EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS

SCHER

Opinion on

"Effectiveness of vapour retardants in reducing risks to human health from paint strippers containing dichloromethane"

ETVREAD Final Report 01 April 2004

Adopted by the SCHER
during the 4th plenary of 18 March 2005

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1. BACKGROUND

The ETVAREAD study was launched by the Commission to evaluate the existing scientific information in the literature on the effectiveness of vapour retardants in reducing risk to human health from paint strippers containing dichloromethane (DCM). The study includes additional laboratory tests that could deliver useful data for the evaluation.

DCM is a well known chlorinated solvent with a high vapour pressure. DCM is also known as one of the strongest paint strippers that can be applied easily and efficiently for many different paint stripping applications. However, DCM could pose risks of accidental exposure due to its high vapour pressure. Some accidents are known where the preparation was not used in a professional manner with the appropriate protective equipment.

ETVAREAD was asked to investigate a variety of different paint strippers containing DCM. They found different emissions of DCM during the application depending on the specific formulation of the product. The purpose of the investigation was to define specifications for paint stripper products containing DCM that could answer the question of whether such products pose unacceptable risks to human health. Based on the outcome of the investigation, the Commission would consider launching a proposal restricting the marketing and use of specific paint stripper products which pose unacceptable risks.

ETVAREAD also investigated some alternative paint strippers containing no DCM, but it was not the primary aim to establish an extensive risk assessment on all available paint strippers.

In order to reduce the risk for consumers, ETVAREAD defines certain paint stripper specifications that should not be placed on the market. For instance, such products should not have a weight loss exceeding 1.85% and the container size should not exceed 500 ml. Furthermore, they recommend certain container requirements, safety warning and sale instructions.

For professional users, ETVAREAD recommends the same maximum weight loss, warning, instructions and the prescription of appropriate protective equipment.

2. TERMS OF REFERENCE

The SCHER is requested to assess the overall scientific quality of the ETVAREAD report. In considering this, the Committee is asked to comment on the methodology, finding, conclusions and recommendation in the report.

3. OPINION

ETVAREAD obtained 17 different paint strippers for testing, and results from 10 of those are presented in the report. The compositions of the products are not given, and only two of them are declared to contain vapour retardants, one of them having twice the concentration of the other. The “evaporation reduction rate” was known for some of the products, but the description of that parameter in an annex does not help the reader as it describes “percentage weight loss” and the formula given is wrong. This test must be difficult to reproduce between laboratories as it is based on the use of a fume hood with the fan off. The air flow over the glass dish is critical for

this test and that may be very different in different laboratories (and may also vary in one fume hood due to different meteorological conditions).

3.1. Exposure assessment

The paint strippers have been tested by the application of 350 mL on 1 m^2 of chipboard in a 15 m^3 room with an air exchange rate of 4 as standard. The standard procedure included 5 minutes application, 10 minutes effecting and 10 minutes removal time. The average DCM concentration in the air during the procedure was measured in a sample taken with an active carbon test tube, and an infrared analyser also measured the actual concentration continuously.

There seems to be no investigation of the reproducibility of the tests, the only uncertainty presented in the results is that given for the test tubes by its manufacturer. No comparison of the results from the two analytical methods is given in the report, and no validation of either of the methods has been given.

Taking into account that the uncertainty in the results may be larger than what is indicated in the figures in the report it is difficult to say if there are any significant differences between the different experiments. The only comparison that can be made between paint strippers with and without vapour retardants present is between the three Kluthe products (Figure 4 in the report). The emission from the product with the lower concentration of retardant is not significantly different from that from the product without retardant even if only the uncertainty from the adsorbent tubes is taken into account. If other uncertainties are also taken into account it may even be difficult to see an influence of the higher concentration of the retardant.

The conclusion that can be drawn is that the measured TWA 25 min for the standard test of 10 of the 17 products was between 400 and 1700 ppm. The standard procedure used an air exchange rate of 4 which is higher than normal. The air intake was positioned low and the outlet high (in some experiments the other way around) on the opposite wall giving optimal conditions. The concentrations in "normal" conditions may therefore be higher. Another important factor is that the DCM vapours have a higher density than air resulting in higher concentrations close to the floor and thus giving children in the working area a higher exposure.

The only results presented from the infrared measurements are given in Figure 6 in the report. If the mechanism for the vapour retardation is that the additives form a skin on the surface when the solvent is evaporated, these results do not support a substantial effect of the retardants. This would have decreased the evaporation mainly during the effecting period, not so much during the application and removal.

The expected levels of DCM (11 to 160 ppm) discussed in the risk reduction section and in the conclusions are based on an air ventilation rate of 10 to 30 which are unrealistic.

The indication of a decreased emission when the surface was painted could be expected as the paint will dilute the DCM concentration in the stripper.

Recently a similar study (maybe from the same laboratory) was published (Rühl et al., 2004). Air concentrations between 1122 and 6719 mg/m^3 (330 to 1980 ppm) were measured from the 24 products studied in a setup very similar to that described in the ETVAREAD report. Rühl et al. (2004) also refer to other German measurements where paint stripping outdoors gave 158 to 2275 mg/m^3 (46 to 670 ppm) DCM in the air with a mean of 524 mg/m^3 (154 ppm). This

publication also mentions that vapour retardants may be effective on horizontal but not on vertical surfaces.

The ETVAREAD report only addresses exposure via inhalation, which is very important due to the high vapour pressure of DCM. However, dermal exposure should also be taken into consideration. Wearing of gloves is not sufficient to protect workers, because currently, there is no material available, which can completely resist DCM. Breakthrough times of different gloves can vary considerably. Latex gloves or gloves based on butyl polymers usually have breakthrough times between 2 and 8 minutes (Rühl, 2003). Only fluoropolymer gloves (fluorocarbon rubber) provide good protection for a time period of up to 150 minutes. However, fluoropolymer gloves are usually not used during paint stripping due to their high costs (50 € per pair). Therefore dermal exposure may be considerable.

3.2. Effect assessment

The ETVAREAD report does not contain an extensive effect assessment and the SCHER therefore made the following compilation of effects related to inhalation of DCM.

The adverse health effects of DCM have been evaluated by IMM (1998), and the US ATSDR, (2000). The carcinogenicity of DCM has been evaluated by IARC (1999), and the US EPA (2002). The present assessment was partly derived from these documents.

The primary route of uptake of DCM in humans is considered to be inhalation (ATSDR, 2000). In addition, DCM can also be absorbed through the skin. The permeability rate in viable human skin was determined to be 24 $g/m^2/h$ (Ursin et al., 1995). The acute toxicity of DCM is low, and the most important acute toxic effect is on the CNS and elevated COHb levels. These effects are reversible, however fatalities have been reported. The typical effects of high exposure to solvents are often of neurobehavioral and cardio toxicological nature.

3.2.1. Fatalities

The ETVAREAD report contains the following information on fatalities related to the use of DCM containing paint strippers:

- A total of six fatalities have been reported among private users of various products of paint removers in the period 1960-2001. The causes of death were cardio-respiratory arrest, cerebral or pulmonary oedema. No information on exposure levels was reported in these cases, but it is assumed a too high level of DCM in the working area, as the material was not used according to the instructions, with low ventilation or in closed rooms.

- Twenty four fatalities have been reported in connection with professional use of DCM, of which 20 were connected with paint stripping processes. Eleven of these deaths were linked to paint removal in dipping tanks. In all these cases, improper use, non-compliance with safety regulations, lack of ventilation or the use of large quantities of paint removers were reported. The causes of death were oedema. An estimate of the concentration of DCM in air was only given in a few cases, and was then reported to be higher than 30.000 ppm.

- No fatalities were reported when DCM containing paint remover was used in accordance with the proper instructions.

3.2.2. Metabolism

Dichloromethane is metabolized by oxidative metabolism mediated by the ethanol inducible CYP2E1 leading to formyl chloride which decomposes to carbon monoxide that binds to haemoglobin to form COHb. An alternative pathway involves the conjugation with reduced glutathione catalysed by GSTT1. The conjugate, S-chloromethylglutathione is highly reactive. However, CYP2E1 has a much higher affinity for DCM compared to GST, and is the most important pathway at relevant human exposure levels, whereas the GSH dependent pathway becomes qualitatively relevant at high exposure concentrations. Difference in the metabolism of DCM is assumed to play an important role in the interspecies differences seen in the toxic response.

3.2.3. Central Nervous System effects

DCM affects the central nervous system and causes impairment of behavioural or sensory responses at high concentrations. CNS effects have been reported in humans occupationally and accidentally exposed to high levels of DCM. The LOEL for neurobehavioral changes (vigilance disturbance and impaired combined tracking monitoring performance) in humans was observed at exposure to 690 mg/m^3 (193 ppm) for 1.5 to 3 hours (Putz et al., 1979). Winneke (1981) attributed impaired psychological performance in volunteers following 3-4 hours exposure to 300 ppm of DCM.

Some epidemiological studies have investigated neurophysiological and psychological symptoms in occupationally exposed workers, but no statistically significant increases were demonstrated (Cherry et al., 1981; Lash et al., 1991; Bukowski et al., 1992; Soden, 1993)

Acute studies in animals show that DCM affects the central nervous system, consistent with findings in humans. Narcotic effects were observed in several animal species, including monkeys exposed to 10 000 ppm for up to 4 hrs.

Chronic exposure of gerbils to 210 ppm DCM for 3 months results in changes in neurotransmitter amino acids and brain enzymes. A lower DNA concentration was also reported in the hippocampus and cerebellum, probably due to cell loss (IMM, 1998).

3.2.4. Ischemic heart disease and carboxyhaemoglobin

Carbon monoxide is formed in the oxidative P450-mediated metabolism of DCM. Carbon monoxide binds strongly to haemoglobin as COHb. As the metabolic pathway is saturated at high concentrations, a maximum of <10% COHb in blood is normally reached, although occasionally still higher levels have been measured, Human exposure to 170-700 mg/m^3 (47.6-196 ppm) for 7.5 h leads to COHb levels of 1.8-6.8 % (IMM, 1998).

The formation of COHb most likely produces the cardiotoxic effects that have been seen in some studies. Several epidemiological studies have been performed in order to investigate the relationship between occupational exposure to DCM and cardiovascular disease. These studies were inconclusive. An excess of cardiovascular mortality was reported in one study with exposure of 490-1700 mg/m^3 (137- 476 ppm), but further follow-up studies did not provide compelling evidence of an increased risk (Ott et al., 1983).

3.2.5. Genotoxicity

The mutagenicity of DCM has been investigated in both *in vitro* and *in vivo* test systems. Large inter-species differences in genotoxic response have been reported, and effects are only seen at high exposure levels. After inhalation exposure of mice to DCM for 10 days at concentrations of 4000 ppm, a significantly increased frequency of sister chromatid exchanges and level of chromosomal aberrations in lung and bone marrow cells were reported in mice, whereas no evidence of chromosomal abnormalities was observed in rat bone cells following 6 months of exposure by inhalation for up to 3500 ppm DCM.

In addition, DNA-protein cross-links were detected in mouse liver at doses ranging from 500-4000 ppm, whereas no cross-links were detected in mouse lung, suggesting different mechanisms of genotoxicity in the two organs. Increased lung cell proliferations were observed in mouse lung at doses higher than 1500 ppm following 3 days of exposure. In a series of bacterial mutagenicity tests, the activity of DCM was strongest in *Salmonella typhimurium* TA 1535 modified to express the mammalian GSTT1 gene, indicating a role of GSTT1 in the activation of DCM to its mutagenic metabolite. Mutagenic activity was also reported in wild-type *Escherichia coli* following activation by mouse liver microsomes, a characteristic shared by cross-linking agents in mammalian mutagenicity tests. In Chinese hamster ovary cells and freshly prepared mouse hepatocytes, DCM induced DNA single-strand breaks, an effect not observed in rat hepatocytes. It was concluded that the mutagenic activity most likely was produced by the glutathione conjugate.

No studies regarding genotoxic effects in humans after inhalation exposure to DCM was identified. An increased level of chromosomal damage has been reported in workers occupationally exposed for DCM, but this group had a concomitant exposure for styrene, and thus could not be linked to DCM exclusively.

3.2.6. Carcinogenicity

Excess of mortality from cancer has been found in some studies of workers chronically exposed to DCM. The fatalities included elevated risk of cancer of biliary passages and liver (Lanes et al., 1990), pancreas (Hearne et al., 1987) and brain (Heineman et al., 1994). However, there seems to be no consistent pattern in tumour appearance, and the results have not been confirmed when other cohorts were examined (Hearne et al., 1990; Lanes et al., 1990; Tomenson et al., 1997). The occurrence of biliary cancer is interesting as the GSTT1 enzyme is expressed at a high level in the bile duct cells in humans.

In mice and rats, inhalation of very high levels of DCM significantly increased the incidence of liver and lung cancer and benign mammary gland tumours (NTP, 1986). In $B6C3F_1$ mice, doses at and above 2000 ppm for 6 hrs/day, 5 days/week and 102 weeks significantly increased the incidence of liver cancer compared to historical controls. In male F344/N rat a statistically significant risk of liver cancer was observed at 4000 ppm.

The species and organ specificity is anticipated to be linked to the GSTT1 activity. *In vitro* studies show that mouse GSTT1 more efficiently catalyze the conjugation of DCM with GSH than the human form. Furthermore, the enzyme is expressed at a higher level in mouse than in human, making it unlikely that humans have sufficient capacity to activate DCM for this compound to be considered to represent a carcinogenic risk (Sherratt et al., 2002).

Based upon the current evidence, DCM was classified by IARC as a group 2B carcinogen, by the EC as a Carc3, and by the US EPA as "reasonably anticipated to be a human carcinogen".

3.3. Risk characterisation

The most sensitive effect from short term inhalation exposure seems to be on the CNS, and 193 ppm DCM in air gave neurobehavioral changes in humans after 1.5 to 3 hours. The SCHER does not see any reason to disregard this as the LOAEL in the risk characterisation, although ATSDR used a higher level (300 ppm).

The ETVAREAD report uses the 300 ppm as a LOAEL and applies uncertainty factors of 10 for intraspecies variation and 3 for the conversion of a LOAEL to a NOAEL. They conclude that 10 ppm is an acceptable level of DCM for acute exposure in air. The SCHER does not support the reduction of these uncertainty factors mentioned in the "Conclusions and recommendations" in the ETVAREAD report.

The concentrations measured in the exposure investigations by ETVAREAD were in the range 400 to 1700 ppm. Those are all higher than the LOAELs discussed here, and obviously the exposure to DCM during use of paint strippers based on this compound is of concern.

The COHb formation was the basis for the recommendations from WHO Europe on air quality guidelines for ambient air (WHO, 1998). A maximum allowable increase of 0,1% in COHb from DCM led to a 24h guideline value of 3 mg/m^3 (0.84 ppm), and a weekly average of 0.45 mg/m^3 (0.13 ppm) (IMM, 1998). COHb formation seems to be the basis for most occupational threshold limit values for DCM. The Swedish occupational exposure limit value (8 h time-weighted average) is 120 mg/m^3 (33.6 ppm), while OSHA has decided on 25 ppm and ACGIH on 50 ppm.

Furthermore for the risk assessment, it has to be considered that dermal exposure may contribute considerably to the overall exposure. It can be speculated that dermal absorption may be even increased by the presence of the vapour retardants, as they may increase the DCM concentration on the skin.

4. CONCLUSIONS

The ETVAREAD report describes an experimental setup to determine the DCM emissions from the use of paint strippers. It is difficult to judge the influence of vapour retardants as the composition of the tested products are not given and the uncertainty in the measurements is not properly determined. It is also difficult to translate the laboratory results to real life situations as a rather high air exchange rate under optimal conditions was used. The measured DCM concentrations seem, however, to be in rather good agreement with what has been found in other studies referenced in the report. A shortcoming in the exposure assessment is that the dermal absorption has not been accounted for.

Neurobehavioral changes have been reported in humans after acute exposure to 193 and 300 ppm DCM in air. These values were exceeded in all experimental studies described in the report, and it is obvious that the exposure to DCM released from paint removers is of concern.

A major concern for the toxicity of DCM is the especially susceptible populations. Children are more susceptible due to a potential for higher exposure, as they have a higher ventilation rate than adults and the concentration of DCM may be higher at floor level. Genetically susceptible

individuals include persons who are carriers of the unfavourable genotypes of the enzymes involved in the biotransformation of DCM. Furthermore, people with predisposing disease of CVD may be a higher risk than healthy individuals, due to the toxicity of carbon monoxide formed by biotransformation of DCM.

The most critical parameter influencing the exposure to DCM from paint strippers is the ventilation rate, but there are data on unacceptable levels also for outdoor use, It may be very difficult to obtain sufficient ventilation during winter in a basement room with small windows and no low ventilation ducts.

The unacceptably high concentrations of DCM measured in air in the ETVAREAD study was obtained using 350 mL paint remover on a 1 m^2 surface. Larger volumes and/or larger areas will give even higher exposure.

Some substances used as alternatives to DCM in paint strippers are listed in the ETVAREAD report. There is, however, no information on their toxicological properties and the release of them from the products, so the SCHER is not able to assess them.

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6. LIST OF ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists,
ATSDR	Toxic Substances and Disease Registry
CNS	Central Nervous System
COHb	Carboxyhaemoglobin
DCM	Dichloromethane

EPA	Environmental Protection Agency
ETVAREAD	Expert Team for Vapour Retarding Additives
GSH	Glutathione
GST	Glutathione S-transferases
GSTT1	Glutathione S-transferase T1
IARC	International Agency for Research on Cancer
IMM	Institute of Environmental Medicine
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
NOAEL	No Observed Adverse Effect Level
OSHA	Occupational Health and Safety Administration
TWA	Time-Weighted Average
WHO	World Health Organization.

7. ACKNOWLEDGEMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are: Prof. H. Autrup, Prof. W. Hanke, Prof. Bo Jansson (rapporteur), and Prof. A. Steenhout.

Dr. I. Mangelsdorf is also acknowledged for valuable contributions.