	10	III B
Carbontetrachloride	+	s	5	A 2	10	III B
Vinyl chloride	+	s	5	A 1	(TRK) 2	III A 1
Vinylidene chloride	+	l	5	---	2	III B
1,2-Dichloroethene	n.d.	n.d.	200	---	200	III B
Trichloroethene	+	in	50	---	50	III B
Tetrachloroethene	-	l	50	---	50	III B
1,2-Dichloroethane	+	s	10	---	---	III A 2
1,1,1-Trichloroethane	+	in	350	---	200	---
1,1,2-Trichloroethane	-	l	10	---	10	III B
1,1,2,2-Tetrachloroethane	+	s	1	---	1	III B
Hexachloroethane	o	l	1	---	1	---
Allyl choride	+	s	1	---	1	III B

n.d. = no data avaiable; in = inadequate experiment; s = sufficient evidence; l = limited evidence
TLV = Threshold limit value (USA);
MAK = Maximale Arbeitsplatzkonzentration (Germany) (Maximum concentrations at the workplace)
TRK = Technische Richtkonzentration (Germany) (Technical Exposure Limit assigned only for hazardous materials for which MAK values cannot be established)
Category USTLV-list A 1 = confirmed carcinogens
A 2 = suspected human carcinogens
MAK-list III A 1 confirmed carcinogens
III A 2 carcinogen in animal experimentation only
III B suspected carcinogens
1) Data from Eder (1991)

The carcinogenic risk for humans of these compounds , is considered to be low, except vinyl chloride.
No threshold can be established for carcinogenic compounds (III A1 and A2 in the MAK-list). In order to limit exposure to suspected carcinogens for protection against cancer exposure limits have to be established for the work place or tolerance values for drinking water, food and air. These values are established not only on a scientific toxicological but also on a socioeconomic basis.

Occupational risk

Highest exposures occur at the work places. Except vinyl chloride, no epidemiological evidence for a correlation of cancer and occupational exposure was found. The MAK value of tetrachloroethylene of 50ppm (335 mg/m^3), for instance, seems rather high at first glance. Nevertheless, according to the definition of MAK values and current knowledge these exposures at work places do not impair health.

Environmental risk

Uptake of volatile chlorinated hydrocarbons from drinking water, food and air is, in general, much lower than occupational exposure.European guidelines recommend a tolerance value of 1μg/l and the German and European (CEC) guidelines for the sum of these compounds is 10μg/l in drinking water. Assuming that a human drinks about 2l water per day, a total amount of 2μg or a daily dose of 0.0280μg per kg for a person with a body weight of 70kg is taken up. With the most sensitive animal species the lowest dose where tumors were observed with methylene chloride, as an example, was 60mg/kg. The dose of 0.028μg/kg is lower by a factor of 2 million. This example shows that the risk from uptake of these compounds via drinking water is negligible if the tolerance value is adhered to.

In principle, the same is valid for uptake via food and air. Chlorinated hydrocarbons can, however be oxidized in the atmosphere to numerous reactive intermediates which can contribute to mutagenicity and cancer. The risk assessment for these secondary products is, however, presently impossible.

Conclusion

Both the environmental and the occupational risk of C_1- and C_2-chlorinated hydrocarbons for mutation and cancer are low if the tolerance values, threshold values or technical exposure limits are adhered to. The situation is, however, different with some oxygen-containing chlorinated hydrocarbons such as bis-(chloromethyl)-ether or 2-chloroacrolein which are extremely strong carcinogens or mutagens. The role of the so called secondary products formed by oxidation of chlorocarbons in air or by chlorination of drinking water is also unclear to date.

1 Eder E, Chemosphere 23, 1991; 1783-1801